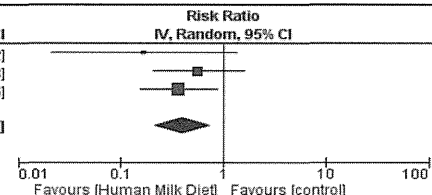
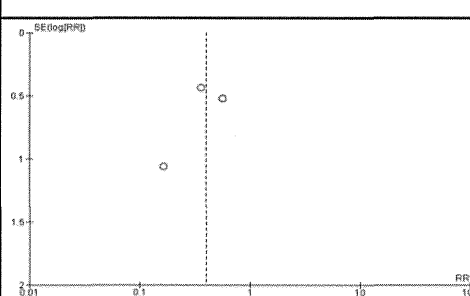
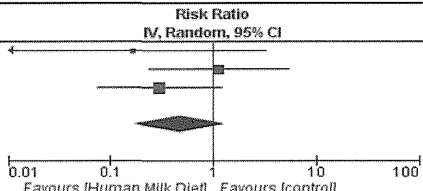
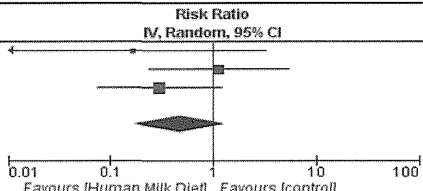
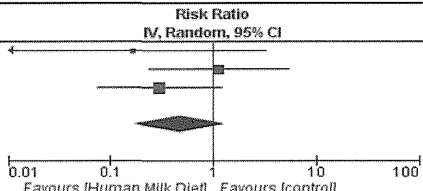
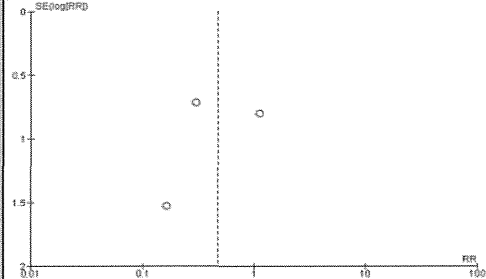


CQ2 メタアナリシス(1)

| CQ                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | CQ2:極低出生体重児の消化管機能障害発症の予防に母乳投与は有効か？ |                   |                                     |                                                          |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|-------------------|-------------------------------------|----------------------------------------------------------|----------------------------------|---------------------------|--------------------------|-------------------|------------------|--------|----------------------------------|-----------------|---|----|---|----|------|-------------------|---------------|---|----|----|----|-------|-------------------|---------------|---|-----|----|----|-------|-------------------|-----------------------|--|------------|--|------------|---------------|--------------------------|--------------|----|--|----|--|--|--|
| P                     | 極低出生体重児 (出生体重1.5kg以下、早産児)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                    |                   | I                                   | 母乳投与                                                     |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| C                     | 母乳投与をしない(ミルク)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                    |                   | O                                   | 消化管機能障害 (NEC/MRI/FIP) の予防 (発症)                           |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| 研究デザイン                | RCT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                    | 文献数               | 3                                   | コード<br>Cristofalo 2013<br>Schanler 2005<br>Sullivan 2010 |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| モデル                   | ランダム効果                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 方法                                 |                   | Inverse-variance method (RevMan5.3) |                                                          |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| 効果指標                  | リスク比                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 統合値                                |                   | 0.40 ( 0.21 - 0.75 ) P= 0.004       |                                                          |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| Forest plot           | <table><thead><tr><th>Study or Subgroup</th><th>Human Milk Diet<br/>Events</th><th>Human Milk Diet<br/>Total</th><th>Control<br/>Events</th><th>Control<br/>Total</th><th>Weight</th><th>Risk Ratio<br/>IV, Random, 95% CI</th></tr></thead><tbody><tr><td>Cristofalo 2013</td><td>1</td><td>29</td><td>5</td><td>24</td><td>9.2%</td><td>0.17 [0.02, 1.32]</td></tr><tr><td>Schanler 2005</td><td>5</td><td>78</td><td>10</td><td>88</td><td>37.5%</td><td>0.56 [0.20, 1.58]</td></tr><tr><td>Sullivan 2010</td><td>8</td><td>138</td><td>11</td><td>69</td><td>53.3%</td><td>0.36 [0.15, 0.86]</td></tr><tr><td><b>Total (95% CI)</b></td><td></td><td><b>245</b></td><td></td><td><b>181</b></td><td><b>100.0%</b></td><td><b>0.40 [0.21, 0.75]</b></td></tr><tr><td>Total events</td><td>14</td><td></td><td>26</td><td></td><td></td><td></td></tr></tbody></table> <p>Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 1.17, df = 2 (P = 0.56); I<sup>2</sup> = 0%<br/>Test for overall effect: Z = 2.86 (P = 0.004)</p>  |                                    |                   |                                     |                                                          | Study or Subgroup                | Human Milk Diet<br>Events | Human Milk Diet<br>Total | Control<br>Events | Control<br>Total | Weight | Risk Ratio<br>IV, Random, 95% CI | Cristofalo 2013 | 1 | 29 | 5 | 24 | 9.2% | 0.17 [0.02, 1.32] | Schanler 2005 | 5 | 78 | 10 | 88 | 37.5% | 0.56 [0.20, 1.58] | Sullivan 2010 | 8 | 138 | 11 | 69 | 53.3% | 0.36 [0.15, 0.86] | <b>Total (95% CI)</b> |  | <b>245</b> |  | <b>181</b> | <b>100.0%</b> | <b>0.40 [0.21, 0.75]</b> | Total events | 14 |  | 26 |  |  |  |
| Study or Subgroup     | Human Milk Diet<br>Events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Human Milk Diet<br>Total           | Control<br>Events | Control<br>Total                    | Weight                                                   | Risk Ratio<br>IV, Random, 95% CI |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| Cristofalo 2013       | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 29                                 | 5                 | 24                                  | 9.2%                                                     | 0.17 [0.02, 1.32]                |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| Schanler 2005         | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 78                                 | 10                | 88                                  | 37.5%                                                    | 0.56 [0.20, 1.58]                |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| Sullivan 2010         | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 138                                | 11                | 69                                  | 53.3%                                                    | 0.36 [0.15, 0.86]                |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| <b>Total (95% CI)</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <b>245</b>                         |                   | <b>181</b>                          | <b>100.0%</b>                                            | <b>0.40 [0.21, 0.75]</b>         |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| Total events          | 14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                    | 26                |                                     |                                                          |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
|                       | コメント: 検索した文献においては、母乳とMRI、FIPの関連を述べたものはなく、NECの発症のみ、についての解析となった。                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                    |                   |                                     |                                                          |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| Funnel plot           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                    |                   |                                     |                                                          |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| その他の解析                | 施行せず                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    |                   |                                     |                                                          |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| メタリグレーション             | コメント:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                    |                   |                                     |                                                          |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |
| 感度分析                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                    |                   |                                     |                                                          |                                  |                           |                          |                   |                  |        |                                  |                 |   |    |   |    |      |                   |               |   |    |    |    |       |                   |               |   |     |    |    |       |                   |                       |  |            |  |            |               |                          |              |    |  |    |  |  |  |

CQ2 メタアナリシス(2)

| CQ                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | CQ2:極低出生体重児の消化管機能障害発症の予防に母乳投与は有効か？ |        |         |                                                          |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|--------|---------|----------------------------------------------------------|-------------------|------------------------------------------------------------------------------------|----------------------------------|----------------------------------|--|--------|----------------------------------|----------------------------------|--------|-------|--------|-------|-----------------|---|----|---|----|-------|-------------------|------------------------------------------------------------------------------------|---------------|---|----|---|----|-------|-------------------|---------------|---|-----|---|----|-------|-------------------|----------------|--|-----|--|-----|--------|-------------------|-------------------|--|--|--|--|--|--|---------------------------------------------------------------------|--|--|--|--|--|--|----------------------------------------------|--|--|--|--|--|--|
| P                                                                                        | 極低出生体重児(出生体重1.5kg以下、早産児)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                    |        | I       | 母乳投与                                                     |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| C                                                                                        | 母乳投与をしない(ミルク)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |        | O       | 生命予後を改善(死亡)                                              |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| 研究デザイン                                                                                   | RCT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                    | 文献数    | 3       | コード<br>Cristofalo 2013<br>Schanler 2005<br>Sullivan 2010 |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| モデル                                                                                      | ランダム効果                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                    | 方法     |         | Inverse-variance method (RevMan5.3)                      |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| 効果指標                                                                                     | リスク比                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                    | 統合値    |         | 0.47 ( 0.17 - 1.29 ) P= 0.15                             |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Forest plot                                                                              | <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">Human Milk Diet</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th rowspan="2">Risk Ratio<br/>IV, Random, 95% CI</th><th rowspan="2">Risk Ratio<br/>IV, Random, 95% CI</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th></tr></thead><tbody><tr><td>Cristofalo 2013</td><td>0</td><td>29</td><td>2</td><td>24</td><td>11.2%</td><td>0.17 [0.01, 3.31]</td><td rowspan="4"></td></tr><tr><td>Schanler 2005</td><td>3</td><td>78</td><td>3</td><td>88</td><td>39.6%</td><td>1.13 [0.23, 5.43]</td></tr><tr><td>Sullivan 2010</td><td>3</td><td>138</td><td>5</td><td>69</td><td>49.3%</td><td>0.30 [0.07, 1.22]</td></tr><tr><td>Total (95% CI)</td><td></td><td>245</td><td></td><td>181</td><td>100.0%</td><td>0.47 [0.17, 1.29]</td></tr><tr><td colspan="7">Total events 6 10</td></tr><tr><td colspan="7">Heterogeneity: Tau² = 0.02; Chi² = 2.05, df = 2 (P = 0.36); I² = 2%</td></tr><tr><td colspan="7">Test for overall effect: Z = 1.46 (P = 0.15)</td></tr></tbody></table> |                                    |        |         |                                                          | Study or Subgroup | Human Milk Diet                                                                    |                                  | Control                          |  | Weight | Risk Ratio<br>IV, Random, 95% CI | Risk Ratio<br>IV, Random, 95% CI | Events | Total | Events | Total | Cristofalo 2013 | 0 | 29 | 2 | 24 | 11.2% | 0.17 [0.01, 3.31] |  | Schanler 2005 | 3 | 78 | 3 | 88 | 39.6% | 1.13 [0.23, 5.43] | Sullivan 2010 | 3 | 138 | 5 | 69 | 49.3% | 0.30 [0.07, 1.22] | Total (95% CI) |  | 245 |  | 181 | 100.0% | 0.47 [0.17, 1.29] | Total events 6 10 |  |  |  |  |  |  | Heterogeneity: Tau² = 0.02; Chi² = 2.05, df = 2 (P = 0.36); I² = 2% |  |  |  |  |  |  | Test for overall effect: Z = 1.46 (P = 0.15) |  |  |  |  |  |  |
|                                                                                          | Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Human Milk Diet                    |        | Control |                                                          |                   | Weight                                                                             | Risk Ratio<br>IV, Random, 95% CI | Risk Ratio<br>IV, Random, 95% CI |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Events                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Total                              | Events | Total   |                                                          |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Cristofalo 2013                                                                          | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 29                                 | 2      | 24      | 11.2%                                                    | 0.17 [0.01, 3.31] |  |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Schanler 2005                                                                            | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 78                                 | 3      | 88      | 39.6%                                                    | 1.13 [0.23, 5.43] |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Sullivan 2010                                                                            | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 138                                | 5      | 69      | 49.3%                                                    | 0.30 [0.07, 1.22] |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Total (95% CI)                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 245                                |        | 181     | 100.0%                                                   | 0.47 [0.17, 1.29] |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Total events 6 10                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |        |         |                                                          |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Heterogeneity: Tau² = 0.02; Chi² = 2.05, df = 2 (P = 0.36); I² = 2%                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |        |         |                                                          |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Test for overall effect: Z = 1.46 (P = 0.15)                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |        |         |                                                          |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| コメント： 検索したStudyのセッティングでは、外科的治療が必要になった場合は転院(調査対象圏外への移動)となる場合が多く、死亡の全エピソードを確認できていないと推測された。 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |        |         |                                                          |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Funnel plot                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                    |        |         |                                                          |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| その他の解析                                                                                   | 施行せず                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                    |        |         |                                                          |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| メタリグレーション                                                                                | コメント:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                    |        |         |                                                          |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| 感度分析                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |        |         |                                                          |                   |                                                                                    |                                  |                                  |  |        |                                  |                                  |        |       |        |       |                 |   |    |   |    |       |                   |                                                                                    |               |   |    |   |    |       |                   |               |   |     |   |    |       |                   |                |  |     |  |     |        |                   |                   |  |  |  |  |  |  |                                                                     |  |  |  |  |  |  |                                              |  |  |  |  |  |  |

## CQ2 SR レポートのまとめ

極低出生体重児における母乳投与に関して、2次スクリーニングに残った文献13編と、その引用文献1編を加えた14編を対象として検討をおこなった。内訳はシステマティックレビュー4編、RCT5編、コホート研究4編、症例対象研究1編であった。システマティックレビュー4編は最も新しいもので2007年のものであったが、検討できるスタディがないとして、最終的な結論に至っていなかったため、本検討では結果を利用できないと判断した。次に、RCT5編について検討を行った。RCT2編（Ghandehari 2012, Lucas 1996）はPICOに合致しないと考えられたため、検討対象から除外した。RCT3編での検討を行った。

### 【CQ2 極低出生体重児の消化管機能障害発症の予防に母乳投与は有効か？】

3編のRCTを対象に、消化管機能障害の発症の有無、死亡、ミルクカードなどのイレウスの発症の有無の各Outcomeに関するSRを行った。

まず、消化管機能障害の発症のOutcomeについては、今回対象とした3編の文献中には、NEC、FIP、MRIのなかでNECについてしか検討をされていなかったため、NEC発症をOutcomeとして検討を行った。FIP、MRIを扱った文献がないことは2次スクリーニングの文献選定時点で判明し、本SRではFIP、MRIについての検討はできないと判断した。NECの発症については、外科手術が必要なNEC、または、BELL分類でStg2以上の診断基準を満たす症例に相当する症例をNEC発症症例と設定して解析を行った。その結果、NEC発症は母乳投与群で有意に少なく（RR 0.40 [0.21-0.75] p=0.004）、母乳投与（または、ウシ由来の栄養投与の回避）はNECの発症を抑制すると考えられた。

3編のRCTの対象患者は、いずれも本ガイドライン（出生体重1.5kg以下、早産児）の対象と完全に一致はしていないものの、過半数は対象と一致すると考えられた。介入については、Cristofalo 2013、Schanler 2005 は対象を母乳が使えない児に限定しており、その上で、人工乳（牛乳由来のもの）を使用するか、ドナー母乳（母親のものでない母乳）を使用するかの2群について、RCTが行われていた。また、Sullivan 2010 では、母乳栄養を希望され、母乳栄養が可能な児を対象として、その上で、母乳強化剤としてヒト母乳由来の製剤を使うか、ウシ（牛乳）由来の製剤を使うかについてRCTが行われていた。また、3文献の対象となる施設では、外科的な介入の必要性が発生した場合は、搬送などによりStudyの検討圏外に移動する場合があり、NEC発症以外の検討項目については脱落症例となってしまうことから正確性の高い検討は不能であると考えられた。

この3編のRCTの検討における「介入」は母乳を使用することであるが、Sullivan 2010においては、母乳の存在によるBenefitよりもウシ由来の栄養成分を使用することによるRiskに注目し、母乳投与群をウシ由来の成分の栄養剤を除外した群として設定していた。この研究は単独でNECの発症に有意な差を示しており、ウシ由来の栄養成分が経腸栄養として使われることが、NECの発症要因となっている可能性が示唆された。

また、生命予後のOutcomeについては、対象とした3編のRCTでは研究観察期間中の死亡のみ

について記載しており、一般に予後として検討したい長期予後についての情報はなかった。短期予後について MA で検討したところ、上記母乳群で死亡率が低い傾向はあったものの、有意差は認めなかった。(RR 0.47 [0.17-1.29] p=0.15) セッティング上、転医・搬送症例が脱落してしまうことから、死亡症例全例のピックアップができないと考えられたため、死亡 Outcome のエビデンスは低いと考えられた。

最後に母乳に関連した腸閉塞（ミルクカードなど）の発症の Outcome であるが、これについては評価した文献が見つからず、現時点での SR での評価はできないと考えられた。

## CQ 2 Future research question

極低出生体重児における早期からの母乳栄養は、現在、一般には母乳に分泌された免疫成分の移行が期待されるとされ、NEC などの感染をベースとした腸管機能障害の発症には抑制的に働くと考えられている。そのため、一般に母乳の投与は推奨され、否定はされることが少ない。本 CQ の検討においても、結果として、母乳投与による NEC の発症が抑制効果を確認し、母乳投与は利益が多いという結論に到達した。しかし、一方で、Sullivan 2010 のように、母乳投与の利益よりも、ウシ（牛乳）由来のタンパク成分が投与されることの不利益に着目し、RCT で有意差を示している研究もある。また、今回、最終検討の対象とならなかった観察研究には、同じ母乳投与群であっても、早期に母乳投与をすすめ PN を早く離脱した群のほうが NEC の発症が多かった、とした文献もあり、NEC の発症についてはまだまだ多くの因子が複雑に絡み合っていると推測される。

また、今回、該当する Study がなく検討できなかった FIP、MRI について、また、母乳投与の長期予後への影響、ミルクカードなどの腸閉塞症状への影響などについては、今後の課題項目として検討される必要があると考えられた。

### CQ 3

#### 推奨提示

|          |                                                                    |
|----------|--------------------------------------------------------------------|
| CQ3      | 極低出生体重児の消化管機能障害発症の予防にプロバイオティクス投与は有効か？                              |
| 推奨草案     | 極低出生体重児においては、消化管機能障害とりわけ壊死性腸炎発症を低下するエビデンスがあるため、プロバイオティクス投与を提案する。   |
| エビデンスの強さ | B（中）                                                               |
| 推奨の強さ    | 1（強い）：「実施する」、または、「実施しない」ことを推奨する<br>②（弱い）：「実施する」、または、「実施しない」ことを提案する |

#### 推奨作成の経過

##### 【CQ 設定の背景】

本邦の新生児医療においてプロバイオティクス投与は、標準的に汎用されている治療のひとつである。しかし、極低出生体重児において、消化管機能障害（NEC、FIP、MRI）における予防に対する有効性は依然明らかではない。そのため、「極低出生体重児の消化管機能障害発症の予防にプロバイオティクス投与は有効か？」というCQにおいて、NECの発症の低下および死亡率の改善を益とし、プロバイオティクスによる敗血症を害とし、プロバイオティクス投与の現段階における知見を整理した。

##### 【文献検索とスクリーニング】

すでに、8編のシステマティックレビュー（SR）<sup>1) - 8)</sup>により、プロバイオティクスの投与によるNECの発症予防効果が見られている。しかし、Minds2014のGrade評価に基づく論文が1つのみ（7）であり、近年報告された4つの介入研究および観察研究4編も追加して、再度、介入研究を評価することとなった。

##### 【介入研究の評価】

25の介入研究よりSRをおこなった。消化管機能障害（NEC、FIP、MRI）発症、特にNECの発症および、生命予後の改善の各アウトカムにおいては、中程度の質のエビデンスが得られた。しかし、MRI/FIPの合併症については検討対象とされておらず、解析を行うことができなかった。

唯一、NECの発症については、プロバイオティクス投与を選択した群が投与しなかった群よりも有意に頻度が低いという解析結果となった（ $P < 0.00001$ ）。これは、プロバイオティクス投与を選択することはNECの発症率を下げ、その結果、予後を改善するという内容を支持するエビデンスであると考えられた。

本検討の最大の制限事項は、非直接性であった。対象としたRCTにおいてそれぞれのプロバイオティクスの使用については完全にはコンセンサスがなく、実際には施設間での差が大きい状況であると考えられた。本邦でも一部のプロバイオティクスは現在も提供を受けている製品でもある<sup>9)</sup>。そ

のためプロバイオティクス投与の有無による評価を行う本検討においては、無視できない非直接性であると考えられた。一方、有意差はないが、敗血症の報告はゼロではなかった。

#### 【観察研究の評価】

介入研究と同様に、NECの予防と死亡率低下が関連している結果を得た。しかし、介入研究と同様にプロバイオティクスの使用については研究・施設間でのコンセンサスは得られなかった。一方、害もあるため、児の状況に応じた適切なプロバイオティクスの使用を行うことが適切と思われた。

#### 【まとめ】

プロバイオティクス投与を選択した群で、有意にNECの発症頻度とともに死亡率が低下していた。一方、極低出生体重児においては、プロバイオティクスが因果関係は不明であっても害がないという確証もないため、児の状況に応じてプロバイオティクスを適切に使用するべきと思われた。

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### CQ3 一般向けサマリー

プロバイオティクスという整腸剤は、日本の極低出生体重児の入院中には標準的に使用されている治療薬です。このプロバイオティクスの投与により、重篤な病気である壊死性腸炎（NEC）の発症数とともに死亡数が大きく減っています。しかし、プロバイオティクスの種類はとても多く、また投与量や投与時期、方法など決まったものではありません。赤ちゃんの状態によっては投与できない場合や、まれにプロバイオティクス投与による敗血症が生じる可能性もあります。そのため、「赤ちゃんのお腹の状況に応じて、適切にプロバイオティクスを使用することがよい」と提案しました。

## CQ 3 定性的システマティックレビュー

|       |                     |                                           |
|-------|---------------------|-------------------------------------------|
| CQ    | 3                   | 極低出生体重児の消化管機能障害発症の予防にプロバイオティクス投与は有効か？     |
| P     | 消化管機能障害を発症した極低出生体重児 |                                           |
| I     | プロバイオティクス           |                                           |
| C     | 無治療／プロバイオティクス投与なし   |                                           |
| 臨床的文脈 |                     | 消化管機能障害を発症した極低出生体重児に対する適切なプロバイオティクスの検討である |

|             |                                                                              |
|-------------|------------------------------------------------------------------------------|
| O1          | 消化管機能障害 (NEC/MRI/FIP) の予防                                                    |
| 非直接性のまとめ    | いずれの研究もエンドポイントをNECとしてアウトカムを設定していたため、消化管機能障害 (NEC/MRI/FIP) としての非直接性はあると考えられた。 |
| バイアスリスクのまとめ | いずれの研究も中程度のバイアスリスクが存在すると判断された                                                |
| 非一貫性その他のまとめ | NECとしてアウトカムを設定しているため、非一貫性はある程度存在すると考えられた                                     |
| コメント        | エビデンスとしては比較的信頼できる(中程度)と評価した。結果としてプロバイオティクス投与によるNEC発生率に有意な差を認めた評価が多かった。       |

|             |                                                                        |
|-------------|------------------------------------------------------------------------|
| O2          | 生命予後の改善                                                                |
| 非直接性のまとめ    | いずれの研究もエンドポイントを死亡率としてアウトカムを設定していたため、非直接性は比較的低いと考えられた。                  |
| バイアスリスクのまとめ | いずれの研究も中程度のバイアスリスクが存在すると判断された                                          |
| 非一貫性その他のまとめ | 研究によりどの時点での死亡であるかの設定などが異なり、非一貫性はある程度存在すると考えられた                         |
| コメント        | エビデンスとしては比較的信頼できる(中程度)と評価した。結果としてプロバイオティクス投与による死亡率の低下に有意な差を認めた評価が多かった。 |

|             |                                                    |
|-------------|----------------------------------------------------|
| O3          | 敗血症 (プロバイオティクス関連)                                  |
| 非直接性のまとめ    | 今回のレビューで敗血症に関してエビデンスを評価するに足る研究はなかった。               |
| バイアスリスクのまとめ | バイアスリスクは中程度であると判断した                                |
| 非一貫性その他のまとめ | 研究により敗血症との関連性の有無が不明であり、非一貫性はある程度存在すると考えられた         |
| コメント        | プロバイオティクスによる敗血症が発生している結果もあり、安全性の確保についての評価は不可能であった。 |

# CQ3 メタアナリシス(1)

| CQ                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | CQ3:極低出生体重児の消化管機能障害発症の予防にプロバイオティクス投与は有効か？ |        |                                                       |                                     |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|--------|-------------------------------------------------------|-------------------------------------|--------------------------|------------|----------------------------------|----------------------------------|--|--------|----------------------------------|----------------------------------|--------|-------|--------|-------|-------------|---|----|----|-----|------|-------------------|--|-------------|-----|------|-----|------|-------|-------------------|--------------|---|-----|----|-----|-------|-------------------|---------------|----|-----|----|-----|-------|-------------------|-----------------------|--|-------------|--|-------------|---------------|--------------------------|--------------|-----|--|-----|--|--|--|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|--|--|--|
| P                                                                                                                                                           | 極低出生体重児(出生体重1.5kg以下、早産児)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                           |        | I                                                     | プロバイオティクス                           |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| C                                                                                                                                                           | 無治療群・プロバイオティクス投与無し                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                           |        | O                                                     | 消化管機能障害(NEC/MRI/FIP)の予防             |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| 研究デザイン                                                                                                                                                      | 観察                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                           | 文献数    | 4                                                     | コード                                 |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
|                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                           |        | Hartel 2014, Janvier 2014, Bonsante 2014, Hunter 2012 |                                     |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| モデル                                                                                                                                                         | ランダム効果                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                           | 方法     |                                                       | Inverse-variance method (RevMan5.3) |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| 効果指標                                                                                                                                                        | リスク比                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                           | 統合値    |                                                       | 0.20 ( 0.14 - 0.30 ) P= <0.00001    |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| Forest plot                                                                                                                                                 | <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">Pribiotics</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th rowspan="2">Risk Ratio<br/>IV, Random, 95% CI</th><th rowspan="2">Risk Ratio<br/>IV, Random, 95% CI</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th></tr></thead><tbody><tr><td>Hunter 2012</td><td>2</td><td>79</td><td>35</td><td>232</td><td>7.0%</td><td>0.17 [0.04, 0.68]</td><td rowspan="5"></td></tr><tr><td>Hartel 2014</td><td>116</td><td>3789</td><td>280</td><td>1562</td><td>55.7%</td><td>0.17 [0.14, 0.21]</td></tr><tr><td>Janvier 2014</td><td>5</td><td>294</td><td>31</td><td>317</td><td>14.0%</td><td>0.17 [0.07, 0.44]</td></tr><tr><td>Bonsante 2014</td><td>10</td><td>347</td><td>62</td><td>783</td><td>23.3%</td><td>0.36 [0.19, 0.70]</td></tr><tr><td><b>Total (95% CI)</b></td><td></td><td><b>4509</b></td><td></td><td><b>2894</b></td><td><b>100.0%</b></td><td><b>0.20 [0.14, 0.30]</b></td></tr><tr><td>Total events</td><td>133</td><td></td><td>408</td><td></td><td></td><td></td><td></td></tr><tr><td colspan="8">Heterogeneity: Tau<sup>2</sup> = 0.06; Chi<sup>2</sup> = 4.67, df = 3 (P = 0.20); I<sup>2</sup> = 36%<br/>Test for overall effect: Z = 7.93 (P &lt; 0.00001)</td></tr></tbody></table> |                                           |        |                                                       |                                     | Study or Subgroup        | Pribiotics |                                  | Control                          |  | Weight | Risk Ratio<br>IV, Random, 95% CI | Risk Ratio<br>IV, Random, 95% CI | Events | Total | Events | Total | Hunter 2012 | 2 | 79 | 35 | 232 | 7.0% | 0.17 [0.04, 0.68] |  | Hartel 2014 | 116 | 3789 | 280 | 1562 | 55.7% | 0.17 [0.14, 0.21] | Janvier 2014 | 5 | 294 | 31 | 317 | 14.0% | 0.17 [0.07, 0.44] | Bonsante 2014 | 10 | 347 | 62 | 783 | 23.3% | 0.36 [0.19, 0.70] | <b>Total (95% CI)</b> |  | <b>4509</b> |  | <b>2894</b> | <b>100.0%</b> | <b>0.20 [0.14, 0.30]</b> | Total events | 133 |  | 408 |  |  |  |  | Heterogeneity: Tau <sup>2</sup> = 0.06; Chi <sup>2</sup> = 4.67, df = 3 (P = 0.20); I <sup>2</sup> = 36%<br>Test for overall effect: Z = 7.93 (P < 0.00001) |  |  |  |  |  |  |  |
|                                                                                                                                                             | Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Pribiotics                                |        | Control                                               |                                     |                          | Weight     | Risk Ratio<br>IV, Random, 95% CI | Risk Ratio<br>IV, Random, 95% CI |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| Events                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Total                                     | Events | Total                                                 |                                     |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| Hunter 2012                                                                                                                                                 | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 79                                        | 35     | 232                                                   | 7.0%                                | 0.17 [0.04, 0.68]        |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| Hartel 2014                                                                                                                                                 | 116                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 3789                                      | 280    | 1562                                                  | 55.7%                               | 0.17 [0.14, 0.21]        |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| Janvier 2014                                                                                                                                                | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 294                                       | 31     | 317                                                   | 14.0%                               | 0.17 [0.07, 0.44]        |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| Bonsante 2014                                                                                                                                               | 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 347                                       | 62     | 783                                                   | 23.3%                               | 0.36 [0.19, 0.70]        |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| <b>Total (95% CI)</b>                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>4509</b>                               |        | <b>2894</b>                                           | <b>100.0%</b>                       | <b>0.20 [0.14, 0.30]</b> |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| Total events                                                                                                                                                | 133                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                           | 408    |                                                       |                                     |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.06; Chi <sup>2</sup> = 4.67, df = 3 (P = 0.20); I <sup>2</sup> = 36%<br>Test for overall effect: Z = 7.93 (P < 0.00001) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                           |        |                                                       |                                     |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| コメント: NECのみで評価                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                           |        |                                                       |                                     |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| Funnel plot                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                           |        |                                                       |                                     |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
|                                                                                                                                                             | コメント: NECのみで評価                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                           |        |                                                       |                                     |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| その他の解析                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                           |        |                                                       | コメント:                               |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| メタリグレーション                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                           |        |                                                       |                                     |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |
| 感度分析                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                           |        |                                                       |                                     |                          |            |                                  |                                  |  |        |                                  |                                  |        |       |        |       |             |   |    |    |     |      |                   |  |             |     |      |     |      |       |                   |              |   |     |    |     |       |                   |               |    |     |    |     |       |                   |                       |  |             |  |             |               |                          |              |     |  |     |  |  |  |  |                                                                                                                                                             |  |  |  |  |  |  |  |

### CQ 3 メタアナリシス(2)

| CQ                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | CQ3:極低出生体重児の消化管機能障害発症の予防にプロバイオティクス投与は有効か？ |                                   |                    |                                                                                                                                                                                                                                                                                                                                                    |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
|-----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-----------------------------------|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|----------------------------------|-------------------------|--------|----------------------------------|------|----------------------------------|------------|-------|--------|------|-------------------|------|--|---------------|-------|--------|------|-------------------|------|--|-------------|------|------|------|-------------------|------|--|------------|-------|--------|------|-------------------|------|--|--------------|-------|--------|------|-------------------|------|--|-------------------|------|------|------|--------------------|------|--|------------|-------|-------|--|---------------|------|--|-------------|--------|--------|-------|-------------------|------|--|------------|-------|-------|------|-------------------|------|--|--------------|-------|-------|------|-------------------|------|--|-------------------------|------|-------|------|-------------------|------|--|---------------|------|------|------|-------------------|------|--|------------|-------|--------|------|-------------------|------|--|------------|-------|-------|------|-------------------|------|--|-----------|-------|--------|------|-------------------|------|--|---------------|------|------|------|-------------------|------|--|--------------|------|-------|------|-------------------|------|--|------------|------|------|------|--------------------|------|--|----------|-------|--------|------|-------------------|------|--|--------------|-------|--------|------|-------------------|------|--|--------------|------|------|------|-------------------|------|--|----------|-------|--------|------|-------------------|------|--|--------------|------|-------|------|-------------------|------|--|-----------|-------|-------|------|-------------------|------|--|---------------|------|------|--|---------------|------|--|----------------|--|--|--|------------------|-------------------|--|--------------|--|--|--|--------|--|--|-----------------------------------------------------------------------------------------------------------|--|--|--|--|--|--|-------------------------------------------------|--|--|--|--|--|--|
| P                                                                                                         | 極低出生体重児(出生体重1.5kg以下、早産児)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                           |                                   | I                  | プロバイオティクス                                                                                                                                                                                                                                                                                                                                          |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |   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| C                                                                                                         | 無治療群・プロバイオティクス投与無し                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                           |                                   | O                  | 消化管機能障害(NEC/MRI/FIP)の予防                                                                                                                                                                                                                                                                                                                            |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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            |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| 研究デザイン                                                                                                    | RCT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 文献数                                       | 25                                | コード                | Nandhini 2015, Dilli 2015, Oncel 2014, Patole 2014, Saengtawesin 2014, Mansoni 2014, Totsu 2014, Jacobs 2013, Demirel 2013, Serce 2013 ,Fernandez-Carrocer 2013, Al-Hosni 2012, Rojas 2012, Sari 2011, Braga 2011, Mihatsch 2010, Samanta 2009, Rouge 2009, Lin 2008, Manzoni 2008, Manzoni 2006, Lin 2005, Bin-Nun 2005, Dani 2002, Kitajima 1997 |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
|                                                                                                           | モデル                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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                                                                                                                                                                                                         | Inverse-variance method (RevMan5.3) |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| 効果指標                                                                                                      | リスク比                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 統合値                                       | 0.46 ( 0.36 - 0.60 ) P= <0.000001 |                    |                                                                                                                                                                                                                                                                                                                                                    |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Forest plot                                                                                               | <table><thead><tr><th>Study or Subgroup</th><th>Probiotics<br/>Events Total</th><th>Placebo<br/>Events Total</th><th>Weight</th><th>Risk Ratio<br/>IV, Random, 95% CI</th><th>Year</th><th>Risk Ratio<br/>IV, Random, 95% CI</th></tr></thead><tbody><tr><td>Dilli 2015</td><td>6 200</td><td>30 200</td><td>8.3%</td><td>0.20 [0.09, 0.47]</td><td>2015</td><td></td></tr><tr><td>Nandhini 2015</td><td>8 108</td><td>16 110</td><td>9.3%</td><td>0.51 [0.23, 1.14]</td><td>2015</td><td></td></tr><tr><td>Patole 2014</td><td>0 77</td><td>1 76</td><td>0.6%</td><td>0.33 [0.01, 7.95]</td><td>2014</td><td></td></tr><tr><td>Oncel 2014</td><td>8 200</td><td>10 200</td><td>7.4%</td><td>0.80 [0.32, 1.99]</td><td>2014</td><td></td></tr><tr><td>Mansoni 2014</td><td>0 238</td><td>14 258</td><td>0.3%</td><td>0.04 [0.00, 0.62]</td><td>2014</td><td></td></tr><tr><td>Saengtawesin 2014</td><td>1 31</td><td>1 29</td><td>0.9%</td><td>0.94 [0.06, 14.27]</td><td>2014</td><td></td></tr><tr><td>Totsu 2014</td><td>0 153</td><td>0 130</td><td></td><td>Not estimable</td><td>2014</td><td></td></tr><tr><td>Jacobs 2013</td><td>11 548</td><td>24 551</td><td>12.0%</td><td>0.46 [0.23, 0.93]</td><td>2013</td><td></td></tr><tr><td>Serce 2013</td><td>7 104</td><td>7 104</td><td>6.0%</td><td>1.00 [0.36, 2.75]</td><td>2013</td><td></td></tr><tr><td>Demirel 2013</td><td>6 135</td><td>7 136</td><td>5.4%</td><td>0.86 [0.30, 2.50]</td><td>2013</td><td></td></tr><tr><td>Fernandez-Carrocer 2013</td><td>6 75</td><td>12 75</td><td>7.1%</td><td>0.50 [0.20, 1.26]</td><td>2013</td><td></td></tr><tr><td>Al-Hosni 2012</td><td>3 50</td><td>4 51</td><td>3.0%</td><td>0.77 [0.18, 3.25]</td><td>2012</td><td></td></tr><tr><td>Rojas 2012</td><td>6 176</td><td>10 184</td><td>6.3%</td><td>0.63 [0.23, 1.69]</td><td>2012</td><td></td></tr><tr><td>Braga 2011</td><td>0 119</td><td>4 112</td><td>0.7%</td><td>0.10 [0.01, 1.92]</td><td>2011</td><td></td></tr><tr><td>Sari 2011</td><td>6 110</td><td>10 111</td><td>6.4%</td><td>0.61 [0.23, 1.61]</td><td>2011</td><td></td></tr><tr><td>Mihatsch 2010</td><td>2 93</td><td>4 90</td><td>2.2%</td><td>0.48 [0.09, 2.58]</td><td>2010</td><td></td></tr><tr><td>Samanta 2009</td><td>5 91</td><td>15 95</td><td>6.5%</td><td>0.35 [0.13, 0.92]</td><td>2009</td><td></td></tr><tr><td>Rouge 2009</td><td>2 45</td><td>1 49</td><td>1.1%</td><td>2.18 [0.20, 23.21]</td><td>2009</td><td></td></tr><tr><td>Lin 2008</td><td>4 217</td><td>14 217</td><td>5.1%</td><td>0.29 [0.10, 0.85]</td><td>2008</td><td></td></tr><tr><td>Manzoni 2008</td><td>0 151</td><td>10 168</td><td>0.8%</td><td>0.05 [0.00, 0.90]</td><td>2008</td><td></td></tr><tr><td>Manzoni 2006</td><td>1 39</td><td>3 41</td><td>1.3%</td><td>0.35 [0.04, 3.23]</td><td>2006</td><td></td></tr><tr><td>Lin 2005</td><td>2 180</td><td>10 187</td><td>2.8%</td><td>0.21 [0.05, 0.94]</td><td>2005</td><td></td></tr><tr><td>Bin-Nun 2005</td><td>1 72</td><td>10 73</td><td>1.5%</td><td>0.10 [0.01, 0.77]</td><td>2005</td><td></td></tr><tr><td>Dani 2002</td><td>4 295</td><td>8 290</td><td>4.4%</td><td>0.49 [0.15, 1.61]</td><td>2002</td><td></td></tr><tr><td>Kitajima 1997</td><td>0 46</td><td>0 45</td><td></td><td>Not estimable</td><td>1997</td><td></td></tr><tr><td colspan="4">Total (95% CI)</td><td>3553 3582 100.0%</td><td>0.46 [0.36, 0.60]</td><td></td></tr><tr><td colspan="4">Total events</td><td>89 225</td><td></td><td></td></tr><tr><td colspan="4">Heterogeneity: Tau<sup>2</sup> = 0.01; Chi<sup>2</sup> = 22.51, df = 22 (P = 0.43); I<sup>2</sup> = 2%</td><td></td><td></td><td></td></tr><tr><td colspan="4">Test for overall effect: Z = 5.99 (P &lt; 0.00001)</td><td></td><td></td><td></td></tr></tbody></table> |                                           |                                   |                    |                                                                                                                                                                                                                                                                                                                                                    | Study or Subgroup                   | Probiotics<br>Events Total       | Placebo<br>Events Total | Weight | Risk Ratio<br>IV, Random, 95% CI | Year | Risk Ratio<br>IV, Random, 95% CI | Dilli 2015 | 6 200 | 30 200 | 8.3% | 0.20 [0.09, 0.47] | 2015 |  | Nandhini 2015 | 8 108 | 16 110 | 9.3% | 0.51 [0.23, 1.14] | 2015 |  | Patole 2014 | 0 77 | 1 76 | 0.6% | 0.33 [0.01, 7.95] | 2014 |  | Oncel 2014 | 8 200 | 10 200 | 7.4% | 0.80 [0.32, 1.99] | 2014 |  | Mansoni 2014 | 0 238 | 14 258 | 0.3% | 0.04 [0.00, 0.62] | 2014 |  | Saengtawesin 2014 | 1 31 | 1 29 | 0.9% | 0.94 [0.06, 14.27] | 2014 |  | Totsu 2014 | 0 153 | 0 130 |  | Not estimable | 2014 |  | Jacobs 2013 | 11 548 | 24 551 | 12.0% | 0.46 [0.23, 0.93] | 2013 |  | Serce 2013 | 7 104 | 7 104 | 6.0% | 1.00 [0.36, 2.75] | 2013 |  | Demirel 2013 | 6 135 | 7 136 | 5.4% | 0.86 [0.30, 2.50] | 2013 |  | Fernandez-Carrocer 2013 | 6 75 | 12 75 | 7.1% | 0.50 [0.20, 1.26] | 2013 |  | Al-Hosni 2012 | 3 50 | 4 51 | 3.0% | 0.77 [0.18, 3.25] | 2012 |  | Rojas 2012 | 6 176 | 10 184 | 6.3% | 0.63 [0.23, 1.69] | 2012 |  | Braga 2011 | 0 119 | 4 112 | 0.7% | 0.10 [0.01, 1.92] | 2011 |  | Sari 2011 | 6 110 | 10 111 | 6.4% | 0.61 [0.23, 1.61] | 2011 |  | Mihatsch 2010 | 2 93 | 4 90 | 2.2% | 0.48 [0.09, 2.58] | 2010 |  | Samanta 2009 | 5 91 | 15 95 | 6.5% | 0.35 [0.13, 0.92] | 2009 |  | Rouge 2009 | 2 45 | 1 49 | 1.1% | 2.18 [0.20, 23.21] | 2009 |  | Lin 2008 | 4 217 | 14 217 | 5.1% | 0.29 [0.10, 0.85] | 2008 |  | Manzoni 2008 | 0 151 | 10 168 | 0.8% | 0.05 [0.00, 0.90] | 2008 |  | Manzoni 2006 | 1 39 | 3 41 | 1.3% | 0.35 [0.04, 3.23] | 2006 |  | Lin 2005 | 2 180 | 10 187 | 2.8% | 0.21 [0.05, 0.94] | 2005 |  | Bin-Nun 2005 | 1 72 | 10 73 | 1.5% | 0.10 [0.01, 0.77] | 2005 |  | Dani 2002 | 4 295 | 8 290 | 4.4% | 0.49 [0.15, 1.61] | 2002 |  | Kitajima 1997 | 0 46 | 0 45 |  | Not estimable | 1997 |  | Total (95% CI) |  |  |  | 3553 3582 100.0% | 0.46 [0.36, 0.60] |  | Total events |  |  |  | 89 225 |  |  | Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 22.51, df = 22 (P = 0.43); I <sup>2</sup> = 2% |  |  |  |  |  |  | Test for overall effect: Z = 5.99 (P < 0.00001) |  |  |  |  |  |  |
|                                                                                                           | Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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                                                                                                                                                                                                         | Year                                | Risk Ratio<br>IV, Random, 95% CI |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Dilli 2015                                                                                                | 6 200                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 30 200                                    | 8.3%                              | 0.20 [0.09, 0.47]  | 2015                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Nandhini 2015                                                                                             | 8 108                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 16 110                                    | 9.3%                              | 0.51 [0.23, 1.14]  | 2015                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Patole 2014                                                                                               | 0 77                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1 76                                      | 0.6%                              | 0.33 [0.01, 7.95]  | 2014                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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| Oncel 2014                                                                                                | 8 200                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 10 200                                    | 7.4%                              | 0.80 [0.32, 1.99]  | 2014                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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| Mansoni 2014                                                                                              | 0 238                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 14 258                                    | 0.3%                              | 0.04 [0.00, 0.62]  | 2014                                                                                                                                      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| Saengtawesin 2014                                                                                         | 1 31                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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                                                                                                                                                                                                         |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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| Totsu 2014                                                                                                | 0 153                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| Jacobs 2013                                                                                               | 11 548                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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                                                                                                                                                                                                         |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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| Serce 2013                                                                                                | 7 104                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| Demirel 2013                                                                                              | 6 135                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 7 136                                     | 5.4%                              | 0.86 [0.30, 2.50]  | 2013                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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| Fernandez-Carrocer 2013                                                                                   | 6 75                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 12 75                                     | 7.1%                              | 0.50 [0.20, 1.26]  | 2013                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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| Al-Hosni 2012                                                                                             | 3 50                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 4 51                                      | 3.0%                              | 0.77 [0.18, 3.25]  | 2012                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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| Rojas 2012                                                                                                | 6 176                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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                                                                                                                                                                                                         |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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| Braga 2011                                                                                                | 0 119                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 4 112                                     | 0.7%                              | 0.10 [0.01, 1.92]  | 2011                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |   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| Sari 2011                                                                                                 | 6 110                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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                                                                                                                                                                                                         |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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            |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Mihatsch 2010                                                                                             | 2 93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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                                                                                                                                                                                                         |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Samanta 2009                                                                                              | 5 91                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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                                                                                                                                                                                                         |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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            |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Rouge 2009                                                                                                | 2 45                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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                                                                                                                                                                                                         |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |   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| Lin 2008                                                                                                  | 4 217                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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                                                                                                                                                                                                         |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Manzoni 2008                                                                                              | 0 151                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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                                                                                                                                                                                                         |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Manzoni 2006                                                                                              | 1 39                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 3 41                                      | 1.3%                              | 0.35 [0.04, 3.23]  | 2006                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Lin 2005                                                                                                  | 2 180                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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                                                                                                                                                                                                         |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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| Bin-Nun 2005                                                                                              | 1 72                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 10 73                                     | 1.5%                              | 0.10 [0.01, 0.77]  | 2005                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |          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| Dani 2002                                                                                                 | 4 295                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 8 290                                     | 4.4%                              | 0.49 [0.15, 1.61]  | 2002                                                                                                                                                                                                                                                                                                                                               |                                     |                                  |                         |        |                                  |      |                                  |            |       |        |      |                   |      |  |               |       |        |      |                   |      |  |             |      |      |      |                   |      |  |            |       |        |      |                   |      |  |              |       |        |      |                   |      |  |                   |      |      |      |                    |      |  |            |       |       |  |               |      |  |             |        |        |       |                   |      |  |            |       |       |      |                   |      |  |              |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |               |      |      |  |               |      |  |                |  |  |  |                  |                   |  |              |  |  |  |        |  |  |                                                                                                           |  |  |  |  |  |  |                                                 |  |  |  |  |  |  |
| Kitajima 1997                                                                                             | 0 46                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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    |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |   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| Total (95% CI)                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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    |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |   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| Total events                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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    |       |       |      |                   |      |  |                         |      |       |      |                   |      |  |               |      |      |      |                   |      |  |            |       |        |      |                   |      |  |            |       |       |      |                   |      |  |           |       |        |      |                   |      |  |               |      |      |      |                   |      |  |              |      |       |      |                   |      |  |            |      |      |      |                    |      |  |          |       |        |      |                   |      |  |              |       |        |      |                   |      |  |              |      |      |      |                   |      |  |          |       |        |      |                   |      |  |              |      |       |      |                   |      |  |           |       |       |      |                   |      |  |   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| Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 22.51, df = 22 (P = 0.43); I <sup>2</sup> = 2% |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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| Test for overall effect: Z = 5.99 (P < 0.00001)                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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| コメント: NECのみで評価                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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| Funnel plot                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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|                                                                                                           | コメント: NECのみで評価                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             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| その他の解析                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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| メタリグレーション                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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| 感度分析                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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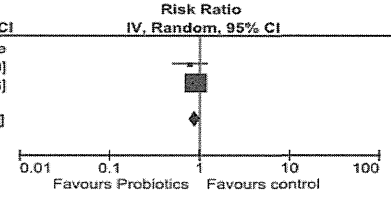
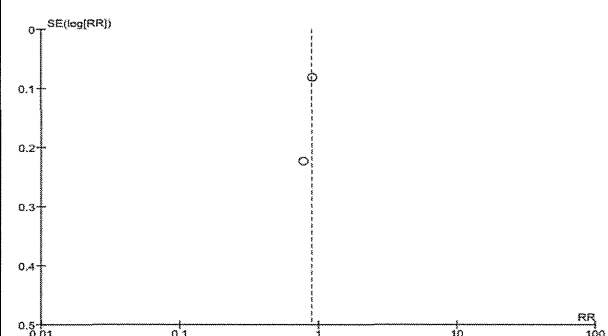
CQ 3    メタアナリシス(3)

| CQ                                                                                                      |                          | CQ3:極低出生体重児の消化管機能障害発症の予防にプロバイオティクス投与は有効か？                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |             |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
|---------------------------------------------------------------------------------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------|--------|-------------------------------------|--------------------------|-------------------------------------------------------|--|-------------------|------------|--|---------|--|--------|----------------------------------|------|----------------------------------|--------|-------|--------|-------|-------------|---|----|---|-----|------|-------------------|------|--|--------------|----|-----|----|-----|------|-------------------|------|---------------|---|-----|----|-----|------|-------------------|------|-------------|-----|------|-----|------|-------|-------------------|------|-----------------------|--|-------------|--|-------------|--|---------------|--------------------------|--|---------------|--|-----|--|-----|--|--|--|--|---------------------------------------------------------------------------------------------------------|--|--|--|--|--|--|--|--|------------------------------------------------|--|--|--|--|--|--|--|--|
| P                                                                                                       | 極低出生体重児(出生体重1.5kg以下、早産児) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |             | I      | プロバイオティクス                           |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| C                                                                                                       | 無治療群・プロバイオティクス投与無し       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |             | O      | 生命予後の改善                             |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| 研究デザイン                                                                                                  |                          | 観察                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         | 文献数         |        | 4                                   | コード                      | Hartel 2014, Janvier 2014, Bonsante 2014, Hunter 2012 |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| モデル                                                                                                     |                          | ランダム効果                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         | 方法          |        | Inverse-variance method (RevMan5.3) |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| 効果指標                                                                                                    |                          | リスク比                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         | 統合値         |        | 0.72 ( 0.61 - 0.86 ) P= 0.0002      |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| Forest plot                                                                                             |                          | <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">Probiotics</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th rowspan="2">Risk Ratio<br/>IV, Random, 95% CI</th><th rowspan="2">Year</th><th rowspan="2">Risk Ratio<br/>IV, Random, 95% CI</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th></tr></thead><tbody><tr><td>Hunter 2012</td><td>0</td><td>79</td><td>7</td><td>232</td><td>0.4%</td><td>0.19 [0.01, 3.36]</td><td>2012</td><td rowspan="4"></td></tr><tr><td>Janvier 2014</td><td>20</td><td>294</td><td>31</td><td>317</td><td>9.8%</td><td>0.70 [0.41, 1.19]</td><td>2014</td></tr><tr><td>Bonsante 2014</td><td>8</td><td>347</td><td>37</td><td>783</td><td>5.0%</td><td>0.49 [0.23, 1.04]</td><td>2014</td></tr><tr><td>Hartel 2014</td><td>291</td><td>3789</td><td>160</td><td>1562</td><td>84.8%</td><td>0.75 [0.62, 0.90]</td><td>2014</td></tr><tr><td colspan="2"><b>Total (95% CI)</b></td><td colspan="2"><b>4509</b></td><td colspan="2"><b>2894</b></td><td><b>100.0%</b></td><td><b>0.72 [0.61, 0.86]</b></td><td></td></tr><tr><td colspan="2">Total events:</td><td colspan="2">319</td><td colspan="2">235</td><td colspan="3"></td></tr><tr><td colspan="9">Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 2.03, df = 3 (P = 0.57); I<sup>2</sup> = 0%</td></tr><tr><td colspan="9">Test for overall effect: Z = 3.73 (P = 0.0002)</td></tr></tbody></table> |         |             |        |                                     |                          |                                                       |  | Study or Subgroup | Probiotics |  | Control |  | Weight | Risk Ratio<br>IV, Random, 95% CI | Year | Risk Ratio<br>IV, Random, 95% CI | Events | Total | Events | Total | Hunter 2012 | 0 | 79 | 7 | 232 | 0.4% | 0.19 [0.01, 3.36] | 2012 |  | Janvier 2014 | 20 | 294 | 31 | 317 | 9.8% | 0.70 [0.41, 1.19] | 2014 | Bonsante 2014 | 8 | 347 | 37 | 783 | 5.0% | 0.49 [0.23, 1.04] | 2014 | Hartel 2014 | 291 | 3789 | 160 | 1562 | 84.8% | 0.75 [0.62, 0.90] | 2014 | <b>Total (95% CI)</b> |  | <b>4509</b> |  | <b>2894</b> |  | <b>100.0%</b> | <b>0.72 [0.61, 0.86]</b> |  | Total events: |  | 319 |  | 235 |  |  |  |  | Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.03, df = 3 (P = 0.57); I <sup>2</sup> = 0% |  |  |  |  |  |  |  |  | Test for overall effect: Z = 3.73 (P = 0.0002) |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                       | Probiotics               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Control |             | Weight | Risk Ratio<br>IV, Random, 95% CI    | Year                     | Risk Ratio<br>IV, Random, 95% CI                      |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
|                                                                                                         | Events                   | Total                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Events  | Total       |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| Hunter 2012                                                                                             | 0                        | 79                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 7       | 232         | 0.4%   | 0.19 [0.01, 3.36]                   | 2012                     |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| Janvier 2014                                                                                            | 20                       | 294                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 31      | 317         | 9.8%   | 0.70 [0.41, 1.19]                   | 2014                     |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| Bonsante 2014                                                                                           | 8                        | 347                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 37      | 783         | 5.0%   | 0.49 [0.23, 1.04]                   | 2014                     |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| Hartel 2014                                                                                             | 291                      | 3789                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 160     | 1562        | 84.8%  | 0.75 [0.62, 0.90]                   | 2014                     |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| <b>Total (95% CI)</b>                                                                                   |                          | <b>4509</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         | <b>2894</b> |        | <b>100.0%</b>                       | <b>0.72 [0.61, 0.86]</b> |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| Total events:                                                                                           |                          | 319                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         | 235         |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.03, df = 3 (P = 0.57); I <sup>2</sup> = 0% |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |             |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| Test for overall effect: Z = 3.73 (P = 0.0002)                                                          |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |             |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
|                                                                                                         |                          | コメント: 死亡率として評価                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         |             |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| Funnel plot                                                                                             |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |             |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
|                                                                                                         |                          | コメント: 死亡率として評価                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         |             |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| その他の解析                                                                                                  |                          | コメント:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |             |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| メタリグレーション                                                                                               |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |             |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |
| 感度分析                                                                                                    |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |             |        |                                     |                          |                                                       |  |                   |            |  |         |  |        |                                  |      |                                  |        |       |        |       |             |   |    |   |     |      |                   |      |  |              |    |     |    |     |      |                   |      |               |   |     |    |     |      |                   |      |             |     |      |     |      |       |                   |      |                       |  |             |  |             |  |               |                          |  |               |  |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |  |

## CQ3 メタアナリシス(4)

| CQ                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | CQ3:極低出生体重児の消化管機能障害発症の予防にプロバイオティクス投与は有効か？ |                                     |                                       |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |     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--------|--------|-------|------------------------|--|-----------|-------|-------|------|------------------------|--|---------------|------|------|------|-------------------------|--|------------|------|------|------|------------------------|--|--------------|------|-------|------|------------------------|--|--------------|-------|--------|------|------------------------|--|----------|-------|-------|------|------------------------|--|--------------|------|------|------|------------------------|--|--------------|------|------|------|------------------------|--|----------|-------|--------|------|------------------------|--|-----------|-------|-------|------|------------------------|--|---------------|------|-------|------|------------------------|--|----------------|------|------|--------|-------------------|--|--------------|-----|-----|--|--|--|------------------------------------------------------------------------------------------------------------|--|--|--|--|--|------------------------------------------------|--|--|--|--|--|
| P                                                                                                          | 極低出生体重児(出生体重1.5kg以下、早産児)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                           |                                     | I                                     | プロバイオティクス                                                                                                                                                                                                                                                                                                                                          |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |     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                        |  |  |  |  |  |
| C                                                                                                          | 無治療群・プロバイオティクス投与無し                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                           |                                     | O                                     | 生命予後の改善                                                                                                                                                                                                                                                                                                                                            |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| 研究デザイン                                                                                                     | RCT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 文献数                                       | 25                                  | コード                                   | Nandhini 2015, Dilli 2015, Oncel 2014, Patole 2014, Saengtawesin 2014, Mansoni 2014, Totsu 2014, Jacobs 2013, Demirel 2013, Serce 2013, Fernandez-Carrocer 2013, Al-Hosni 2012, Rojas 2012, Sari 2011, Braga 2011, Mihatsch 2010, Samanta 2009, Rouge 2009, Lin 2008, Manzoni 2008, Manzoni 2006, Lin 2005, Bin-Nun 2005, Dani 2002, Kitajima 1997 |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| モデル                                                                                                        | ランダム効果                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 方法                                        | Inverse-variance method (RevMan5.3) |                                       |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| 効果指標                                                                                                       | リスク比                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 統合値                                       | 0.69 ( 0.56 - 0.85 ) P= <0.0004     |                                       |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Forest plot                                                                                                | <table><thead><tr><th>Study or Subgroup</th><th>Probiotics<br/>Events Total</th><th>Placebo<br/>Events Total</th><th>Weight</th><th>Risk Ratio<br/>IV, Random, 95% CI Year</th><th>Risk Ratio<br/>IV, Random, 95% CI</th></tr></thead><tbody><tr><td>Dilli 2015</td><td>6 200</td><td>14 200</td><td>4.2%</td><td>0.43 [0.17, 1.09] 2015</td><td></td></tr><tr><td>Nandhini 2015</td><td>10 108</td><td>9 110</td><td>4.9%</td><td>1.13 [0.48, 2.68] 2015</td><td></td></tr><tr><td>Oncel 2014</td><td>12 200</td><td>17 200</td><td>6.6%</td><td>0.71 [0.35, 1.44] 2014</td><td></td></tr><tr><td>Saengtawesin 2014</td><td>0 31</td><td>0 29</td><td></td><td>Not estimable 2014</td><td></td></tr><tr><td>Totsu 2014</td><td>2 153</td><td>0 130</td><td>0.5%</td><td>4.25 [0.21, 87.80] 2014</td><td></td></tr><tr><td>Patole 2014</td><td>0 77</td><td>0 76</td><td></td><td>Not estimable 2014</td><td></td></tr><tr><td>Mansoni 2014</td><td>9 238</td><td>18 258</td><td>5.7%</td><td>0.54 [0.25, 1.18] 2014</td><td></td></tr><tr><td>Jacobs 2013</td><td>27 548</td><td>28 551</td><td>10.6%</td><td>0.97 [0.58, 1.62] 2013</td><td></td></tr><tr><td>Fernandez-Carrocer 2013</td><td>1 75</td><td>7 75</td><td>1.0%</td><td>0.14 [0.02, 1.13] 2013</td><td></td></tr><tr><td>Serce 2013</td><td>5 104</td><td>4 104</td><td>2.4%</td><td>1.25 [0.35, 4.52] 2013</td><td></td></tr><tr><td>Demirel 2013</td><td>5 135</td><td>5 136</td><td>2.6%</td><td>1.01 [0.30, 3.40] 2013</td><td></td></tr><tr><td>Al-Hosni 2012</td><td>3 50</td><td>4 51</td><td>1.9%</td><td>0.77 [0.18, 3.25] 2012</td><td></td></tr><tr><td>Rojas 2012</td><td>48 176</td><td>54 184</td><td>17.4%</td><td>0.93 [0.67, 1.29] 2012</td><td></td></tr><tr><td>Braga 2011</td><td>26 119</td><td>27 112</td><td>11.9%</td><td>0.91 [0.56, 1.45] 2011</td><td></td></tr><tr><td>Sari 2011</td><td>3 110</td><td>3 111</td><td>1.6%</td><td>1.01 [0.21, 4.89] 2011</td><td></td></tr><tr><td>Mihatsch 2010</td><td>2 91</td><td>1 89</td><td>0.7%</td><td>1.96 [0.18, 21.19] 2010</td><td></td></tr><tr><td>Rouge 2009</td><td>2 45</td><td>4 49</td><td>1.5%</td><td>0.54 [0.10, 2.83] 2009</td><td></td></tr><tr><td>Samanta 2009</td><td>4 91</td><td>14 95</td><td>3.3%</td><td>0.30 [0.10, 0.87] 2009</td><td></td></tr><tr><td>Manzoni 2008</td><td>6 151</td><td>12 168</td><td>4.1%</td><td>0.56 [0.21, 1.45] 2008</td><td></td></tr><tr><td>Lin 2008</td><td>2 217</td><td>9 217</td><td>1.7%</td><td>0.22 [0.05, 1.02] 2008</td><td></td></tr><tr><td>Manzoni 2006</td><td>5 39</td><td>6 41</td><td>3.2%</td><td>0.88 [0.29, 2.64] 2006</td><td></td></tr><tr><td>Bin-Nun 2005</td><td>3 72</td><td>8 73</td><td>2.4%</td><td>0.38 [0.11, 1.38] 2005</td><td></td></tr><tr><td>Lin 2005</td><td>7 180</td><td>20 187</td><td>5.1%</td><td>0.36 [0.16, 0.84] 2005</td><td></td></tr><tr><td>Dani 2002</td><td>0 295</td><td>2 290</td><td>0.5%</td><td>0.20 [0.01, 4.08] 2002</td><td></td></tr><tr><td>Kitajima 1997</td><td>7 46</td><td>20 45</td><td>6.0%</td><td>0.34 [0.16, 0.73] 1997</td><td></td></tr><tr><td>Total (95% CI)</td><td>3551</td><td>3581</td><td>100.0%</td><td>0.69 [0.56, 0.85]</td><td></td></tr><tr><td>Total events</td><td>195</td><td>286</td><td></td><td></td><td></td></tr><tr><td colspan="6">Heterogeneity: Tau<sup>2</sup> = 0.04; Chi<sup>2</sup> = 26.08, df = 22 (P = 0.25); I<sup>2</sup> = 16%</td></tr><tr><td colspan="6">Test for overall effect: Z = 3.54 (P = 0.0004)</td></tr></tbody></table> |                                           |                                     |                                       |                                                                                                                                                                                                                                                                                                                                                    | Study or Subgroup | Probiotics<br>Events Total | Placebo<br>Events Total | Weight | Risk Ratio<br>IV, Random, 95% CI Year | Risk Ratio<br>IV, Random, 95% CI | Dilli 2015 | 6 200 | 14 200 | 4.2% | 0.43 [0.17, 1.09] 2015 |  | Nandhini 2015 | 10 108 | 9 110 | 4.9% | 1.13 [0.48, 2.68] 2015 |  | Oncel 2014 | 12 200 | 17 200 | 6.6% | 0.71 [0.35, 1.44] 2014 |  | Saengtawesin 2014 | 0 31 | 0 29 |  | Not estimable 2014 |  | Totsu 2014 | 2 153 | 0 130 | 0.5% | 4.25 [0.21, 87.80] 2014 |  | Patole 2014 | 0 77 | 0 76 |  | Not estimable 2014 |  | Mansoni 2014 | 9 238 | 18 258 | 5.7% | 0.54 [0.25, 1.18] 2014 |  | Jacobs 2013 | 27 548 | 28 551 | 10.6% | 0.97 [0.58, 1.62] 2013 |  | Fernandez-Carrocer 2013 | 1 75 | 7 75 | 1.0% | 0.14 [0.02, 1.13] 2013 |  | Serce 2013 | 5 104 | 4 104 | 2.4% | 1.25 [0.35, 4.52] 2013 |  | Demirel 2013 | 5 135 | 5 136 | 2.6% | 1.01 [0.30, 3.40] 2013 |  | Al-Hosni 2012 | 3 50 | 4 51 | 1.9% | 0.77 [0.18, 3.25] 2012 |  | Rojas 2012 | 48 176 | 54 184 | 17.4% | 0.93 [0.67, 1.29] 2012 |  | Braga 2011 | 26 119 | 27 112 | 11.9% | 0.91 [0.56, 1.45] 2011 |  | Sari 2011 | 3 110 | 3 111 | 1.6% | 1.01 [0.21, 4.89] 2011 |  | Mihatsch 2010 | 2 91 | 1 89 | 0.7% | 1.96 [0.18, 21.19] 2010 |  | Rouge 2009 | 2 45 | 4 49 | 1.5% | 0.54 [0.10, 2.83] 2009 |  | Samanta 2009 | 4 91 | 14 95 | 3.3% | 0.30 [0.10, 0.87] 2009 |  | Manzoni 2008 | 6 151 | 12 168 | 4.1% | 0.56 [0.21, 1.45] 2008 |  | Lin 2008 | 2 217 | 9 217 | 1.7% | 0.22 [0.05, 1.02] 2008 |  | Manzoni 2006 | 5 39 | 6 41 | 3.2% | 0.88 [0.29, 2.64] 2006 |  | Bin-Nun 2005 | 3 72 | 8 73 | 2.4% | 0.38 [0.11, 1.38] 2005 |  | Lin 2005 | 7 180 | 20 187 | 5.1% | 0.36 [0.16, 0.84] 2005 |  | Dani 2002 | 0 295 | 2 290 | 0.5% | 0.20 [0.01, 4.08] 2002 |  | Kitajima 1997 | 7 46 | 20 45 | 6.0% | 0.34 [0.16, 0.73] 1997 |  | Total (95% CI) | 3551 | 3581 | 100.0% | 0.69 [0.56, 0.85] |  | Total events | 195 | 286 |  |  |  | Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 26.08, df = 22 (P = 0.25); I <sup>2</sup> = 16% |  |  |  |  |  | Test for overall effect: Z = 3.54 (P = 0.0004) |  |  |  |  |  |
| Study or Subgroup                                                                                          | Probiotics<br>Events Total                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Placebo<br>Events Total                   | Weight                              | Risk Ratio<br>IV, Random, 95% CI Year | Risk Ratio<br>IV, Random, 95% CI                                                                                                                                                                                                                                                                                                                   |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Dilli 2015                                                                                                 | 6 200                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 14 200                                    | 4.2%                                | 0.43 [0.17, 1.09] 2015                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Nandhini 2015                                                                                              | 10 108                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 9 110                                     | 4.9%                                | 1.13 [0.48, 2.68] 2015                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Oncel 2014                                                                                                 | 12 200                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 17 200                                    | 6.6%                                | 0.71 [0.35, 1.44] 2014                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Saengtawesin 2014                                                                                          | 0 31                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0 29                                      |                                     | Not estimable 2014                    |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Totsu 2014                                                                                                 | 2 153                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0 130                                     | 0.5%                                | 4.25 [0.21, 87.80] 2014               |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                        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| Patole 2014                                                                                                | 0 77                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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                    |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Mansoni 2014                                                                                               | 9 238                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 18 258                                    | 5.7%                                | 0.54 [0.25, 1.18] 2014                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |     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| Jacobs 2013                                                                                                | 27 548                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 28 551                                    | 10.6%                               | 0.97 [0.58, 1.62] 2013                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Fernandez-Carrocer 2013                                                                                    | 1 75                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 7 75                                      | 1.0%                                | 0.14 [0.02, 1.13] 2013                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Serce 2013                                                                                                 | 5 104                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 4 104                                     | 2.4%                                | 1.25 [0.35, 4.52] 2013                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |     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                        |  |  |  |  |  |
| Demirel 2013                                                                                               | 5 135                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 5 136                                     | 2.6%                                | 1.01 [0.30, 3.40] 2013                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |     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                        |  |  |  |  |  |
| Al-Hosni 2012                                                                                              | 3 50                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 4 51                                      | 1.9%                                | 0.77 [0.18, 3.25] 2012                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |     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                        |  |  |  |  |  |
| Rojas 2012                                                                                                 | 48 176                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 54 184                                    | 17.4%                               | 0.93 [0.67, 1.29] 2012                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Braga 2011                                                                                                 | 26 119                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 27 112                                    | 11.9%                               | 0.91 [0.56, 1.45] 2011                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Sari 2011                                                                                                  | 3 110                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3 111                                     | 1.6%                                | 1.01 [0.21, 4.89] 2011                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Mihatsch 2010                                                                                              | 2 91                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1 89                                      | 0.7%                                | 1.96 [0.18, 21.19] 2010               |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Rouge 2009                                                                                                 | 2 45                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 4 49                                      | 1.5%                                | 0.54 [0.10, 2.83] 2009                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Samanta 2009                                                                                               | 4 91                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 14 95                                     | 3.3%                                | 0.30 [0.10, 0.87] 2009                |                                                                                                                                                                                                                                                                                                                                                    |                   |                            |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |        |        |       |                        |  |           |       |       |      |                        |  |               |      |      |      |                         |  |            |      |      |      |                        |  |              |      |       |      |                        |  |              |       |        |      |                        |  |          |       |       |      |                        |  |              |      |      |      |                        |  |              |      |      |      |                        |  |          |       |        |      |                        |  |           |       |       |      |                        |  |               |      |       |      |                        |  |                |      |      |        |                   |  |              |     |     |  |  |  |                                                                                                            |  |  |  |  |  |                                                |  |  |  |  |  |
| Manzoni 2008                                                                                               | 6 151                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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| Lin 2008                                                                                                   | 2 217                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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| Manzoni 2006                                                                                               | 5 39                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| Bin-Nun 2005                                                                                               | 3 72                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| Lin 2005                                                                                                   | 7 180                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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| Dani 2002                                                                                                  | 0 295                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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                    |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |     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| Kitajima 1997                                                                                              | 7 46                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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                    |                         |        |                                       |                                  |            |       |        |      |                        |  |               |        |       |      |                        |  |            |        |        |      |                        |  |                   |      |      |  |                    |  |            |       |       |      |                         |  |             |      |      |  |                    |  |              |       |        |      |                        |  |             |        |        |       |                        |  |                         |      |      |      |                        |  |            |       |       |      |                        |  |              |       |       |      |                        |  |               |      |      |      |                        |  |            |        |        |       |                        |  |            |     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| Total (95% CI)                                                                                             | 3551                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| Total events                                                                                               | 195                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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                        |  |  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 26.08, df = 22 (P = 0.25); I <sup>2</sup> = 16% |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Test for overall effect: Z = 3.54 (P = 0.0004)                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| コメント： 死亡率として評価                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Funnel plot                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| コメント： 死亡率として評価                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| その他の解析                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| メタリグレーション                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| 感度分析                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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CQ 3    メタアナリシス(5)

| CQ                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | CQ3:極低出生体重児の消化管機能障害発症の予防にプロバイオティクス投与は有効か？ |        |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|--------|-------------------------------------|-----------------------------------------|-------------------------------|------------|------------|---------|--|--------|------------|--|--------|-------|--------|-------|--------------------|-------------------------------|---------------|---|-----|---|-----|--|---------------|--|-------------|----|----|----|-----|-------|-------------------|--|-------------|-----|------|-----|------|-------|-------------------|--|----------------|--|------|--|------|--------|-------------------|--|--------------|-----|--|-----|--|--|--|--|---------------------------------------------------------------------------------------------------------|--|--|--|--|--|--|----------------------------------------------|--|--|--|--|--|--|
| P                                                                                                       | 極低出生体重児(出生体重1.5kg以下、早産児)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                           |        | I                                   | プロバイオティクス                               |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| C                                                                                                       | 無治療群・プロバイオティクス投与無し                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                           |        | O                                   | 敗血症(プロバイオティクス関連)                        |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| 研究デザイン                                                                                                  | 観察                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                           | 3      | コード                                 | Hartel 2014, Bonsante 2014, Hunter 2012 |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
|                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                           |        |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| モデル                                                                                                     | ランダム効果                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 方法                                        |        | Inverse-variance method (RevMan5.3) |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| 効果指標                                                                                                    | リスク比                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 統合値                                       |        | 0.89 ( 0.76 - 1.03 ) P= 0.11        |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Forest plot                                                                                             | <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">Probiotics</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th colspan="2">Risk Ratio</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>IV, Random, 95% CI</th><th>Risk Ratio IV, Random, 95% CI</th></tr></thead><tbody><tr><td>Bonsante 2014</td><td>0</td><td>347</td><td>0</td><td>783</td><td></td><td colspan="2">Not estimable</td></tr><tr><td>Hunter 2012</td><td>19</td><td>79</td><td>72</td><td>232</td><td>11.7%</td><td colspan="2">0.77 [0.50, 1.20]</td></tr><tr><td>Hartel 2014</td><td>427</td><td>3789</td><td>195</td><td>1562</td><td>88.3%</td><td colspan="2">0.90 [0.77, 1.06]</td></tr><tr><td>Total (95% CI)</td><td></td><td>4215</td><td></td><td>2577</td><td>100.0%</td><td colspan="2">0.89 [0.76, 1.03]</td></tr><tr><td>Total events</td><td>446</td><td></td><td>267</td><td></td><td></td><td colspan="2"></td></tr><tr><td colspan="7">Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.41, df = 1 (P = 0.52); I<sup>2</sup> = 0%</td></tr><tr><td colspan="7">Test for overall effect: Z = 1.58 (P = 0.11)</td></tr></tbody></table>  |                                           |        |                                     |                                         | Study or Subgroup             | Probiotics |            | Control |  | Weight | Risk Ratio |  | Events | Total | Events | Total | IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI | Bonsante 2014 | 0 | 347 | 0 | 783 |  | Not estimable |  | Hunter 2012 | 19 | 79 | 72 | 232 | 11.7% | 0.77 [0.50, 1.20] |  | Hartel 2014 | 427 | 3789 | 195 | 1562 | 88.3% | 0.90 [0.77, 1.06] |  | Total (95% CI) |  | 4215 |  | 2577 | 100.0% | 0.89 [0.76, 1.03] |  | Total events | 446 |  | 267 |  |  |  |  | Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.41, df = 1 (P = 0.52); I <sup>2</sup> = 0% |  |  |  |  |  |  | Test for overall effect: Z = 1.58 (P = 0.11) |  |  |  |  |  |  |
|                                                                                                         | Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Probiotics                                |        | Control                             |                                         |                               | Weight     | Risk Ratio |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Events                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Total                                     | Events | Total                               | IV, Random, 95% CI                      | Risk Ratio IV, Random, 95% CI |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Bonsante 2014                                                                                           | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 347                                       | 0      | 783                                 |                                         | Not estimable                 |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Hunter 2012                                                                                             | 19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 79                                        | 72     | 232                                 | 11.7%                                   | 0.77 [0.50, 1.20]             |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Hartel 2014                                                                                             | 427                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 3789                                      | 195    | 1562                                | 88.3%                                   | 0.90 [0.77, 1.06]             |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Total (95% CI)                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 4215                                      |        | 2577                                | 100.0%                                  | 0.89 [0.76, 1.03]             |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Total events                                                                                            | 446                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                           | 267    |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.41, df = 1 (P = 0.52); I <sup>2</sup> = 0% |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                           |        |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Test for overall effect: Z = 1.58 (P = 0.11)                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                           |        |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| コメント: 敗血症の原因の不確実さあり                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                           |        |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| Funnel plot                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                           |        |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
|                                                                                                         | コメント:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                           |        |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| その他の解析                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                           |        |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| メタリグレーション                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                           |        |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |
| 感度分析                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                           |        |                                     |                                         |                               |            |            |         |  |        |            |  |        |       |        |       |                    |                               |               |   |     |   |     |  |               |  |             |    |    |    |     |       |                   |  |             |     |      |     |      |       |                   |  |                |  |      |  |      |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                         |  |  |  |  |  |  |                                              |  |  |  |  |  |  |

## CQ 3 メタアナリシス(6)

| CQ                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | CQ3:極低出生体重児の消化管機能障害発症の予防にプロバイオティクス投与は有効か？ |                              |                   |                                                                                                                                                                                                                                                                                                                          |                                     |                                  |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |  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----|------|--|-------------|---|-----|---|-----|--|---------------|------|--|-------------------------|---|----|---|----|--|---------------|------|--|--------------|----|-----|----|-----|------|-------------------|------|--|---------------|----|----|----|----|------|-------------------|------|--|------------|----|-----|----|-----|------|-------------------|------|--|------------|----|-----|----|-----|------|-------------------|------|--|-----------|---|-----|---|-----|--|---------------|------|--|---------------|----|----|----|----|------|-------------------|------|--|--------------|----|----|----|----|------|-------------------|------|--|------------|----|----|----|----|------|-------------------|------|--|----------|----|-----|----|-----|------|-------------------|------|--|--------------|---|-----|----|-----|------|-------------------|------|--|--------------|----|----|----|----|------|-------------------|------|--|----------|----|-----|----|-----|------|-------------------|------|--|--------------|----|----|----|----|------|-------------------|------|--|-----------|----|-----|----|-----|------|-------------------|------|--|---------------|---|----|---|----|------|-------------------|------|--|----------------|--|------|--|------|--------|-------------------|--|--|--------------|--|-----|--|-----|--|--|--|--|------------------------------------------------------------------------------------------------------------|--|--|--|--|--|--|--|--|----------------------------------------------|--|--|--|--|--|--|--|--|
| P                                                                                                          | 極低出生体重児(出生体重1.5kg以下、早産児)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  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              | プロバイオティクス         |                                                                                                                                                                                                                                                                                                                          |                                     |                                  |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| C                                                                                                          | 無治療群・プロバイオティクス投与無し                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 敗血症(プロバイオティクス関連)  |                                                                                                                                                                                                                                                                                                                          |                                     |                                  |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |  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| 研究デザイン                                                                                                     | RCT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 文献数                                       | 23                           | コード               | Nandhini 2015, Dilli 2015, Patole 2014, Saengtawesin 2014, Totsu 2014, Jacobs 2013, Demirel 2013, Serce 2013 ,Fernandez-Carrocer 2013, Al-Hosni 2012, Rojas 2012, Sari 2011, Braga 2011, Mihatsch 2010, Samanta 2009, Rouge 2009, Lin 2008, Manzoni 2008, Manzoni 2006, Lin 2005, Bin-Nun 2005, Dani 2002, Kitajima 1997 |                                     |                                  |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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            |    |    |    |    |      |                   |      |  |           |    |     |    |     |      |                   |      |  |               |   |    |   |    |      |                   |      |  |                |  |      |  |      |        |                   |  |  |              |  |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
|                                                                                                            | モデル                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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              |                   | 方法                                                                                                                                                                                                                                                                                                                       | Inverse-variance method (RevMan5.3) |                                  |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| 効果指標                                                                                                       | リスク比                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 統合値                                       | 0.88 ( 0.73 - 1.07 ) P= 0.20 |                   |                                                                                                                                                                                                                                                                                                                          |                                     |                                  |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |           |    |     |    |     |      |                   |      |  |               |   |    |   |    |      |                   |      |  |                |  |      |  |      |        |                   |  |  |              |  |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Forest plot                                                                                                | <table><thead><tr><th>Study or Subgroup</th><th>Probiotics<br/>Events</th><th>Probiotics<br/>Total</th><th>Placebo<br/>Events</th><th>Placebo<br/>Total</th><th>Weight</th><th>Risk Ratio<br/>IV, Random, 95% CI</th><th>Year</th><th>Risk Ratio<br/>IV, Random, 95% CI</th></tr></thead><tbody><tr><td>Nandhini 2015</td><td>18</td><td>108</td><td>7</td><td>110</td><td>3.6%</td><td>2.62 [1.14, 6.02]</td><td>2015</td><td></td></tr><tr><td>Dilli 2015</td><td>16</td><td>200</td><td>23</td><td>200</td><td>5.4%</td><td>0.70 [0.38, 1.28]</td><td>2015</td><td></td></tr><tr><td>Patole 2014</td><td>0</td><td>77</td><td>0</td><td>76</td><td></td><td>Not estimable</td><td>2014</td><td></td></tr><tr><td>Totsu 2014</td><td>6</td><td>153</td><td>10</td><td>130</td><td>2.8%</td><td>0.51 [0.19, 1.36]</td><td>2014</td><td></td></tr><tr><td>Saengtawesin 2014</td><td>2</td><td>31</td><td>1</td><td>29</td><td>0.6%</td><td>1.87 [0.18, 19.55]</td><td>2014</td><td></td></tr><tr><td>Serce 2013</td><td>19</td><td>104</td><td>25</td><td>104</td><td>6.2%</td><td>0.76 [0.45, 1.29]</td><td>2013</td><td></td></tr><tr><td>Jacobs 2013</td><td>0</td><td>548</td><td>0</td><td>551</td><td></td><td>Not estimable</td><td>2013</td><td></td></tr><tr><td>Fernandez-Carrocer 2013</td><td>0</td><td>75</td><td>0</td><td>75</td><td></td><td>Not estimable</td><td>2013</td><td></td></tr><tr><td>Demirel 2013</td><td>20</td><td>135</td><td>21</td><td>136</td><td>5.8%</td><td>0.96 [0.55, 1.69]</td><td>2013</td><td></td></tr><tr><td>Al-Hosni 2012</td><td>13</td><td>50</td><td>16</td><td>51</td><td>5.2%</td><td>0.83 [0.45, 1.54]</td><td>2012</td><td></td></tr><tr><td>Rojas 2012</td><td>28</td><td>176</td><td>33</td><td>184</td><td>7.0%</td><td>0.89 [0.66, 1.40]</td><td>2012</td><td></td></tr><tr><td>Braga 2011</td><td>40</td><td>119</td><td>42</td><td>112</td><td>8.6%</td><td>0.90 [0.63, 1.27]</td><td>2011</td><td></td></tr><tr><td>Sari 2011</td><td>0</td><td>110</td><td>0</td><td>111</td><td></td><td>Not estimable</td><td>2011</td><td></td></tr><tr><td>Mihatsch 2010</td><td>28</td><td>91</td><td>29</td><td>89</td><td>7.4%</td><td>0.94 [0.61, 1.45]</td><td>2010</td><td></td></tr><tr><td>Samanta 2009</td><td>13</td><td>91</td><td>28</td><td>95</td><td>5.5%</td><td>0.48 [0.27, 0.88]</td><td>2009</td><td></td></tr><tr><td>Rouge 2009</td><td>13</td><td>45</td><td>15</td><td>49</td><td>5.2%</td><td>0.94 [0.51, 1.76]</td><td>2009</td><td></td></tr><tr><td>Lin 2008</td><td>40</td><td>217</td><td>24</td><td>217</td><td>6.9%</td><td>1.67 [1.04, 2.67]</td><td>2008</td><td></td></tr><tr><td>Manzoni 2008</td><td>7</td><td>151</td><td>29</td><td>168</td><td>3.8%</td><td>0.27 [0.12, 0.60]</td><td>2008</td><td></td></tr><tr><td>Manzoni 2006</td><td>19</td><td>39</td><td>22</td><td>41</td><td>7.4%</td><td>0.91 [0.59, 1.40]</td><td>2006</td><td></td></tr><tr><td>Lin 2005</td><td>22</td><td>180</td><td>36</td><td>187</td><td>6.7%</td><td>0.63 [0.39, 1.04]</td><td>2005</td><td></td></tr><tr><td>Bin-Nun 2005</td><td>31</td><td>72</td><td>24</td><td>73</td><td>7.5%</td><td>1.31 [0.86, 2.00]</td><td>2005</td><td></td></tr><tr><td>Dani 2002</td><td>14</td><td>295</td><td>12</td><td>290</td><td>4.1%</td><td>1.15 [0.54, 2.44]</td><td>2002</td><td></td></tr><tr><td>Kitajima 1997</td><td>0</td><td>46</td><td>1</td><td>45</td><td>0.3%</td><td>0.33 [0.01, 7.80]</td><td>1997</td><td></td></tr><tr><td>Total (95% CI)</td><td></td><td>3113</td><td></td><td>3123</td><td>100.0%</td><td>0.88 [0.73, 1.07]</td><td></td><td></td></tr><tr><td>Total events</td><td></td><td>349</td><td></td><td>398</td><td></td><td></td><td></td><td></td></tr><tr><td colspan="9">Heterogeneity: Tau<sup>2</sup> = 0.08; Chi<sup>2</sup> = 34.73, df = 18 (P = 0.01); I<sup>2</sup> = 48%</td></tr><tr><td colspan="9">Test for overall effect: Z = 1.29 (P = 0.20)</td></tr></tbody></table> |                                           |                              |                   |                                                                                                                                                                                                                                                                                                                          | Study or Subgroup                   | Probiotics<br>Events             | Probiotics<br>Total | Placebo<br>Events                | Placebo<br>Total | Weight | Risk Ratio<br>IV, Random, 95% CI | Year | Risk Ratio<br>IV, Random, 95% CI | Nandhini 2015 | 18 | 108 | 7 | 110 | 3.6% | 2.62 [1.14, 6.02] | 2015 |  | Dilli 2015 | 16 | 200 | 23 | 200 | 5.4% | 0.70 [0.38, 1.28] | 2015 |  | Patole 2014 | 0 | 77 | 0 | 76 |  | Not estimable | 2014 |  | Totsu 2014 | 6 | 153 | 10 | 130 | 2.8% | 0.51 [0.19, 1.36] | 2014 |  | Saengtawesin 2014 | 2 | 31 | 1 | 29 | 0.6% | 1.87 [0.18, 19.55] | 2014 |  | Serce 2013 | 19 | 104 | 25 | 104 | 6.2% | 0.76 [0.45, 1.29] | 2013 |  | Jacobs 2013 | 0 | 548 | 0 | 551 |  | Not estimable | 2013 |  | Fernandez-Carrocer 2013 | 0 | 75 | 0 | 75 |  | Not estimable | 2013 |  | Demirel 2013 | 20 | 135 | 21 | 136 | 5.8% | 0.96 [0.55, 1.69] | 2013 |  | Al-Hosni 2012 | 13 | 50 | 16 | 51 | 5.2% | 0.83 [0.45, 1.54] | 2012 |  | Rojas 2012 | 28 | 176 | 33 | 184 | 7.0% | 0.89 [0.66, 1.40] | 2012 |  | Braga 2011 | 40 | 119 | 42 | 112 | 8.6% | 0.90 [0.63, 1.27] | 2011 |  | Sari 2011 | 0 | 110 | 0 | 111 |  | Not estimable | 2011 |  | Mihatsch 2010 | 28 | 91 | 29 | 89 | 7.4% | 0.94 [0.61, 1.45] | 2010 |  | Samanta 2009 | 13 | 91 | 28 | 95 | 5.5% | 0.48 [0.27, 0.88] | 2009 |  | Rouge 2009 | 13 | 45 | 15 | 49 | 5.2% | 0.94 [0.51, 1.76] | 2009 |  | Lin 2008 | 40 | 217 | 24 | 217 | 6.9% | 1.67 [1.04, 2.67] | 2008 |  | Manzoni 2008 | 7 | 151 | 29 | 168 | 3.8% | 0.27 [0.12, 0.60] | 2008 |  | Manzoni 2006 | 19 | 39 | 22 | 41 | 7.4% | 0.91 [0.59, 1.40] | 2006 |  | Lin 2005 | 22 | 180 | 36 | 187 | 6.7% | 0.63 [0.39, 1.04] | 2005 |  | Bin-Nun 2005 | 31 | 72 | 24 | 73 | 7.5% | 1.31 [0.86, 2.00] | 2005 |  | Dani 2002 | 14 | 295 | 12 | 290 | 4.1% | 1.15 [0.54, 2.44] | 2002 |  | Kitajima 1997 | 0 | 46 | 1 | 45 | 0.3% | 0.33 [0.01, 7.80] | 1997 |  | Total (95% CI) |  | 3113 |  | 3123 | 100.0% | 0.88 [0.73, 1.07] |  |  | Total events |  | 349 |  | 398 |  |  |  |  | Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> = 34.73, df = 18 (P = 0.01); I <sup>2</sup> = 48% |  |  |  |  |  |  |  |  | Test for overall effect: Z = 1.29 (P = 0.20) |  |  |  |  |  |  |  |  |
|                                                                                                            | Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Probiotics<br>Events                      | Probiotics<br>Total          | Placebo<br>Events | Placebo<br>Total                                                                                                                                                                                                                                                                                                         | Weight                              | Risk Ratio<br>IV, Random, 95% CI | Year                | Risk Ratio<br>IV, Random, 95% CI |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |     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| Nandhini 2015                                                                                              | 18                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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| Dilli 2015                                                                                                 | 16                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 200               | 5.4%                                                                                                                                                                                                                                                                                                                     | 0.70 [0.38, 1.28]                   | 2015                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Patole 2014                                                                                                | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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| Totsu 2014                                                                                                 | 6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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              | 130               | 2.8%                                                                                                                                                                                                                                                                                                                     | 0.51 [0.19, 1.36]                   | 2014                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Saengtawesin 2014                                                                                          | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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              | 29                | 0.6%                                                                                                                                                                                                                                                                                                                     | 1.87 [0.18, 19.55]                  | 2014                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Serce 2013                                                                                                 | 19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 104               | 6.2%                                                                                                                                                                                                                                                                                                                     | 0.76 [0.45, 1.29]                   | 2013                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Jacobs 2013                                                                                                | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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| Fernandez-Carrocer 2013                                                                                    | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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              | 75                |                                                                                                                                                                                                                                                                                                                          | Not estimable                       | 2013                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Demirel 2013                                                                                               | 20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 136               | 5.8%                                                                                                                                                                                                                                                                                                                     | 0.96 [0.55, 1.69]                   | 2013                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Al-Hosni 2012                                                                                              | 13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 51                | 5.2%                                                                                                                                                                                                                                                                                                                     | 0.83 [0.45, 1.54]                   | 2012                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Rojas 2012                                                                                                 | 28                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 184               | 7.0%                                                                                                                                                                                                                                                                                                                     | 0.89 [0.66, 1.40]                   | 2012                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |  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| Braga 2011                                                                                                 | 40                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 112               | 8.6%                                                                                                                                                                                                                                                                                                                     | 0.90 [0.63, 1.27]                   | 2011                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |  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| Sari 2011                                                                                                  | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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              | 111               |                                                                                                                                                                                                                                                                                                                          | Not estimable                       | 2011                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |  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| Mihatsch 2010                                                                                              | 28                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 89                | 7.4%                                                                                                                                                                                                                                                                                                                     | 0.94 [0.61, 1.45]                   | 2010                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |  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| Samanta 2009                                                                                               | 13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 95                | 5.5%                                                                                                                                                                                                                                                                                                                     | 0.48 [0.27, 0.88]                   | 2009                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |  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| Rouge 2009                                                                                                 | 13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 49                | 5.2%                                                                                                                                                                                                                                                                                                                     | 0.94 [0.51, 1.76]                   | 2009                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Lin 2008                                                                                                   | 40                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 217               | 6.9%                                                                                                                                                                                                                                                                                                                     | 1.67 [1.04, 2.67]                   | 2008                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |  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| Manzoni 2008                                                                                               | 7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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              | 168               | 3.8%                                                                                                                                                                                                                                                                                                                     | 0.27 [0.12, 0.60]                   | 2008                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Manzoni 2006                                                                                               | 19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 41                | 7.4%                                                                                                                                                                                                                                                                                                                     | 0.91 [0.59, 1.40]                   | 2006                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |  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| Lin 2005                                                                                                   | 22                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 187               | 6.7%                                                                                                                                                                                                                                                                                                                     | 0.63 [0.39, 1.04]                   | 2005                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   |      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |  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| Bin-Nun 2005                                                                                               | 31                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 73                | 7.5%                                                                                                                                                                                                                                                                                                                     | 1.31 [0.86, 2.00]                   | 2005                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Dani 2002                                                                                                  | 14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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              | 290               | 4.1%                                                                                                                                                                                                                                                                                                                     | 1.15 [0.54, 2.44]                   | 2002                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Kitajima 1997                                                                                              | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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              | 45                | 0.3%                                                                                                                                                                                                                                                                                                                     | 0.33 [0.01, 7.80]                   | 1997                             |                     |                                  |                  |        |                                  |      |                                  |               |    |     |   |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |             |   |    |   |    |  |               |      |  |            |   |     |    |     |      |                   |      |  |                   |   |    |   |    |      |                    |      |  |            |    |     |    |     |      |                   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| Total (95% CI)                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Total events                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> = 34.73, df = 18 (P = 0.01); I <sup>2</sup> = 48% |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Test for overall effect: Z = 1.29 (P = 0.20)                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| コメント: 敗血症の原因の不確かさあり                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Funnel plot                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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|                                                                                                            | コメント:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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| その他の解析                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| メタリグレーション                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| 感度分析                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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|      |  |             |   |     |   |     |  |               |      |  |                         |   |    |   |    |  |               |      |  |              |    |     |    |     |      |                   |      |  |               |    |    |    |    |      |                   |      |  |            |    |     |    |     |      |                   |      |  |            |    |     |    |     |      |                   |      |  |           |   |     |   |     |  |               |      |  |               |    |    |    |    |      |                   |      |  |              |    |    |    |    |      |                   |      |  |            |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |   |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |          |    |     |    |     |      |                   |      |  |              |    |    |    |    |      |                   |      |  |           |    |     |    |     |      |                   |      |  |               |   |    |   |    |      |                   |      |  |                |  |      |  |      |        |                   |  |  |              |  |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |

### CQ3 SR レポートのまとめ

極低出生体重児に発症した消化管機能障害において、プロバイオティクス投与は有効か？という CQ に対し、SCOPE の採用条件を策定して文献検索をおこなった結果、対象となった研究は SR8 編、RCT が 4 編、観察研究 4 編が基準を満たした。しかし、消化管機能障害の全般に関する評価（NEC、FIP、MRI）ではなく、最新の SR でも最新の論文をカバーしておらず、体重に規定されるデータ解析やプロバイオティクスの投与量・期間・種類の統一がされていないため、SR をやり直すことになった。患者・家族・医療者にとって最も重要な Outcome として、消化管機能障害（NEC、FIP、MRI）の予防（益）、生命予後の改善（益）、敗血症（プロバイオティクス関連）（害）の計 3 点をアウトカムに設定してシステマティックレビューを行った。なお、消化管機能障害の予防（益）は、その発症（害）として算出し、生命予後は死亡（害）として算出することで、代用の Outcome とした。

#### アウトカム 1. 消化管機能障害（NEC、FIP、MRI）の予防

今回対象とした RCT25 研究（SR8 編）、観察研究 4 編のすべてで NEC の発症としての Outcome が設定されていた。メタアナリシスではプロバイオティクス投与群で NEC の発症が低い傾向があった(0.44 [0.31-0.63]  $P < 0.000001$ )。primary outcome として設定していることもあり、比較的信頼できる結果であると判断した。エビデンスの質としては高いと判断した。結果、プロバイオティクス投与群では NEC においては予防効果があると判断した。

#### アウトカム 2. 生命予後の改善

今回対象とした RCT25 研究（SR8 編）、観察研究 4 編のすべてで 生命予後の改善としての Outcome が、死亡数として設定されていた。メタアナリシスではプロバイオティクス投与群で死亡率が低い傾向があった(0.71[0.61-0.82]  $P < 0.000001$ )。primary outcome として設定している場合と NEC の発症後の secondary outcome として設定されている場合があるが、比較的信頼できる結果であると判断した。エビデンスの質としては中程度と判断した。結果、プロバイオティクス投与群では生命予後の改善が見込まれると判断した。

#### アウトカム 3. 敗血症（プロバイオティクス関連）

今回対象とした RCT23 研究（SR8 編）、観察研究 3 編のすべてで敗血症の出現としての Outcome が設定されていた。しかし、文献によっては敗血症の原因がプロバイオティクス投与によるものかどうか不明であり、エビデンスの質としては低い印象であった。メタアナリシスではプロバイオティクス投与群で死亡率が低い傾向があった(0.88[0.76-1.03]  $P = 0.10$ )が、プロバイオティクス投与による害の報告もあった。

以上を踏まえてシステマティックレビューをまとめる。

消化管機能障害（NEC、FIP、MRI）の予防、生命予後の改善の各アウトカムにおいては、中程度の質のエビデンスが得られた。NEC の予防と死亡率も低下が関連している一方、害もあるため、児の状況に応じた適切なプロバイオティクスの使用を行うことが適切と思われた。

### CQ3 Future research question

今回のシステマティックレビューでは、消化管機能障害（NEC、FIP、MRI）のうち NEC の予防、生命予後の改善に関して、エビデンスを得た **CQ** に対する推奨を提案することができた。しかし、プロバイオティクス関連の敗血症に関しては、十分なエビデンスを得ることができなかった。プロバイオティクスの種類・投与方法を統一して、今後はこれらの点の評価を目的とした **RCT** 研究が行われ、エビデンスを得ることで、**CQ** に対するより適切な推奨を出すことができるのではないかと考えられた。

## CQ 4

### 推奨提示

|          |                                           |
|----------|-------------------------------------------|
| CQ4      | 極低出生体重児の消化管機能障害発症の予防にグリセリン浣腸は有効か？         |
| 推奨草案     | 極低出生体重児の消化管機能障害発症予防に対するグリセリン浣腸の有効性は不明である。 |
| エビデンスの強さ | D（非常に弱い）                                  |

### 推奨作成の経過

#### 【CQ 設定の背景】

グリセリン浣腸は本邦では低出生体重児に広く日常的に行われている処置である。極低出生体重児の消化管機能障害（特に MRI）にも予防的に行われているが、使用基剤、使用量、使用方法、使用期間は施設によってさまざまである。今回、グリセリン浣腸の有効性の有無を消化管機能障害（NEC、FIP、MRI）の発症の予防、生命予後の改善、胎便排泄遅延の改善、頭蓋内出血の増加をアウトカムとして設定し解析を行った。

#### 【文献検索とスクリーニング】

2 次スクリーニング解析後の 6 論文の解析を行ったが、対象となった研究は SR1 件、RCT が 3 件、コホートが 1 件であり、SR 一件は以下の 3 件の RCT を含んでいるため、RCT を中心としての検討となった。

#### 【観察研究の評価】

消化管機能（NEC、FIP、MRI）の発症の予防、生命予後の改善、胎便排泄遅延の改善、頭蓋内出血の増加についての検討では、介入方法（基剤、使用量、期間）など各種バイアスの存在、検討数が少ないこともあり、エビデンスの質は低かった。MA の結果からは CQ の求めるものとは異なるが、消化管機能障害の発症に関しては NEC のみが対象疾患であり、生命予後に関しては 3 つの RCT では死亡率に明らかな差はないが、胎便排泄遅延の改善には寄与する可能性が示唆された。頭蓋内出血の発症も明らかな差は認めなかったが、検討を行っている研究論文は一つしか存在せず、さらなる検討が必要と思われる。

#### 【まとめ】

当研究班全体で総合的に検討を行った結果、CQ4 におけるグリセリン浣腸の消化管機能障害（NEC、FIP、MRI）発症予防についての有効性は不明であった。

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- 2) Shinde S, Kabra NS, et al. Glycerin suppository for promoting feeding tolerance in

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4) Haiden N, Jilma B, et al. Small volume enemas do not accelerate meconium evacuation in very low birth weight infants. J Pediatr Gastroenterol Nutr. 2007 Feb 44(2) 270-3

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#### CQ 4 一般向けサマリー

今回世界中の過去の研究からグリセリン浣腸が消化管機能障害を予防するかどうかを調べましたが、グリセリン浣腸に関しての報告が少ないこと、また、浣腸の使用方法（基剤、使用量、期間）などが違うため、メリットもデメリットも不明でした。

けれども、日本では、グリセリン浣腸は、極低出生体重児だけでなく腸の動きの悪い赤ちゃんに標準的に行っている治療なので、これからも児の症状、全身状態を考えて適切に使用してください。

# CQ4 定性的システマティックレビュー

|       |                          |                               |
|-------|--------------------------|-------------------------------|
| CQ    | 4                        | 極低出生体重児の消化管機能障害発症の予防に浣腸は有効か？  |
| P     | 極低出生体重児(出生体重1.5kg以下、早産児) |                               |
| I     | グリセリン浣腸(もしくは坐剤)          |                               |
| G     | グリセリン浣腸(もしくは坐剤)を行わなかった群  |                               |
| 臨床的文脈 |                          | 極低出生体重児の消化管機能障害の予防に関する検討項目である |

|             |                                                                         |
|-------------|-------------------------------------------------------------------------|
| O1          | 極低出生体重児に対するグリセリン浣腸(もしくは坐剤)は、消化管機能障害(NEC/MRI/FIP)の発症を予防する                |
| 非直接性のまとめ    | 採用論文はいずれもNECの発症のみをアウトカムとしており、臨床上グリセリン浣腸を行う主な目的となるMRIの発症の予防については言及されていない |
| バイアスリスクのまとめ | 盲検化がされていないstudyがあることなどよりバイアスリスクは中程度に存在する                                |
| 非一貫性その他のまとめ | studyによりプロトコールが異なること、NECの判定基準が明確でないものもあることなどから、非一貫性は高い                  |
| コメント        | アウトカムの設定が対象論文と異なるため、エビデンスの強度は低くせざるを得ないが、介入群でNECが多い傾向は認められた              |

|             |                                                      |
|-------------|------------------------------------------------------|
| O2          | 極低出生体重児に対するグリセリン浣腸(もしくは坐剤)は、生命予後を改善する                |
| 非直接性のまとめ    | 対象が論文により異なること、日本では使用不可能な坐剤のデータであることから、非直接性は中程度にある    |
| バイアスリスクのまとめ | ランダム化について記載のない論文があったため、バイアスリスクがある可能性がある              |
| 非一貫性その他のまとめ | 対象症例数が少なく、また死亡率も少ないため、正確な評価は困難である                    |
| コメント        | 少ない症例数ではあるが、グリセリン浣腸(もしくは坐剤)の使用の有無での生存率には差がない結果となっている |

|             |                                                           |
|-------------|-----------------------------------------------------------|
| O3          | 極低出生体重児に対するグリセリン浣腸(もしくは坐剤)は、胎便排泄遅延の発生を改善する                |
| 非直接性のまとめ    | 唯一データが利用可能であったstudyでは、坐剤を使用しており、非直接性は相応にある                |
| バイアスリスクのまとめ | 対象となった論文で盲検化に関してバイアスリスクが存在する                              |
| 非一貫性その他のまとめ | 対象studyが一つのみであり、非一貫性、非確実性に関して評価は不可能である                    |
| コメント        | 対象studyが一つのみであり、エビデンスとしては弱いだが、グリセリン坐剤は胎便排泄遅延を改善することが示唆された |

|             |                                                                         |
|-------------|-------------------------------------------------------------------------|
| O4          | 極低出生体重児に対するグリセリン浣腸(もしくは坐剤)は、頭蓋内出血の発症を増加させる                              |
| 非直接性のまとめ    | 唯一データが利用可能であったstudyでは、坐剤を使用しており、非直接性は相応にある                              |
| バイアスリスクのまとめ | 対象となった論文で盲検化に関してバイアスリスクが存在する                                            |
| 非一貫性その他のまとめ | 対象studyが一つのみであり、非一貫性、非確実性に関して評価は不可能である                                  |
| コメント        | 対象studyが一つのみであり、エビデンスとしては弱いだが、グリセリン坐剤の害の一つである可能性のある頭蓋内出血を増加させないことが示唆された |

CQ4 メタアナリシス(1)

| CQ                                                                                                      |        | CQ4:極低出生体重児の消化管機能障害発症の予防に浣腸は有効か？                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
|---------------------------------------------------------------------------------------------------------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|-------|---------|-------------------------------------|--------------------------------------|--------------------|----------------|------|---------|--|--------|------------|------|--------|-------|--------|-------|--------------------|-------------|----|----|----|----|-------|-------------------|------|------------|----|----|----|----|-------|-------------------|------|-------------|----|----|----|----|------|-------------------|------|----------------|--|----|--|----|--|--------|-------------------|--|--------------|--|----|--|----|--|--|--|--|---------------------------------------------------------------------------------------------------------|--|--|--|--|--|--|--|----------------------------------------------|--|--|--|--|--|--|--|
| P                                                                                                       | 低出生体重児 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |       | I       | グリセリン浣腸                             |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| C                                                                                                       | 無治療    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |       | O       | 消化管機能障害 (NEC/MRI/FIP) の予防           |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| 研究デザイン                                                                                                  |        | RCT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                | 文献数   | 3       | コード                                 | Heiden 2007, Khadr 2011, Shinde 2014 |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| モデル                                                                                                     |        | ランダム効果                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                | 方法    |         | Inverse-variance method (RevMan5.3) |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| 効果指標                                                                                                    |        | リスク比                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                | 統合値   |         | 0.94 ( 0.87 - 1.02 ) P= 0.13        |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| Forest plot                                                                                             |        | <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">Glycerin enema</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th>Risk Ratio</th><th rowspan="2">Year</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>IV, Random, 95% CI</th></tr></thead><tbody><tr><td>Heiden 2007</td><td>39</td><td>42</td><td>38</td><td>39</td><td>68.5%</td><td>0.95 [0.86, 1.05]</td><td>2007</td></tr><tr><td>Khadr 2011</td><td>25</td><td>29</td><td>24</td><td>25</td><td>23.9%</td><td>0.90 [0.76, 1.06]</td><td>2011</td></tr><tr><td>Shinde 2014</td><td>19</td><td>25</td><td>20</td><td>25</td><td>7.6%</td><td>0.95 [0.71, 1.28]</td><td>2014</td></tr><tr><td colspan="2">Total (95% CI)</td><td colspan="2">96</td><td colspan="2">89</td><td>100.0%</td><td>0.94 [0.87, 1.02]</td><td></td></tr><tr><td colspan="2">Total events</td><td colspan="2">83</td><td colspan="2">82</td><td colspan="3"></td></tr><tr><td colspan="2">Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.37, df = 2 (P = 0.83); I<sup>2</sup> = 0%</td><td colspan="6"></td></tr><tr><td colspan="2">Test for overall effect: Z = 1.51 (P = 0.13)</td><td colspan="6"></td></tr></tbody></table> |                |       |         |                                     |                                      | Study or Subgroup  | Glycerin enema |      | Control |  | Weight | Risk Ratio | Year | Events | Total | Events | Total | IV, Random, 95% CI | Heiden 2007 | 39 | 42 | 38 | 39 | 68.5% | 0.95 [0.86, 1.05] | 2007 | Khadr 2011 | 25 | 29 | 24 | 25 | 23.9% | 0.90 [0.76, 1.06] | 2011 | Shinde 2014 | 19 | 25 | 20 | 25 | 7.6% | 0.95 [0.71, 1.28] | 2014 | Total (95% CI) |  | 96 |  | 89 |  | 100.0% | 0.94 [0.87, 1.02] |  | Total events |  | 83 |  | 82 |  |  |  |  | Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.37, df = 2 (P = 0.83); I <sup>2</sup> = 0% |  |  |  |  |  |  |  | Test for overall effect: Z = 1.51 (P = 0.13) |  |  |  |  |  |  |  |
|                                                                                                         |        | Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Glycerin enema |       | Control |                                     | Weight                               |                    | Risk Ratio     | Year |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
|                                                                                                         |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Events         | Total | Events  | Total                               |                                      | IV, Random, 95% CI |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
|                                                                                                         |        | Heiden 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 39             | 42    | 38      | 39                                  | 68.5%                                | 0.95 [0.86, 1.05]  | 2007           |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
|                                                                                                         |        | Khadr 2011                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 25             | 29    | 24      | 25                                  | 23.9%                                | 0.90 [0.76, 1.06]  | 2011           |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| Shinde 2014                                                                                             | 19     | 25                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 20             | 25    | 7.6%    | 0.95 [0.71, 1.28]                   | 2014                                 |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                          |        | 96                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                | 89    |         | 100.0%                              | 0.94 [0.87, 1.02]                    |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| Total events                                                                                            |        | 83                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                | 82    |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.37, df = 2 (P = 0.83); I <sup>2</sup> = 0% |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| Test for overall effect: Z = 1.51 (P = 0.13)                                                            |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
|                                                                                                         |        | <p>コメント: NECの発生のみを評価している</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| Funnel plot                                                                                             |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
|                                                                                                         |        | <p>コメント: Publication biasはないと考えてよい</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
|                                                                                                         |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
|                                                                                                         |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
|                                                                                                         |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| その他の解析                                                                                                  |        | 施行せず                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                |       |         |                                     | コメント:                                |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| メタリグレーション                                                                                               |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |
| 感度分析                                                                                                    |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |       |         |                                     |                                      |                    |                |      |         |  |        |            |      |        |       |        |       |                    |             |    |    |    |    |       |                   |      |            |    |    |    |    |       |                   |      |             |    |    |    |    |      |                   |      |                |  |    |  |    |  |        |                   |  |              |  |    |  |    |  |  |  |  |                                                                                                         |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |