厚生労働行政推進調査事業費補助金（新興・再興感染症及び予防接種政策推進研究事業）

ワクチンの有効性・安全性の臨床評価と
ＶＰＤの疾病負荷に関する疫学研究

平成29～令和元年度　総合研究報告書

令和 2 年 3 月

研究代表者　　廣田　良夫

Ⅰ. 総合研究報告書

Ⅲ. 研究成果の刊行物・別刷り

目　次

厚生労働行政推進調査事業費補助金　（新興・再興感染症及び予防接種政策推進研究事業）
総合研究報告書

ワクチンの有効性・安全性の臨床評価と VPD の疾病負荷に関する疫学研究

研究代表者　廣田　良夫　医療法人相生会臨床疫学研究センター長・保健医療経営大学長

研究要旨

厚生労働省意向による特定研究

１）ポリオ感受性分科会

①　2011～2013 年に実施した「ポリオワクチンの互換性に関する免疫原性・安全性試験」の対象児では、接種後５年間に中和抗体価 1:8 未満まで低下した者は、A 群（sOPV → sIPV → sIPV → sIPV）11 人のうち２人（18%）、B 群（sOPV → wIPV → wIPV → wIPV）49 人のうち３人（6%）であった。また、いずれの群も抗体価の半減期の中央値は２年であり、抗体保有割合 100%を維持できる期間は最長で接種６年後までと推計された（福岡、2013～2018 年、前向き cohort study）。

２）B 型肝炎ワクチン安全性分科会

①　製法変更された B 型肝炎ワクチン（ヘプタバックス -Ⅱ®）を接種した小児 100 人（男 51 人、２ヵ月児 98 人、３ヵ月児 2 人）では、延べ 298 回接種のうち、局所反応を 64 件（21%）、38℃以上の発熱を 13 件（4%）に認めたが、概ね発現後３日以内に消失した。重篤な有害事象は認めなかった（福岡、2018 年、前向き cohort study）。

３）定点モニタリング分科会

①　６歳未満児 1,007 人（平均 2.7 歳）では、PCR 陽性インフルエンザに対するワクチン接種の調整オッズ比（OR）は、１回接種で 0.58（0.32-1.06）、２回接種で 0.59（0.40-0.86）であった（大阪、福岡、2016/17 シーズン、症例対照研究 , test-negative design）。

②　６歳未満児 1,015 人（平均 2.8 歳）では、PCR 陽性インフルエンザに対するワクチン接種の調整オッズ比（OR）は、１回接種で 0.43（0.25-0.75）、２回接種で 0.37（0.24-0.55）であった（大阪、福岡、2017/18 シーズン、症例対照研究 , test-negative design）。

③　３歳未満児 399 人（平均 1.3 歳）では、PCR 陽性インフルエンザに対するワクチン接種の調整オッズ比（OR）は、１回接種で 0.25（0.04-1.55）、２回接種で 0.53（0.22-1.28）であった（大阪、福岡、2018/19 シーズン、症例対照研究 , test-negative design）。

４）埼玉株／香港株ワクチン免疫原性分科会

①　20 歳以上の健康成人では、香港株単価ワクチン接種により香港株のみならず埼玉株や流行野生株（A/ 大阪 /188/2017、大阪株）に対しても良好な免疫原性（中和抗体）を示した。埼玉株に対する抗体応答は：香港株単価ワクチン接種群で平均上昇倍数が 5.3 倍、抗体応答割合が 50%；埼玉株単価ワクチン接種群では各々4.2 倍と 46%であった。大阪株に対する抗体応答は：香港株単価ワクチン接種群で平均上昇倍数が 2.7 倍、抗体応答割合が 32%；埼玉株単価ワクチン接種群では各々1.3 倍と 4%であった（福岡、2017/18 シーズン、無作為化比較試験）。

５）インフルエンザワクチンの株選定の在り方に関する検討

①　ワクチンの安定供給、および国内外におけるインフルエンザワクチンの多様化に対応するため、

ワクチン株選定の在り方を検討した。WHO によるワクチン株選定会議を基軸とした一般的な株選定の流れの下、「国内での選定過程」「海外での選定過程」「それぞれの長所・短所」や関連する課題等を整理した。

6）HPV ワクチンの安全性に関する文献抄訳

① 現在積極的勧奨を差し控えている HPV ワクチンについて、科学的に公平な立場から安全性に関するエビデンスを整理した。「PRISMA 声明」に基づいたシステマティックレビューにより、HPV ワクチンの安全性・有効性に関する先行文献を抽出し、抄訳集を作成した。

プロジェクト研究

7）インフルエンザ分科会

【免疫原性】

① ３シーズン連続して A/H1N1pdm09 株含有ワクチンを接種した健康成人 119 人（26～66 歳）では、シーズンを経るに従って、接種前・接種後の幾何平均抗体価（GMT）および平均上昇倍数が有意に低下していた（１・２・３シーズン目の接種後 GMT は 61 → 53 → 51、平均上昇倍数は 1.49 → 1.30 → 1.25）（東京、福岡、2014/15～2016/17 シーズン、前向き cohort study）。

② 大学の教職員・学生 34 人（男 20 人、平均 36 歳）では、ストレス指数が中等度の者で、インフルエンザワクチン接種後の AH1 型に対する抗体応答割合および抗体保有割合が高かった（福岡、2017/18 シーズン、前向き cohort study）。

③ 大学生 13 人（男 2 人、平均 21 歳）では、接種後の抗体保有割合は AH1pdm09：91％、AH3：100％、B（Victoria）：54％、B（Yamagata）：91％であり、ワクチン接種歴を有する者では AH1pdm09 や B（Yamagata）の抗体保有割合が高かった（福岡、2018/19 シーズン、前向き cohort study）。

【有効性】

① ６歳未満児 2,694 人（平均 2.8 歳）では、迅速診断陽性インフルエンザに対するワクチン接種の調整 OR は 0.61（0.50-0.75）であった。型別にみると、A 型に対する調整 OR は 0.64（0.52-0.79）、B 型に対する調整 OR は 0.41（0.24-0.73）であり、いずれも有意差を認めた（石川、2016/17 シーズン、症例対照研究 , test-negative design）。

② ６歳未満児 2,539 人（平均 2.8 歳）では、迅速診断陽性インフルエンザに対するワクチン接種の調整 OR は 0.57（0.46-0.70）であった。型別にみると、A 型に対する調整 OR は 0.52（0.40-0.69）、B 型に対する調整 OR は 0.61（0.48-0.78）であり、いずれも有意差を認めた（石川、2017/18 シーズン、症例対照研究 , test-negative design）。

③ ６歳未満児 2,250 人（平均 2.7 歳）では、迅速診断陽性インフルエンザに対するワクチン接種の調整 OR は 0.44（0.35-0.55）であった。型別でみると、A 型に対する調整 OR は 0.44（0.35-0.55）、B 型に対しては発症者が少なく算出できなかった（石川、2018/19 シーズン、症例対照研究 , test-negative design）。

④ 小学生（４校：2,120 人）では、A 型インフルエンザ（迅速診断）に対するワクチン接種の調整 OR は 0.71（0.48-1.04）であった（土浦市、2016/17 シーズン、前向き cohort study）。

⑤ 小学生（４校：2,077 人）では、ワクチン接種の調整 OR は A 型インフルエンザ（迅速診断）に対して 0.34（0.19-0.61）、B 型インフルエンザに対して 0.85（0.63-1.15）であった（土浦市、2017/18 シーズン、前向き cohort study）。

⑥ 小学生（４校：2,077 人）では、ワクチン接種の調整 OR は A 型インフルエンザ（迅速診断）に対して 0.56（0.40-0.78）であった。B 型インフルエンザに対しては発症者が少なく算出できなかった（土浦市、2018/19 シーズン、前向き cohort study）。

⑦　小学生 193 人（平均 8.8 歳）では、迅速診断陽性インフルエンザに対するワクチン接種の調整 OR は 1.07（0.24-4.86）、主流行の B 型に対する調整 OR は 0.65（0.12-3.49）であり、いずれも推計の精度が非常に悪く、ワクチンの有効性を論じることが出来なかった（福岡、2017/18 シーズン、症例対照研究、test-negative design）。
⑧　一般住民 243 人（１歳から 64 歳）では、PCR 陽性インフルエンザ（H1N1pdm）に対するワクチン接種の調整 OR は 1～64 歳で 0.29（0.12-0.68）、１～12 歳で 0.51（0.19-1.39）、13～64 歳で 0.08（0.01-0.47）であった（東京、2009/10 シーズン、症例対照研究 , test-negative design）。
⑨　一般住民 378 人（１歳から 64 歳）では、PCR 陽性インフルエンザに対するワクチン接種の調整 OR は 1～64 歳で 0.34（0.19-0.60）１～12 歳で 0.37（0.19-0.70）、13～64 歳で 0.34（0.19-1.26）であった（東京、2010/11 シーズン、症例対照研究 , test-negative design）。

【安全性】
①　妊婦 10,631 人（平均 32.0 歳）では、妊娠転帰として「流産・死産・早産・低出生体重・先天奇形のいずれか 1 つ以上」を呈した者は、妊娠中にインフルエンザワクチン接種を受けた 4,244 人で 11％、非接種の 6,387 人で 14％であり、妊婦に対するインフルエンザワクチン接種の安全性が示唆された（大阪、2013/14 シーズン、前向き cohort study）。

【費用対効果】
①　妊婦に対するインフルエンザワクチンの費用対効果は、接種費用を 1 回接種 3,529 円、接種率を「接種プログラムあり」60％、「接種プログラムなし」27％とした場合、接種プログラムの増分費用効果比（ICER）は 7,779,356 円 /QALY であり、WHO の基準（３× GDP）に基づくと費用効果的であることが示された。

【微生物検索・病原診断】
①　2016/17 シーズンの大阪府におけるインフルエンザ流行株の抗原性は、全国の分離株と同様の傾向であった。
②　2017/18 シーズンの大阪府におけるインフルエンザ流行株の抗原性解析では、AH1pdm 亜型は総て 6B.1 に属し、AH3 亜型は 3C.2a1b、3C.2a2、3C.2a3 に含まれた。
③　2018/19 シーズンの大阪府におけるインフルエンザ流行株の抗原性解析では、AH1pdm 亜型は全国の解析株と同様のサブクレード内に属し、AH3 亜型は全国の解析株の半数が属する 1 つのサブクレード内に属した。
④　いずれのシーズンでも、インフルエンザ陰性の検体から、他の呼吸器ウイルスが検出された。インフルエンザ様疾患を呈する患者の中には他の呼吸器ウイルスを原因とする者が混在し、ワクチン有効性の過小評価の一因となることが示唆された。

８）百日咳分科会
①　検査陽性の百日咳症例 95 人（中央値 8.0 歳）、検査陰性対照 50 人（中央値 6.4 歳）では、DTaP ワクチン４回接種（ref. 未接種）の百日咳発症に対する調整 OR は、6 歳未満児で 0.10（0.01-1.20）であったが、6 歳以上児では 1.18（0.10-13.9）となった。また、ワクチン４回接種者では、年齢 9 歳以上、接種後経過年数 5.9 年以上、で百日咳発症に対する OR が有意に上昇した（2017 年 10 月～、症例対照研究 , test-negative design）。
②　LAMP 陽性の百日咳症例 17 人（平均 7.8 歳）、LAMP 陰性の対照患者 29 人（平均 4.3 歳）、他疾患の対照患者 77 人（平均 4.9 歳）における症例対照研究では、百日咳に対する DTaP ワクチン４回接種の OR は、test-negative control との比較で 0.24（0.004-3.61）、他疾患の対照患者との比較で 0.07

（0.000-0.45）であった（高知、2012 年、症例対照研究）。
③　LAMP 陽性の百日咳症例 121 人（平均 8.3 歳）、LAMP 陰性対照 282 人（平均 7.2 歳）では、DTaP ワクチン４回接種（ref. 未接種）の百日咳発症に対する OR は 0.27（0.05-1.67）であった。しかし、ワクチン４回接種者では、接種後経過年数 4.0 年以上で百日咳発症に対する OR が有意に上昇した（高知、2012 年、2018 年、症例対照研究 , test-negative design）。
④　就学前の DTaP ワクチン追加接種を始めた地域およびその周辺地域において、百日咳の疾病負荷の変化、追加接種の有効性を検討する（宮崎、2018 年～、記述疫学＋症例対照研究 , test-negative design）。
⑤　妊婦 977 人では、妊娠中に百日咳含有ワクチンが接種可能なら「接種する」と回答した者は 279 人（29％）であった（熊本、三重、2016 年、横断研究）。
⑥　妊婦に対する百日咳ワクチンの費用効果は、児の百日咳の発症率および接種費用に大きく影響を受けるが、費用効率的と考えられるシナリオが複数存在した。今後、妊婦に対する百日咳ワクチン接種の定期接種化を検討する際の基礎情報として重要である。

９）高齢者肺炎分科会（肺炎球菌ワクチン）

①　65 歳以上高齢者で、肺炎症例 127 人（平均 75.7 歳）と病院対照 542 人（平均 75.6 歳）では、ワクチン接種の肺炎に対する調整 OR は、肺炎球菌ワクチン 1.19（0.77-1.82）、インフルエンザワクチン 0.85（0.55-1.31）であった（2016 年 10 月～、症例対照研究）。
②　65 歳以上の高齢者では、定期接種化が肺炎球菌ワクチン接種の主要な規定要因であることが示唆された。接種の最たる契機は、市町村からの案内（50％）であり、市町村による直接的な対象者個人へのアプローチが接種促進に有効と考えられた。

10）新規ワクチン検討分科会

①　６歳未満児 454 人では、迅速診断陽性ロタウイルス胃腸炎に対するワクチン接種の調整 OR は 0.26（0.15-0.45）であり、胃腸炎の初期症状が重篤な例に対して、より高い有効率を示した（福岡、奈良、2018～2019 シーズン、症例対照研究 , test-negative design）。
②　６歳未満児 1,798 人では、迅速診断陽性ロタウイルス胃腸炎に対するワクチン接種の調整 OR は 0.44（0.34-0.58）であり、胃腸炎の初期症状が重篤な例に対して、より高い有効率を示した（佐賀、福岡、奈良、2018～2019 シーズン、症例対照研究 , test-negative design）。
③　１歳半検診受診児 1,282 人では、ロタウイルスワクチンの接種率は 73％であり、保護者がロタウイルス胃腸炎を重症だと思うこと、ワクチンが効くと思うこと、小児科での勧め、雑誌やネットでの情報、保護者の学歴、世帯年収、が接種と正の関連を示した（金沢、2017～2018 年、横断研究）。
④　おたふくかぜワクチンの安全性に関する文献的考察では、国内で承認使用されている２種類（星野株、鳥居株）のおたふくかぜ単抗原ワクチン接種後の無菌性髄膜炎の発生頻度は、2010 年以降、3～4 万人に 1 人であり、年齢別の検討では１歳以下の発生頻度が最も低いことを示す文献が散見された。
⑤　企業が医療機関等から収集したおたふくかぜワクチン（鳥居株）接種後の有害事象報告について、年次推移を検討したところ、ワクチン接種後の無菌性髄膜炎の発生頻度は 2001 年以降に減少し、直近の 2016～2018 年では 10 万接種あたり 2.78（1.94-3.62）であった（1992～2018 年、記述疫学）。
⑥　40～73 歳の医療従事者 266 人（男 106 人）では、風疹抗体陰性者が 11.7％、麻疹抗体陰性者が 0.4％、水痘抗体陰性者が 0.4％、ムンプス抗体陰性者が 3.8％であった。麻疹、ムンプスに関しては抗体陽性者でも学会基準値以下の抗体価である者が多く（麻疹 31.6％、ムンプス 41.0％）、国内の成人への感染症対策としてワクチンの追加接種やキャッチアップ接種を検討する必要性が示唆された（川崎、2018 年、横断研究）。
⑦　４価髄膜炎菌結合体ワクチンの接種を受けた 56 歳以上の者 21 人（男 11 人、年齢中央値 61 歳）

では、局所反応 10%、全身反応 10%を認めたが、重篤な有害事象は認めなかった（東京、川崎、前向き cohort study）。

⑧　高齢者に対する帯状疱疹ワクチンの費用効果は、接種費用を弱毒生水痘ワクチン（VVL）１回接種 8,000 円、組換え帯状疱疹ワクチン（RZV）２回接種 30,000 円とし、１QALY 獲得に対する支払意志額（WTP, Willingness-to-pay）を 500 万円に設定した場合、用いたワクチンの種類に拘らず、全ての接種プログラムの増分費用効果比（ICER, Incremental cost-effectiveness ratio）は WTP を上回り、費用効果的であった。

⑨　高齢者施設入所者 1,345 人（男 404 人、年齢中央値 86 歳）では、追跡期間中に 37 人が下痢症を発現したが、*Clostridioides difficile* 感染症（CDI）やノロウイルスの検査陽性者はいなかった（大阪、2018～2019 年、前向き cohort study）。

11）広報啓発分科会

米国予防接種諮問委員会（US-ACIP）の勧告 2017 年版、2018 年版、2019 年版を翻訳し、（財）日本公衆衛生協会より出版した。

はじめに

かつて我が国では、インフルエンザワクチン無効論が台頭した時期があった。最近では、子宮頸がん予防ワクチンの接種後に広範な疼痛や運動障害が発生したことから、積極的勧奨が一時中止されている。このように予防接種を取り巻く環境には、科学的根拠の不足と解明の困難性という障壁が常に横たわっている。

予防接種を健全な形で普及していくためには、ワクチンの有効性や安全性に関する的確な情報を整備蓄積することが必要である。言うまでもなく、有効性や安全性の評価はヒト集団から得られた情報に基づかねばならないが、我が国では実験結果に基づいた推論が独り歩きしている例もある。

ワクチンギャップの克服に向けて大きな前進を遂げつつある現在、ワクチンの有効性・安全性評価に関する分析疫学研究を担う本研究班の役割は大きく、責任は重い。

A.　研究目的

ワクチンを巡る国外および国内の諸課題について、疫学、小児科、内科、臨床薬理、微生物、医療経済などの専門家、及び第一線の開業医が共同で疫学研究に取り組む。

主要課題としては以下の項目があげられる：生・不活化ポリオワクチン混合接種後の抗体持続を検討し、追加接種の必要性と時期の決定に必要なデータを提示する；製造変更された B 型肝炎ワクチンの安全性を評価する；インフルエンザワクチンの有効性について、abstract universal statements（要約された普遍的見解）を得る；A（H3N2）埼玉株／香港株を用いたインフルエンザワクチンの免疫原性を検討し、株変更（埼玉株→香港株）の影響を評価する；インフルエンザワクチンの株選定の在り方を検討する；HPV ワクチンの安全性・有効性を評価する；小学生やハイリスク集団を対象にインフルエンザワクチンの有効性や免疫原性を検討する；百日咳（DTaP）ワクチンの有効性、接種後経過年数の影響などを調査する；高齢者肺炎に対する肺炎球菌ワクチンの有効性およびインフルエンザワクチンの併用効果を検討する；開発導入や定期接種化が近年行われた（あるいは行われる見込みの）ワクチンを対象として、ワクチンの免疫原性や有効性、安全性、費用対効果を検討する；ワクチンの健全な普及に必要な基盤情報として、米国予防接種諮問委員会の勧告「インフルエンザの予防と対策」を翻訳し出版する。

インフルエンザワクチンを巡る従来の問題には、予防接種全般に係る課題が集約されているようである。前記の主要課題に関して、研究を継続しつつ研究ネットワークを確立維持することは、予防接種全般に係る緊急な問題に対応できる体制の確立維持につながると考えられる。

B.　研究方法

厚生労働省意向による特定研究

1）ポリオ感受性分科会（分科会長：廣田　良夫）

2011～2013 年度に実施した互換性試験（Sabin 株由来 OPV と DTaP-IPV、Wild 株由来 IPV）の被験者 153 人について、抗体持続状況を５年後まで実測、10 年後まで推計した。

2）B 型肝炎ワクチン安全性分科会
（分科会長：廣田　良夫）

製法変更された B 型肝炎ワクチン（ヘプタバックス -Ⅱ®）の安全性を評価するため、福岡県の小児科医院５施設において、B 型肝炎ワクチンの定期接種で受診した小児 100 人（生後２ヵ月以上６ヵ月未満）を対象に、１回目から３回目の各接種後 28 日までに発現した有害事象及び副反応を調査した。

3）定点モニタリング分科会
（分科会長：福島　若葉）

米国、EU などと同じ手法（test-negative 症例対照研究）により、季節性インフルエンザワクチンの有効性を継続的にモニタリングする。インフルエンザ様疾患で受診した６歳未満児（大阪・福岡の９診療所、800～1000 人）に PCR 検査を実施し、PCR 陽性者を症例、陰性者を対照とする。2013/14～2017/18 シーズンは６歳未満児を対象としたが、2018/19 シーズンは規定接種量の少ない３歳未満児を対象に、ワクチン有効性を検討した。

4）A(H3N2) 埼玉株／香港株ワクチン免疫原性分科会（分科会長：福島　若葉）

インフルエンザ H3 の埼玉株と香港株の単価ワクチンを作成し、健康成人 50 人ずつに１回接種し、埼玉株、香港株および流行株に対する抗体を測定した。

5）インフルエンザワクチンの株選定の在り方に関する検討（分科会長：福島　若葉）

インフルエンザワクチンの安定供給、およびワクチンの多様化への対応に資するため、インフルエンザワクチン製造株の選定に関わる各ステークホルダー［国立感染症研究所インフルエンザウイルス研究センター、製造販売会社など］の意見を集約し、ワクチン株選定の在り方を検討した。

6）HPV ワクチンの安全性に関する文献抄訳（分科会長：大藤　さとこ）

科学的に公平な立場からの堅固なエビデンスを整理するため、HPV ワクチンの安全性に関する先行研究のシステマティックレビューを「PRISMA（システマティックレビューおよびメタアナリシスのための優先的報告項目）声明」に基づいて実施し、抄訳集を作成した。

プロジェクト研究

7）インフルエンザ分科会（分科会長:原　めぐみ）

不活化インフルエンザワクチンの免疫原性と有効性、安全性、費用対効果を検討した。免疫原性は、健康成人を対象に２件（福岡・東京：入江、および福岡：織田）の研究で調査した。接種前、接種後、流行後に血清を採取し、HI 価を測定。幾何平均抗体価（geometric mean titer: GMT）、平均上昇倍数（mean fold rise: MFR）、抗体保有割合（seroprotection proportion（sP）：HI 価≧ 1:40 の割合）、抗体応答割合（seroresponse proportion（sR）：接種前 HI 価と比し４倍以上上昇した者の割合）を算出し、国際基準に則って評価した。有効性については、小学生（土浦：山口）を対象とした前向きコーホート研究、および６歳未満児（石川：中村）、小学生（福岡：福島）、一般住民（東京：齋藤）を対象とした症例対照研究（test-negative design）の手法により評価した。安全性については、妊婦（大阪：大藤）を対象とした前向きコーホート研究により、妊娠転帰に及ぼす影響を評価した。また、妊婦に対するインフルエンザワクチン接種について、費用効果分析を行った（近藤）。

加えて、シーズン中の流行ウイルスを解析し、インフルエンザのウイルス学的特性を明らかにするとともに、インフルエンザ陰性検体の病原検索を行った（大阪：森川）。

8）百日咳分科会（分科会長：岡田　賢司）

現行の予防接種プログラムによるワクチン有効性を検討し、接種後経過年数の影響などを評価するため、多施設共同症例対照研究を実施した。20 歳未満の百日咳患者を症例とし、同性・同年齢の友人対照３人、病院対照３人を選定した。加えて、百日咳検査陰性の対照を登録し、test-negative 症例対照研究の側面からも検討した。解析では、DTaP ワクチ

ンの有効性、および百日咳発症に対するその他の関連因子を検討した。

9）高齢者肺炎分科会（分科会長：鈴木　幹三）

高齢者肺炎に対するワクチン予防効果を検討するため、多施設共同症例対照研究を実施した。65～90歳の肺炎患者（誤嚥性肺炎は除外）を症例とし、出生年度・性が対応する病院対照を５人選定した。解析では、高齢者肺炎に対する肺炎球菌ワクチンの有効性およびインフルエンザワクチンの併用効果を検討した。

10）新規ワクチン検討分科会

（分科会長：中野　貴司）

接種普及に関心が高い複数のワクチン（ロタウイルスワクチン、おたふくかぜワクチン、帯状疱疹ワクチンなど）について、有効性、安全性、費用対効果を検討した。また、児や保護者におけるロタウイルス胃腸炎の疾病負担、ロタウイルスワクチンの接種行動に関連する因子、医療従事者における Vaccine preventable diseases の抗体保有状況、高齢者施設入所者における感染性胃腸炎の疾病負荷を検討した。

11）広報啓発分科会（分科会長：大藤　さとこ）

米国 CDC と連絡を取りながら、米国予防接種諮問委員会（ACIP）の勧告について、発行時期、注意点や変更点などについての情報を収集した。若手研究者を中心に同勧告を共同翻訳し、一般財団法人・日本公衆衛生協会より出版した。

（倫理面への配慮）

本研究全般に関して、「博多クリニック臨床試験審査委員会（医療法人相生会博多クリニック院長設置）」の承認を得た。また、研究分担者においても、必要に応じて所属機関の倫理委員会より承認を得た。

C.　主要分科会のまとめ

厚生労働省意向による特定研究

１）ポリオ感受性分科会（分科会長：廣田　良夫）

本邦での不活化ポリオワクチン（IPV）導入（2012）に先立ち、本研究班において「ポリオワクチン (OPV、IPV、DPT-IPV) の互換性に関する免疫原性・安全性試験」（以下「ポリオワクチン互換性試験」）を実施した（登録時月齢 3ヵ月～45ヵ月）。その結果、ワクチンの組み合わせ・接種順序にかかわらず、3 回の接種で防御レベル 1:8 を上回る抗体（NA）が誘導され、4 回目の booster dose により抗体価は更に上昇した。

その後、追加接種の必要性などを検討するため、ポリオワクチン互換性試験に参加して 4 回接種を完了した小児 153 人を対象に、抗体価の推移を 5 年間追跡した（2013～2018 年）。結果指標は幾何平均抗体価および抗体保有割合 (1:8 以上を示した者の割合) である。また、抗体価 1:8 を下回ったものについては、抗体価推移を個別に評価した。

Sabin 株・Wild 株いずれに対しても幾何平均抗体価は、4 回目接種後から接種 1 年後にかけて急速に低下し、接種 1 年後以降は緩やかに低下した。なお、Wild 株に対する幾何平均抗体価は、Sabin 株よりもやや早く低下する傾向を認めた。個々の児の抗体価についてみると、Wild 株 Type I、Sabin 株 Type I または Sabin 株 Type III に対して、接種 5 年後までに防御レベル 1:8 を下回ったものが 5 人いた。なお、抗体価半減期の中央値は、ワクチン組合せのグループや抗原に関わらず 2 年であり、半減期に基づく抗体保有割合の外挿値が 100% を維持できた期間は最長でも接種 6 年後までであった。

２）B 型肝炎ワクチン安全性分科会

（分科会長：廣田　良夫）

福岡県の小児科診療所 5 施設において、「ヘプタバックス－Ⅱ® 水性懸濁注シリンジ 0.25 ｍL」の安全性を確認する多施設共同、前向き観察研究を実施した。2018 年 9 月より、B 型肝炎ワクチンの定期接種のため受診した小児（生後2ヵ月以上6ヵ月未満、男女）100 人に対し、代諾者の同意を取得し、接種から 28 日間の研究対象者の健康状態を健康観察日誌に記録した。健康状態の調査項目は、体温（腋窩）、接種部位反応（紅斑、腫脹、硬結など）、全身症状、使用薬剤等である。定期接種 3 回全てにおいてこの調査を行った。本研究で観察された副反応・有害事象に関する所見に、本製剤の定期接種での使用において、安全性を懸念すべきものはないと考えられた。

３）定点モニタリング分科会

（分科会長：福島　若葉）

2013/14 シーズン以降、わが国の小児における

インフルエンザワクチン有効性を大阪府と福岡県で継続的にモニタリングしている。2016/17 および 2017/18 シーズンは 6 歳未満小児を対象とし、2018/19 シーズンは規定接種量の少ない 3 歳未満小児に対象を絞り、ワクチン有効性を評価した。

多施設共同症例・対照研究（test-negative design）の手法で研究を実施した。大阪府内と福岡県内の小児科診療所（2016/17 シーズンと 2017/18 シーズン：9 施設、2018/19 シーズン：7 施設）において、各シーズンのインフルエンザ流行中にインフルエンザ様疾患で受診した小児を登録した（2016/17 シーズン：6 歳未満小児 1,007 人、2017/18 シーズン：6 歳未満小児 1,015 人、2018/19 シーズン：3 歳未満小児 399 人）。登録時に、調査シーズンのインフルエンザワクチン接種に関する情報を診療録あるいは母子健康手帳から転記し、鼻汁吸引液を採取した。結果指標は real-time RT-PCR で病原診断した検査確定インフルエンザであり、条件付き多重ロジスティック回帰モデルによりワクチン有効率を算出した。

2016/17 シーズン（6 歳未満小児）：ワクチン有効率は、1 回接種で 42%（95% CI：－ 6%～68%）、2 回接種で 41%（95% CI：14%～60%）であり、2 回接種で有意な発病防止効果を認めた。主流行株であった A(H3N2) 型に対しても、2 回接種は有意な効果を示した（37%、95% CI：16%～58%）。年齢層別（1～2 歳／3～5 歳）にみると、これまでのシーズンと同様、若年層でより高いワクチン有効率を認めた（55% vs. 34%）。また、調査シーズンのインフルエンザワクチン接種が 1 回でも、これまでに合計 2 回以上ワクチン接種を受けている場合、あるいは前シーズンにワクチン接種を受けている場合は、2 回接種と同等の有効率である可能性が示唆された。

2017/18 シーズン（6 歳未満小児）：ワクチン有効率は、1 回接種で 57%（95% CI：25%～75%）、2 回接種で 63%（95% CI：45%～76%）であり、ともに有意な発病防止効果を認めた。型・亜型別の分析では、最も多く検出された B(Yam) 型に対して 2 回接種は有意な効果を示した（有効率 60%、95% CI：35%～76%）。調査シーズンは、インフルエンザワクチンの A(H3N2) 株が当初選定の埼玉株（卵馴化による抗原性の変化が小さい）から香港株（卵馴化による抗原性の変化が大きい）への変更を余儀なくされたものの、A(H3N2) 型に対しても有意な効果であった（有効率 67%、95% CI：29～85%）。年齢層別（1～2 歳／3～5 歳）にみると、これまでのシーズンと同様、若年層でより高いワクチン有効率を認めた（80% vs. 37%）。また、昨シーズン調査結果と同じく、調査シーズンのインフルエンザワクチン接種が 1 回であっても、これまでに合計 2 回以上ワクチン接種を受けている場合、あるいは前シーズンにワクチン接種を受けている場合は、2 回接種と同等の有効率である可能性が示唆された。

2018/19 シーズン（3 歳未満小児）：ワクチン有効率は、1 回接種で 75%（95% CI：-55%～96%）、2 回接種で 47%（95% CI：-28%～78%）であった。いずれも発病を予防する傾向を認めたが、統計学的に有意ではなかった。有意差を検出できなかった理由として、結果的に流行期間外の登録となってしまった者が多かったこと、福岡において流行のピークに登録できなかったことが影響したと考えられる。有効率の点推定値は、過去の調査と比べて大きな相違はないと考えられた。

6 歳未満小児におけるインフルエンザワクチン 2 回接種の有効率は、過去 3 シーズン（2013/14～2015/16 シーズン）の結果もあわせると、5 シーズン連続で有意であり、2 回接種により発病リスクが 1/2 程度に低下することが示された。若年層でより高いワクチン有効率を認めたこと、調査シーズンの接種回数が 1 回であっても過去接種の既往がある場合は 2 回接種と同等の効果が示唆されたことについても、複数シーズンで確認できたことから、結果の頑健性が示された。

国際水準からみても遜色のない、質の高い統一的な疫学手法で、インフルエンザワクチン有効性を継続的にモニタリングすることにより、わが国の小児における "abstract universal statements（要約された普遍的見解）" を導くことができており、予防接種政策に還元できる。2018/19 シーズンの 3 歳未満小児を対象とした調査では、当初予定していた解析対象者数を確保できず、有意差を検出できなかったが、今後はこれまで蓄積済みの情報もあわせた統合解析なども予定している。従って、3 歳未満の若年小児における堅固なエビデンスの提供に向けて十分に活用できる。

4）A(H3N2) 埼玉株／香港株ワクチン免疫原性分科会（分科会長：福島　若葉）

インフルエンザ A/ 埼玉 /103/2014（CEXP002）

(H3N2) 株（以下、埼玉株）、およびインフルエンザ A/ 香港 /4801/2014（X-263）（H3N2）株（以下、香港株）の免疫原性・安全性を確認するため、無作為化比較試験を実施した。それぞれの株を含む研究用の単価インフルエンザワクチン（以下、埼玉株ワクチンおよび香港株ワクチン）を作成し、20 歳以上の健康成人男女 100 人を無作為に 2 群に分け、埼玉株ワクチン、香港株ワクチンを各 50 人に 1 回接種した。ワクチン接種は、2017 年 10 月～11 月に実施し、接種前（S0）および接種 3 週間後（S1）に血清を採取した。

免疫原性は、香港株、埼玉株および A/ 大阪 /188/2017（H3N2）(以下大阪株) を用いて中和抗体価を測定し、接種後の幾何平均抗体価（GMT）、GMT 上昇倍数、抗体応答割合、抗体保有割合（任意に≧ 1:40 と設定）を算出して評価を行った。

香港株に対する中和抗体価：香港株ワクチン接種群の S1 の GMT は 1:546、GMT 上昇倍数は 5.5 倍、抗体応答割合は 50%、接種後の抗体保有割合は 96%であった。埼玉株ワクチン接種群では、各々、1:260、4.5 倍、40%、92%であった。

埼玉株に対する中和抗体価：香港株ワクチン接種群の S1 の GMT は 1:116、GMT 上昇倍数は 5.3 倍、抗体応答割合は 50%、接種後の抗体保有割合は 86%であった。埼玉株ワクチン接種群では、各々。1:61、4.2 倍、46%、68%であった。

大阪株に対する中和抗体価：香港株ワクチン接種群の S1 の GMT は 1:17、GMT 上昇倍数は 2.7 倍、抗体応答割合は 32%、接種後の抗体保有割合は 28%であった。埼玉株ワクチン接種群では、各々、1:9、1.3 倍、4%、6%であった。

香港株ワクチン接種は、ホモである香港株だけでなく、ヘテロである埼玉株に対しても、埼玉株ワクチン接種と同等あるいはより良好な免疫原性を示した。また、香港株ワクチン接種は、流行野生株である大阪株に対しても、埼玉株ワクチン接種より良好な免疫原性を示した。これは、香港株ワクチンがより広い範囲の株に対して免疫原性を有する可能性を示唆している。

安全性については、軽微な副反応を認めたが、重篤な有害事象の報告はなかった。また、2 群における副反応発現頻度には有意差を認めなかった。

5）インフルエンザワクチンの株選定の在り方に関する検討（分科会長：福島　若葉）

わが国における「インフルエンザワクチン株選定の在り方」について検討するため、株選定に関わる国立感染症研究所およびワクチンメーカー（国内メーカー5 社、外資系メーカー3 社）に対する聞き取り調査を行い、「世界保健機関（WHO）によるインフルエンザワクチン株選定会議を基軸とした一般的な株選定の流れ」や「国内での選定過程」「海外での選定過程」「それぞれの長所・短所」を整理した。また、関連事項として「製造候補株、リアソータント株」「名古屋議定書」「製造候補株の増殖性と生産性の評価」「力価試験の試薬」「国家検定」「市場性、需給バランス」「生物学的製剤基準」等の顕在する、或いは潜在する課題を整理した。これらの内容は、今後のワクチン株選定において有用な基礎情報であり、総ての関係者で共有かつ知識の継承を通じて、より的確なワクチン株選定が可能となり、効果的な予防接種政策の樹立に向かうであろう。

6）HPV ワクチンの安全性に関する文献抄訳
（分科会長：大藤　さとこ）

HPV ワクチンの安全性に関する先行研究のシステマティックレビューを「PRISMA（システマティックレビューおよびメタアナリシスのための優先的報告項目）声明」に基づいて実施し、抄訳集を作成した。ワクチンの安全性に関しては、HPV ワクチン接種群では、コントロール群と比べて、局所反応の発生割合が高く、統計学的有意差を認めたが、症状は接種後 1 週間以内に自然軽快した。全身反応、重篤な有害事象、慢性疾患の新規発症、自己免疫疾患の新規発症、妊娠転帰に関しては、HPV ワクチン接種群とコントロール群で発生割合はほとんど同様であった。一部の観察研究において、HPV ワクチン群で中枢神経系疾患や一部の自己免疫疾患の発生率が高いことを示した研究も認めたが、研究手法による限界や Publication bias の可能性も考えられる。ワクチン有効性に関しては、HPV ワクチン群で、HPV 初感染や持続感染、CIN や尖圭コンジローマの発生割合が下がり、高いワクチン有効率が多くの文献で示されていた。本抄訳集は、HPV ワクチンの有用性を検討する際の基礎資料として、参考にする価値があり、HPV ワクチンの健全な普及に貢献すると考えられる。

プロジェクト研究

7）インフルエンザ分科会（分科会長:原　めぐみ）

不活化インフルエンザワクチンの免疫原性、有効性、安全性、費用対効果を評価することを目的とした。免疫原性については、①医療施設職員におけるワクチン抗原 A/H1N1pdm09 への繰り返し曝露の影響（東京・福岡、2014/15～2016/17 シーズン、前向き cohort 研究：入江）、②健常成人における免疫原性とそれに影響を与える因子（福岡、2017/18 シーズン、2018/19 シーズン、前向き cohort 研究：織田ら）；有効性については、③小学生における迅速診断陽性インフルエンザに対する有効性（土浦、2016/17 シーズン、2017/18 シーズン、2018/19 シーズン、前向き cohort 研究：山口）、④小学生における迅速診断陽性インフルエンザに対する有効性（福岡、2017/18 シーズン、症例対照研究 , test-negative design：福島）、⑤ 6 歳未満児における迅速診断陽性インフルエンザに対する有効性（石川、2016/17 シーズン、2017/18 シーズン、2018/19 シーズン、症例対照研究 test-negative design：中村）、⑥一般住民における PCR 検査陽性インフルエンザに対する有効性（東京、2009/2010 シーズン、2010/11 シーズン、症例対照研究 test-negative design：齋藤）；安全性については、⑦妊婦に対する安全性（大阪、2013/14 シーズン、前向き cohort 研究：大藤）；費用対効果については、⑧妊婦に対するインフルエンザ予防接種の費用対効果（近藤ら）を評価した。

免疫原性については、①ワクチン抗原 A/H1N1pdm09 への繰り返し曝露により接種後の幾何平均抗体価および平均上昇倍数は毎年有意に減少した。②健常成人に対するインフルエンザワクチンの免疫原性には、接種前抗体価とストレス指標（2017/18 シーズン調査）や過去のインフルエンザワクチン接種歴（2018/19 シーズン調査）が関連していた。有効性については、③小学生の迅速診断陽性インフルエンザに対するワクチン有効率は、A/H3 亜型が主流行の 2016/17 シーズンは A 型に対し 29%；A 型 2 種と B 型の混合流行の 2017/18 シーズンは A 型に対し 66%、B 型に対し 15%；A 型が主流行の 2018/19 シーズンは A 型に対し 44%と推計した。④小学生の迅速診断陽性インフルエンザに対する有効率は－ 7%（主流行の B 型に対して 35%）であった。⑤ 6 歳未満児の迅速診断陽性インフルエンザに対する有効率は、2016/17 シーズンで 39%（A 型に対し 36%、B 型に対し 59%）、2017/18 シーズンで 43%（A 型に対し 48%、B 型に対し 39%）、2018/19 シーズンで 56%（A 型に対し 56%、B 型は算出できず）と推定した。⑥ 2009/2010/2011 インフルエンザシーズンに伊豆大島で収集したデータを test-negative design で再解析し PCR 検査陽性インフルエンザに対する有効率は、2009/10 シーズン：A/H1N1pdm09 に対して 1～12 歳、13～64 歳でそれぞれ 49%、92%、2010/11 シーズン：A/H1N1pdm09 に対して 87%、73%、A/H3 に対して 1～12 歳は 59%、13～64 歳は検出不能、B に対して 46%、－ 5%と推定した。安全性については、⑦妊婦 10,631 人（ワクチン接種率 40%）において、ワクチン接種を受けた妊娠週数に拘らず、妊婦に対するインフルエンザワクチン接種が、妊娠転帰を悪化させるという所見は認めなかった。費用対効果については、⑧妊婦に対するインフルエンザ予防接種プログラムの増分費用効果比（プログラムなしと比較する）は、¥7,779,356/QALY であり、WHO の基準（3 × GDP）に基づくと、費用効果的であることを示した。

また、インフルエンザシーズン中の流行ウイルスを解析し、インフルエンザのウイルス学的特性を明らかにするとともに、インフルエンザ陰性検体の病原検索を行った。3 シーズンのインフルエンザ流行状況を見ると、2016/17 シーズンは A/H3 亜型がほぼ単独流行であり、地域小流行的に A/H1N1pdm09 亜型、B 型 Victoria 系統、同 Yamagata 系統が検出された。2017/18 シーズンは、A 型と B 型の検出比がほぼ 1 対 1 であり B 型 Yamagata 系統が主流行であった。2018/19 シーズンは、A/H1N1pdm09 亜型、AH3 亜型がそれぞれ 4 割以上を占め、B 型 Yamagata 系統、B 型 Victoria 系統は散発的であった。全国データでは A/H3 亜型が若干多い結果であったが、大阪府内は全国集計と異なり A/H1N1pdm09 亜型が多く検出された。HA 全長の塩基配列の解析は、全国データと同じ傾向を示した。インフルエンザウイルスが検出されなかった事例はそれぞれ 12.7%、6.7%、7.7%で、各シーズンともそのうちの半数で他の呼吸器ウイルスが検出された。

これらの研究により得られた成果は、今後のインフルエンザワクチン施策の判断資料となりうる。また、Test-negative design による有効性検討は、インフルエンザの疾病特性を踏まえると、インフルエン

ザワクチン有効性の評価手法として有用ではあるものの、わが国の小学生を対象として適用する場合は、集団特性を考慮した工夫が必要と考えられた。

8）百日咳分科会（分科会長：岡田　賢司）

本分科会の目的は、百日咳含有ワクチンの有効性を疫学の視点から検討することである。そこで、砂川・神谷、および岡田・大藤は、国内で開発された安全性の高い無細胞精製百日咳ワクチンの有効性を検討した。また、砂川らは、重症化しやすい早期乳児への百日咳対策として、欧米で行われている妊婦への百日咳含有ワクチン接種が国内で可能かどうかを調査し、星らは妊婦への百日咳含有ワクチンの費用対効果を検討した。

有効性に関して、①「地域流行に対するワクチンを用いた百日咳の予防に関する研究」により、2012年～2013 年及び 2018 年に高知県某市で発生した百日咳の流行下での、乳幼児期に接種されているDPT 4 回接種についての百日咳含有ワクチン接種の有効性を評価した。ワクチン 4 回接種者の OR は未接種者に対して 0.27(0.05-1.67）であったが、４回接種後４年以上経過した者は、２年未満の者と比較して有意に発症者が増加しワクチン効果の減衰傾向が認められた。②これまで本研究班で行ってきた友人対照および病院対照による多施設共同・症例対照研究に、検査陰性対照の登録を追加し、ワクチン接種後の効果減弱に関する検討を行った。現行の百日咳含有ワクチン接種後、経年的に有効率が低下した。百日咳含有ワクチン接種後、5 年以上経過すると、4 回百日咳含有ワクチンを接種していても百日咳発症のリスクが有意に上昇した。

両研究とも、現行の百日咳含有ワクチン４回接種後、効果の減弱が明らかとなり、（１）５回目の追加接種が必要であること、（２）追加接種時期としては就学前が望ましいことを提案した。

妊婦への百日咳含有ワクチン接種については、妊婦 977 人における質問票調査の結果、「百日咳含有ワクチン」の接種希望は約 30％であり、接種希望と関連する要因は「妊婦への百日咳含有ワクチン接種が必要」「出生児への予防効果がある」であった。また、妊婦への百日咳含有ワクチンの有効性・安全性に関する正しい知識の普及には、正確な情報を医師が妊婦へ提供することが重要であると考えられた。費用対効果については、妊婦に対する百日咳含有ワクチン接種は、QALY を費用効果の基準に用いる、あるいは WHO の判断基準による、のいずれの方法でも、費用効果的と考えられるシナリオが存在した。

9）高齢者肺炎分科会（分科会長：鈴木　幹三）

2010 年 10 月～2014 年 9 月に多施設共同症例対照研究（症例 161 人、対照 308 人）を実施したが、2014 年 10 月、高齢者に対する肺炎球菌ワクチン接種が定期接種化されたため、有効性に関する先行研究の実施要領を一部修正して新規に症例対照研究を行った。2016 年 10 月より、41 施設の協力を得て多施設共同症例対照研究を実施した。症例は 65～90 歳の市中肺炎患者、対照は、症例と性、出生年度、外来受診日が対応する同一機関受診患者５人を選定した。患者背景として、インフルエンザワクチン接種歴、肺炎球菌ワクチン接種歴、年齢、性別、身長・体重（BMI）、ADL、基礎疾患、６歳以下の小児との同居、血液検査所見、喫煙・飲酒習慣等の情報を収集した。また、肺炎に関する疾患情報（確定診断日、症状、検査結果など）も併せて収集した。2019 年 11 月時点で、解析対象者数は 669 人（症例 127 人、対照 542 人）であり、肺炎球菌性肺炎は 127 人中29 人（23%）であった。肺炎に対する調整 OR は、インフルエンザワクチン接種 0.85(95％ CI：0.55-1.31)、肺炎球菌ワクチン接種1.19(0.77-1.82）となった。23 価莢膜多糖体ワクチン接種 5 年以内に限定した肺炎球菌ワクチンの調整 OR は 1.26(0.82-1.96）であった。結果指標を肺炎球菌性肺炎に限定した解析では、肺炎球菌ワクチン接種の粗 OR は1.13(95％ CI：0.50-2.56）であった。

また、高齢者肺炎球菌ワクチン定期接種化の影響に関する横断研究では、定期 B 類の高齢者肺炎球菌ワクチンについて定期接種年齢該当者すなわち費用助成対象者において接種率が高いことを明らかにした。接種の最たる契機は、市町村からの案内（50％）であり、市町村による直接的な対象者個人へのアプローチが接種促進に有効と考えられた。

これらの結果は、肺炎球菌ワクチン定期接種化後の高齢者肺炎に対するワクチン有効性を示すものであり、今後の高齢者への予防接種施策に有用と考えられる。

10）新規ワクチン検討分科会（分科会長：中野　貴司）

新しく導入や定期接種化されたワクチン、あるいは今後の定期接種化や普及が想定されるワクチンについて検討することを目的とした。具体的には以下の内容になる。

ロタウイルスワクチンの有効性（2018 シーズン、2019シーズン）、ワクチン接種行動に関連する要因、およびロタウイルス胃腸炎による児や保護者への疾病負担を調査した。また、おたふくかぜワクチン接種後の有害事象、医療従事者における麻疹・風疹・水痘・ムンプスに対する抗体保有状況、56 歳以上の者における髄膜炎菌ワクチンの免疫原性・安全性、帯状疱疹ワクチンの費用対効果、高齢者施設入所者の下痢症に関する疫学調査を実施した。

ロタウイルスワクチンは、佐賀県、福岡県、奈良県の医療機関 6 施設において、2 か月以上 6 歳未満の乳幼児 1669 人を対象に test-negative design による症例対照研究を行い、有効性を評価した。症例対照研究によるロタウイルスワクチンの有効性は、接種の調整 OR（95％信頼区間）は①ロタウイルス胃腸炎（RVGE）に対し 0.44（0.34-0.58）、②重症 RVGE に対し 0.15（0.07-0.32）、③点滴または入院 RVGE に対し 0.09（0.03-0.27）であった。2 歳以下と 3 歳以上の 2 群に分けて検討したところ、いずれのアウトカムについても調整 OR は 2 歳以下の群の方が低かった。金沢市の 1 歳半健診での調査では、ロタウイルスワクチンの接種率は 72.9％であり、保護者がロタウイルス胃腸炎を重症だと思うこと、ワクチンが効くと思うこと、小児科で勧められたこと、雑誌やネットの情報を見たことは、保護者が児にワクチンを接種することと正の関連を、ワクチンの接種費用や副反応への心配は有意な関連を認めなかった。それらを調整しても相対的貧困は接種と負の関連を示した。約 3 割の幼児が感染性胃腸炎で医療機関受診があり、ロタウイルス胃腸炎の割合は 7.1％であった。児が感染性胃腸炎にかかると主に母親が看病をし、その半数以上が仕事を休んでいた。これらの研究結果は、定期接種化に際して有用であった。

鳥居株おたふくかぜワクチンについては、企業が医療機関等から収集した接種後の有害事象報告およびワクチン出荷数の情報を使用し、1992～2018 年度におけるワクチン接種後の無菌性髄膜炎の発症頻度（/10 万ドーズ）とその内容を検討した。鳥居株おたふくかぜワクチン接種後の無菌性髄膜炎の発症頻度（/10 万ドーズ）は、1990 年代は 10 万ドーズあたり 10 前後を推移していたが、2001 年以降、有意に減少し、2001～2003 年の発症頻度（/10 万ドーズ）は 3.91（2.46-5.36）、直近の 2016～18 年の頻度（/10 万ドーズ）は 2.78（1.94-3.62）であった。また、接種後の有害事象例では、ムンプスウイルスの自然感染時と同様に、一定期間は一定の頻度で髄液からワクチン株ウイルスが検出され、その期間は比較的長期に及ぶ可能性も考えられた。現行のおたふくかぜワクチンの副反応としての無菌性髄膜炎の出現頻度が、１万回接種前後に１例程度という範囲で議論されていること、２社から販売されているワクチンの年間出荷量がそれぞれ約 60 万本と推計されることを考慮すると、安全性に関する詳細な結論を導くためには、市販ワクチンを接種された多数例に対する前向き観察研究を計画し、詳細な臨床症状に関する情報や症状を認めた場合には髄液を含めたウイルス学的検査の情報を収集解析する必要がある。

40歳以上の医療関係者で抗体陰性者が最も多かったのは風疹、次いでムンプスであった。麻疹については、日本環境感染学会による医療関係者のためのワクチンガイドライン第 2 版で呈示された「基準を満たさない抗体価」を有する者の占める割合が高かった。これらの結果は、2019 年から開始された成人男性に対する第 5 期の風疹定期接種は適切な施策であり、病院職員への院内感染対策としても大切なワクチンであることを示唆する。麻疹抗体価の結果より、第 5 期風疹定期接種および VPD 院内感染対策に MR ワクチンを用いることは妥当と考えられた。医療関係者に対する予防接種指針とともに、国内の成人への感染症対策として、ワクチン追加接種やキャッチアップ接種に関する方策を検討する必要がある。

髄膜炎菌ワクチンの安全性について、接種部位の局所反応は接種部位の圧痛 1 人、接種上肢の動かしにくさ 1 人、全身反応は 2 人（倦怠感 2 件、筋肉痛 2 件、頭痛 1 件）に認めたが、37.5℃以上の発熱はみられなかった。重篤な有害事象をきたした症例は無かった。

帯状疱疹ワクチン 2 製剤（弱毒生水痘ワクチン、不活化サブユニットワクチン）の費用対効果については、接種費用が 8,000 円（生ワクチン１回接種）と 30,000 円（不活化ワクチン２回接種

計）に、１QALY 獲得に対する支払い意思額（WTP, Willingness-to-pay） を 5,000,000 円 /QALY に設定した場合、用いたワクチンの種類に関わらず、全ての接種プログラムの増分費用効果比（ICER, Incremental cost-effectiveness ratio）は WTP を下回り費用効果的であった。

高齢者施設入所者 1345 人の下痢症に関する調査では、2018 年 11 月～2019 年 8 月に 37 人が下痢を発現したが（罹患率：1.34/10,000 person-days）、ノロウイルスやクロストリジウム・ディフィシルの陽性者はいなかった。調査年度の感染性胃腸炎の流行規模が小さかったことを考慮し、追跡調査を延長し、結論を導く予定である。

新たに開発されたワクチン、公的接種が検討されているワクチンは、その有効性と安全性や費用対効果を検証し、解析結果を社会に情報発信する必要があるため、予防接種施策に活用できる有用なデータの提供に努めたい。

11）広報啓発分科会（分科会長：大藤　さとこ）

我が国におけるインフルエンザの予防と対策が、世界的な観点で標準的と考えられる手法によって行われるようになることに寄与する。

毎年８月ごろに米国の予防接種諮問委員会（ACIP）が刊行する勧告（2017/18 版、2018/19 版、2019/20 版）を翻訳し日本公衆衛生協会より出版した。

本勧告では 2010 年より、月齢６ヵ月以上のすべての人々に対する普遍的接種（universal vaccination）を勧奨している。また、月齢６ヵ月から８歳未満児への接種回数について、過去に合計２回以上ワクチン接種を受けたことがある場合には当該シーズンのワクチン接種は１回接種でよいと記載されている。このほか、各シーズンに入手可能な各ワクチンの適応や禁忌・慎重投与、卵アレルギーのある人への接種、などが明記されている。

本勧告のワクチン適応等は、米国 ACIP によるものであり、我が国の予防接種法に規定されているものとは異なるが、インフルエンザワクチン接種の実施における日常の保健医療活動の指針として、学術的に参考とする価値があり、インフルエンザの予防と対策の標準的な手法の普及に貢献すると考えられる。

D.　研究結果と考察

厚生労働省意向による特定研究

１）ポリオ感受性分科会

①　入江らは、2011～2013 年度に実施した互換性試験（Sabin 株由来 OPV と DTaP-IPV、Wild 株由来 IPV）の被験者 153 人について、抗体持続状況を５年後まで実測、10年後まで推計した（2013～2018年、前向き cohort study）。なお、2011～2013 年に実施した試験では、下記の４群について検討し、sOPV、DTaP-sIPV、wIPV の組み合わせ・接種順序にかかわらず、初回免疫後にはすべての者で防御レベル（中和抗体価1：8）を大きく上回る抗体が誘導され、追加免疫後には booster 効果が得られたことを確認している。

・A 群（11人）：１期初回（sOPV→DTaP-sIPV→DTaP-sIPV）⇒１期追加（DTaP-sIPV）
・B 群（49人）：１期初回（sOPV → wIPV → wIPV）⇒１期追加（wIPV）
・C 群（50人）：１期初回（DTaP-sIPV → DTaP-sIPV → wIPV）⇒１期追加（wIPV）
・D 群（43人）：１期初回（wIPV → wIPV → DTaP-sIPV）⇒１期追加（DTaP-sIPV）

各群の追加免疫から１年後の抗体価が得られた 120 人、２年後の抗体価が得られた 103 人、３年後の抗体価が得られた 94 人、４年後の抗体価が得られた 85 人、５年後の抗体価が得られた 88 人を解析対象とした。

(1) Sabin 株に対する幾何平均抗体価は、追加免疫後から１年後にかけて急速に減少した後（1 年後 / 追加免疫後：0.08～0.24）、接種２年後以降は緩やかに減少した（2 年後 /1 年後：0.75～1.00、3 年後 /2 年後：0.53～0.85、4 年後 /3 年後：0.24～0.56、5 年後 /4 年後：0.58～0.86）。なお、３年後から４年後にかけての低下、および４年後から５年後にかけての低下は、接種ワクチン、抗原に拘わらず、有意であった。

(2) Wild 株に対する幾何平均抗体価も同様の傾向を示したが、接種２年後以降の減少程度は Sabin 株よりも大きかった（1年後 / 追加免疫後：0.10～0.27、2 年後 /1 年後：0.33～0.67、3 年後 /2 年後：0.39～1.10、4 年後 /3 年後：0.37～0.82、5 年後 /4 年後：0.55～1.04）。

(3) 接種後５年間で抗体価が 1：8 を下回った者は：A 群で Wild 株 Type Ⅰ に対して２人（18％）；

B 群で Sabin 株 Type Ⅲと Wild 株 Type Ⅲに対して１人、Sabin 株 Type Ⅰと Wild 株 Type Ⅰに対して１人、Sabin 株 Type Ⅲに対して１人の合計３人（6%）であった。

(4) 接種１年後から５年後までに３点以上の抗体価が測定できた 103 人（A 群７、B 群 37、C 群 32、D 群 27）を対象に、10 年後までの抗体価を推定したところ、いずれの群も抗体価の半減期の中央値は２年であり、抗体保有割合が 100%を維持できた期間は最長で接種６年後までであった。

以上の結果から、就学前の時期に追加接種を実施する必要性が示唆された。

２）B 型肝炎ワクチン安全性分科会

① 伊藤らは、製法（アジュバントの総量、リン酸／アルミニウムモル比）が変更された B 型肝炎ワクチン（ヘプタバックス -Ⅱ®）の安全性成績を収集するため、福岡県の小児科医院５施設において、B 型肝炎ワクチンの定期接種で受診した小児 100 人（男 51 人、２ヵ月児 98 人、３ヵ月児 2 人）を対象に、接種後 28 日間の安全性を評価した（2018 年、前向き cohort study）。調査項目は、体温、接種部位反応、全身反応、使用薬剤などである。１回目接種から３回目接種後 28 日までに発現した有害事象及び副反応の種類、重症度、発現までの日数、持続日数および発現割合について検討した。100 人のうち 97 人が本製剤の３回接種を完了した。逸脱例１人（２回目接種にバイアル製剤を使用）は解析に含めた。３回目接種に来院しなかった追跡不能例２人は２回目接種までの情報を解析に含めた。延べ 298 回接種のうち、局所反応は 64 件（21%）に認め、１回目接種時に 10%、２回目接種時に 25%、３回目接種時に 30%で局所反応を認めた。ほとんどの局所反応は発現後３日以内に消失した。本剤接種との関連が否定できない 38℃以上の発熱が 13 件（4%）であったが、１件を除き発現後３日以内に解熱した。重篤な有害事象は認めなかった。本研究で観察された副反応・有害事象に関する所見に、本製剤の定期接種での使用において、安全性を懸念すべきものはないと考えられた。

３）定点モニタリング分科会

① 福島らは、インフルエンザワクチンの有効性を継続的にモニタリングするため、多施設共同症例対照研究（test-negative design）を実施した（2016/17 シーズン、症例対照研究）。大阪府および福岡県の小児科診療所９施設において、流行期間中（大阪：2017 年第２週～10 週、福岡：2017 年第３週～11 週）にインフルエンザ様疾患（ILI）で受診した６歳未満の小児 1,007 人（平均 2.7 歳、男 538 人）を解析対象とした。鼻汁吸引検体を用いて real-time RT-PCR 法による病原診断を行い、インフルエンザウイルス陽性者を症例、インフルエンザウイルス陰性者を対照（test-negative control）とした。調査シーズンのインフルエンザワクチン接種に関する情報は、診療録あるいは母子健康手帳から転記した。症例と対照のワクチン接種率を比較し、多重ロジスティック回帰モデルにより PCR 陽性インフルエンザに対するワクチン有効率（VE）を（１－ OR）× 100%により算出した。PCR 陽性インフルエンザは 369 人で、亜型は A/H3N2 型が最も多かった。PCR 陽性インフルエンザに対するワクチン接種の調整 OR は１回接種で 0.58（0.32-1.06）、２回接種で 0.59（0.40-0.86）、有効率はそれぞれ 42%、41%であり、２回接種の有効率は有意差を認めた。年齢階級別にみると、若年層でより高いワクチン有効率を認めた（２回接種の有効率は１～２歳：55%、３～５歳：34%）。調査シーズンのワクチン接種が１回でも、過去に合計２回以上ワクチン接種を受けている、あるいは昨シーズンにワクチン接種を受けている場合には、２回接種と同等の有効率である可能性が示唆された。

また、2017/18 シーズンも、大阪府と福岡県の２地域で、同内容の調査を実施した（2017/18 シーズン、症例対照研究、test-negative design）。大阪府および福岡県の小児科診療所９施設において、流行期間中（大阪・福岡：2018 年第２週～10 週）に ILI で受診した６歳未満の小児 1,015 人（平均 2.8 歳、男 561 人）を解析対象とした。PCR 陽性インフルエンザは 436 人で、亜型は B(Yam) 型が最も多かった。PCR 陽性インフルエンザに対するワクチン接種の調整 OR は１回接種で 0.43（0.25-0.75）、２回接種で 0.37（0.24-0.55）、有効率はそれぞれ 57%、63%であり、１回接種、２回接種とも有意な発病防止効果を認めた。年齢階級別にみると、若年層でより高いワクチン有効率を認めた（２回接種の有効率は１～２歳：80%、３～５歳：37%）。また、調査シーズンのワクチン接種が１回でも、過去に合計２回以上ワ

クチン接種を受けている、あるいは昨シーズンにワクチン接種を受けている場合には、２回接種と同等の有効率である可能性が示唆された。

さらに、2018/19 シーズンは、大阪府と福岡県の２地域で、規定接種量の少ない３歳未満児を対象に、同内容の調査を実施した（2018/19 シーズン、症例対照研究、test-negative design）。大阪府および福岡県の小児科診療所７施設において、流行期間中（大阪：2019 年第３週～10 週、福岡：2019 年第４週～12 週）に ILI で受診した３歳未満の小児 399 人（平均 1.3 歳、男 216 人）を解析対象とした。PCR 陽性インフルエンザは 122 人で、亜型は AH3 型が最も多かった。PCR 陽性インフルエンザに対するワクチン接種の調整 OR は１回接種で 0.25(0.04-1.55)、２回接種で 0.53(0.22-1.28)、有効率はそれぞれ 75%、47%であり、１回接種、２回接種とも OR が低下する傾向を認めたが、統計学的有意な有効性を検出するには至らなかった。有意差を検出しえなかった原因として、流行ピークでの登録を逃したことによる検出力不足の影響が考えられる。インフルエンザワクチン有効性の研究では、十分な対象者数の確保および流行ピークを捉えるため、調査開始時期を適格に決定する必要性が示唆された。

４）埼玉株／香港株ワクチン免疫原性分科会

① 福島らは、インフルエンザワクチンの H3 株に対する免疫原性・安全性に関して、埼玉株と香港株の無作為化比較試験を実施した（2017/18 シーズン、無作為化比較試験）。20 歳以上の健康成人 100 人を無作為に２群に分け、本研究用に作成した単価インフルエンザワクチン（埼玉株ワクチン、香港株ワクチン）を各 50 人に１回接種した。ワクチン接種は、2017 年 10 月～11 月に実施し、接種前および接種３週間後に血清を採取した。免疫原性は、ワクチン株の香港株、埼玉株、および流行野生株の A/大阪 /188/2017 (H3N2) 株（以下、大阪株）に対する中和抗体価を測定し、接種後の幾何平均抗体価(GMT)、GMT 上昇倍数、抗体応答割合、抗体保有割合（任意に≧ 1:40 と設定）を算出して評価した。安全性は、接種から１週間以内に発現した副反応および有害事象の発現について評価した。香港株に対する抗体応答は：香港株ワクチン接種群で、GMT 上昇倍数 5.5 倍、抗体応答割合 50%、接種後の抗体保有割合96%；埼玉株ワクチン接種群では各々、4.5 倍、40%、92%であった。また、埼玉株に対する抗体応答は：香港株ワクチン接種群で、GMT 上昇倍数 5.3 倍、抗体応答割合 50%、接種後の抗体保有割合 86%；埼玉株ワクチン接種群では各々、4.2 倍、46%、68%であった。さらに、大阪株に対する抗体応答は：香港株ワクチン接種群で、GMT 上昇倍数 2.7 倍、抗体応答割合 32%、接種後の抗体保有割合 28%；埼玉株ワクチン接種群では各々、1.3 倍、4%、6%であった。香港株ワクチンは、ホモである香港株に対してのみならず、ヘテロである埼玉株に対しても良好な免疫原性を示した。また、流行野生株の大阪株に対しても、埼玉株ワクチンより良好な免疫原性を示した。安全性に関しては、重篤な有害事象は認めず、２群の副反応発現頻度に有意差を認めなかった。

５）インフルエンザワクチンの株選定の在り方に関する検討（分科会長：福島　若葉）

① 福島らは、わが国における「インフルエンザワクチン株選定の在り方」について検討するため、株選定に関わる国立感染症研究所およびワクチンメーカー（国内メーカー５社、外資系メーカー３社）に対する聞き取り調査を行った。そして、世界保健機関（WHO）によるインフルエンザワクチン株選定会議を基軸とした一般的な株選定の流れの下、「国内での選定過程」「海外での選定過程」「それぞれの長所・短所」を整理するとともに、関連事項として「製造候補株、リアソータント株」「名古屋議定書」「製造候補株の増殖性と生産性の評価」「力価試験の試薬」「国家検定」「市場性、需給バランス」「生物学的製剤基準」等についても、顕在する、或いは潜在する課題を整理した。これらの内容は、選定されたインフルエンザワクチン製造株の影響がワクチン供給までの全プロセスに及ぶことを理解する一助となるものであり、今後のワクチン株選定において有用な基礎情報となる。また、今後の改善を通じて変化していく課題の全般を、総ての関係者が共有し、各々の分野でそのような知識が継承されることになれば、より的確なワクチン株選定が可能となり、効果的な予防接種政策の樹立に向かうであろう。

６）HPV ワクチンの安全性に関する文献抄訳（分科会長：大藤　さとこ）

① 大藤らを中心に計 26 人の班員が共同して、

HPV ワクチンの有用性を検討する基礎資料として、HPV ワクチンの安全性・有効性に関する抄訳集を作成した。HPV ワクチンの安全性について記載した文献について、「PRISMA（システマティックレビューおよびメタアナリシスのための優先的報告項目）声明」に基づいた系統的レビューを行い、該当文献を抽出した。抽出した 140 文献の内容を要約すると、ワクチンの安全性に関しては、HPV ワクチン接種群では、コントロール群と比べて、局所反応の発生割合が高く、統計学的有意差を認めたが、症状は接種後１週間以内に自然軽快した。全身反応、重篤な有害事象、慢性疾患の新規発症、自己免疫性疾患の新規発症、妊娠転帰に関しては、HPV ワクチン接種群とコントロール群で発生割合はほとんど同様であった。一部の観察研究において、HPV ワクチン群で中枢神経系疾患や一部の自己免疫疾患の発生率が高いことを示した研究も認めたが、研究手法による限界や Publication bias の可能性も考えられる。ワクチン有効性に関しては、HPV ワクチン群で、HPV 初感染や持続感染、CIN や尖圭コンジローマの発生割合が下がり、高いワクチン有効率が多くの文献で示されていた。

プロジェクト研究

７）インフルエンザ分科会

① 入江、都留らは、治験を専門とする医療機関（東京・福岡の３施設）の職員を対象に、インフルエンザワクチン毎年接種の免疫応答への影響を検討した（2014/15～2016/17 シーズン、前向き cohort study）。登録時に、年齢、性、ワクチン接種歴、既往歴、などの背景因子の情報を収集した。また、対象者にインフルエンザワクチンを１回接種し（2014/15 シーズンは３価、2015/16 シーズン・2016/17 シーズンは４価）、接種前、接種４週後、流行後に HI 価測定のための採血を実施した。３シーズン連続してワクチン接種を受けた 26～66 歳の健康成人 119 人を解析対象とした。３シーズンの A/H1 抗原はいずれも A/H1N1pdm09 であったため、当該ワクチン抗原 A/H1N1pdm09 への繰り返し曝露が免疫原性に与える影響を評価した。シーズンを経るに従って、接種前・接種後の GMT は低下した。１シーズン目の接種後 GMT は 61、２シーズン目の接種後 GMT は 53、３シーズン目の接種後 GMT は 51 であり、１シーズン目と比べると、２シーズン目で 0.87 倍（95% CI：0.78-0.97）、３シーズン目で 0.84 倍（0.75-0.94）、有意に低下していた。接種前後の上昇倍数で見ても、１シーズン目の上昇倍数は 1.49、２シーズン目の上昇倍数は 1.30、３シーズン目の上昇倍数は 1.25 であり、１シーズン目と比べると、２シーズン目で 0.87 倍（95% CI：0.78-0.97）、３シーズン目で 0.84 倍（0.75-0.94）、有意に上昇倍数が低下していた。同一ワクチン抗原への繰り返し曝露は、同抗原に対する免疫原性を低下させる可能性が示唆された。

② 織田らは、大学の教職員および学生 34 人（男 20 人、平均 36 歳）を対象に、インフルエンザワクチンの免疫原性を検討した（2017/18 シーズン、前向き cohort study）。登録時に、自記式質問票により、ワクチン接種歴、既往歴、基礎疾患、インフルエンザ罹患歴、ストレス指数などの背景因子の情報を収集した。研究協力施設において対象者にインフルエンザワクチンを１回接種し、接種前、接種４週後、流行後に採血を行い、HI 抗体価を測定した。免疫原性の評価尺度として、GMT、平均上昇倍数、抗体応答割合、抗体保有割合を算出し、ワクチンの免疫原性に影響を及ぼす要因として、年齢、ワクチン接種歴、ストレス指数、接種前抗体価との関連を検討した。AH1 型に対しては、接種前抗体価が高いと接種後の抗体保有割合が低い傾向を認め、ストレス指数が中等度の者で接種後の抗体応答割合および抗体保有割合が高かった。B 型に対しては、Victoria 系統と Yamagata 系統のいずれに対しても、接種前抗体価が高い者で接種後の抗体応答割合が有意に低かった。

また、2018/19 シーズンには、大学生 13 人（男 2 人、平均 21 歳）を対象に、インフルエンザワクチンの免疫原性を検討した（2018/19 シーズン、前向き cohort study）。登録時に、自記式質問票により、年齢、性別、ワクチン接種歴、インフルエンザ罹患歴、基礎疾患などの背景因子の情報を収集した。研究協力施設において対象者にインフルエンザワクチンを１回接種し、接種前、接種４週後、流行後に採血を行い、HI 抗体価を測定した。免疫原性の評価尺度として、GMT、平均上昇倍数、抗体応答割合、抗体保有割合を算出し、ワクチンの免疫原性に影響を及ぼす要因として、ワクチン接種歴、インフルエンザ罹患歴との関連を検討した。接種４週後の GMT は AH1pdm09：128、AH3：309、B（Victoria）：42、B（Yamagata）：70、抗体保有割合

は AH1pdm09：91％、AH3：100％、B（Victoria）：54％、B（Yamagata）：91％であった。AH1pdm09 および B（Yamagata）に対しては、ワクチン接種歴を有する者で、抗体応答割合や抗体保有割合が高い傾向を認めた。B（Yamagata）に対しては、接種前と比べた接種後 GMT の平均上昇倍数は 1.0 であり、抗体上昇が低かった。

③　山口は、茨城県土浦市の小学生（４校：2,120 人）を対象に、インフルエンザワクチンの有効性を検討した（2016/17 シーズン、前向き cohort study）。2017 年１月上旬に基礎調査を行い、年齢、性別、兄弟姉妹数、基礎疾患の有無、インフルエンザワクチン接種歴、罹患歴、等の情報を収集した。また、2017 年１月から３月の追跡期間中、インフルエンザに罹患した場合は、学校に届け出る欠席報告書と一緒に、本研究用のアンケート（発熱時期、インフルエンザの型、抗ウイルス薬処方等）を提出するよう依頼した。解析では、ワクチン接種回数が１回のみの児童はワクチン接種群に入れて検討した。１回以上ワクチンを接種したと回答したのは 1,030 人（接種率 51%）であった。４校全体の A 型インフルエンザの発病率は 17%、B 型インフルエンザの発病率は 1％であり、ワクチン有効率（95%CI）は主流行である A 型インフルエンザに対して 29%（－4-52%）であった。有熱期間は、A 型、B 型ともにワクチン接種群と非接種群の間で有意差を認めなかった。抗インフルエンザ薬の種類による有熱時間の有意差は認めなかった。

2017/18 シーズンにも、茨城県土浦市の小学生（４校：2,077 人）を対象に、同内容の調査を実施した（2017/18 シーズン、前向き cohort study）。１回以上ワクチンを接種したと回答したのは 897 人（接種率 47%）であった。４校全体の A 型インフルエンザの発病率は 6%、B 型インフルエンザの発病率は 31％であり、ワクチン有効率（95%CI）は A 型インフルエンザに対して 66％（39-81％）、B 型インフルエンザに対して 15％（－ 15-37％）であった。有熱期間は、A 型ではワクチン接種群と非接種群の間で有意差を認めなかったが、B 型では接種群が非接種群に比べて平均 7.6 時間短かった（P=0.01）。抗インフルエンザ薬の種類による有熱時間の有意差は認めなかった。

さらに、2018/19 シーズンにも、茨城県土浦市の小学生（４校：2,077 人）を対象に、同内容の調査を実施した（2018/19 シーズン、前向き cohort study）。１回以上ワクチンを接種したと回答したのは 901 人（接種率 50%）であった。４校全体の A 型インフルエンザの発病率は 26%、B 型インフルエンザの発病率は 0.002％であり、ワクチン有効率（95%CI）は A 型インフルエンザに対して 44%（22-60%）であった。有熱時間は、A 型ではワクチン接種群と非接種群の間で有意差を認めなかった。抗インフルエンザ薬の種類による有熱時間の有意差は認めなかった。

④　中村らは、石川県内の 13 医療機関の小児科外来において、インフルエンザ抗原検出用迅速診断（以下、迅速診断）キットによる病原診断を用いた症例対照研究を実施した（石川、2016/17 シーズン、症例対照研究、test-negative design）。2016/17 シーズンの流行期間中（定点あたり患者数５人以上の期間と定義）に、ILI で受診した生後９ヵ月から６歳未満の小児 2,694 人（平均 2.8 歳）を登録した。インフルエンザワクチン接種歴に関する情報は、問診や母子健康手帳等で確認した。登録時に採取した鼻腔拭い液または鼻汁検体を用いて、迅速診断キットによる病原診断を行った。症例と対照のワクチン接種率を比較し、多重ロジスティック回帰モデルにより迅速診断キット陽性インフルエンザに対するワクチン有効率（VE）を（１－ OR）× 100％により算出した。モデルには、年齢、就園の有無、同胞の有無、昨シーズンのインフルエンザ罹患歴、発症週数、発症から診断までの日数、診断時までの最高体温、昨シーズンのワクチン接種歴、今シーズンのワクチン接種状況を含めた。迅速診断キット陽性インフルエンザは 1,390 人で、うち A 型が 1,248 人であった。迅速診断キット陽性インフルエンザに対するワクチン接種の VE は 39%(25-50%)、A 型に対する VE は 36％（21-48％）、B 型に対する VE は 59％（27-76％）であり、いずれも有意なワクチン有効性を示した。年齢別では、０～１歳児における VE は 20％（－11-48％）であり有意な有効性を認めなかったが、２～３歳児では 53％（32-67％）、４～５歳児では 40％（6-61％）と有意なワクチン有効性を示した。また、３～５歳児で、接種回数別の VE を比較したところ、１回接種の VE は 37％（5-58％）、２回接種の VE は 43％（16-62％）であり、１回接種と２回接種の VE は同様であった。

2017/18 シーズンにも、石川県内の 13 医療機

関の小児科外来において、同内容の調査を実施した（2017/18 シーズン、症例対照研究、test-negative design）。2017/18 シーズンの流行期間中に、ILI で受診した生後９ヵ月から６歳未満の小児2,539人（平均 2.8 歳）を解析対象とした。迅速診断陽性インフルエンザは 1,055 人で、うち A 型が 402 人、B 型が 653 人であった。迅速診断陽性インフルエンザに対するワクチン接種の VE は 43％（30-54％）、A 型に対する VE は 48％（31-60％）、B 型に対する VE は 39％（22-52％）であり、いずれも有意なワクチン有効性を示した。年齢別では、０～１歳児における VE は 46％、２～３歳児では 46％、４～５歳児では 31％と、いずれの年齢層においても有意なワクチン有効性を示した。

さらに、2018/19 シーズンにも、石川県内の 13 医療機関の小児科外来において、同内容の調査を実施した（2018/19 シーズン、症例対照研究、test-negative design）。2018/19 シーズンの流行期間中に、ILI で受診した生後９ヵ月から６歳未満の小児 2,250 人（平均 2.7 歳）を解析対象とした。迅速診断陽性インフルエンザは 1,060 人で、うち A 型が 1,056 人、B 型が 4 人であった。迅速診断陽性インフルエンザに対するワクチン接種の VE は 56％（45-65％）、A 型に対する VE は 56％（45-65％）と有意なワクチン有効性を示したが、B 型に対する VE は算出できなかった。

これまで2015/16～2018/19シーズンまでの4シーズンに渡り、同手法による検討を継続しているが、2018/19 シーズンのワクチン有効率は過去 3 シーズンよりも高かった。4 シーズンのデータを統合して、年齢別のワクチン有効率を検討したところ、０歳児の VE は 0％（－ 60-38％）、１歳児では 29％（15-41％）、２歳児では 47％（33-58％）、３歳児では 40％（21-54％）、４歳児では 47％（29-60％）、５歳児では 36％（14-52％）であり、０歳児のワクチン有効率は他の年齢層に比べて明らかに低かった。３歳以上児で、接種回数別のワクチン有効率を検討したところ、１回接種の有効率は 65％（44-79％）、２回接種の有効率は 75％（60-84％）であり、ともに有意なワクチン有効性を示し、１回接種と２回接種の有効性には有意差を認めなかった。同じ手法で実施した４シーズンの結果も合わせて総合的に考えると、流行ウイルスの型・亜型の変化にも拘らず、全体の VE は概ね 30～50％前後であった。

⑤　福島らは、小学生におけるインフルエンザワクチンの有効性を検討するため、迅速診断キットによる病原診断を用いた症例対照研究を実施した（2017/18 シーズン、症例対照研究、test-negative design）。福岡県の小児科診療所５施設において、流行期間中（2018 年第２週～10 週）に ILI で受診した小学生 193 人（平均 8.8 歳、男 103 人）を解析対象とした。鼻汁吸引検体あるいは鼻かみで鼻汁を採取し、迅速診断キットによる病原診断を行い、陽性者を症例、陰性者を対照（test-negative control）とした。調査シーズンのインフルエンザワクチン接種に関する情報は、診療録あるいは母子健康手帳から転記した。症例と対照のワクチン接種率を比較し、多重ロジスティック回帰モデルにより迅速診断陽性インフルエンザに対するワクチン有効率（VE）を（１－ OR）× 100％により算出した。モデルには、性別、年齢、発症から診断までの日数、同胞の有無、基礎疾患による通院、過去1年間の受診回数、昨シーズンのワクチン接種歴、昨シーズンの医師診断インフルエンザ歴、試料採取方法を調整変数とし、参加施設、発症週数、診断時までの最高体温を層化変数に含めた。迅速診断陽性インフルエンザは 134 人で、うち B 型が 113 人を占めた。迅速診断陽性インフルエンザに対するワクチン接種の調整 OR は１回接種で 0.33（0.05-2.47）、２回接種で 2.55（0.39-16.57）であった。主流行である B 型に対するワクチン接種の調整 OR は１回接種で 0.20（0.02-2.09）、２回接種で 1.40（0.19-10.45）であり、いずれも推計の精度が非常に悪く、ワクチンの有効性を論じることが出来なかった。その原因として、「小学生は若年小児と比べて既存免疫の影響がより大きいこと」「検査診断の誤分類が影響したこと」「小学生には Test-negative design が適用しにくい可能性」などが考えられた。

⑥　齋藤は、東京都大島町の全医療機関において、PCR 検査による病原診断を用いた症例対照研究により、インフルエンザワクチンの有効性を検討した（2009/10～2010/11 シーズン、症例対照研究、test-negative design）。2009/10 シーズンおよび 2010/11 シーズンのインフルエンザ流行期（2009 年 47 週～2010 年 10 週；2011 年２週～15 週）に ILI で受診した１歳から 64 歳の患者を対象とした。患者から検体を採取し、PCR 検査で陽性者を症例、陰性者を対照（test-negative control）とした。調査シーズン

のインフルエンザワクチン接種に関する情報は、診療録あるいはインフルエンザワクチン接種の問診票から情報を得た。症例と対照のワクチン接種率を比較し、多重ロジスティック回帰モデルによりPCR陽性インフルエンザに対するワクチン有効率（VE）を（１－OR）× 100％により算出した。モデルには、発症から受診までの日数、インフルエンザ感染者への接触歴、2009/10 シーズンの３価季節性ワクチン接種歴・単価新型ワクチン接種歴、AH1pdm09罹患歴、性別、年齢カテゴリーを含めた。2009/10シーズンはPCR陽性インフルエンザ（AH1pdm09）140 人、対照 103 人を比較した。PCR陽性インフルエンザ（AH1pdm09）に対するワクチン接種のVEは全年齢で71％（32-88％）、１～12歳児で49％（－ 39-81％）、13～64 歳で 92％（53-99％）であった。2010/11 シーズンのPCR陽性インフルエンザは 221 人で、うちAH1pdm09 型が 78 人、AH3 型が 41 人、B 型が 112 人であった。PCR陽性インフルエンザに対するワクチン接種のVEは全年齢で66％（40-81％）、１～12 歳児で 63%(30-80％)、13～64 歳で 69％（－ 20-92％）であった。型・亜型別ではAH1pdm09 型に対するVEは全年齢で 84％(60-93％)、１～12 歳児で 87%(62-96%)、13～64歳で 77％（－ 21-96％）、AH3 型に対するVEは全年齢で 69％（15-89％）、１～12 歳児で 58%(－ 33-87%)、13～64歳では算出不能、B 型に対するVEは全年齢で42％（－ 10-70％）、１～12歳児で46%(－11-73%)、13～64歳で－9％(－430-84％）であった。

⑦ 浦江、大藤らは、大阪産婦人科医会の協力のもと、妊婦に対するインフルエンザワクチン接種の安全性として、妊娠転帰に対する影響を検討した（2013/14 シーズン、前向き cohort study）。2013 年 10 月～12 月に、大阪府下の産科医療機関に通院していた妊婦 10,631 人を調査対象とした。登録時に自記式質問票を用いて、2013/14 シーズンのインフルエンザワクチン接種、妊娠前の身長・体重、基礎疾患、妊娠中の喫煙・飲酒などの情報を収集した。シーズン終了後（2014 年５月）にも自記式質問票調査を行い、登録時以降のワクチン接種の有無について情報を得た。さらに、妊婦の担当医への質問票調査を行い、対象妊婦の妊娠転帰について追跡を行った。解析では、妊娠転帰（流産・死産・早産・低出生体重・先天奇形）を結果指標として発生率を算出し、logistic regression model によりワクチン接種の妊娠転帰に対するオッズ比（OR）および 95％信頼区間（95％ CI）を算出した。対象妊婦 10,631 人のうちワクチン接種者は 4,244 人（40％）であった。ワクチン接種を受けた妊婦では、非接種の妊婦と比べて、「流産・死産・早産・低出生体重・先天奇形のいずれか 1 つ以上」を呈した者が有意に少なく（11％ vs. 14％）、調整 OR は 0.81(0.71-0.92）と有意に低下した。妊娠週数別に検討したところ、妊娠初期にワクチン接種を受けた妊婦における「流産・死産・早産・低出生体重・先天奇形のいずれか 1 つ以上」の発生率は、非接種の妊婦と同様であり（13％ vs. 13％）、調整 OR も 1.04(0.80-1.35）と関連を認めなかった。一方、妊娠中期・妊娠後期にワクチン接種を受けた妊婦では、非接種の妊婦と比べて、これらの妊娠転帰の発生率が低く（妊娠中期：12％ vs. 15％、妊娠後期：10％ vs. 13％）、調整 OR も有意な低下を認めた（妊娠中期：OR=0.79、95％ CI=0.62-0.99、 妊娠後期：OR=0.69、95％ CI=0.56-0.86)。本研究結果により、ワクチン接種を受けた妊娠週数に拘らず、妊婦に対するインフルエンザワクチン接種が妊娠転帰を悪化させるという所見は認めず、妊婦に対するインフルエンザワクチン接種の安全性が示唆された。

⑧ 近藤らは、妊婦に対するインフルエンザワクチン接種について、費用効果分析を行なった。接種対象者は 10 月～翌 3 月までの期間中に妊娠週数が満 12 週以上となる 20～49 歳の妊婦とした。「接種プログラムあり」と「接種プログラムなし」の費用の差を分子とし、効果の差を分母として、増分費用効果比（ICER）を求めた。効果の指標を QALY とし、ICER を、追加的に 1QALY 獲得するための追加費用とした。モデルは以下の仮定に基づき構築した：１）接種対象者は 10 月～翌 3 月までの期間中に妊娠週数が満 12 週以上となる 20～49 歳の妊婦、２）接種は妊娠 12 週～臨月までのいずれかの時期に受ける、３）妊娠 12 週目が 10 月以降の場合は、妊娠 12 週になった時点で接種できる、４）ワクチンは 10 月～翌 3 月まで十分に供給、５）接種者は接種 4 週後から効果が発現、６）インフルエンザシーズンは 10～4 月、７）妊婦と児へのワクチン効果は 1 シーズンのみ。接種費用は 1 回接種 3,529 円とし、接種率は「接種プログラムあり」で 60％、「接種プログラムなし」で 27％とした。妊婦と児のインフルエンザ罹患による外来受診率、入院割合、ワクチ

ン効果は既報のデータを用いた。費用効果分析の結果、「接種プログラムなし」に比べて、「接種プログラムあり」の増分効果は 0.00009 QALYs、ICER は ￥7,779,356/QALY であり、WHO の基準（３× GDP）に基づくと、費用効果的であることが示された。妊婦に対するインフルエンザワクチン接種は費用対効果に優れ、将来定期接種の含める候補として検討する価値がある。

⑨　森川らは、大阪府におけるインフルエンザ流行のウイルス学的特徴を検討した（2016/17～2018/19 シーズン、ウイルス学的解析）。MDCK 細胞を用いてウイルス分離を行い、real-time RT-PCR 法によりインフルエンザウイルスの遺伝子検査を実施した。分離したインフルエンザウイルス株の一部は、塩基配列を解析し、ワクチン株との比較、地域特異性、流行時期との関連を検討した。また、インフルエンザウイルスが検出されなかった検体については、10 種類の呼吸器ウイルスを検査し、病原体検索を行った。

2016/17 シーズンは、291 検体のうち 254 検体（87%）からインフルエンザウイルスが検出された。内訳は、A/H3 亜型 86%（219 検体）、A/H1N1pdm09 亜型 4%、B 型 Victoria 系統 4%、同 Yamagata 系統 5% であった。A 型流行株について、HA 遺伝子全長の系統樹解析を行った結果、2016/17 シーズンの大阪府におけるインフルエンザ流行株の抗原性は、全国の分離株における傾向と類似していることが明らかになった。インフルエンザウイルス陰性の 37 検体のうち、11 検体から１種類、５検体から２種類の呼吸器ウイルスが検出された。

2017/18 シーズンは、255 検体のうち 238 検体（93%）からインフルエンザウイルスが検出された。内訳は、A/H1N1pdm09 亜型 13%（32 検体）、A/H3 亜型 36%（93 検体）、B 型 Victoria 系統 2%（5 検体）、同 Yamagata 系統 48%（108 検体）であり、A 型と B 型の検出比がほぼ１対１であった。A 型流行株について、HA 遺伝子全長の系統樹解析を行った結果、2017/18 シーズンの大阪府におけるインフルエンザ流行株の抗原性は、AH1pdm 亜型は総て 6B.1 に属し、AH3 亜型は 3C.2a1b、3C.2a2、3C.2a3 に含まれた。インフルエンザウイルス陰性の 17 検体のうち、8 検体から他の呼吸器ウイルスが検出された。

2018/19 シーズンは、168 検体のうち 155 検体（92%）からインフルエンザウイルスが検出された。内訳は、AH1pdm09 亜型 47%（73 検体）、AH3 亜型 45%（69 検体）、B 型 Victoria 系統 3%（4 検体）、同 Yamagata 系統 6%（9 検体）であり、シーズン前半は AH1pdm09 亜型、後半は AH3 亜型が主流となった。A 型流行株について、HA 遺伝子全長の系統樹解析を行った結果、2018/19 シーズンの大阪府におけるインフルエンザ流行株の抗原性は、AH1pdm 亜型は全国の解析データと同様なサブクレード内でのアミノ酸置換の多様性が見られ、AH3 亜型は全国の解析株の半数が属した１つの群にすべてが属する結果となった。インフルエンザウイルス陰性の 13 検体のうち、8 検体から他の呼吸器ウイルスが検出された。インフルエンザ集団発生事例の 2 検体からインフルエンザウイルスではなくアデノウイルス、エンテロウイルスが検出された事例があった。

いずれのシーズンの調査においても、インフルエンザ様疾患を呈する患者の中には、他の呼吸器ウイルスを原因とする者が混在し、ワクチン有効性の過小評価の一因となることが示唆された。

８）百日咳分科会

①　岡田らは、百日咳を専門とする小児科医が所属する 15 医療機関の協力を得て、多施設共同症例対照研究を実施し、現行の DTaP ワクチンの有効性および接種後経過年数の影響などを検討した（2017 年 10 月～、症例対照研究）。症例は「小児呼吸器感染症診療ガイドライン」により百日咳と確定診断された 20 歳未満の患者、対照は各症例に対し性・年齢（学年）が対応する同病院の他疾患患者３人（病院対照）および症例の友人３人（友人対照）とし、さらに臨床的百日咳ではあるが百日咳検査で陰性を示した患者を検査陰性対照（Test-negative control）として登録することとした。自記式質問票により、ワクチン接種歴、基礎疾患、感染暴露機会（通園・通学・兄弟数など）、受動喫煙、社会経済学的因子、などの情報を収集する。解析では、症例と病院対照・友人対照の比較による従来の症例対照研究手法でワクチン有効性を検討するのみならず、症例と年齢がマッチしていない検査陰性対照を比較することによりワクチン接種後経過年数によるワクチン有効性への影響についても検討する（test-negative design）。2019 年 11 月時点で登録された症例 128 人、対照 223 人のうち、質問票の回答があった月齢 3ヵ月以上の症例 95 人、対照 169 人（友人対照 48

人、病院対照 71 人、検査陰性対照 50 人）を解析対象とした。Test-negative design の手法により、症例 vs. 検査陰性対照で DTaP ワクチンの有効性を検討した結果、4 回接種（ref. 未接種）の有効率は 61％（95％ CI：－ 128-93％）であった。また、年齢層別にワクチン有効率を検討したところ、6 歳未満児では 4 回接種の有効率は 90％（95％ CI：－ 20-99％、P=0.07）と境界域の有効性を示したが、6 歳以上児では 4 回接種の有効率は－ 18％（P=0.90）であった。ワクチン４回接種者に限定して年齢や接種後経過年数の影響を検討したところ、年齢 9 歳以上（OR=4.46, 95%CI：1.47-13.5）、接種後経過年数 5.9 年以上（OR=6.29, 95%CI：1.71-23.1）で、百日咳発症に対する OR が有意に上昇した。百日咳含有ワクチン 4 回接種の有効率は 6 歳以上児では減弱し、年齢 9 歳以上、接種後経過年数 5.9 年以上では百日咳の発症リスクが上昇していることから、就学前から小学校低学年の段階で追加接種が必要と考えられる。

② 砂川らは、高知県の１医療機関で、test-negative design による症例対照研究と従来の症例対照研究を実施し、DTaP ワクチンの有効性を検討した（2012 年、症例対照研究）。百日咳の症状を呈し LAMP 法による検査で陽性となった17人を症例、陰性となった 29 人を対照（test-negative control）とした。また、症例と同じ日に呼吸器疾患以外の症状で同病院を受診した者 77 人を「従来の症例対照研究」による対照とした。平均年齢は、症例が 7.8 歳、test-negative control が4.3歳、従来の対照が4.9歳であり、症例はいずれの対照と比しても年齢が高かった。しかし、性別、DTaP ワクチン接種回数、４回接種時の年齢には有意差を認めなかった。DTaP ワクチン４回接種（ref. 未接種）の百日咳発症に対する OR（95％ CI）は、test-negative control との比較では0.24（0.004-3.61）、従来の対照との比較では 0.07（0.000-0.45）であり、従来の症例対照研究手法による検討では有意なワクチン有効性を認めた。Test-negative design による症例対照研究手法では有意なワクチン有効性を検出しえなかったが、対照が少なかったことによる検出力不足が影響した可能性がある。また、test-negative design による症例対照研究手法ではワクチン有効性が過小評価される可能性が報告されており、それも一因となったかもしれない。Test-negative design による検討では、LAMP 法の実施時期により偽陰性となり誤分類が生じやすくなる可能性があるが、症例と test-negative control の検査時期は同様であった。Test-negative design による症例対照研究手法で DTaP ワクチン有効性を検討する場合、百日咳検査の実施時期の精査、百日咳検査の実施状況による selection bias の可能性、交絡因子の存在などについて注意深く配慮すれば、DTaP ワクチンの有効性研究の一手法として有用であると考えられる。

また、高知県の１医療機関で、test-negative design による症例対照研究を実施し、DTaP ワクチンの有効性を検討した（2012 年、2018 年、症例対照研究、test-negative design）。2012 年 8 月～2013 年 8 月、2018 年 1 月～7 月の期間に、百日咳の症状を呈して小児科を受診し、LAMP 法による検査で陽性となった 121 人を症例、陰性となった 282 人を対照（test-negative control）とした。症例と対照は、性別、DTaP ワクチンの接種回数は同様であったが、年齢は症例の方が高かった（平均 8.3 歳 vs 7.2 歳、P=0.001）。DTaP ワクチン４回接種（ref. 未接種）の百日咳発症に対する OR（95％ CI）は 0.27（0.05-1.67）であり、ワクチン有効率は73％であった。４回接種後の経過年数毎の有効率を検討したところ（ref. 未接種）、2 年未満 92％、2～4 年未満 82％、4～6 年未満 71％、6～8 年未満 67％、8～10 年未満 69％、10～14 年未満 33％、と接種後 2 年未満のみ有意な有効率を認めた。また、４回接種者を対象とし、経過年数の影響を検討したところ、2 年未満と比較し、接種後 4.0-5.9 年で百日咳発症に対する OR が有意に増加し（OR=3.8, 95%CI: 1.2-11.9）、以降も有意な OR 上昇を認めた。

これらの結果を受けて、宮崎県宮崎市および高鍋保健所管内で、就学前の DTaP ワクチン追加接種による百日咳の疾病負荷の変化、追加接種の有効性を検討するための研究に着手した（2018 年～、記述疫学＋症例対照研究、Test-negative design）。

別途、2016 年度に熊本県・三重県の２医療機関を受診した妊婦 1,287 人を対象に、百日咳含有ワクチン接種に関する意識調査を実施した（2016 年、横断研究）。自記式質問票により、百日咳含有ワクチン接種の意向、ワクチンや疾患に関する知識、態度に関する情報を得た。有効回答 977 人のうち、妊娠中に百日咳含有ワクチンが接種可能なら「接種する」と回答した者は 279 人（29％）であった。接種の意向に関連する項目は、「ジカウイルスワクチンを妊娠中であれば希望する」、「海外で実施している

妊婦用の百日咳含有ワクチンは怖くない」、妊婦への百日咳ワクチンが「必要と思う」、「効果あると思う」、「出生児への予防効果があると思う」であった。これらの情報は、妊婦への百日咳ワクチン接種を検討する際の貴重な情報となることが期待される。

③　近藤らは、諸外国で妊婦への Tdap ワクチン接種が推奨されており、わが国で 2016 年２月から DTaP ワクチンの青年・成人への追加接種が可能となったことを受けて、今後の妊婦への百日咳含有ワクチンの適用可能性を踏まえ、妊婦に対する百日咳ワクチン接種についての費用効果分析を行なった。QALY を効果の指標とした費用効果分析の手法を用いた。海外の報告を参照して３ヵ月未満児の百日咳発症率を５レベルに設定し、接種費用は 2,000 円～10,000 円の幅で９レベルに設定した。これらの発症率と接種費用の組み合わせから 45 のシナリオを設定し、「接種プログラムなし」と比較した。妊婦に対するワクチン効果は約４年間で減衰するという報告に従い、妊婦の方はマルコフ・モデルを用いた。児は生後３ヵ月から DPT-IPV の定期接種が始まるため、その後の百日咳罹患は母親からの移行抗体に影響されないと考え、判断樹モデルを用いた。モデルに組み入れた疫学データは国内の文献から、ワクチン効果は海外の文献から引用した。１QALY 獲得あたりの増分費用は 500 万円を費用効果の判断基準に用いた場合、45 シナリオのうち 29 シナリオが費用効果的であった。一方、WHO がワクチン接種の費用効果の判断基準として推奨している GDP × 3 を用いた場合には、45 シナリオのうち 36 シナリオが費用効果的であった。わが国の妊婦に対する百日咳予防接種の効率性は、児の百日咳の発症率および接種費用に大きく影響されるが、定期予防接種に将来含める候補として検討する価値があることが示唆された。

9）高齢者肺炎分科会（肺炎球菌ワクチン）

①　中島らは、高齢者肺炎に対するインフルエンザワクチンと肺炎球菌ワクチンの予防効果を検討するため、41 施設の協力を得て多施設共同症例対照研究を実施している（2016年10月～、症例対照研究）。症例は協力医療機関において新たに肺炎と診断された 65～90 歳の患者である。対照は、症例と性・出生年度・外来受診日が対応する同一機関受診患者とし、１症例につき５対照を選定した。背景因子として、インフルエンザワクチン接種歴、肺炎球菌ワクチン接種歴、年齢、性別、基礎疾患、血液検査所見、喫煙、飲酒、６歳未満の同居家族、ADL、等の情報を収集した。また、肺炎に関する情報（確定診断日、症状、検査結果など）も併せて収集した。2019 年 11 月までに登録された症例 132 人、対照 583 人のうち、検討項目に欠損のない症例 127 人（うち肺炎球菌性肺炎29人）、対照542人を解析対象とした。インフルエンザワクチン接種率は症例 38％、対照 42％、肺炎球菌ワクチン接種率は症例 55％、対照 54％であった。なお、肺炎球菌ワクチン接種者には、PPSV23 のみ接種、PCV13 のみ接種、両方接種、ワクチンタイプ不明の者を含めて解析した。肺炎に対する調整 OR は、インフルエンザワクチン接種 0.85（0.55-1.31）、肺炎球菌ワクチン接種 1.19（0.77-1.82）であった。結果指標を肺炎球菌性肺炎に限定し、肺炎球菌ワクチン接種を PPSV23 の５年以内の接種に限定した解析では、インフルエンザワクチン接種の粗 OR は 1.15（0.49-2.73）、肺炎球菌ワクチン接種は 1.13（0.50-2.56）であった。2019 年 12 月で、症例、対照の登録を終了し、最終解析を実施中である。

②　近藤らは、調査会社に登録されている 65 歳から 79 歳のモニターを対象にインターネット調査を行い、高齢者肺炎球菌ワクチンの定期接種化による接種への影響を検討した（2015年12月、横断研究）。調査内容は、肺炎球菌ワクチン接種の有無、接種の契機、年齢、性別、配偶者の有無、世帯収入、学歴、職業、治療状況、喫煙習慣、インフルエンザワクチン接種などである。回答者は3,889人（男1,830人、平均年齢 70.8 歳）であり、肺炎球菌ワクチン接種を受けていた者は 1,304 人（34％）であった。接種者のうち、定期接種化後に接種した人は 742 人（57％）、定期接種の導入時点での接種者は 562 人であった。定期接種の導入時点での未接種者 3,327 人を対象に、肺炎球菌ワクチン接種を結果指標として、単変量解析を行った結果、定期接種対象（ref. 非対象）では接種に対する OR（95％ CI）が 12.3（10.0-15.2）に上昇した。接種の最たる契機は、市町村からの案内（50％）であり、次いで、かかりつけ医からの勧め（17％）、TV コマーシャル（13％）であった。市町村による直接的な対象者個人へのアプローチが接種促進に有効であると考えられた。

10）新規ワクチン検討分科会

① 荒木らは、福岡県・奈良県の３小児科医療機関を受診した２ヵ月から６歳未満児を対象に、多施設共同症例対照研究（test-negative design）を行い、ロタウイルスワクチンの有効性を検討した（2018～2019 シーズン、症例対照研究）。急性胃腸炎症状で病院時間内に受診したすべての乳幼児に対して、ロタウイルス迅速診断検査を実施し、陽性者を症例、陰性者を対照とした。これらの対象者から、自記式質問票により、ワクチン接種歴、性、年齢、出生体重、母乳保育、基礎疾患、集団保育、同胞の有無などの情報を得た。また、胃腸炎の臨床所見、治療状況については、病院診療録から情報を得た。なお、ロタウイルス胃腸炎の罹患歴を有する者、最終接種から２週間以内に急性胃腸炎を発症した者は除外した。2018 シーズンの対象患者は 493 人、同意が得られた患者は 484 人であり、うちロタウイルス胃腸炎の罹患歴を有した 30 人を除外し、454 人を対象とした。迅速診断の結果、ロタウイルス陽性症例は 78 人、陰性対照は 376 人であった。迅速診断陽性ロタウイルス胃腸炎に対するワクチン接種の調整 OR は 0.26（0.15-0.45）であり、有効率は 74％と有意な発病防止効果を認めた。重症度別の検討では、Severity score ５点以上、７点以上の胃腸炎に対する有効率はそれぞれ 81％（59-91％）、91％（64-98％）であり、初期症状が重篤な例に対して、より高い有効率を示した。年齢別の検討では、１歳代、２歳代、３歳以上の有効率はそれぞれ 83％（59-95％）、80％（19-95％）、63％（－ 4-87％）であった。

② 原らは、佐賀県・福岡県・奈良県の６小児科医療機関を受診した２ヵ月から６歳未満児を対象に、多施設共同症例対照研究（test-negative design）を行い、ロタウイルスワクチンの有効性を検討した（2018～2019 シーズン、症例対照研究）。方法は、①荒木らの研究と同じである。2018 シーズン・2019 シーズンの対象患者は 2031 人、同意が得られた患者は 1798 人であり、うちロタウイルス胃腸炎の罹患歴を有した 129 人を除外し、1669 人を対象とした。迅速診断の結果、ロタウイルス陽性症例は 317 人、陰性対照は 1352 人であった。迅速診断陽性ロタウイルス胃腸炎に対するワクチン接種の調整 OR は 0.44（0.34-0.58）であり、有効率は 56％と有意な発病防止効果を認めた。重症度別の検討では、Severity score ７点以上の胃腸炎に対する有効率は 85％（68-93％）であり、初期症状が重篤な例に対して、より高い有効率を示した。年齢別の検討では、０～２歳、３～５歳の有効率はそれぞれ 59％（43-71％）、47％（17-67％）であった。

別途、金沢市の１歳半検診受診児を対象に、ロタウイルスワクチン接種行動に関連する要因および児・保護者のロタウイルス胃腸炎の疾病負荷を検討した（2017～2018 年、横断研究）。１歳半検診を受診した児（目標 1,000 人）の保護者に協力を依頼し、児の基礎情報（性、出生年月、出生時体重、健診時体重、集団保育、基礎疾患、家族数、兄弟数など）、ロタウイルスワクチン接種状況、ロタウイルス胃腸炎およびロタウイルスワクチンに関する知識や考え、感染性胃腸炎の罹患歴、児や保護者への負担について、調査票を用いた聞き取り調査を行った。受診者 1,303 人のうち 1,282 人（98％）から回答を得た。ロタウイルスワクチンの接種率は 73％であり、保護者がロタウイルス胃腸炎を重症だと思うこと、ワクチンが効くと思うこと、小児科での勧め、雑誌やネットでの情報、保護者の学歴、世帯年収、が接種と正の関連を示した。ワクチンの接種費用や副反応への心配は有意な関連を認めなかった。接種しない理由としては、定期接種でない（37％）、接種費用（30％）などが上位を占めた。感染性胃腸炎の既往は 394 人（31％）に認めたが、ロタウイルス胃腸炎の割合は 7％と低かった。児が感染性胃腸炎にかかると主に母親が看病し、仕事を休んでいることが明らかになった。世帯所得と世帯人数から相対的貧困を評価し、ロタウイルスワクチン接種との関連を検討したところ、相対的貧困状態にあるものでは接種に対する調整 OR が 0.49（0.26-0.90）となり、接種と有意な負の関連を示した。ロタウイルスワクチンの接種推進には、ワクチンに関する正しく適切な情報提供とともに、接種費用の補助が重要な要因であることが示唆された。

③ 中野らは、川崎医科大学総合医療センターの 40 歳以上の職員 266 人（男性 106 人、年齢：40～73 歳）を対象に、ワクチン予防可能疾患に対する抗体保有状況を検討した（2018 年、横断研究）。2018 年 10 月～12 月に、対象者の血清を採取し、風疹・麻疹・水痘・ムンプスの抗体価を測定した。風疹の抗体陰性（HI 価＜ 8）は 31 人（11.7％）、麻疹の抗体陰性（EIA-IgG）は 1 人（0.4％）、水痘の抗体陰性（EIA-IgG ＜ 2.0）は 1 人（0.4％）、ムンプ

スの抗体陰性（EIA-IgG）は10人（3.8％）であった。しかし、麻疹やムンプスは、抗体陽性者でも学会基準値以下の抗体価の者の占める割合が高かった（麻疹 31.6％、ムンプス 41.0％）。水痘は、基準を満たす抗体価を有する者が多かったが（98.1％）、今回の対象者はワクチン開発以前の世代であり、自然感染によるものと考えられた。医療関係者に対する予防接種指針とともに、国内の成人への感染症対策として、ワクチン追加接種やキャッチアップ接種を含めた方策を検討する必要がある。

また、東京・川崎の２医療機関のワクチン外来を受診した 56 歳以上の者を対象に、４価髄膜炎菌結合体ワクチンの免疫原性および安全性を検討している（2018～2020 年、前向き cohort study）。４価髄膜炎菌結合体ワクチンは、2015 年５月からわが国でも承認製剤の接種が可能となったが、承認前には 2～55 歳の者を対象とした臨床試験が実施されたのみであり、56 歳以上の者における免疫原性および安全性のデータが乏しい。そこで、本研究では、４価髄膜炎菌結合体ワクチンの接種を希望して協力医療機関を受診した56歳以上の者23人を対象として、ワクチンの免疫原性および安全性を検討中である。対象者にワクチンを１回筋肉内に注射し、接種前・接種４週後に抗体価測定のための採血を行う。免疫原性の評価は、SBA-BR（Serum bactericidal assay using baby rabbit complement）で測定した髄膜炎菌抗原（A、C、Y および W-135）に対する抗体保有割合（1：128 以上の者の割合）、GMT および抗体陽転割合にて行う。また、安全性の評価として、接種後４週間の副反応および有害事象の調査を行った。2020 年１月時点で、接種 4 週後の安全性評価が完了した 21 人（男性 11 人、年齢中央値 61 歳）では、接種部位の局所反応を 2 人（10％）、全身反応を 2 人（10％）に認めたが、重篤な有害事象は認めなかった。免疫原性評価については、24 人全例のペア血清の採取が完了した時点で、海外の抗体価測定施設に検体を送付し、抗体価を測定する予定である。

別途、おたふくかぜワクチンの安全性について、文献的考察を行った。おたふくかぜワクチンは、定期接種化の検討対象であるが、かつて多発した MMR ワクチン接種後の無菌性髄膜炎という副反応の懸念から、厚生科学審議会の審議過程では「より安全性が期待できるワクチン」の承認が前提とされてきた。しかし、新たな MMR ワクチンの国内開発には時間を要すことが考えられる。一方で、おたふくかぜの疾病負荷として、ムンプス難聴の懸念が改めて認識されている。そこで、国内で承認使用されている２種類（星野株、鳥居株）のおたふくかぜ単抗原ワクチンに関する既報告をレビューしたところ、1989 年から使用された国産 MMR ワクチン統一株（Urabe-AM9 株）接種後の無菌性髄膜炎の発生頻度は 0.16％（634 人に 1 人）であったが、星野株おたふくかぜワクチン接種後の無菌性髄膜炎の発生頻度は 1994-1998 年で 1 万人に 1 人、2003-2009 年で 2 万人に 1 人、2010 年以降で 3-4 万人に 1 人、と経年的に減少傾向が認められる。鳥居株おたふくかぜワクチンについても、2004-2015 年調査で 3 万人に 1 人である。また、2000-2003 年に実施した単抗原ムンプスワクチン３製剤（星野株、鳥居株、宮原株）の安全性に関する調査では、接種後 30 日間の無菌性髄膜炎の発生頻度は 1 歳以下で 0.016％、2 歳 0.021％、3-4 歳 0.066％、5 歳以上 0.096％と、接種年齢が高いほど無菌性髄膜炎の発生頻度は高くなる。同様の報告は、鳥居株ワクチン接種後の無菌性髄膜炎の発生頻度を検討した報告でも認められた。おたふくかぜの疾病負荷や新たな MMR ワクチンの開発に要する時間を鑑みると、現行の単抗原おたふくかぜワクチンの安全性および有効性を再評価することも必要であろう。

また、1992 年 4 月～2018 年 12 月までに、企業が医療機関等から収集したおたふくかぜワクチン（鳥居株）接種後の全ての有害事象に関して、臨床経過やウイルス学的検査などの情報に着目して検討した（1992～2018 年、記述疫学）。死亡例 1 人（1 歳女児）は、PCV13、Hib、水痘、MR ワクチンとの同時接種事例であり、既往歴として乳アレルギー、QT 延長症候群があり、接種4日後に低酸素性虚血性脳症、心不全にて死亡した症例であった。接種 16 日後に発熱・頭痛・嘔吐を認めた 8 歳男児は、採取した髄液からワクチン株ムンプスウイルスが検出されたことから無菌性髄膜炎の診断名で 10 日間入院し、軽快退院した。基礎疾患としてクラインフェルター症候群を有した 6 歳男児は、接種 67 日後に発熱・頭痛があり、採取した髄液からワクチン株ムンプスウイルスが検出されたことから無菌性髄膜炎の診断名で 20 日間入院し、軽快退院した。このほか、接種 32 日後に脳炎症状を呈した 1 歳女児、接種 28 日後に水痘ワクチンを接種し同日に ADEM を発症した

3 歳男児などがあった。ワクチン接種後に中枢神経系の有害事象を認めた場合、ワクチンによる副反応か、他の原因によるものかの判断が必要となるが、十分な臨床的およびウイルス学的情報がないと、因果関係の評価は必ずしも容易ではない。おたふくかぜワクチン接種後の有害事象例では、ムンプスウイルスの自然感染時と同様に、一定期間は一定の頻度で髄液からワクチン株ウイルスが検出されるが、2ヵ月を超えて検出される症例もある。現行のおたふくかぜワクチン接種後の無菌性髄膜炎の出現頻度が10万本に1例程度、2社の推計ワクチン出荷量が年間 60 万本であることから、ワクチンの安全性に関する結論を得るには、市販されたワクチンの前向き全数調査により、詳細な臨床症状の収集や髄液のウイルス学的検査も行う必要があるかもしれない。

④ 大藤らは、おたふくかぜワクチン（鳥居株）接種後の有害事象について、無菌性髄膜炎の発症頻度の年次推移を中心に検討した（1992～2018 年、記述疫学）。1992 年 4 月～2018 年 12 月までに、企業が医療機関等から収集したおたふくかぜワクチン（鳥居株）接種後の全ての有害事象報告を解析対象とした。また、おたふくかぜワクチン（鳥居株）の出荷数の情報を元に、おたふくかぜワクチン（鳥居株）接種後の有害事象の発症頻度（/10 万ドーズ）を算出した。1992～2018 年の 27 年間に 8,262,121 ドーズのおたふくかぜワクチン（鳥居株）が出荷され、688 人から 1,034 件の有害事象報告があった。発症頻度（/10 万ドーズ）は、全有害事象が 8.33、無菌性髄膜炎が 4.19、脳炎 0.33、ムンプス 0.80、ムンプス合併症 0.25、その他 3.78 であり、無菌性髄膜炎が全有害事象の半数を占めた。ワクチン接種後の無菌性髄膜炎の発症頻度は、1990 年代は 10 万ドーズ当たり 10 前後を推移したが、2001 年以降、有意に減少していた。1998～2000 年の発症頻度（/10 万ドーズ）は 7.90（95% CI：5.61-10.18）であったが、2001～2003 年の発症頻度（/10 万ドーズ）は 3.91（2.46-5.36）に半減し、直近の 2016～18 年の発症頻度（/10 万ドーズ）は 2.78（1.94-3.62）であった。ワクチン接種後の無菌性髄膜炎の報告が減少した背景には、無菌性髄膜炎の発症と関連するエコーウイルスの流行が最近落ち着いているため誤分類の影響が少ないこと、2000 年にワクチン製造工程でシードウイルスを1代継代したことで副反応が減少した可能性、2008 年以降に無菌性髄膜炎の発症が少ない1歳早期での接種が推奨されるようになったこと、など複数の要因が関与した可能性が考えられた。

⑤ 近藤らは、現在、わが国で使用できる２種類の帯状疱疹ワクチン（国産乾燥弱毒生水痘ワクチン（VVL）と乾燥組換え帯状疱疹ワクチン（RZV））について、費用効果分析を行なった。VVL 接種プログラム、RZV 接種プログラムと「プログラムなし」の費用の差を分子とし、効果の差を分母として、増分費用効果比（ICER）を求めた。効果の指標を QALY とし、ICER を、追加的に 1QALY 獲得するための追加費用とした。接種年齢の異なる４つの接種ストラテジー（65～84歳；70～84歳；75～84歳；80～84 歳）を設定した。接種費用は VVL １回接種 8,000 円、RZV ２回接種 30,000 円とし、接種率はそれぞれ 40.8%（ただし RZV の２回目接種は 32.6%）とした。性・年齢別の帯状疱疹の発症率、帯状疱疹後神経痛の発症率は国内調査のデータを用いた。ワクチン効果は海外の文献から引用した。プログラムなしに比べて、８つの接種プログラムは総て QALY の増加と罹病のための医療費の減少がみられた。しかし、接種に要する費用が、減少した医療費を上回ったため、全体としては費用の増加を要することとなった。１QALY 獲得に対する支払意志額（WTP, Willingness-to-pay）を 500 万円に設定した場合、用いたワクチンの種類に拘らず、全ての接種プログラムの ICER は WTP を上回り、費用効果的であった。

⑥ 吹田らは、高齢者施設入所者を対象に、感染性胃腸炎の疾病負荷を検討している（2018～2019 年、前向き cohort study）。高齢者施設入所者は感染性胃腸炎のハイリスクグループと考えられるが、Clostridioides difficile 感染症（CDI）やノロウイルス胃腸炎に関しては、現在ワクチンが開発中である。そこで、ワクチンが導入される前の実態を把握するため、大阪介護老人保健施設協会の協力を得て、高齢者施設入所者における感染性胃腸炎の罹患率及び入院率を評価し、そのリスク因子を検討する。対象は、大阪府下の介護老人保健施設 10 施設に入所している高齢者であり、利用期間が１ヵ月未満のショートステイ利用者および人工肛門造設者は除外する。調査期間中の下痢症の発現を追跡し、下痢症を発現した対象者にはノロウイルスおよび Clostridioides difficile 迅速診断キットによる検査を実施し、病原診断を行う。2018 年 11 月～2019 年 8 月の入所者 1,345 人を対象に実施した解析では、37 人が下痢症

を発現したが、検査陽性者はいなかった。下痢症の罹患率は 1.33（95％ CI：0.90-1.76）/10,000 人年であり、80 歳以下の者、甲状腺疾患を有する者で、下痢症の罹患率が高かった（罹患率は、それぞれ 2.52/10,000 人年、5.15/10,000 人年）。当初は調査期間として 1 年間を予定していたが、半年間の延長を行い、より詳細な実態把握を行う予定である。

11）広報啓発分科会

① 大藤らを中心に、平成 29 年度 18 人、平成 30 年度 24 人、令和元年度 26 人の班員が共同して、米国予防接種諮問委員会（US-ACIP）の勧告 2017 年版「Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practice (ACIP) — United States, 2017–2018 Influenza Season（MMWR Recomm Rep. 2017; 66 (2): 1-20）」、2018 年版「Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practice (ACIP) — United States, 2018–2019 Influenza Season（MMWR Recomm Rep. 2018; 67 (3): 1-20）」、2019 年版「Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practice (ACIP) — United States, 2019–20 Influenza Season（MMWR Recomm Rep. 2019; 68 (3): 1-21）」を翻訳し、（財）日本公衆衛生協会より出版した（「インフルエンザの予防と対策、2017 年度版」入江伸・福島若葉・大藤さとこ・伊藤一弥（編集）、廣田良夫・葛西健（監修）；「インフルエンザの予防と対策、2018 年度版」入江伸・福島若葉・大藤さとこ・伊藤一弥（編集）、廣田良夫（監修）；「インフルエンザの予防と対策、2019 年度版」入江伸・福島若葉・大藤さとこ・伊藤一弥（編集）、廣田良夫（監修））。本勧告はインフルエンザの予防と対策において世界標準に位置づけられており、インフルエンザに関する最新の知識を普及させるために広く活用されるものである。

F. 健康危険情報

なし

Ⅱ．研究成果の刊行に関する一覧表

【書 籍】

著者氏名	論文タイトル名	書籍名の編集者名	書籍名	出版社名	出版地	出版年	ページ
入江 伸、伊藤一弥、福島若葉、大藤さとこ、他	インフルエンザの予防と対策	廣田良夫	2019 年版　米国予防接種諮問委員会(ACIP)勧告、インフルエンザの予防と対策	(財)日本公衆衛生協会	東京	2020	
中島 啓	肺炎球菌ワクチンとインフルエンザワクチン	中島　啓	レジデントのための呼吸器診療最適解	医学書院	東京	2020	175-7
岡田賢司	百日咳	藤田次郎,竹末芳生,舘田一博	感染症最新の治療 2019-2021	南江堂	東京	2019	102-3
岡田賢司	百日咳	浦部昌夫,島田和幸,川合眞一	今日の処方 改訂第 6 版	南江堂	東京	2019	553-4
岡田賢司	4 種混合ワクチン	寺田喜平	よくわかる予防接種のキホン第 2 版	中外医学社	東京	2019	119-38
中野貴司他	海外渡航者のためのワクチンガイドライン/ガイダンス 2019	日本渡航医学会　ガイドライン作成委員会	海外渡航者のためのワクチンガイドライン/ガイダンス 2019	協和企画	東京	2019	
中野貴司（分担執筆）	年齢別 これから必要なワクチン「髄膜炎菌」	中山久仁子	おとなのワクチン	南山堂	東京	2019	112-6
入江　伸、福島若葉、大藤さとこ、伊藤一弥、他	インフルエンザの予防と対策	廣田良夫	2018 年版　米国予防接種諮問委員会（ACIP）勧告、インフルエンザの予防と対策	(財)日本公衆衛生協会	東京	2019	全 46p
Hara M.	Influenza and influenza vaccination in Japanese elderly	Washio M, Kiyohara C.	Health Issues and Care System for the Elderly	Springer	Germany	2018	117-83
中野貴司	髄膜炎菌ワクチン	岡部信彦、他	予防接種の手びき 2018-19 年度版	近代出版	東京	2018	325-32
岡田賢司	DPT-IPV（百日咳、ジフテリア、破傷風、ポリオ）	岡部信彦、他	予防接種の手びき 2018-19 年度版	近代出版	東京	2018	152-73
岡田賢司	4 種混合ワクチン	寺田喜平	よくわかる予防接種のキホン	中外医学社	東京	2018	119-38
岡田賢司	百日咳	日本臨床ウイルス学会	ウイルス検査法臨床と検査室のための手引き	春恒社	東京	2018	233-9
岡田賢司	百日せきワクチン	日本ワクチン学会	ワクチン 基礎から臨床まで	朝倉書店	東京	2018	58-68
入江　伸、福島若葉、大藤さとこ、伊藤一弥、他	インフルエンザの予防と対策	廣田良夫、葛西健	2017 年版　米国予防接種諮問委員会（ACIP）勧告、インフルエンザの予防と対策	(財)日本公衆衛生協会	東京	2018	全 46p
鈴木幹三、太田千晴、丹羽俊朗	成人の肺炎球菌ワクチンと、インフルエンザワクチンの同時接種の安全性と効果について	編著：中野貴司	予防接種の現場で困らない「まるわかりワクチン Q&A」第 2 版	日本医事新報社	東京	2017	261-2
鈴木幹三、中村　敦、永坂博彦	成人の肺炎球菌ワクチンを複数回接種すると局所の副反応が出やすいと聞きますが、再接種の安全性について	編著：中野貴司	予防接種の現場で困らない「まるわかりワクチン Q&A」第 2 版	日本医事新報社	東京	2017	263-5

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
福島若葉	不活化インフルエンザワクチンの有効性評価について，近年よく使用されている test-negativedesign の概要，日本での成績，解釈の際に注意すべき点は.	編著： 中野貴司	予防接種の現場で困らない「まるわかりワクチン Q&A」第 2 版	日本医事新報社	東京	2017	332-4
福島若葉	2009 年に出現した A(H1N1)pdm09 ウイルスのワクチンによる予防効果について	編著： 中野貴司	予防接種の現場で困らない「まるわかりワクチン Q&A」第 2 版	日本医事新報社	東京	2017	335-6
岡田賢司	百日咳	日本感染症学会	感染症専門医テキスト第 I 部解説編 改訂第 2 版	南江堂	東京	2017	1055-61
岡田賢司	百日咳	三島理晃	呼吸器疾患　診断治療アプローチ 2　呼吸器感染症	中山書店	東京	2017	122-7
岡田賢司	百日咳菌	日本小児感染症学会	日常診療に役立つ　小児感染症マニュアル 2017	東京医学社	東京	2017	57-64

【雑　誌】

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ohfuji S, Deguchi M, Tachibana D, Koyama M, Takagi T, Yoshioka T, Urae A, Ito K, Kase T, Maeda A, Kondo K, Fukushima W, Hirota Y; Osaka Pregnant Women Influenza Study Group.	Safety of influenza vaccination on adverse birth outcomes among pregnant women: a prospective cohort study in Japan	Int J Infect Dis.	93	68–76	2020
Ohfuji S, Ito K, Inoue M, Ishibashi M, Kumashiro H, Hirota Y, Kayano E, Ota N.	Safety of live attenuated varicella-zoster vaccine in patients with underlying illnesses compared with healthy adults: A prospective cohort study.	BMC Infect Dis.	19(1)	95	2019
Ohfuji S, Kondo K, Ito K, Kase T, Maeda A, Fukushima W, Masuda T, Kano M.	Nationwide epidemiologic study of norovirus-related hospitalization among Japanese older adults.	BMC Infect Dis.	19(1)	400	2019
Suzuki K, Kondo K, Washio M, Kan S, Adachi S, Imai S, Yoshimura K, Ota C, Ohfuji S, Fukushima W, Maeda A, Hirota Y, and the Study Group for Pneumonia in the Elderly Individuals.	Preventive effects of pneumococcal and influenza vaccines on community-acquired pneumonia in older individualsin Japan: A case-control study.	Hum Vaccin Immunother.	15(9)	2171-7	2019
Ozasa K, Fukushima W	Commentary: Test negative design reduces confounding by healthcare-seeking attitude in case-control studies	J Epidemiol.	29(8)	279-81	2019
Araki K, Hara M, Shimanoe C, Nishida Y, Matsuo M, Tanaka K	Case-Control Study of Rotavirus Vaccine Effectiveness Compared to Test-Negative Controls or Hospital Controls	J Epidemiol.	29(8)	282-7	2019
Takechi M, Fukushima W, Nakano T, Inui M, Ohfuji S, Kase T, Ito K, Kondod K, Maeda, Shimizu H, Hirota Y.	Nationwide survey on pediatric inpatients with hand, foot and mouth disease, herpangina, and associated complications during epidemic period in Japan: Estimated number of hospitalized patients and factors associated with severe cases.	J Epidemiol.	29(9)	354-362	2019
Masahiro A, Nakashima K, Ohfuji S.	Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine in Patients with Chronic Lung Diseases: A Self-Controlled Case Series Study.	J Clin Immunol Immunother.	5	14	2019
Nakayama T, Suga S, Okada K, Okabe N	Persistence of Antibodies against Diphtheria, Tetanus, Pertussis, and PoliovirusTypes I, II, and III Following Immunization with DTaP Combined with Inactivated Wild-Type Polio Vaccine (DTaP-wIPV)	Jpn J Infect Dis.	72(1)	49-52	2019
Ozaki T, Goto Y, Nishimura N, Nakano T, Kumihashi H, Kano M, Ohfuji S.	Effects of a Public Subsidy Program for Mumps Vaccine on Reducing the Disease Burden in Nagoya City, Japan.	Jpn J Infect Dis.	72(2)	106-11	2019
Hoshi SL, Seposo X, Shono A, Okubo I, Kondo M.	Cost-effectiveness of Recombinant Zoster Vaccine (RZV) and Varicella Vaccine Live (VVL) against herpes zoster and post-herpetic neuralgia among adults aged 65 and over in Japan.	Vaccine.	37(27)	3588-97	2019
Nakashima K, Aoshima M, Ohfuji S, Yamawaki S, Nemoto M,Hasegawa S, Noma S, Misawa M, Hosokawa N, Yaegashi M, Yoshihito Otsuka Y.	Immunogenicity of simultaneous versus sequential administration of a 23-valent pneumococcal polysaccharide vaccine and a quadrivalent influenza vaccine in older individuals: A randomized, open-label, non-inferiority trial.	Hum Vaccin Immunother.	14(8)	1923-30	2018

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ohfuji S, Deguchi M, Tachibana D, Koyama M,Takagi T, Yoshioka T, Urae A,Ito K, Kase T, Maeda A,Kondo K, Fukushima W,Hirota Y; Osaka Pregnant Women Influenza Study Group.	Protective effect of maternal influenza vaccination on influenza in their infants: a prospective cohort study.	J Infect Dis.	217(6)	878-86	2018
Oda K, Nishimura H, Watanabe O, Kubo T, Shindo S.	A case report on parainfluenza virus type 4a infection in a 1-year-old boy with biphasic fever.	J Thorac Dis.	10(19)	S2305-8	2018
Ito K, Mugitani A, Irie S, Ishibashi M, Takasaki Y, Shindo S, Yokoyama T, Yamashita Y, Shibao K, Koyanagi H, Fukushima W, Ohfuji S, Maeda A, Kase T, Hirota Y.	Prior vaccinations improve immunogenicity of inactivated influenza vaccine in young children aged 6 months to 3 years: A cohort study.	Medicine (Baltimore)	97(29)	e11551.	2018
Hara M., Nakagomi O	Role of rotavirus vaccination on an emerging G8P[8] rotavirus strain causing an outbreak in central Japan	Vaccine	36(34)	5109	2018
Hoshi SL, Seposo X, Okubo I, Kondo M.	Cost-effectiveness analysis of pertussis vaccination during pregnancy in Japan.	Vaccine	36(34)	5133-40	2018
Araki K, Hara M, Tsugawa T, Shimanoe C, Nishida Y, Matsuo M, Tanaka K.	Effectiveness of monovalent and pentavalent rotavirus vaccines in Japanese children.	Vaccine	36(34)	5187-93	2018
Shono A,Hoshi SL, Kondo M	The impact on vaccination coverage following introduction of a routine pneumococcal vaccination programme for the elderly in Japan.	Vaccine	36(39)	5886-90	2018
Matsushita M, Takeuchi S,Kumagai N, Morio M, Matsushita C, Arise K, Awatani T.	Booster influenza vaccination confers additional immune responses in an elderly, rural communitydwelling population.	Am J Infect Control.	46(4)	462-3	2018
Hoshi SL, Kondo M, Okubo I.	Economic evaluation of routine infant rotavirus immunisation programme in Japan.	Hum Vaccin Immunother.	13(5)	1115-25	2017
Nakashima K, Aoshima M, Ohfuji S, Suzuki K, Katsurada M, Katsurada N,Misawa M, Otsuka Y, Kondo K &Hirota Y	Immunogenicity of trivalent influenza vaccine in patients with lung cancer undergoing anticancer chemotherapy.	Hum Vaccin Immunother.	13(3)	543-50	2017
Ohfuji S, Ito K, Ishibashi M, Shindo S, Takasaki Y, Yokoyama T, Yokoyama T, Yamashita Y, Shibao K, Nakano T, Tsuru T, Irie S, Hirota Y.	Immunogenicity study to investigate the interchangeability among three different types of polio vaccine: A cohort study in Japan.	Medicine (Baltimore)	96(23)	e7073	2017
Hoshi SL, Kondo M,Okubo I.	Response to Curran and Mrkvan, Letter to the Editor: Response to publication by Hoshi SL et al.: Cost-effectiveness of varicella vaccine against herpes zoster and post-herpetic neuralgia for elderly in Japan.	Vaccine	35(51)	7080	2017

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ohfuji S, Kobayashi M, Ide Y, Egawa Y, Saito T, Kondo K, Ito K, Kase T, Maeda A, Fukushima W, Hirota Y.	Key points in evaluating immunogenicity of pandemic influenza vaccines: A lesson from immunogenicity studies of influenza A(H1N1) pdm09 vaccine.	Vaccine	35(39)	5303-8	2017
Hirota Y,Ozasa K,Nakano T	Vaccine epidemiology : Its role in promoting sound immunization programs in Japan.	Vaccine	35(36)	4787-90	2017
Hara M, Hirota Y.	Basic principle of population-based cohort study to evaluate influenza vaccine effectiveness among elderly Japanese.	Vaccine	35(36)	4791-5	2017
Fukushima W,Hirota Y	Basic principle of test-negative design in evaluating influenza vaccine effectiveness.	Vaccine	35(36)	4796 -800	2017
Ohfuji S, Okada K, Nakano T, Ito H, Hara M, Kuroki H, Hirota Y	Control selection and confounding factors: A lesson from a Japanese case-control study to examine acellular pertussis vaccine effectiveness.	Vaccine	35(36)	4801-5	2017
Kondo K, Suzuki K, Washio M, Ohfuji S, Fukushima W, Maeda A, Hirota Y and the Study Group forPheumonia in the Elderly Individuals.	Effectiveness of 23 valent pneumococcal polysaccharide vaccine and seasonal influenza vaccine for pneumonia among the elderly -selection of controls in a case-controle study.	Vaccine	35(36)	4806-10	2017
Ohfuji S, Deguchi M,Tachibana D, Koyama M,Takagi T, Yoshioka T,Urae A, Fukushima W,Hirota Y for the Osaka PregnantWomen Influenza Study Group.	Estimating influenza disease burden amongpregnant women:application of self-control method.	Vaccine	35(36)	4811-6	2017
Fukushima W,Ozasa K,Okumura A,Mori M,Hosoya M,Nakano T,Tanabe T,Yamaguchi N,Suzuki H,Mori M,Hatayama H,Ochiai H,Kondo K,Ito K,Ohfuji S,Nakamura Y,Hirota Y.	Oseltamivir use and severe abnomal behavior in Japanese children and adolescents with influenza: Is a self-controlled case series study applicable?	Vaccine	35(36)	4817-24	2017
Hoshi SL, Kondo M, Okubo I.	Cost-effectiveness of varicella vaccine against herpes zoster and post-herpetic neuralgia for elderly in Japan.	Vaccine	35(24)	3264-71	2017
福島若葉	ワクチンの効果	BIO Clinica	34(2)	11-5	2019
福島若葉, 森川佐依子, 松本一寛, 藤岡雅司, 松下享, 久保田恵巳, 八木由奈, 武知哲久, 高崎好生, 進藤静生, 山下祐二, 横山隆人, 清松由美, 廣井聡, 中田恵子, 前田章子, 伊藤一弥, 大藤さとこ, 加瀬哲男, 廣田良夫.	6 歳未満児におけるインフルエンザワクチンの有効性：2013/14～2017/18 シーズンのまとめ（厚生労働省研究班報告として）.	病原微生物検出情報（IASR）	40(11)	194-5	2019
岡田賢司	百日咳	小児内科　増刊号	51	696-9	2019

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
中野貴司	定期接種化の検討状況、特にポリオ追加接種とおたふくかぜワクチンについて.	臨床とウイルス	47(4)	310-8	2019
岡田賢司	4 種混合ワクチン	臨床と研究	96(2)	41-8	2019
中野貴司	海外渡航者の感染予防～初めて打つワクチン、追加するワクチン	臨床と研究	96(12)	1463-8	2019
岡田賢司	百日咳含有（DTP）ワクチン	臨床と微生物	46(2)	65-9	2019
中野貴司	成人への予防接種－欧米との比較を含めて	臨床と微生物	46(2)	99-104	2019
岡田賢司	くすぶり続ける百日咳の流行	チャイルドヘルス	21(5)	38-42	2018
福島若葉	インフルエンザワクチンの有効性：その評価手法とともに再考する	外来小児科	21(3)	435-40	2018
福島若葉	Test-negative design によるインフルエンザワクチンの有効性評価	感染症	48(2)	64-8	2018
中野貴司	侵襲性髄膜炎菌感染症とは	健康教室	69(1)	94-7	2018
岡田賢司	百日咳	検査と技術	46(6)	610-4	2018
中野貴司	思春期以降のワクチン－髄膜炎菌－	治療	100(8)	920-4	2018
岡田賢司	百日咳	小児科診療　増刊号	81	108-9	2018
中野貴司	渡航前の感染対策（ワクチンを中心に）	小児科診療	81(4)	427-35	2018
岡田賢司	病原体診断に基づく百日咳の疾病負荷の評価と今後の課題	小児科臨床	71(9)	165-70	2018
山村佳子、三原由佳、中谷圭吾、岡田賢司	来院時心肺停止状態であった乳児百日咳の 1 例	小児感染免疫	30(3)	252-7	2018
福島若葉、森川佐依子、藤岡雅司、松下　享、久保田恵巳、八木由奈、高崎好生、進藤静生、山下祐二、横山隆人、清松由美、廣井　聡、中田恵子、前田章子、伊藤一弥、大藤さとこ、加瀬哲男、廣田良夫	6 歳未満児におけるインフルエンザワクチンの有効性：2013/14～2016/17 シーズンのまとめ（厚生労働省研究班報告として）	病原微生物検出情報(IASR)	39(11)	197-9	2018
岡田賢司	百日咳含有ワクチン	臨床と微生物	45(2)	35-8	2018
牟田広美	ロタウィルスワクチンの接種方法に関する実態調査～日本外来小児科学会員への調査結果から～	外来小児科	20(3)	362-8	2017
岡田賢司、富樫武弘、田邊康祐、山地雅子、Pride M、Gurtman A、吉田瑞樹、Thompson A、Gruber WC、Scott DA	日本人乳幼児における 7 価肺炎球菌結合型ワクチンと DTaP 同時接種時の安全性，忍容性および免疫原性	小児感染免疫	28(4)	225-35	2017
中田恵子、上林大起、森川佐依子、大塚真紀	海外での感染が疑われた患者からの EV-D68 家族内感染事例	病原微生物検出情報(IASR)	39(1)	9-11	2017

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
福島若葉、森川佐依子、藤岡雅司、松下　享、久保田恵巳、武知哲久、高崎好生、進藤静生、山下祐二、横山隆人、清松由美、廣井　聡、中田恵子、前田章子、伊藤一弥、大藤さとこ、加瀬哲男、廣田良夫	6 歳未満児におけるインフルエンザワクチンの有効性：2013/14 ～ 2015/16 シーズンのまとめ（厚生労働省研究班報告として）	病原微生物検出情報(IASR)	38(11)	223-4	2017
岡田賢司	百日咳ワクチン・DTP ワクチン	化学療法の領域増刊号	33	64-74	2017

研究班構成員名簿

平成29年～令和元年度　ワクチンの有効性・安全性の臨床評価と VPDの疾病負荷に関する疫学研究班　班員名簿

区　分	氏　名	所　属	職　名
顧　問	武内可尚	川崎市立川崎病院	名誉院長
顧　問	柏木征三郎	九州大学医学部	元教授
研究代表者	廣田良夫	医療法人相生会臨床疫学研究センター 保健医療経営大学	センター長 学長
研究分担者	福島若葉	大阪市立大学大学院医学研究科公衆衛生学	教授
	大藤さとこ	大阪市立大学大学院医学研究科公衆衛生学	准教授
	岡田賢司	学校法人福岡学園　福岡看護大学 基礎・基礎看護部門　基礎・専門基礎分野	教授
	中野貴司	川崎医科大学 小児科学	教授
	原　めぐみ	佐賀大学医学部社会医学講座予防医学分野	准教授
	森川佐依子	大阪健康安全基盤研究所　森ノ宮センター　ウイルス課	主任研究員
	浦江明憲	株式会社メディサイエンスプラニング	代表取締役会長兼社長
	入江　伸	医療法人相生会	理事長
	都留智巳	医療法人相生会ピーエスクリニック	院長
	砂川富正	国立感染症研究所感染症疫学センター	室長
	近藤正英	筑波大学医学医療系	教授
	織田慶子	保健医療経営大学	教授
	齋藤智也	国立保健医療科学院健康危機管理研究部	上席主任研究官
	中島　啓	亀田総合病院呼吸器内科	部長
研究協力者	鈴木幹三	名古屋市立大学大学院医学研究科地域包括医療学	寄附講座講師
	小笹晃太郎	公益財団法人放射線影響研究所 疫学部	部長
	葛西　健	世界保健機関西太平洋地域事務局（WPRO）	事務局長
	山口真也	霞ヶ浦医療センター小児科	小児周産期診療部長
	越田理恵	金沢市保健局	局長
	磯部充久	さいたま市健康科学研究センター　保健科学課　代謝免疫係	主任
	松下雅英	高知大学医学部家庭医療学講座	准教授
	田中好太郎	国立感染症研究所　感染症疫学センター	協力研究員
	前田章子	大阪市立大学大学院医学研究科公衆衛生学	研究員
	松井珠乃	国立感染症研究所感染症疫学センター第一室	室長
	菅野恒治	菅野小児科医院	院長
	高崎好生	高崎小児科医院	院長
	進藤静生	医療法人　しんどう小児科	理事長
	横山　隆	医療法人　横山小児科医院	顧問
	横山隆人	医療法人　横山小児科医院	院長
	山下祐二	医療法人　やました小児科医院	院長
	芝尾敬吾	医療法人　しばおクリニック	院長
	清松由美	医療法人きよまつ小児科医院	院長
	渡辺憲治	兵庫医科大学　腸管病態解析学	特任准教授
	山上博一	医療法人藤井会　石切生喜病院　消化器内科	部長
	大津　寧	久留米大学医療センター小児科	講師
	田中征治	久留米大学医学部小児科	講師
	津村直幹	つむら診療所	副院長
	棚成嘉文	医療法人 和田医院　和田小児科	院長
	山崎和子	聖マリアンナ医科大学リウマチ・膠原病・アレルギー内科	助教

区　分	氏　名	所　属	職　名
研究協力者	井手悠一郎	聖マリア学院大学看護学部	准教授
	Timothy M. Uyeki	Centers for Disease Control and Prevention	疫学専門家
	中村英夫	中村小児科医院	院長
	川合秀治	介護老人保健施設 竜間之郷	代表者
	仲田裕行	介護老人保健施設 ケーアイ	施設長
	伊藤一弥	保健医療経営大学 医療法人相生会　臨床疫学研究センター	教授
	村田節子	福岡看護大学　看護学部看護学科　健康支援部門　成人看護学	教授
	中村　敦	名古屋市立大学医学研究科臨床感染制御学	病院教授
	吉村邦彦	東京有隣会有隣病院	診療部長
	村端真由美	三重大学　大学院医学系研究科看護学専攻 小児看護学	准教授
	岩本里美	厚生連足助病院感染制御課	感染制御課長
	矢野久子	名古屋市立大学看護学部	教授
	藤岡雅司	ふじおか小児科	院長
	松下　享	松下こどもクリニック	院長
	久保田恵巳	くぼたこどもクリニック	院長
	八木由奈	八木小児科	副院長
	吉田英樹	大阪市保健所	所長
	近藤亨子	大阪市立大学大学院医学研究科　研究支援プラットフォーム生物統計部門	技術職員・医学博士
	出口昌昭	市立岸和田市民病院	副院長
	加瀬哲男	大阪市立大学大学院医学研究科公衆衛生学	特任講師
	三原由佳	刈谷豊田総合病院小児科	小児科医師
	本村知華子	国立病院機構福岡病院小児科	小児科医長
	藤野元子	済生会中央病院　小児科	副医長
	吉川哲史	藤田医科大学医学部小児科	教授
	宮田章子	さいわいこどもクリニック	院長
	荒木　薫	佐賀大学保健管理センター	助教
	青木才一志	あおき小児科	院長
	牟田広実	いいづかこども診療所	院長
	毛利陽子	毛利医院	院長
	太田光博	太田小児科内科医院	副院長
	坂西信平	坂西内科医院	副院長
	廣井　聡	大阪健康安全基盤研究所感染症部ウイルス課	主任研究員
	中田恵子	大阪健康安全基盤研究所感染症部ウイルス課	主任研究員
	麦谷　歩	医療法人相生会墨田病院	医師
	江藤　隆	医療法人相生会博多クリニック	医師
	石橋元規	医療法人相生会臨床研究部門　臨床研究・治験推進部	部長
	吉原達也	医療法人相生会福岡みらい病院臨床研究センター	医師
	神代弘子	医療法人相生会臨床研究部門　臨床研究・治験推進部	課長
	三浦由子	医療法人相生会福岡みらい病院臨床研究センター	臨床検査技師
	真部順子	医療法人相生会福岡みらい病院臨床研究センター	企画部
	平塚磁郎	医療法人相生会墨田病院	臨床検査技師
	千色純子	医療法人相生会墨田病院	看護師
	河野優二	医療法人相生会墨田病院	臨床検査技師

区　分	氏　名	所　属	職　名
研究協力者	本間太一	医療法人相生会墨田病院	臨床検査技師
	洲崎みどり	医療法人相生会ピーエスクリニック	看護係長
	神谷　元	国立感染症研究所感染症疫学センター	主任研究官
	安藤由香	岡山労災病院 小児科	部長
	大平文人	大阪精神医療センター 救急・急性期診療部	副部長
	土橋酉紀	国立感染症研究所感染症疫学センター	主任研究官
	松本道明	高知県衛生研究所　総務企画課	専門員
	八幡裕一郎	国立感染症研究所感染症疫学センター	主任研究官
	森畑東洋一	もりはた小児科	院長
	高橋琢理	国立感染症研究所感染症疫学センター	研究員
	浜田文彦	医療法人慈孝会 はまだ小児科	院長
	小林祐介	埼玉県保健医療部南部保健所	医員
	河上祥一	医療法人社団 愛育会 福田病院	病院長
	星　淑玲	筑波大学医学医療系　保健医療政策学・医療経済学	研究員
	庄野あい子	明治薬科大学　公衆衛生・疫学研究室	講師
	樋口恵美	ほほえみクリニック	院長
	山本和英	かずクリニック	院長
	菅　栄	医療法人開生会かいせい病院	院長
	太田千晴	豊川市民病院呼吸器内科	部長
	宇佐美郁治	旭労災病院	院長
	岩島康仁	岩島医院	副院長
	吉川理子	三宿病院　呼吸器科	部長
	宮下修行	関西医科大学　内科学第一講座	診療教授
	丹羽俊朗	浜田・浅井医院　呼吸器科	部長
	住田千鶴子	稲沢市民病院	看護部長
	伊藤功朗	公立小浜病院	非常勤医師
	南里純代	大阪市立十三市民病院医療安全対策室	感染管理認定看護師
	宮川浩一	みやがわクリニック	理事長
	白石　訓	大阪市立十三市民病院呼吸器内科	部長
	武田博明	済生会山形済生病院トータルクオリティーマネージメント	センター長
	永坂博彦	永坂内科医院	院長
	土田文宏	済生会山形済生病院呼吸器内科	副部長
	佐藤千紗	済生会山形済生病院呼吸器内科	副医長
	西塚　碧	済生会山形済生病院呼吸器内科	医師
	坪井永保	坪井病院	理事長
	中浜　力	中浜医院	院長
	上田章人	藤立病院	病院長
	迎　寛	長崎大学病院呼吸器内科	教授
	宮崎泰可	長崎大学病院呼吸器内科	講師
	東山康仁	北松中央病院	理事長
	塚本美鈴	北松中央病院呼吸器内科	医長
	早川富博	愛知厚生連足助病院	名誉院長
	名倉明日香	稲沢市民病院消化器内科	医長
	平山達朗	長崎大学病院呼吸器内科	医員

区　分	氏　名	所　属	職　名
研究協力者	城下彰宏	亀田総合病院呼吸器内科	医師
	山城　信	沖縄県立中部病院	医師
	喜舎場朝雄	沖縄県立中部病院	部長
	田中純太	魚沼基幹病院	医師
	高田俊範	魚沼基幹病院新潟大学地域医療教育センター魚沼基幹病院	センター長・副院長
	榊原智博	東北労災病院	医師
	西　耕一	石川県立中央病院	科長
	西辻　雅	石川県立中央病院	医師
	寺島　毅	東京歯科大学市川総合病院	教授
	松崎　透	東京歯科大学市川総合病院	講師
	中島隆裕	東京歯科大学市川総合病院	講師
	黒田　葵	東京歯科大学市川総合病院	助教
	岩見枝理	東京歯科大学市川総合病院	臨床専攻医
	飛野和則	飯塚病院	部長
	吉峯晃平	飯塚病院	医師
	田坂定智	弘前大学呼吸器内科学講座	教授
	富井啓介	神戸市立医療センター中央市民病院	副院長
	桜川敬子	神戸市立医療センター中央市民病院	CRC
	中川　淳	神戸市立医療センター中央市民病院	医師
	平林亮介	神戸市立医療センター中央市民病院呼吸器内科	医師
	塚尾仁一	福井県立病院　呼吸器内科	医師
	黒沼幸治	札幌医科大学医学部呼吸器・アレルギー内科講座	講師
	青島正大	亀田総合病院呼吸器内科	顧問
	牧野英記	松山赤十字病院	副部長
	西垂水和隆	今村総合病院	部長
共同研究者	松本一寛	大阪市立大学大学院医学研究科公衆衛生学	大学院生
	迎　恵美子	大阪市立大学大学院医学研究科公衆衛生学	大学院生
	松浦知香	大阪市立大学大学院医学研究科公衆衛生学	大学院生
	出口晃史	大阪市立大学大学院医学研究科公衆衛生学	研究員
	吹田安佐詠	大阪市立大学大学院医学研究科公衆衛生学	大学院生
	田中孝明	川崎医科大学総合医療センター小児科	講師
	伊東宏明	亀田総合病院　小児科	部長
	田中敏博	JA静岡厚生連　静岡厚生病院　小児科	診療部長
	福島慎二	東京医科大学病院渡航者医療センター感染制御部・感染症科	講師
	笠井正志	兵庫県立こども病院 感染症内科	部長
	山本裕子	医療法人やまもと医院	副院長
	髙杉尚志	医療法人髙杉会　高杉こどもクリニック	院長
	三宅真砂子	三宅内科小児科医院	副院長
	上田美子	清音クリニック	副院長
	津川　毅	札幌医科大学小児科	特任講師
	武知茉莉亜	株式会社電通パブリックリレーションズ	
	守田貴子	純真学園大学保健医療学部　医療工学科	准教授
	来海和彦	KMバイオロジクス株式会社 研究部	次長
	松浦健太	KMバイオロジクス株式会社　ワクチン事業部門　第二製造部1課	課長

区　分	氏　名	所　属	職　名
共同研究者	Emmanuel Vidor	Global Medical Affairs, Sanofi Pasteur SA（France）	Global Medical Expert
	Su Peing Ng	Global Medical Affairs, Sanofi Pasteur SA（France）	Head
	酒井伸夫	デンカ生研株式会社　ワクチン学術部	ワクチン企画推進部長
	丸山裕一	デンカ生研株式会社　ワクチン研究部	部長
	三森重孝	デンカ生研株式会社　ワクチン研究部	部長代理
	本條健太	一般財団法人　阪大微生物病研究会 BMS センターサーベイランス課	課長
	明地正晃	一般財団法人　阪大微生物病研究会メディカルアフェアーズ部	部長
	小林真之	MSD 株式会社　メディカルアフェアーズ ワクチン領域	ディレクター

International Journal of Infectious Diseases 93 (2020) 68–76

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Safety of influenza vaccination on adverse birth outcomes among pregnant women: A prospective cohort study in Japan

Satoko Ohfuji[a,b,*], Masaaki Deguchi[c], Daisuke Tachibana[d], Masayasu Koyama[d], Tetsu Takagi[e], Takayuki Yoshioka[f], Akinori Urae[g], Kazuya Ito[a,h], Tetsuo Kase[a,b], Akiko Maeda[a], Kyoko Kondo[i], Wakaba Fukushima[a,b], Yoshio Hirota[a,h,j], for the Osaka Pregnant Women Influenza Study Group[1]

[a] Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-shi, Osaka 545-8585, Japan
[b] Research Center for Infectious Disease Sciences, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-shi, Osaka 545-8585, Japan
[c] Department of Obstetrics and Gynecology, Kishiwada City Hospital, 1001, Gakuhara-cho, Kishiwada-shi, Osaka 596-8501, Japan
[d] Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-shi, Osaka 545-8585, Japan
[e] Takagi Ladies Clinic, 1-13-44, Kamihigashi, Hirano-ku, Osaka-shi, Osaka 547-0002, Japan
[f] Osaka Branch, Mediscience Planning Inc., 3-6-1, Hiranomachi, Chuo-ku, Osaka-shi, Osaka 541-0052, Japan
[g] Head Office, Mediscience Planning Inc., 1-11-44, Akasaka, Minato-ku, Tokyo 107-0052, Japan
[h] College of Healthcare Management, 960-4, Takayanagi, Setaka-machi, Miyama-shi, Fukuoka, 835-0018, Japan
[i] Osaka City University Hospital, 1-4-3, Asahi-machi, Abeno-ku, Osaka-shi, Osaka 545-8585, Japan
[j] Clinical Epidemiology Research Center, SOUSEIKAI, 3-5-1, Kashii-Teriha, Higashi-ku, Fukuoka-shi, Fukuoka 813-0017, Japan

ARTICLE INFO

Article history:
Received 29 November 2019
Received in revised form 9 January 2020
Accepted 19 January 2020

Keywords:
Adverse birth outcomes
Influenza vaccine
Pregnant women
Prospective cohort study
Vaccine safety

ABSTRACT

Background: Pregnant women are in the highest priority group for receiving influenza vaccination. However, they may be reluctant to receive the vaccination due to concerns about the influence of vaccination on the fetuses.
Methods: This prospective cohort study of 10 330 pregnant women examined the safety of influenza vaccination in terms of adverse birth outcomes. Influenza vaccination during pregnancy was determined from questionnaires before and after the 2013/2014 influenza season. All subjects were followed until the end of their pregnancy. Adverse birth outcomes, including miscarriage, stillbirth, preterm birth, low birth weight, and malformation, were assessed by obstetrician reports.
Results: Adverse birth outcomes were reported for 641 (10%) of the 6387 unvaccinated pregnant women and 356 (9%) of the 3943 vaccinated pregnant women. Even after adjusting for potential confounders, vaccination during pregnancy showed no association with the risk of adverse birth outcomes (odds ratio 0.90, 95% confidence interval 0.76–1.07). Vaccination during the first or second trimester displayed no association with adverse birth outcomes, whereas vaccination during the third trimester was associated with a decreased risk of adverse birth outcomes (odds ratio 0.70, 95% confidence interval 0.51–0.98).
Conclusions: Influenza vaccination during pregnancy did not increase the risk of adverse birth outcomes, regardless of the trimester in which vaccination was performed, when compared to unvaccinated pregnant women.

Introduction

In November 2012, the World Health Organization presented a position paper placing pregnant women in the highest priority group to receive influenza vaccination, due to the expectations of vaccine effectiveness in preventing influenza among mothers and their infants (World Health Organization, 2012). Indeed, several epidemiological studies have indicated that maternal influenza

* Corresponding author at: Corresponding author at: Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-shi, Osaka 545-8585, Japan.
E-mail address: satop@med.osaka-cu.ac.jp (S. Ohfuji).
[1] Other members of the study group are listed in the Appendix A.

https://doi.org/10.1016/j.ijid.2020.01.033

vaccination provides effective protection against infant influenza (Benowitz et al., 2010; Black et al., 2004; Ohfuji et al., 2018; Steinhoff et al., 2012; Zaman et al., 2008). In general, however, pregnant women tend to be concerned about the influence of vaccines on the fetuses, which may lead to some reluctance to undergo vaccination. In fact, a previous study identified concerns about vaccine safety as the most significant reason for pregnant women not undergoing influenza vaccination (Prospero et al., 2019). Particularly in Japan, influenza vaccination for pregnant women is performed as 'voluntary vaccination'. In this situation, positive vaccination behaviors among pregnant women are likely to remain suboptimal until the safety concerns regarding effects on fetuses can be addressed.

A review of previous reports on the safety of influenza vaccination among pregnant women revealed no studies examining the influence of influenza vaccination among Japanese pregnant women on adverse birth outcomes. Since the Japanese population tends to show greater concern about vaccine safety than other populations (Hanley et al., 2015; Nakayama, 2019), this lack of evidence among the relevant population might present a barrier to achieving adequate coverage with influenza vaccination for pregnant women. Additionally, the proportions of preterm delivery, low birth weight infants, and malformed infants vary between countries (Källén, 2012; Morisaki et al., 2017; Sepkowitz, 1995).

We therefore conducted a prospective cohort study to examine vaccine safety in comparison with the incidence of adverse birth outcomes (including miscarriage, stillbirth, preterm birth, low birth weight, and congenital malformation) between vaccinated and unvaccinated pregnant women in Japan. In general, pregnant women who receive influenza vaccination are likely to be older or to have an underlying illness such as hypertension or diabetes, representing conditions that may bring about a higher incidence of adverse birth outcomes. In this study, the safety of influenza vaccination in pregnant women was evaluated with consideration of the effect of differences in such background characteristics.

Methods

Study subjects

This study was conducted with the cooperation of 117 maternity hospitals and clinics affiliated with the Obstetrical Gynecological Society of Osaka, Japan. Study subjects comprised Japanese pregnant women (regardless of gestational week) attending the collaborating hospitals and clinics before the beginning of the 2013/14 influenza season (i.e., between October and December 2013). In Japan, pregnant women typically undergo influenza vaccination at a maternity clinic or primary care clinic between October and December, as a voluntary vaccination. All study subjects received an explanation of the study from their obstetrician and verbally provided informed consent prior to participation.

The study protocol was approved by the Ethics Committee at the Osaka City University Graduate School of Medicine, and was performed in accordance with the Declaration of Helsinki.

Information collection

At the time of recruitment, study subjects completed a self-administered questionnaire to provide the following information: date of recruitment, age, gestational age at recruitment, expected date of birth, height and weight before pregnancy, smoking and alcohol drinking habits, underlying illnesses, influenza vaccination status for the 2013/14 season, and month of vaccination for vaccinated subjects. The accuracy of gestational age at recruitment was confirmed by referring to the expected date of birth. To collect information on receipt of influenza vaccination after responding to the questionnaire at recruitment, the study subjects were sent a second questionnaire after the end of the 2013/14 influenza season (May 2014). In this post-season questionnaire, besides vaccination status for the 2013/14 season and month of vaccination, we also asked the following questions about pregnancy outcomes and their babies: date of delivery and birth weight and height of their babies. To confirm these self-reported pregnancy outcomes and neonatal characteristics, the obstetrician-in-charge was contacted and asked to provide the following information from the medical records of each subject: pregnancy outcome (live birth, miscarriage, or stillbirth), and if a live birth was delivered, the date of delivery, gestational week at delivery, birth weight and height, Apgar scores at 1 min and 5 min, and presence and name of any congenital malformations. In addition, information on pregnancy-induced complications (i.e., multiple pregnancy, pregnancy-induced hypertension, gestational diabetes, hospitalization due to threatened miscarriage, placenta previa, fetal growth restriction, abruptio placentae, and intrauterine infection) was also collected by their obstetricians.

Statistical analysis

The primary exposure was influenza vaccination during pregnancy, determined from information on the month of vaccination and month of delivery. Subjects who received vaccination in the same month as the delivery, or for whom information on the month of vaccination was unavailable were excluded from the analysis.

The study outcome was adverse birth outcomes including miscarriage (termination of pregnancy before gestational week 22), stillbirth (dead at birth or after gestational week 22), preterm birth (live birth at less than gestational week 37), and/or low birth weight (birth weight <2500 g) for all study subjects. Miscarriage and stillbirth included therapeutic abortions. Information on low birth weight was primarily based on information from the obstetrician. If information was unavailable from the obstetrician, complementary data were obtained from the self-administered questionnaire. In addition, Apgar scores at 1 min and 5 min were also assessed using three categories: 0–3, very low; 4–6, low; 7–10, healthy. Also, for women in the first trimester, congenital malformation was assessed as another study outcome. Genetic and chromosomal abnormalities were not included in congenital malformation, because these occur at conception and are uninfluenced by vaccination. For detailed analyses, congenital malformations were classified into 10 categories by organ system (i.e., central nervous system; ophthalmological, otological, or orofacial; cardiac; respiratory; cleft lip and/or cleft palate; gastrointestinal; genitourinary or renal; muscular or limb defects; or other), according to International Classification of Diseases 10th revision (ICD-10) codes, and were compared between unvaccinated and vaccinated women.

With regard to explanatory variables, age was categorized into <30, 30–34, and >34 years old. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2), and then classified into three categories according to conventional cut-off values. Gestational age was defined as gestational week at the time of vaccination for vaccinated women or at the time of recruitment for unvaccinated women, and was categorized into first trimester (<16 weeks), second trimester (16–27 weeks), and third trimester (>27 weeks). Gestational age at vaccination was calculated using the information on the month of vaccination, gestational age at recruitment, and date at recruitment, and considering the date of vaccination as the 15th day (median) of the month. Calendar month at the start of pregnancy was calculated by information on

the date of recruitment and gestational age at recruitment, and was classified into four seasons. The following influenza-related high-risk conditions were included according to a previous report: chronic respiratory disorders (including asthma), cardiovascular disorders (excluding isolated hypertension), kidney disease, liver disease, neurological disorders, blood disorders, metabolic disorders (including diabetes), immunocompromised states (such as malignant tumors, connective tissue disorders, inflammatory bowel disease, and chronic rheumatism), and obesity (BMI $\geq$ 25.0 kg/m^2) (Centers for Disease Control and Prevention, 2013). Underlying obstetric and gynecological illnesses were included as infertility, myoma uteri, ovarian diseases, endometriosis, diseases in the neck of the uterus including severe dysplasia or cancer, endometrial polyp, adenomyosis uteri, habitual miscarriage, etc.

A logistic regression model was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for associations between influenza vaccination during pregnancy and adverse birth outcomes. The multivariate model included all variables related to vaccination status (i.e., exposure variables) or adverse birth outcomes (i.e., outcome index) showing values of $p < 0.05$ in the univariate analyses. The Chi-square test and Wilcoxon rank-sum test were used where appropriate.

In addition, in order to separately evaluate the influence of influenza vaccination on adverse birth outcomes according to gestational week, stratified analyses by trimester were conducted.

All analyses were two-tailed and were conducted using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

Results

Of the 20 420 pregnant Japanese women recruited, 12 838 responded to the post-season questionnaire. Among these, 301 vaccinated women were excluded, because vaccination had been performed in the month of delivery; whether the vaccination had been performed before or after delivery was thus unclear. Another 233 vaccinated women were excluded because of a lack of information on the month of vaccination. Information on birth outcomes was then obtained for 10 330 women from their obstetricians, and these women therefore comprised the subjects for analysis (Figure 1). Table 1 shows the characteristics of the study subjects. A total of 3943 women (38%) received influenza vaccination during pregnancy. Among these, about one-third had received the vaccination during each of the first, second, and third trimesters. Vaccinated women were older and more likely to have underlying obstetric and gynecological illnesses, whereas unvaccinated women appeared to show higher frequencies of obesity, hypertension, or fetal growth restriction as pregnancy-induced complications, and of having smoking or alcohol drinking habits during pregnancy.

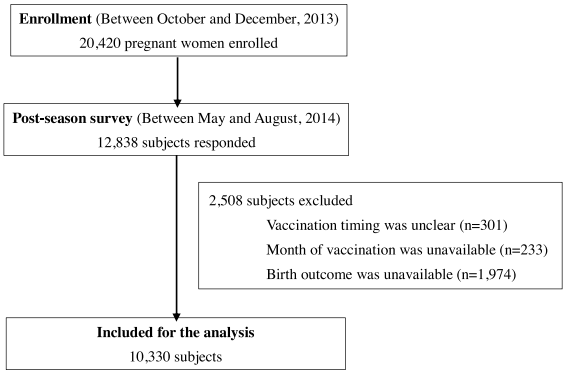


Figure 1. The enrollment process for the study.

Table 2 shows birth outcomes for the study subjects. Miscarriage or stillbirth was reported for 0.1% of subjects, each with similar proportions in unvaccinated and vaccinated women. Preterm birth occurred in 4.1% of subjects, again with similar proportions in the two groups. On the other hand, low birth weight was significantly more frequent among unvaccinated women than among women vaccinated during pregnancy (8% vs. 7%).

A total of 997 subjects (10%) reported miscarriage, stillbirth, preterm birth, and/or low birth weight as adverse birth outcomes (Table 3). Women who had received influenza vaccination during pregnancy reported slightly fewer adverse birth outcomes compared with unvaccinated women, although the difference was not significant (9% vs. 10%, respectively; $p = 0.09$). In addition, pregnant women $\geq$30 years old, with BMI <18.5 kg/m^2, underlying obstetric and gynecological illnesses, pregnancy-induced complications, or a smoking habit during pregnancy were significantly more likely to present with adverse birth outcomes. After considering the effects of these potential confounders in the multivariate analysis, vaccination during pregnancy did not show any significant association with adverse birth outcomes when compared to unvaccinated women (OR 0.90, 95% CI 0.76–1.07). However, age $\geq$30 years, lower BMI before pregnancy, and some pregnancy-induced complications were significantly associated with adverse birth outcomes.

Adverse birth outcomes were examined separately in subgroups according to the trimester at vaccination for vaccinated women or at recruitment for unvaccinated women (Table 4). In the first trimester, although congenital malformation was regarded as one of the adverse birth outcomes, no significant difference in these adverse birth outcomes was seen between unvaccinated and vaccinated women (13% each). In the second trimester, the proportion of adverse birth outcomes was broadly similar among unvaccinated and vaccinated women. In the third trimester, however, vaccinated women had significantly fewer reports of adverse birth outcomes (6% vs. 9%, respectively), especially for low birth weight (6% vs. 8%, respectively), than unvaccinated women. Even in the multivariate analysis with consideration of the effect of potential confounders, women who received vaccination during the first or second trimester showed no significant elevation in adverse birth outcomes compared with unvaccinated women (first trimester: OR 1.07, 95% CI 0.81–1.40; second trimester: OR 0.87, 95% CI 0.65–1.16). On the other hand, women who received vaccination during the third trimester showed a significantly decreased OR for adverse birth outcomes when compared with unvaccinated women (OR 0.70, 95% CI 0.51–0.98).

Discussion

The study findings demonstrated that influenza vaccination during pregnancy was not associated with any increase in adverse effects on the fetus. This result is consistent with previous studies from other countries. To date, several randomized controlled trials of pregnant women have shown that the incidences of miscarriage, stillbirth, preterm birth, low birth weight, and congenital malformations among influenza vaccination groups were similar to those in placebo groups (Michikawa et al., 2018; Osaka City, 2019; Steinhoff et al., 2012). Most cohort studies have also shown that vaccinated and unvaccinated pregnant women display similar incidences of miscarriage, stillbirth, preterm birth, low birth weight, or congenital malformation in their babies (Baum et al., 2015; Black et al., 2004; Chambers et al., 2013; Chambers et al., 2016; Cleary et al., 2014; de Vries et al., 2014; Fabiani et al., 2015; Fell et al., 2012; Fell et al., 2017; Kharbanda et al., 2017; Ma et al., 2014; Madhi et al., 2014; McHugh et al., 2017; Nordin et al., 2014a;

Table 1
Characteristics of the pregnant women ($N = 10\ 330$).[a]

Characteristics		Total *n* (%)	Unvaccinated *n* (%)	Vaccinated *n* (%)	*p*-Value
Total		10 330 (100)	6387 (62)	3943(38)	
Gestational age at recruitment or vaccination (weeks)	<16 (first trimester)	2826 (27)	1705 (27)	1121 (28)	<0.01
	16–27 (second trimester)	3328 (32)	1738 (27)	1590 (40)	
	>27 (third trimester)	4176 (40)	2944 (46)	1232 (31)	
Calendar month at pregnancy start	March–May (Spring)	3506 (34)	1997 (31)	1509 (38)	<0.01
	June–August (Summer)	2908 (28)	1434 (22)	1474 (37)	
	September–November (Autumn)	1997 (19)	1215 (19)	782 (20)	
	December–February (Winter)	1919 (19)	1741 (27)	178 (5)	
Age (years)	Median (range)	32 (15–51)	32 (15–51)	33 (16–47)	<0.01
	<30	3273 (32)	2273 (36)	1000 (25)	<0.01
	30–34	3673 (36)	2154 (34)	1519 (39)	
	>34	3384 (33)	1960 (31)	1424 (36)	
Body mass index before pregnancy (kg/m^2)	<18.5	1636 (16)	1007 (16)	629 (16)	0.04
	18.5–24.9	7585 (75)	4640 (74)	2945 (76)	
	>24.9	960 (9)	640 (10)	320 (8)	
Influenza-related high-risk conditions	Present	2321 (22)	1456 (23)	865 (22)	0.31
Underlying obstetric and gynecological illness	Present	1916 (19)	1075 (17)	841 (21)	<0.01
Pregnancy-induced complications		*n*/*N* (%)	*n*/*N* (%)	*n*/*N* (%)	
Multiple pregnancy	Present	149/10 328 (1)	91/6386 (1)	58/3942 (1)	0.85
Pregnancy-induced hypertension	Present	338/10 302 (3)	234/6367 (4)	104/3935 (3)	<0.01
Gestational diabetes	Present	276/10 322 (3)	185/6383 (3)	91/3939 (2)	0.07
Hospitalization due to threatened miscarriage	Present	526/10 318 (5)	324/6379 (5)	202/3939 (5)	0.91
Placenta previa	Present	41/10 325 (0.4)	28/6384 (0.4)	13/3941 (0.3)	0.39
Fetal growth restriction	Present	271/10 315 (3)	190/6377 (3)	81/3938 (2)	<0.01
Abruptio placentae	Present	36/10 324 (0.4)	25/6384 (0.4)	11/3940 (0.3)	0.35
Intrauterine infection	Present	81/10 313 (1)	54/6376 (1)	27/3937 (1)	0.37
Smoking habit	Present during pregnancy	306/9645 (3)	261/5983 (4)	45/3662 (1)	<0.01
Alcohol drinking habit	Present during pregnancy	66/9661 (0.7)	54/5996 (0.9)	12/3665 (0.3)	<0.01

[a] Data are expressed as the number (%) unless indicated otherwise.

Table 2
Birth outcomes of the study subjects.[a]

Birth outcomes		Total *n* (%)	Unvaccinated *n* (%)	Vaccinated *n* (%)	*p*-Value
Pregnancy outcomes	Live birth	10 305 (99.8)	6370 (99.7)	3935 (99.8)	0.38
	Miscarriage	11 (0.1)	6 (0.1)	5 (0.1)	
	Stillbirth	14 (0.1)	11 (0.2)	3 (0.1)	
Gestational age at delivery (weeks)	22–36 (preterm birth)	421 (4.1)	258 (4.1)	163 (4.2)	0.81
	37–41	9839 (95.5)	6084 (95.5)	3755 (95.4)	
	42+	45 (0.4)	28 (0.4)	17 (0.4)	
Birth weight (g)	Median (range)	3030 (428–4670)	3032 (484–4670)	3030 (428–4615)	0.39
	<2500 (low birth weight)	812 (7.9)	531 (8.3)	281 (7.1)	0.03
	≥2500	9493 (92.1)	5839 (91.7)	3654 (92.9)	
Apgar score at 1 min	0–3	58 (0.6)	43 (0.7)	15 (0.4)	0.01
	4–6	155 (1.5)	105 (1.7)	50 (1.3)	
	7–10	10 078 (97.9)	6212 (97.7)	3866 (98.3)	
Apgar score at 5 min	0–3	10 (0.1)	8 (0.1)	2 (0.1)	0.16
	4–6	32 (0.3)	22 (0.3)	10 (0.3)	
	7–10	10 233 (99.6)	6323 (99.5)	3910 (99.7)	

[a] Data are expressed as the number (%) unless indicated otherwise.

Olsen et al., 2016; Omon et al., 2011; Oppermann et al., 2012; Oskovi Kaplan and Ozgu-Erdinc, 2018; Pasternak et al., 2012; Regan et al., 2016; Steinhoff et al., 2017; Sugiura-Ogasawara et al., 2019; Vazquez-Benitez et al., 2016). In a previous case–control study, no association was identified between influenza vaccination during pregnancy and miscarriage (Ludvigsson et al., 2013).

In general, concerns have been raised regarding the effect of maternal medications, including vaccination, on the fetus within the first trimester, since the first trimester is a crucial period for embryogenesis of the major organs. However, the present study showed that even pregnant women who received influenza vaccination during the first trimester showed similar incidences of miscarriage, stillbirth, preterm birth, low birth weight, and congenital malformations when compared with unvaccinated women. The results suggest no adverse influences on the fetus, even when providing influenza vaccination to pregnant women in the first trimester.

Besides, pregnant women who received influenza vaccination during the third trimester were less likely to have babies with low birth weight. This was an unexpected finding. One possible interpretation is that recent advances in medical checkups for pregnancy have enabled better diagnosis of fetal growth restriction during pregnancy. Pregnant women diagnosed with fetal growth restriction during the third trimester might thus have been reluctant to receive influenza vaccination. Such a difference in vaccination behavior might result in apparent increases in babies with low birth weight among unvaccinated pregnant women. However, the present study did not collect information about the

Table 3
Association between background characteristics including influenza vaccination and adverse birth outcomes.[a]

Characteristics		Outcomes *n*/*N* (%)	Univariate OR (95% CI) *p*-Value	Multivariate[b] OR (95% CI) *p*-Value
Total		997/10 330 (10)		
Influenza vaccination during pregnancy	Unvaccinated	641/6387 (10)	1.00	1.00
	Vaccinated	356/3943 (9)	0.89 (0.78–1.02)	0.90 (0.76–1.07)
			0.09	0.24
Gestational age at recruitment or vaccination (weeks)	<16 (first trimester)	291/2826 (10)	1.00	1.00
	16–27 (second trimester)	354/3328 (11)	1.04 (0.88–1.22)	1.25 (0.95–1.65)
			0.06	0.12
	>27 (third trimester)	352/4476 (8)	0.80 (0.68–0.94)	1.05 (0.73–1.51)
			<0.01	0.79
			(Trend $p < 0.01$)	(Trend $p = 0.89$)
Calendar month at pregnancy start	March–May (Spring)	358/3506 (10)	1.00	1.00
	June–August (Summer)	292/2908 (10)	0.98 (0.83–1.16)	1.01 (0.78–1.31)
			0.82	0.93
	September–November (Autumn)	213/1997 (11)	1.05 (0.88–1.26)	1.23 (0.86–1.76)
			0.59	0.25
	December–February (Winter)	134/1919 (7)	0.66 (0.54–0.81)	0.79 (0.60–1.03)
			<0.01	0.08
Age (years)	<30	264/3273 (8)	1.00	1.00
	30–34	380/3673 (10)	1.32 (1.12–1.55)	1.34 (1.09–1.64)
			<0.01	<0.01
	>34	353/3384 (10)	1.33 (1.12–1.57)	1.32 (1.06–1.63)
			<0.01	0.01
			(Trend $p < 0.01$)	(Trend $p = 0.01$)
Body mass index before pregnancy (kg/m^2)	<18.5	206/1636 (13)	1.44 (1.22–1.70)	1.45 (1.18–1.78)
			<0.01	<0.01
	18.5–24.9	689/7585 (9)	1.00	1.00
	>24.9	83/960 (9)	0.95 (0.75–1.20)	0.78 (0.55–1.09)
			0.66	0.14
			(Trend $p < 0.01$)	(Trend $p < 0.01$)
Influenza-related high-risk conditions	Absent	768/8009 (10)	1.00	1.00
	Present	229/2321 (10)	1.03 (0.88–1.21)	1.19 (0.95–1.50)
			0.69	0.13
Underlying illnesses in obstetrics and gynecology	Absent	787/8414 (9)	1.00	1.00
	Present	210/1916 (11)	1.19 (1.02–1.40)	0.97 (0.79–1.19)
			0.03	0.76
Pregnancy-induced complications				
Multiple pregnancy	Absent	894/10 179 (9)	1.00	1.00
	Present	102/149 (68)	22.5 (15.9–32.1)	14.8 (9.73–22.4)
			<0.01	<0.01
Pregnancy-induced hypertension	Absent	894/9964 (9)	1.00	1.00
	Present	99/338 (29)	4.21 (3.29–5.37)	3.81 (2.79–5.21)
			<0.01	<0.01
Gestational diabetes	Absent	957/10 046 (10)	1.00	1.00
	Present	37/276 (13)	1.47 (1.03–2.09)	1.41 (0.92–2.16)
			0.03	0.12
Hospitalization due to threatened miscarriage	Absent	821/9792 (8)	1.00	1.00
	Present	172/526 (33)	5.31 (4.37–6.46)	4.45 (3.49–5.68)
			<0.01	<0.01
Placenta previa	Absent	971/10 284 (9)	1.00	1.00
	Present	24/41 (59)	13.5 (7.25–25.3)	17.2 (8.38–35.1)
			<0.01	<0.01
Fetal growth restriction	Absent	768/10 044 (8)	1.00	1.00
	Present	224/271 (83)	57.6 (41.7–79.5)	66.1 (46.4–94.0)
			<0.01	<0.01
Abruptio placentae	Absent	982/10 288 (10)	1.00	1.00
	Present	13/36 (36)	5.36 (2.71–10.6)	6.22 (2.55–15.2)
			<0.01	<0.01
Intrauterine infection	Absent	977/10 232 (10)	1.00	1.00
	Present	15/81 (19)	2.15 (1.22–3.79)	2.13 (1.11–4.07)
			<0.01	0.02
Smoking habit	Absent	887/9339 (9)	1.00	1.00
	Present during pregnancy	43/306 (14)	1.56 (1.12–2.17)	1.45 (0.96–2.19)
			<0.01	0.08
Alcohol drinking habit	Absent	926/9595 (10)	1.00	1.00
	Present during pregnancy	6/66 (9)	0.94 (0.40–2.18)	1.15 (0.44–2.95)
			0.88	0.78

OR, odds ratio; CI, confidence interval.
[a] Miscarriage, stillbirth, preterm birth, or low birth weight were included.
[b] Model included variables in this table.

Table 4
Birth outcomes of study subjects according to trimester.

Birth outcomes		First trimester		*p*-Value	Second trimester		*p*-Value	Third trimester		*p*-Value
		Unvaccinated *n* (%)	Vaccinated *n* (%)		Unvaccinated *n* (%)	Vaccinated *n* (%)		Unvaccinated *n* (%)	Vaccinated *n* (%)	
Adverse birth outcomes[a]	Present	229 (13)	142 (13)	0.56	119 (11)	155 (10)	0.11	265 (9)	87 (6)	0.04
Pregnancy outcomes	Live birth	1697 (99.5)	1116 (99.6)	0.61	1733 (99.7)	1588 (99.9)	0.46	2940 (99.9)	1231 (99.9)	1.00
	Miscarriage	6 (0.4)	5 (0.4)		0 (0)	0 (0)		0 (0)	0 (0)	
	Stillbirth	2 (0.1)	0 (0)		5 (0.3)	2 (0.1)		4 (0.1)	1 (0.1)	
Preterm birth	Present	64 (4)	55 (5)	0.12	97 (6)	79 (5)	0.74	97 (3)	29 (3)	0.07
Low birth weight	Present	148 (9)	86 (8)	0.34	155 (9)	125 (8)	0.27	228 (8)	70 (6)	0.02
Congenital malformation	Present	55 (3.2)	33 (3.0)	0.67	–	–		–	–	
Categories by organ system	Central nervous system	0 (0)	1 (0.1)	0.25						
	Ophthalmological, otological or orofacial	1 (0.1)	3 (0.3)							
	Cardiac	7 (0.4)	3 (0.3)							
	Respiratory	0 (0)	1 (0.1)							
	Cleft lip and/or cleft plate	1 (0.1)	1 (0.1)							
	Gastrointestinal	0 (0)	1 (0.1)							
	Genitourinary or renal	5 (0.3)	2 (0.2)							
	Muscular or limb defects	7 (0.4)	1 (0.1)							
	Others	0 (0)	1 (0.1)							
	Unknown	34 (2.0)	19 (1.7)							

[a] Miscarriage, stillbirth, preterm birth, low birth weight, or congenital malformation were included for women in the first trimester. For women in the second or third trimester, miscarriage, stillbirth, preterm birth, or low birth weight were included.

timing of diagnoses of fetal growth restriction. It is thus difficult to determine how such diagnoses affected the vaccination behaviors of pregnant women.

Various limitations need to be considered when interpreting the results of this study. First, to increase the response rate, we decided to collect information on vaccination month instead of vaccination date, resulting in the exclusion of 301 vaccinated women who had received vaccination in the same month as the delivery. Besides, the trimester at vaccination for vaccinated women might have been misclassified into the neighboring category in some subjects, since calculations were made using information on the month of vaccination, date of recruitment, and gestational week at recruitment, and the date of vaccination was regarded as the 15th of each month. Since we lacked accurate information on the date of vaccination from the clinic at which patients received vaccination, this represents the most important limitation of the present study.

Second, since information on vaccination status and explanatory variables was based on self-reports from pregnant women, some data such as body weight before pregnancy, smoking, and alcohol drinking status might have been underreported. However, the present design using a prospective cohort study is less susceptible to misclassification due to recall errors than a case–control study design. Besides, to confirm the accuracy of self-reported data, the date of delivery and birth weight, which were obtained using two methods (self-report and obstetrician report), were examined by comparing information from both sources. Among the subjects for whom the date of delivery was available from both self-report and obstetrician report ($n = 8227$), the correlation coefficient between self-report and obstetrician report was 0.988 ($p < 0.01$). Among subjects for whom birth weight was available from both reports ($n = 8273$), the correlation coefficient was 1.000 ($p < 0.01$). Based on these confirmations, the self-reported information used in the present study was expected to be relatively reliable.

Third, the subjects analyzed comprised 10 330 women who answered the post-season questionnaire and had birth outcomes provided by their obstetricians, from among the 20 420 women recruited before the season. This follow-up proportion might have affected the study results. For example, if women who experienced miscarriage or stillbirth as the pregnancy outcome tended to be less likely to answer the post-season questionnaire, a selection bias for study subjects would have been present. Actually, considering the number of stillbirths and livebirths in Osaka of 1621 and 69 968 in 2014 (Håberg et al., 2013), the proportion of miscarriage or stillbirth among the present study subjects (0.1%) appeared lower than among the general population (2%). On the other hand, the proportions of preterm birth, low birth weight, or congenital malformation in Japan were reported as 5.1%, 8.3%, and 3–5%, respectively, in 2013 (Nordin et al., 2014b), representing proportions broadly comparable to those in the present study. The possibility of selection bias thus appears low in the assessment of preterm birth, low birth weight, or congenital malformations, but the possibility of selection bias due to study dropout in the assessments of miscarriage or stillbirth cannot be ruled out.

Fourth, since the study subjects were pregnant women under clinical follow-up at obstetric facilities in Osaka Prefecture before the beginning of the 2013/14 influenza season, some concerns remain about the generalizability of the results. Further investigations of different seasons and regions is desirable to confirm the validity of the present study findings.

This study has the following strengths. First, with the cooperation of the Obstetrical Gynecological Society of Osaka, it was possible to investigate the safety of influenza vaccination among pregnant women in a large cohort exceeding 10 000 study subjects, covering 15% of pregnant women in the study area. This also enabled the examination of the effects of the timing of influenza vaccination on adverse birth outcomes. Second, since information on pregnancy outcomes was based on reports from the obstetricians of the study subjects, the accuracy of information was considered high. In fact, the proportions of preterm birth, low birth weight, congenital malformations, and pregnancy-induced complications in the present study were comparable to those of the general population in Japan (Munoz et al., 2005; Nordin et al., 2014b; Sheffield et al., 2012). Additionally, maternal age, BMI, and the proportion of smokers during pregnancy were similar in another study in Japan (Munoz et al., 2005). In addition, the present study detected known risk factors for adverse birth outcomes, such as maternal age, pregnancy-induced complications, and smoking during pregnancy (Irving et al., 2013). These findings suggest the reliability of the study results.

In conclusion, this cohort study indicates that influenza vaccination of pregnant women had no adverse effects on the fetus regardless of the trimester in which the vaccination was performed. The safety of influenza vaccination among pregnant women in Japan was also suggested.

Funding

This work was supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare, Japan (H23-SHINKO-IPPAN-017 and H26-SHINKOGYOSEI-SHITEI-003).

Conflict of interest

SO reports personal fees from speaking and/or teaching arrangements, outside the submitted work; TK reports personal fees from the BIKEN Foundation, outside the submitted work; WF reports personal fees from royalties, personal fees from consulting, personal fees from speaking and/or teaching arrangements, personal fees from scientific advisory committee, and grants outside the submitted work; YH reports grants from the Ministry of Health, Labor, and Welfare, during the conduct of the study; all other authors declare no conflicts of interest.

Author contributions

SO contributed to the study design, data management, statistical analysis, data interpretation, and drafting of the work or revising it critically for important intellectual content. MD, DT, MK, TT, and all members listed in the Appendix contributed to data acquisition and data interpretation. TY and AU contributed to the study design and data management. KI, TK, AM, KK, and WF contributed to the study design and data interpretation. YH contributed to the conception of the design, overall management, data interpretation, and manuscript editing. All authors provided comments on the drafts and have read and approved the final manuscript.

Acknowledgements

We thank all the medical doctors involved for participating in this study despite their busy schedules in medical practice, education, and research.

Appendix A.

Other members of the Osaka Pregnant Women Influenza Study Group are as follows (shown in alphabetical order of affiliation): Shiro Imai (Department of Gynecology and Obstetrics, Aizenbashi Hospital), Eiko Akagaki (Akagaki Ladies Clinic), Mariko Akai (Akai Maternity Clinic), Yoshitsune Azuma (Azuma Ladies Clinic), Shinichi Hamada (Department of Obstetrics and Gynecology, Bell Land General Hospital), Satoru Motoyama (Department of Obstetrics and Gynecology, Chibune General Hospital), Hiroko Chimori (Chimori Medical Clinic), Shoko Nakagawa (Department of Obstetrics and Gynecology, Fuchu Hospital), Takehiko Fukuda (Fukuda Lady's Clinic), Masahisa Hagiwara (Hagiwara Clinic), Hideto Okuda (Hamada Women's Hospital), Takuro Hamanaka (Hamanaka Obstetrics and Gynecology), Seiichi Yamamasu (Obstetrics and Gynecology, Hannan Chuo Hospital), Kenji Hirota (Obstetrics and Gynecology, Hanwasumiyoshi General Hospital), Masataka Oku (Obstetrics and Gynecology, Higashi Osaka City General Hospital), Keizo Hiramatsu (Hiramatsu Obstetrics and Gynecology Clinic), Masanori Hisamatsu (Hisamatsu Maternity Clinic), Yasushi Iijima (Iijima Women's Hospital), Mikio Takehara (Department of Obstetrics and Gynecology, Ikeda City Hospital), Somei Ikeda (Ikeda OB/GYN Clinic), Takeshi Inoue (Inoue Lady's Clinic), Eriko Yamashita (Ishida Hospital), Aisaku Fukuda (The Centre for Reproductive Medicine and Infertility, IVF Osaka Clinic), Itsuko Iwata (Iwata Clinic), Junko Nishio (Department of Obstetrics and Gynecology, Izumiotsu Municipal Hospital), Tateki Tsutsui (Department of Obstetrics and Gynecology, Japan Community Healthcare Organization Osaka Hospital), Kenji Yamaji (Kajimoto Clinic), Takao Kamiya (Kamiya Ladies Clinic), Atsushi Kasamatsu (Department of Obstetrics and Gynecology, Kansai Medical University Hirakata Hospital), Tatsuya Nakajima (Department of Obstetrics and Gynecology, Kansai Medical University Takii Hospital), Kanji Kasahara (Kasahara Clinic), Kenjitsu Kasamatsu (Kasamatsu Obstetrics and Gynecology/Pediatrics), Kawabata Ryoichi (Kawabata Lady's Clinic), Kazume Kawabata (Kawabata Women's Clinic), Kozo Kadowaki (Department of Obstetrics and Gynecology, Kawachi General Hospital), Hiroshi Nomura (Kawashima Ladies Clinic), Tomoyuki Kikuchi (Kikuchi Ladies Clinic), Ayako Suzuki (Department of Obstetrics and Gynecology, Kinki University), Tadayoshi Nagano (Department of Obstetrics and Gynecology, Kitano Hospital), Yoshitsugu Komeda (Komeda Ladies Clinic), Ryousuke Kondo (Kondo Ladies Clinic), Shinjin Konishi (Konishi Ladies Clinic), Hideo Takemura (Kosaka Women's Hospital), Masako Kasumi (Masako Ladies Clinic), Kazuo Masuhiro (Masuhiro Maternity Clinic), Ryoji Ito (Department of Obstetrics and Gynecology, Matsushita Memorial Hospital), Yoshiki Sakamoto (Department of Obstetrics and Gynecology, Mimihara General Hospital), Kouzo Hirai (Minami-Morimachi Ladies Clinic), Yoshimitsu Yamamoto (Department of Obstetrics and Gynecology, Minoh City Hospital), Yoshitaka Kariya (Minoh Ladies Clinic), Osamu Misaki (Misaki Clinic), Akira Miyake (Miyake Clinic), Yasuko Osako (Mom Women's Clinic Osako), Masao Mori (Mori Obstetrics and Gynecology Clinic), Keizo Naka (Naka Ladies Clinic), Yasumasa Tokura (Nakai Clinic), Jun Yoshimatsu (Department of Perinatology and Gynecology, National Cerebral and Cardiovascular Center), Keiji Tatsumi (Department of Obstetrics and Gynecology, National Hospital Organization Osaka National Hospital), Takayoshi Kanda (Department of Obstetrics and Gynecology, National Hospital Organization Osaka Minami Medical Center), Masahiro Nishikawa (Nishikawa Ladies Clinic), Sekio Nishimoto (Nishimoto Ladies Clinic), Yoshihiro Nishioka (Nishioka Clinic), Takao Funato (Department of Obstetrics and Gynecology, Nissay Hospital), Kouichi Nozaki (Nozaki Ladies Clinic), Gengo Ohira (Ohira Ladies Clinic), Yoshiyuki Okamura (Okamura Ladies Clinic), Yuzo Oga (Oga Clinic), Osamu Nakamoto (Department of Obstetrics and Gynecology, Osaka City General Hospital), Shinichi Nakata (Department of Obstetrics and Gynecology, Osaka City Juso Hospital), Tetsuo Nakamura (Department of Obstetrics and Gynecology, Osaka City Sumiyoshi Hospital), Masahiko Takemura (Department of Obstetrics and Gynecology, Osaka General Medical Center), Toshiyuki Sadou (Department of Obstetrics and Gynecology, Osaka Gyoumeikan Hospital), Nobuaki Mitsuda (Department of Obstetrics, Osaka Medical Center and Research Institute for Maternal and Child Health), Daisuke Fujita (Department of Obstetrics and Gynecology, Osaka Medical College), Koji Hisamoto (Department of Obstetrics and Gynecology, Osaka Police Hospital), Shinobu Akada (Department of Obstetrics and Gynecology, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases), Takafumi Nonogaki, Chinami Horiuchi (Department of Obstetrics and Gynecology, Osaka Red Cross Hospital), Yasuhiko Shiki (Department of Obstetrics and Gynecology, Osaka Rousai Hospital), Tadashi Kimura (Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine), Koutaro Kitamura (Obstetrics and Gynecology, PL Hospital), Kazuhide Ogita (Department of Obstetrics and Gynecology, Rinku General Medical Center),

Shigeki Matsuo (Saint Barnabas Hospital), Yoshihito Ikeda (Department of Obstetrics and Gynecology, Saiseikai Ibaraki Hospital), Akihiro Moriyama (Department of Obstetrics and Gynecology, Saiseikai Nakatsu Hospital), Yukiyoshi Ishikawa (Department of Obstetrics and Gynecology, Saiseikai Noe Hospital), Hiroshi Muso (Department of Obstetrics and Gynecology, Saiseikai Senri Hospital), Fuminori Kitada (Department of Obstetrics and Gynecology, Saiseikai Suita Hospital), Toshiya Yamamoto (Department of Obstetrics and Gynecology, Sakai City Hospital), Megumi Takemura (Department of Obstetrics and Gynecology, Sakibana Hospital), Takeshi Sawada (Sawada Ladies Clinic), Kentaro Shimura (Shimura Women's Clinic), Koh Shinyashiki (Shinyashiki Obstetrics and Gynecology), Mitsuhiko Masuda (Department of Obstetrics and Gynecology, Shiseikai Corporate Juridical Person), Tsuneo Shoda (Shoda Medical Clinic), Takamichi Nishizaki (Department of Obstetrics and Gynecology, Suita Municipal Hospital), Yoshinori Suzuki (Suzuki Clinic), Isao Suzuki (Suzuki Obstetrics and Gynecology), Hiroshi Nanjyo (Department of Obstetrics and Gynecology, Taisho Hospital), Keiko Takabatake (Takabatake Women's Clinic), Kikuya Takase (Takase Ladies Clinic), Satoshi Nakago (Department of Obstetrics and Gynecology, Takatsuki General Hospital), Jun Takeyama (Takeyama Ladies Clinic), Takeshi Taniguchi (Taniguchi Hospital), Keiichi Tasaka (Tasaka Clinic), Toshiaki Tatsumi (Tatsumi Ladies Clinic), Atsushi Tokuhira (Department of Obstetrics and Gynecology, Toyonaka Municipal Hospital), Shogo Tsubokura (Tsubokura Women's Clinic), Kayoko Ueda (Ueda Ladies Clinic), Yukiko Uenae (Uenae Ladies Clinic), Takahiko Unno (Unno Maternity Clinic), Hiroshi Yabuki (Yabuki Maternity Clinic), Tokihiro Yanamoto (Yanamoto Maternity Clinic), Yoshihiko Yamada (Department of Obstetrics and Gynecology, Yao Municipal Hospital), Nobuyuki Maruo (Department of Obstetrics and Gynecology, Yodogawa Christian Hospital), Yoshitsugu Takada (Department of Obstetrics and Gynecology, Yoshikawa Hospital).

References

Baum U, Leino T, Gissler M, Kilpi T, Jokinen J. Perinatal survival and health after maternal influenza A(H1N1)pdm09 vaccination: a cohort study of pregnancies stratified by trimester of vaccination. Vaccine 2015;33:4850–7.

Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. Clin Infect Dis 2010;51:1355–61.

Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. Am J Perinatol 2004;21:333–9.

Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices — United States, 2013–14. MMWR Recomm Rep 2013;62:1–43.

Chambers CD, Johnson D, Xu R, Luo Y, Louik C, Mitchell AA, et al. Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants. Vaccine 2013;31:5026–32.

Chambers CD, Johnson DL, Xu R, Luo YJ, Louik C, Mitchell AA, et al. Safety of the 2010-11, 2011-12, 2012-13, and 2013-14 seasonal influenza vaccines in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS. Vaccine 2016;34:4443–9.

Cleary BJ, Rice Ú, Eogan M, Metwally N, McAuliffe F. 2009 A/H1N1 influenza vaccination in pregnancy: uptake and pregnancy outcomes – a historical cohort study. Eur J Obstet Gynecol Reprod Biol 2014;178:163–8.

de Vries L, van Hunsel F, Cuppers-Maarschalkerweerd B, van Puijenbroek E, van Grootheest K. Adjuvanted A/H1N1 (2009) influenza vaccination during pregnancy: description of a prospective cohort and spontaneously reported pregnancy-related adverse reactions in the Netherlands. Birth Defects Res A Clin Mol Teratol 2014;100:731–8.

Fabiani M, Bella A, Rota MC, Clagnan E, Gallo T, D'Amato M, et al. A/H1N1 pandemic influenza vaccination: a retrospective evaluation of adverse maternal, fetal and neonatal outcomes in a cohort of pregnant women in Italy. Vaccine 2015;33:2240–7.

Fell DB, Sprague AE, Liu N, Yasseen 3rd AS, Wen SW, Smith G, et al. Better Outcomes Registry & Network (BORN) Ontario. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. Am J Public Health 2012;102: e33–40.

Fell DB, Savitz DA, Kramer MS, Gessner BD, Katz MA, Knight M, et al. Maternal influenza and birth outcomes: systematic review of comparative studies. BJOG 2017;124:48–59.

Håberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. N Engl J Med 2013;368:333–40.

Hanley SJ, Yoshioka E, Ito Y, Kishi R. HPV vaccination crisis in Japan. Lancet 2015;385:2571.

Irving SA, Kieke BA, Donahue JG, Mascola MA, Baggs J, DeStefano F, et al. Vaccine safety datalink. Trivalent inactivated influenza vaccine and spontaneous abortion. Obstet Gynecol 2013;121:159–65.

Källén B. The problem of confounding in studies of the effect of maternal drug use on pregnancy outcome. Obstet Gynecol Int 2012;2012:148616.

Kharbanda EO, Vazquez-Benitez G, Romitti PA, Naleway AL, Cheetham TC, Lipkind HS, et al. Vaccine safety datalink. First trimester influenza vaccination and risks for major structural birth defects in offspring. J Pediatr 2017;187:234–9.

Ludvigsson JF, Zugna D, Cnattingius S, Richiardi L, Ekbom A, Örtqvist Å, et al. Influenza H1N1 vaccination and adverse pregnancy outcome. Eur J Epidemiol 2013;28:579–88.

Ma F, Zhang L, Jiang R, Zhang J, Wang H, Gao X, et al. Prospective cohort study of the safety of an influenza A(H1N1) vaccine in pregnant Chinese women. Clin Vaccine Immunol 2014;21:1282–7.

Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014;371:918–31.

McHugh L, Andrews RM, Lambert SB, Viney KA, Wood N, Perrett KP, et al. Birth outcomes for Australian mother-infant pairs who received an influenza vaccine during pregnancy, 2012-2014: the FluMum study. Vaccine 2017;35:1403–9.

Michikawa T, Nitta H, Nakayama SF, Yamazaki S, Isobe T, Tamura K, et al. Baseline profile of participants in the Japan environment and children's study (JECS). J Epidemiol 2018;28:99–104.

Morisaki N, Ganchimeg T, Vogel JP, Zeitlin J, Cecatti JG, Souza JP, et al. Impact of stillbirths on international comparisons of preterm birth rates: a secondary analysis of the WHO multi-country survey of Maternal and Newborn Health. BJOG 2017;124:1346–54.

Munoz FM, Greisinger AJ, Wehmanen OA, Mouzoon ME, Hoyle JC, Smith FA, et al. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2005;192:1098–106.

Nakayama T. Causal relationship between immunological responses and adverse reactions following vaccination. Vaccine 2019;37:366–71.

Nordin JD, Kharbanda EO, Vazquez-Benitez G, Lipkind H, Lee GM, Naleway AL. Monovalent H1N1 influenza vaccine safety in pregnant women, risks for acute adverse events. Vaccine 2014a;32:4985–92.

Nordin JD, Kharbanda EO, Vazquez Benitez G, Lipkind H, Vellozzi C, Destefano F, et al. Maternal influenza vaccine and risks for preterm or small for gestational age birth. J Pediatr 2014b;164: 1051-1057.e2..

Ohfuji S, Deguchi M, Tachibana D, Koyama M, Takagi T, Yoshioka T, et al. Protective effect of maternal influenza vaccination on influenza in their infants: a prospective cohort study. J Infect Dis 2018;217:878–86.

Olsen SJ, Mirza SA, Vonglokham P, Khanthamaly V, Chitry B, Pholsena V, et al. The effect of influenza vaccination on birth outcomes in a cohort of pregnant women in Lao PDR, 2014-2015. Clin Infect Dis 2016;63:487–94.

Omon E, Damase-Michel C, Hurault-Delarue C, Lacroix I, Montastruc JL, Oustric S, et al. Non-adjuvanted 2009 influenza A (H1N1)v vaccine in pregnant women: the results of a French prospective descriptive study. Vaccine 2011;29:9649–54.

Oppermann M, Fritzsche J, Weber-Schoendorfer C, Keller-Stanislawski B, Allignol A, Meister R, et al. A(H1N1)v2009: a controlled observational prospective cohort study on vaccine safety in pregnancy. Vaccine 2012;30:4445–52.

Osaka City. Vital statistics: annual number of stillbirth and the proportion (in Japanese).http://www.city.osaka.lg.jp/kenko/cmsfiles/contents/0000277/277916/15H29-06sizannsibou.pdf (Accessed 22 January 2019).

Oskovi Kaplan ZA, Ozgu-Erdinc AS. Prediction of preterm birth: maternal characteristics, ultrasound markers, and biomarkers: an updated overview. J Pregnancy 2018;2018:8367571.

Pasternak B, Svanström H, Mølgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy. JAMA 2012;308:165–74.

Prospero E, Galmozzi S, Paris V, Felici G, Barbadoro P, D'Alleva A, et al. Factors influencing refusing of flu vaccination among pregnant women in Italy: healthcare workers' role. Influenza Other Respi Viruses 2019;13:201–7.

Regan AK, Moore HC, de Klerk N, Omer SB, Shellam G, Mak DB, et al. Seasonal trivalent influenza vaccination during pregnancy and the incidence of stillbirth: population-based retrospective cohort study. Clin Infect Dis 2016;62:1221–7.

Sepkowitz S. International rankings of infant mortality and the United States' vital statistics natality data collecting system–failure and success. Int J Epidemiol 1995;24:583–8.

Sheffield JS, Greer LG, Rogers VL, Roberts SW, Lytle H, McIntire DD, et al. Effect of influenza vaccination in the first trimester of pregnancy. Obstet Gynecol 2012;120:532–7.

Steinhoff MC, Omer SB, Roy E, El Arifeen S, Raqib R, Dodd C, et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. CMAJ 2012;184:645–53.

Steinhoff MC, Katz J, Englund JA, Khatry SK, Shrestha L, Kuypers J, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. Lancet Infect Dis 2017;17:981–9.

Sugiura-Ogasawara M, Ebara T, Yamada Y, Shoji N, Matsuki T, Kano H, et al. Adverse pregnancy and perinatal outcome in patients with recurrent pregnancy loss: multiple imputation analyses with propensity score adjustment applied to a large-scale birth cohort of the Japan Environment and Children's Study. Am J Reprod Immunol 2019;81:e13072.

Vazquez-Benitez G, Kharbanda EO, Naleway AL, Lipkind H, Sukumaran L, McCarthy NL, et al. Risk of preterm or small-for-gestational-age birth after influenza vaccination during pregnancy: caveats when conducting retrospective observational studies. Am J Epidemiol 2016;184:176–86.

World Health Organization. Vaccines against influenza WHO position paper – November 2012. Weekly Epidemiol Rec 2012;87:461–76.

Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med 2008;359:1555–64.

The Journal of Infectious Diseases

MAJOR ARTICLE

Protective Effect of Maternal Influenza Vaccination on Influenza in Their Infants: A Prospective Cohort Study

Satoko Ohfuji,[1,2] Masaaki Deguchi,[4] Daisuke Tachibana,[3] Masayasu Koyama,[3] Tetsu Takagi,[5] Takayuki Yoshioka,[6] Akinori Urae,[8] Kazuya Ito,[1,2] Tetsuo Kase,[1,2] Akiko Maeda,[1] Kyoko Kondo,[7] Wakaba Fukushima,[1,2] and Yoshio Hirota,[1,9,10] for the Osaka Pregnant Women Influenza Study Group[a]

[1]Department of Public Health, [2]Research Center for Infectious Disease Sciences, and [3]Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine, [4]Department of Obstetrics and Gynecology, Kishiwada City Hospital, [5]Takagi Ladies Clinic, [6]Osaka Branch, Mediscience Planning, and [7]Osaka City University Hospital, Osaka, [8]Head Office, Mediscience Planning, Tokyo, and [9]College of Healthcare Management and [10]Clinical Epidemiology Research Center, SOUSEIKAI Global Clinical Research Center, Fukuoka, Japan.

Background. Infants <6 months of age are too young to receive influenza vaccine, despite being at high risk for severe influenza-related complications.

Methods. To examine the effectiveness of maternal influenza vaccination in preventing influenza in their infants, we conducted a prospective cohort study of 3441 infants born at participating hospitals before the 2013–2014 influenza season. At the time of recruitment, their mothers completed a questionnaire about influenza vaccination status for the 2013–2014 season. A follow-up survey was conducted after the end of the 2013–2014 season to collect information regarding influenza diagnosis and hospitalization among infants.

Results. During the 2013–2014 influenza season, 71 infants (2%) had influenza diagnosed, and 13 infants (0.4%) were hospitalized with influenza. Maternal influenza vaccination (especially prenatal vaccination) decreased the odds of influenza among infants. The effectiveness of prenatal vaccination was 61% (95% confidence interval, 16%–81%), whereas that of postpartum vaccination was 53% (−28%–83%). Although maternal influenza vaccination was also associated with a decreased odds of influenza-related hospitalization among infants, vaccine effectiveness (73%) did not reach statistical significance, owing to the limited number of infants hospitalized because of influenza.

Conclusions. The present findings indicated that pregnant women and postpartum women should receive influenza vaccination to protect their infants.

Keywords. Influenza; infants; maternal vaccination; prospective cohort study; vaccine effectiveness.

Infants <6 months of age are too young to receive the influenza vaccine, despite being at high risk for severe influenza-related complications. In the United States, to protect these infants, influenza vaccination has been recommended for individuals who live with or care for these infants, particularly their mothers [1]. In addition, the World Health Organization issued a position paper recommending that pregnant women be accorded the highest priority for seasonal influenza vaccination, owing to expectations of vaccine effectiveness in preventing influenza in mothers and their infants [2].

However, to our knowledge, only 7 studies have reported the effectiveness of maternal influenza vaccination for influenza in infants <6 months of age [3–9]. Moreover, these previous studies have reported inconsistent results. Four studies indicated significant vaccine effectiveness in preventing infant influenza and its related hospitalization [3–6], while the remaining 3 studies did not indicate any effectiveness of maternal influenza vaccination [7–9]. We believe there could be several possible reasons for this inconsistency. Since the previous studies focused on the effectiveness of vaccination of pregnant women, they might not have taken the possible effects of vaccination of postpartum women into consideration. Influenza vaccination of postpartum women may prevent influenza among mothers, which may contribute to protecting their infants from influenza. If, however, these postpartum-vaccinated women were classified as unvaccinated women, it would lead to underestimation of the effectiveness of maternal influenza vaccination. In addition, studies that used acute febrile respiratory illness rather than laboratory-confirmed influenza as a study outcome may have included noninfluenza cases, so that the resultant outcome misclassification would make it more difficult to detect vaccine effectiveness.

Thus, in the present prospective cohort study, which investigated the effectiveness of maternal influenza vaccination in preventing infant influenza and its related hospitalization, maternal

Received 28 September 2017; editorial decision 27 November 2017; accepted 30 November 2017; published online December 5, 2017.

[a]Members of the study group are listed at the end of the text.

Correspondence: S. Ohfuji, MD, PhD, Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545–8585, Japan (satop@med.osaka-cu.ac.jp).

The Journal of Infectious Diseases® 2018;217:878–86

DOI: 10.1093/infdis/jix629

influenza vaccination was divided into prenatal vaccination and postpartum vaccination in the detailed analysis, and the effectiveness of vaccination during each period was estimated separately. In addition, although we used pediatrician-diagnosed influenza as the main study outcome, we considered it an appropriate substitute for laboratory-confirmed influenza because the influenza rapid diagnostic test is routinely performed for infants who visit pediatric hospitals and clinics for medical treatment of acute febrile respiratory illnesses during the influenza season in Japan.

METHODS

Participants

This study was conducted with the cooperation of the 117 maternity hospitals and clinics affiliated with the Obstetrical Gynecological Society of Osaka, Japan. To enroll infants born at the collaborating hospitals and clinics before the start of the 2013–2014 influenza season, 10 720 pregnant women (regardless of gestational age) who were attending these hospitals and clinics between September 2013 and December 2013 were recruited to participate in the present study. At that time, 2812 women were in the first trimester, whereas 3585 and 4323 women were in the second and third trimesters, respectively. A total of 3841 infants were delivered by these women before the start of the 2013–2014 influenza season (ie, between October and December 2013) and were identified as study candidates. Mothers of the participating infants received an explanation of the study from their obstetrician and verbally provided informed consent prior to participation.

The study protocol was approved by the Ethics Committees at the Osaka City University Graduate School of Medicine and was performed in accordance with the Declaration of Helsinki.

Information Collection

At the time of recruitment, data on the following maternal characteristics were obtained by means of a self-administered questionnaire completed by each infant's mother: maternal age, height and weight before pregnancy, underlying illnesses, and influenza vaccination status for the 2013–2014 season.

With respect to the follow-up survey conducted after the 2013–2014 influenza season (ie, May 2014), the mothers were asked to fill out a mail-back questionnaire to collect the following information that had become available since the time of recruitment: for infants, the date and gestational week of birth, birth weight, daycare attendance, influenza diagnosis made by a pediatrician, and hospitalization; and for mothers, influenza vaccination history after recruitment and influenza diagnosis. Mothers of infants who had been hospitalized were also asked to provide the name of the disease that led to hospitalization and the name of the hospital. To confirm this self-reported information on hospitalization, we contacted the pediatricians at the relevant hospitals and asked them to provide the following information from the subject's hospital records: date of admission, date of discharge, name of disease that led to hospitalization, and laboratory data at the time of hospitalization.

In addition, to obtain clinical information about the infants' birth, the obstetrician caring for their mothers was asked to complete a structured questionnaire. The questionnaire gathered information about the infants' date and gestational week of birth, birth weight, presence of congenital malformation, and birth order (ie, the mother's parity status when the infant was delivered).

Statistical Analysis

As an exposure variable, the effect of maternal influenza vaccination was first investigated after categorizing mothers as unvaccinated or receiving vaccination and then after categorizing them as unvaccinated, receiving prenatal vaccination, or receiving postpartum vaccination.

The following 2 outcome measures for infants were used in the present study: pediatrician-diagnosed influenza and hospitalization due to an influenza diagnosis.

With regard to explanatory variables, maternal age was categorized as <29, 30–34, and ≥35 years. The following maternal influenza-related underlying conditions, based on a previous report, were included: chronic respiratory disorders (including asthma), cardiovascular disorders (excluding isolated hypertension), kidney disease, liver disease, neurological disorders, blood disorders, metabolic disorders (including diabetes), immunocompromised state (due to factors such as malignant tumors, connective tissue disorders, inflammatory bowel disease, and chronic rheumatism), and obesity (ie, a body mass index [calculated as the weight in kilograms divided by the height in meters squared] of ≥25.0) [1]. Data regarding the number of siblings of the infants were based on the mother's parity status recorded during the obstetrician-administered questionnaire.

A logistic regression model was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the associations between maternal influenza vaccination and the outcome measures. In the multivariate model, we included all variables in the univariate analyses that were related to both maternal vaccination status (ie, the exposure variable) and infant influenza diagnosis (ie, the outcome index) with P values of <.10. Furthermore, stratified analysis was conducted to examine whether the effectiveness of maternal influenza vaccination against influenza acquisition by their infants varied according to the maternal influenza diagnostic status in the relevant season. The χ^2 and Wilcoxon rank-sum tests were also used where appropriate. All analyses were 2-tailed and were conducted using SAS, version 9.3.

RESULTS

Among 3841 infants, incomplete data on the variables under study caused the exclusion of 400 infants, leaving 3441 infants (89.6%) for analysis. Table 1 shows the characteristics of the study infants and their mothers. Median maternal age was 32 years, and 22% of mothers had influenza-related underlying conditions. A total of 39% of mothers received the influenza vaccine for the 2013–2014 season, and 27% were vaccinated during their pregnancy. A total of 5% of study infants were born prematurely, whereas 9% had a low birth weight. Approximately half the infants had older siblings, and 8% began attending daycare facilities in the 2013–2014 season.

Table 2 shows the association between maternal influenza vaccination and select background characteristics. Unvaccinated mothers were younger than vaccinated mothers. In addition, infants' birth month appeared to affect the timing of maternal vaccination (ie, during the prenatal or postpartum periods). Preterm birth, low birth weight, and congenital malformations were more often observed in infants delivered by unvaccinated mothers. Vaccinated mothers were likely to be multipara, suggesting that their infants had at least 1 older sibling.

Table 1. Characteristics of the Study Infants and their Mothers

Characteristic	Study Subjects (n = 3441)
Among mothers	
Age, y	32 (17–49)
Presence of influenza-related underlying condition(s)	758 (22)
Influenza vaccination status for 2013–2014 season	
Unvaccinated	2101 (61)
Vaccinated	1340 (39)
Timing of influenza vaccination	
Prenatal	943 (27)
Postpartum	397 (12)
Receipt of influenza diagnosis during 2013–2014 season	152 (4)
Among infants	
Birth month	
October	886 (26)
November	1227 (36)
December	1328 (38)
Gestational week	
Overall	39.6 (23.1–42.4)
22–36	179 (5)
37–41	3244 (94)
≥42	18 (1)
Birth weight, g	
Overall	3024 (428–4716)
<2500	317 (9)
≥2500	3124 (91)
Congenital malformation	
Present	155 (5)
Older siblings, no.	
Absent	1825 (53)
1	1137 (33)
≥2	479 (14)
Attends daycare	260 (8)

Data are no. (%) of subjects or median value (range).

During the 2013–2014 influenza season, 71 infants (2%) had influenza diagnosed (Table 3). Univariate analysis revealed that maternal influenza vaccination had a decreasing effect on the occurrence of pediatrician-diagnosed influenza among infants. The proportion of infants with an influenza diagnosis was also lower among those born in December or with a low birth weight. On the other hand, maternal influenza diagnosis, presence of older siblings, and daycare attendance were associated with a higher risk of influenza among infants. Even after considering the effects of these potential confounding factors, maternal vaccination showed a decreasing OR for an influenza diagnosis among infants (OR, 0.42; 95% CI, .22–.78). In particular, prenatal vaccination was associated with a statistically significantly lower OR of 0.39 (95% CI, .19–.84). Although postpartum vaccination also showed a decreasing OR for influenza among infants, it did not reach statistically significant levels, owing to the limited number of study subjects. Conversely, a diagnosis of maternal influenza elevated the OR for a diagnosis of influenza in infants by 36-fold, implicating influenza in mothers as a strong risk factor for influenza virus infection in infants. In addition, the presence of older siblings or daycare attendance also increased the ORs for influenza among infants by approximately 2–3-fold.

Table 4 shows the association between infant hospitalization due to influenza and background characteristics, including maternal vaccination. In multivariate analysis, maternal vaccination decreased the OR for infant hospitalization due to influenza by approximately one fourth, with marginal statistical significance (OR, 0.27; 95% CI, .06–1.24). The OR of prenatal vaccination was also decreased to 0.33, which, however, was not statistically significant. We could not calculate the OR of postpartum vaccination, since there were no hospitalized cases in this category. On the other hand, maternal influenza was associated with a higher risk of infant hospitalization due to influenza, while a greater number of older siblings was also associated with an elevated OR for infant hospitalization. The ORs for these variables were 13.8 (95% CI, 4.42–42.9) and 6.88 (95% CI, 1.27–37.3), respectively.

The effect of maternal influenza vaccination was examined in terms of the status of maternal influenza diagnosis in the 2013–2014 season (Table 5). Among mothers with a diagnosis of influenza in the 2013–2014 season, the proportion of infants with influenza was 33% for unvaccinated mothers, 16% for those with a prenatal vaccination, and 16% for those with a postpartum vaccination. Among mothers without a diagnosis of influenza, the proportions of infants with influenza were much smaller (1% for unvaccinated mothers, 0.4% for those with a prenatal vaccination, and 0.8% for those with a postpartum vaccination).

Table 2. Association Between Maternal Influenza Vaccination and Select Background Characteristics, by Maternal Vaccination Status

Characteristic	Unvaccinated (n = 2101)	Prenatal Vaccination (n = 943)	Postpartum Vaccination (n = 397)	*P*
Among mothers				
Age, y	32 (17–49)	33 (19–47)	33 (17–46)	<.01
Presence of influenza-related underlying condition(s)	457 (22)	213 (23)	88 (22)	.87
Receipt of influenza diagnosis during 2013–2014 season	103 (5)	37 (4)	12 (3)	.17
Among infants				
Birth month				
October	567 (27)	53 (6)	266 (67)	<.01
November	765 (36)	345 (37)	117 (29)	
December	769 (37)	545 (58)	14 (4)	
Gestational week				
22–36	123 (6)	41 (4)	15 (4)	.02
37–41	1969 (94)	896 (95)	379 (95)	
≥42	9 (0.4)	6 (1)	3 (1)	
Birth weight, g				
<2500	215 (10)	74 (8)	28 (7)	.01
≥2500	1886 (90)	869 (92)	369 (93)	
Presence of congenital malformation	114 (5)	24 (3)	17 (4)	<.01
Older siblings, no.				
0	1217 (58)	423 (45)	185 (47)	<.01
1	597 (28)	387 (41)	153 (39)	
≥2	287 (14)	133 (14)	59 (15)	
Attends daycare	166 (8)	55 (6)	39 (10)	.03

Data are no. (%) of subjects or median value (range).

However, the ORs of maternal influenza vaccination were quite similar regardless of whether the mothers received a diagnosis of influenza. Regarding infant hospitalization due to influenza, stratified analysis could not provide meaningful results, since the number of infants hospitalized due to influenza was very limited.

DISCUSSION

The findings of the present study demonstrated that maternal influenza vaccination decreases the occurrence of influenza and its related hospitalization in their infants. Among infants, the vaccine effectiveness of maternal influenza vaccination was 58% (95% CI, 22%–78%) for pediatrician-diagnosed influenza and 73% (95% CI, −24%–94%) for influenza-related hospitalization. These results are consistent with those of previous studies conducted in other countries [3–6].

When we examined the effects of maternal vaccination by dividing it into prenatal vaccination and postpartum vaccination, prenatal vaccination seemed to be more effective in preventing influenza infection in infants; the effectiveness of prenatal vaccination for infants' pediatrician-diagnosed influenza was 61% (95% CI, 16%–81%) and that of postpartum vaccination was 53% (95% CI, −28%–83%). However, we did not conclude that postpartum vaccination had no effect on infant influenza, because the effectiveness of postpartum vaccination was 53% (point estimate) and the number of study subjects with postpartum vaccination was really smaller than the number of those with prenatal vaccination. It is therefore possible that the lack of statistical significance in the effectiveness of postpartum vaccination might have resulted from the lack of statistical power in our study.

There are 2 possible mechanisms for the observed effect of maternal influenza vaccination on decreasing the risk of influenza among infants. The first is through passive immunity, in which maternal antibodies produced in response to prenatal vaccination are transferred to the fetus via the umbilical cord and, thus, protect the infant from contracting influenza. Previous studies have reported this possibility by showing the presence of passive antibodies in umbilical cords and serum samples from infants [10–13]. The second mechanism is that vaccinated mothers have a lower risk of developing influenza, which secondarily results in a reduced risk of influenza among infants. In theory, since prenatal vaccination could have both of these effects and postpartum vaccination only includes the latter mechanism, the difference between the effectiveness of prenatal and postpartum vaccination is probably the effect of passive immunity. From this point of view, the effect of passive immunity could be calculated as only 8%, and the remaining 53% might be explained by the latter mechanism. Hence, prenatal vaccination is expected to be more effective for preventing influenza in infants because it exerts effects through both mechanisms described above. Prenatal vaccination is therefore considered preferable for preventing influenza among infants, although if mothers do not receive influenza vaccination during

Table 3. Association Between Subjects' Background Characteristics, Including Maternal Influenza Vaccination Status, and Pediatrician-Diagnosed Influenza in Infants

		Univariate		Multivariate[a]	
Characteristics	Influenza Cases, n/N (%)	OR (95% CI)	*P*	OR (95% CI)	*P*
Among mothers					
Age, y[b]					
<29	22/1043 (2)	1.07 (.60–1.91)	.81	…	
30–34	25/1269 (2)	1.00		…	
≥35	24/1129 (2)	1.08 (.61–1.90)	.79	…	
Influenza-related underlying conditions					
Absent	59/2683 (2)	1.00		…	
Present	12/758 (2)	0.72 (.38–1.34)	.30	…	
Influenza vaccination during 2013–2014 season					
Absent	56/2101 (3)	1.00		1.00	
Present	15/1340 (1)	0.41 (.23–.73)	<.01	0.42 (.22–.78)	<.01
Timing of influenza vaccination					
Prenatal	10/943 (1)	0.39 (.20–.77)	<.01	0.39[c] (.19–.84)	.02
Postpartum	5/397 (1)	0.47 (.19–1.17)	.10	0.47[c] (.17–1.28)	.14
Influenza diagnosis during 2013–2014 season					
Absent	29/3289 (1)	1.00		1.00	
Present	42/152 (28)	42.9 (25.8–71.5)	<.01	36.0 (21.1–61.4)	<.01
Among infants					
Birth month					
October	24/886 (3)	1.00		1.00	
November	31/1227 (3)	0.93 (.54–1.60)	.80	0.99 (.53–1.82)	.96
December	16/1328 (1)	0.44 (.23–.83)	.01	0.50 (.25–1.01)	.05
Birth weight, g					
<2500	2/317 (1)	0.28 (.07–1.15)	.08	0.26 (.06–1.16)	.08
≥2500	69/3124 (2)	1.00		1.00	
Congenital malformation					
Absent	69/3286 (2)	1.00		…	
Present	2/155 (1)	0.61 (.15–2.51)	.49	…	
Older siblings, no.[d]					
0	17/1825 (1)	1.00		1.00	
1	33/1137 (3)	3.18 (1.76–5.73)	<.01	2.02 (1.06–3.85)	.03
≥2	21/479 (4)	4.88 (2.55–9.32)	<.01	3.29 (1.61–6.71)	<.01
Daycare attendance					
Absent	59/3181 (2)	1.00		1.00	
Present	12/260 (5)	2.56 (1.36–4.83)	<.01	2.05 (.98–4.32)	.06

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Model includes variables in this table.

[b]In univariate analysis, P_{trend} = .46.

[c]The OR was obtained from the model in which maternal influenza vaccination status during the 2013–2014 influenza season (ie, unvaccinated or vaccinated) was replaced by maternal vaccination status that included stratification of vaccination timing (ie, unvaccinated, prenatal vaccination, or postpartum vaccination).

[d]In univariate and multivariate analyses, P_{trend} = <.01.

pregnancy, postpartum vaccination would also be useful in protecting their infants from the threat of influenza.

The present study also showed strong associations between an influenza diagnosis among infants and the presence of influenza in their mothers, the presence of older siblings, and attendance at a daycare facility. In particular, the risk of an influenza diagnosis among infants with mothers who had influenza was 36 times the risk among infants without mothers who had influenza. In general, younger infants, especially those aged <6 months, tend to be kept inside the house during winter; therefore, household members are usually the primary source of influenza virus infection among infants. Mothers in particular tend to have the most contact with infants because they are usually their main caregivers. Hence, if a mother is infected with influenza virus, it is often easily transmitted to their infant. Infants can also be exposed to influenza virus in the daycare setting. Therefore, to protect infants <6 months of age who are too young to be vaccinated, family members living in the same household (particularly mothers) should receive influenza vaccine; the stratified analysis in the present study supported this recommendation by also showing the protective effect of maternal influenza vaccination against influenza among infants

Table 4. Association Between Subjects' Background Characteristics, Including Maternal Influenza Vaccination Status, and Infant Hospitalization Due to an Influenza Diagnosis

		Univariate		Multivariate[a]	
Characteristic	Hospitalized Cases, n/N (%)	OR (95% CI)	*P*	OR (95% CI)	*P*
Among mothers					
Age, y[b]					
<29	5/1043 (0.5)	1.52 (.41–5.69)	.53	…	
30–34	4/1269 (0.3)	1.00		…	
≥35	4/1129 (0.4)	1.12 (.28–4.51)	.87	…	
Influenza-related underlying conditions					
Absent	10/2683 (0.4)	1.00		…	
Present	3/758 (0.4)	1.06 (.29–3.87)	.93	…	
Influenza vaccination during 2013–2014 season					
Absent	11/2101 (0.5)	1.00		1.00	
Present	2/1340 (0.1)	0.28 (.06–1.28)	.10	0.27 (.06–1.24)	.09
Timing of influenza vaccination					
Prenatal	2/943 (0.2)	0.40 (.09–1.83)	.24	0.33[c] (.07–1.56)	.16
Postpartum	0/397 (0)	NA		NA	
Influenza diagnosis during 2013–2014 season					
Absent	7/3289 (0.2)	1.00		1.00	
Present	6/152 (3.9)	19.3 (6.40–58.1)	<.01	13.8 (4.42–42.9)	<.01
Among infants					
Birth month					
October	2/886 (0.2)	1.00		1.00	
November	5/1227 (0.4)	1.81 (.35–9.34)	.48	1.98 (.37–10.5)	.42
December	6/1328 (0.5)	2.01 (.40–9.96)	.40	2.53 (.49–13.0)	.27
Birth weight, g					
<2500	0/317 (0)	NA		NA	
≥2500	13/3124 (0.4)	…		…	
Congenital malformation					
Absent	12/3286 (0.4)	1.00		…	
Present	1/155 (0.6)	1.77 (.23–13.7)	.58	…	
Older siblings, no.[d]					
0	2/1825 (0.1)	1.00		1.00	
1	6/1137 (0.5)	4.84 (.97–24.0)	.05	3.96 (.78–20.2)	.098
≥2	5/479 (1.0)	9.62 (1.86–49.7)	<.01	6.88 (1.27–37.3)	.03
Daycare attendance					
Absent	11/3181 (0.3)	1.00		1.00	
Present	2/260 (0.8)	2.23 (.49–10.1)	.30	1.49 (.31–7.27)	.62

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

[a]Model includes variables in this table.

[b]In univariate analysis, P_{trend} = .93.

[c]The OR was obtained from the model in which maternal influenza vaccination status during the 2013–2014 influenza season (ie, unvaccinated or vaccinated) was replaced by maternal vaccination status that included stratification of vaccination timing (ie, unvaccinated, prenatal vaccination, or postpartum vaccination).

[d]In univariate analysis, P_{trend} <.01; in multivariate analysis, P_{trend} = .02.

whose mothers received a diagnosis of influenza. And if family members contract influenza, protective measures, such as wearing masks and putting some distance between infected family members and the infant, should be taken to avoid transmission to the infant.

In the present study, infants born in December and those with low a birth weight had a lower risk of influenza. These findings are unexpected but might be explained by the possibility that a decreased opportunity for contact with influenza virus results in a lower odds of contracting influenza. Specifically, during the influenza season, infants born in December are younger than those born in October and, thus, have a greater likelihood of remaining indoors in the winter. In addition, because infants with a low birth weight are usually treated in incubators until they reach an adequate weight, they may have spent less time at home during the influenza season than those with a normal or higher birth weight. However, we cannot confirm whether this explanation is accurate, since we did not obtain any information on the frequency of leaving home and the date of hospital discharge after birth. In addition, infants born in December had an increased odds of hospitalization, although the association was not statistically significant. Thus, it seems sensible to have

Table 5. Effect of Maternal Influenza Vaccination on Infants' Influenza, by Presence or Absence of Maternal Influenza Diagnosis During the 2013–2014 Season

	Pediatrician-Diagnosed Influenza			Hospitalization Due to influenza		
Characteristic, by Diagnosis Status	Proportion (%)	OR (95% CI)[a]	*P*	Proportion (%)	OR (95% CI)[a]	*P*
Present (n = 152)						
Influenza vaccination during 2013–2014 season						
Absent	34/103 (33.0)	1.00		5/103 (4.9)	1.00	
Present	8/49 (16.3)	0.41 (.17–.99)	.048	1/49 (2.0)	0.43 (.05–4.06)	.46
Timing of influenza vaccination						
Prenatal	6/37 (16.2)	0.42[b] (.15–1.18)	.099	1/37 (2.7)	0.46[b] (.05–4.45)	.50
Postpartum	2/12 (16.7)	0.36[b] (.07–1.86)	.22	0/12 (0)	NA	
Absent (n = 3289)						
Influenza vaccination during 2013–2014 season						
Absent	22/1998 (1.1)	1.00		6/1998 (0.3)	1.00	
Present	7/1291 (0.5)	0.42 (.18–1.01)	.051	1/1291 (0.1)	0.23 (.03–1.94)	.18
Timing of influenza vaccination						
Prenatal	4/906 (0.4)	0.40[b] (.13–1.19)	.098	1/906 (0.1)	0.30[b] (.04–2.58)	.27
Postpartum	3/385 (0.8)	0.47[b] (.13–1.65)	.24	0/385 (0)	NA	

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

[a]Model includes maternal influenza vaccination status during the 2013–2014 influenza season, birth month, birth weight, older siblings, and daycare attendance.

[b]The OR was obtained from the model in which maternal influenza vaccination status during the 2013–2014 influenza season (ie, unvaccinated or vaccinated) was replaced by maternal vaccination status that included stratification of vaccination timing (ie, unvaccinated, prenatal vaccination, or postpartum vaccination).

reservations about a relationship between birth month and influenza risk among infants.

The present study has the following advantages. First, this is the first study to investigate the effects of maternal vaccination on influenza among infants by using a large cohort of infants (>3000). This enabled us to examine not only the effects of maternal vaccination, but also that of prenatal versus postpartum vaccination, which further helps to elucidate the mechanisms of protective effects of maternal influenza vaccination against influenza among infants. Second, while information on infant hospitalization relied on self-reported data from mothers, the accuracy of the data was ensured by contacting the relevant admitting hospital. Although we were able to obtain information from hospital records for only 54% of infants reported to be hospitalized, almost all information obtained from mothers about the admission date and name of the disease leading to hospitalization was identical to the data from the hospital records. Thus, we believe that the self-reported information about infant hospitalization was reliable. Third, since all study subjects were recruited from within Osaka Prefecture, characteristics of the subjects' exposure to influenza viruses were considered to be similar.

However, this study also had some limitations. First, there may have been some misclassification of infants' influenza diagnoses. However, in Japan, since rapid diagnostic tests are conventionally used in the clinical setting, almost all reports of infant influenza would be expected to be based on the results of rapid tests. On the other hand, the infants' influenza diagnoses would be affected by their mothers' attitudes toward seeking medical attention. For example, febrile infants observed at home without visiting a medical facility may have been classified as not having influenza even if they had contracted the virus. However, since infants were as young as several months olds, most mothers would have taken their infants to the hospital or clinic if they had a fever. Thus, the number of misclassifications of infants' influenza diagnoses, if any, would be expected to be low, compared with the studies targeting older infants. Second, generally speaking, since vaccinated mothers have a higher level of health consciousness than unvaccinated mothers, they might avoid taking their infants outside in the influenza season. If this behavior was different between vaccinated and unvaccinated mothers, the observed vaccine effectiveness in the present study might be biased toward overestimation. Third, since the infants in the present study were all born at obstetric facilities in Osaka Prefecture before the beginning of the 2013–2014 influenza season, there is some concern about the generalizability of the results. Further investigation in different seasons and regions is desirable to confirm the validity of the findings in the present study.

In conclusion, these results indicate that maternal vaccination could protect infants from contracting influenza. Pregnant women should receive influenza vaccination to protect not only themselves but also their infants. If they do not receive influenza vaccination during pregnancy, postpartum vaccination would also be useful in protecting their infants from the threat of influenza.

MEMBERS OF THE STUDY GROUP

Other members in the Osaka Pregnant Women Influenza Study Group are as follows (in alphabetical order of affiliation):

Shiro Imai (Department of Gynecology and Obstetrics, Aizenbashi Hospital), Eiko Akagaki (Akagaki Ladies Clinic), Mariko Akai (Akai Maternity Clinic), Yoshitsune Azuma (Azuma Ladies Clinic), Shinichi Hamada (Department of Obstetrics and Gynecology, Bell Land General Hospital), Satoru Motoyama (Department of Obstetrics and Gynecology, Chibune General Hospital), Hiroko Chimori (Chimori Medical Clinic), Shoko Nakagawa (Department of Obstetrics and Gynecology, Fuchu Hospital), Takehiko Fukuda (Fukuda Lady's Clinic), Masahisa Hagiwara (Hagiwara Clinic), Hideto Okuda (Hamada Women's Hospital), Takuro Hamanaka (Hamanaka Obstetrics and Gynecology), Seiichi Yamamasu (Obstetrics and Gynecology, Hannan Chuo Hospital), Kenji Hirota (Obstetrics and Gynecology, Hanwasumiyoshi General Hospital), Masataka Oku (Obstetrics and Gynecology, Higashi Osaka City General Hospital), Keizo Hiramatsu (Hiramatsu Obstetrics and Gynecology Clinic), Masanori Hisamatsu (Hisamatsu Maternity Clinic), Yasushi Iijima (Iijima Women's Hospital), Mikio Takehara (Department of Obstetrics and Gynecology, Ikeda City Hospital), Somei Ikeda (Ikeda OB/GYN Clinic), Takeshi Inoue (Inoue Lady's Clinic), Eriko Yamashita (Ishida Hospital), Aisaku Fukuda (The Centre for Reproductive Medicine and Infertility, IVF Osaka Clinic), Itsuko Iwata (Iwata Clinic), Junko Nishio (Department of Obstetrics and Gynecology, Izumiotsu Municipal Hospital), Tateki Tsutsui (Department of Obstetrics and Gynecology, Japan Community Healthcare Organization Osaka Hospital), Kenji Yamaji (Kajimoto Clinic), Takao Kamiya (Kamiya Ladies Clinic), Atsushi Kasamatsu (Department of Obstetrics and Gynecology, Kansai Medical University Hirakata Hospital), Tatsuya Nakajima (Department of Obstetrics and Gynecology, Kansai Medical University Takii Hospital), Kanji Kasahara (Kasahara Clinic), Kenjitsu Kasamatsu (Kasamatsu Obstetrics and Gynecology/Pediatrics), Kawabata Ryoichi (Kawabata Lady's Clinic), Kazume Kawabata (Kawabata Women's Clinic), Kozo Kadowaki (Department of Obstetrics and Gynecology, Kawachi General Hospital), Hiroshi Nomura (Kawashima Ladies Clinic), Tomoyuki Kikuchi (Kikuchi Ladies Clinic), Ayako Suzuki (Department of Obstetrics and Gynecology, Kinki University), Tadayoshi Nagano (Department of Obstetrics and Gynecology, Kitano Hospital), Yoshitsugu Komeda (Komeda Ladies Clinic), Ryousuke Kondo (Kondo Ladies Clinic), Shinjin Konishi (Konishi Ladies Clinic), Hideo Takemura (Kosaka Women's Hospital), Masako Kasumi (Masako Ladies Clinic), Kazuo Masuhiro (Masuhiro Maternity Clinic), Ryoji Ito (Department of Obstetrics and Gynecology, Matsushita Memorial Hospital), Yoshiki Sakamoto (Department of Obstetrics and Gynecology, Mimihara General Hospital), Kouzo Hirai (Minami-Morimachi Ladies Clinic), Yoshimitsu Yamamoto (Department of Obstetrics and Gynecology, Minoh City Hospital), Yoshitaka Kariya (Minoh Ladies Clinic), Osamu Misaki (Misaki Clinic), Akira Miyake (Miyake Clinic), Yasuko Osako (Mom Women's Clinic Osako), Masao Mori (Mori Obstetrics and Gynecology Clinic), Keizo Naka (Naka Ladies Clinic), Yasumasa Tokura (Nakai Clinic), Jun Yoshimatsu (Department of Perinatology and Gynecology, National Cerebral and Cardiovascular Center), Keiji Tatsumi (Department of Obstetrics and Gynecology, National Hospital Organization Osaka National Hospital), Takayoshi Kanda (Department of Obstetrics and Gynecology, National Hospital Organization Osaka Minami Medical Center), Masahiro Nishikawa (Nishikawa Ladies Clinic), Sekio Nishimoto (Nishimoto Ladies Clinic), Yoshihiro Nishioka (Nishioka Clinic), Takao Funato (Department of Obstetrics and Gynecology, Nissay Hospital), Kouichi Nozaki (Nozaki Ladies Clinic), Gengo Ohira (Ohira Ladies Clinic), Yoshiyuki Okamura (Okamura Ladies Clinic), Yuzo Oga (Oga Clinic), Osamu Nakamoto (Department of Obstetrics and Gynecology, Osaka City General Hospital), Shinichi Nakata (Department of Obstetrics and Gynecology, Osaka City Juso Hospital), Tetsuo Nakamura (Department of Obstetrics and Gynecology, Osaka City Sumiyoshi Hospital), Masahiko Takemura (Department of Obstetrics and Gynecology, Osaka General Medical Center), Toshiyuki Sadou (Department of Obstetrics and Gynecology, Osaka Gyoumeikan Hospital), Nobuaki Mitsuda (Department of Obstetrics, Osaka Medical Center and Research Institute for Maternal and Child Health), Daisuke Fujita (Department of Obstetrics and Gynecology, Osaka Medical College), Koji Hisamoto (Department of Obstetrics and Gynecology, Osaka Police Hospital), Shinobu Akada (Department of Obstetrics and Gynecology, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases), Takafumi Nonogaki, Chinami Horiuchi (Department of Obstetrics and Gynecology, Osaka Red Cross Hospital), Yasuhiko Shiki (Department of Obstetrics and Gynecology, Osaka Rousai Hospital), Tadashi Kimura (Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine), Koutaro Kitamura (Obstetrics and Gynecology, PL Hospital), Kazuhide Ogita (Department of Obstetrics and Gynecology, Rinku General Medical Center), Shigeki Matsuo (Saint Barnabas Hospital), Yoshihito Ikeda (Department of Obstetrics and Gynecology, Saiseikai Ibaraki Hospital), Akihiro Moriyama (Department of Obstetrics and Gynecology, Saiseikai Nakatsu Hospital), Yukiyoshi Ishikawa (Department of Obstetrics and Gynecology, Saiseikai Noe Hospital), Hiroshi Muso (Department of Obstetrics and Gynecology, Saiseikai Senri Hospital), Fuminori Kitada (Department of Obstetrics and Gynecology, Saiseikai Suita Hospital), Toshiya Yamamoto (Department of Obstetrics and Gynecology, Sakai City Hospital), Megumi Takemura (Department of Obstetrics and Gynecology, Sakibana Hospital), Takeshi Sawada (Sawada Ladies Clinic), Kentaro Shimura (Shimura Women's Clinic), Koh Shinyashiki (Shinyashiki Obstetrics and Gynecology), Mitsuhiko Masuda (Department of Obstetrics and Gynecology, Shiseikai

Corporate Juridical Person), Tsuneo Shoda (Shoda Medical Clinic), Takamichi Nishizaki (Department of Obstetrics and Gynecology, Suita Municipal Hospital), Yoshinori Suzuki (Suzuki Clinic), Isao Suzuki (Suzuki Obstetrics and Gynecology), Hiroshi Nanjyo (Department of Obstetrics and Gynecology, Taisho Hospital), Keiko Takabatake (Takabatake Women's Clinic), Kikuya Takase (Takase Ladies Clinic), Satoshi Nakago (Department of Obstetrics and Gynecology, Takatsuki General Hospital), Jun Takeyama (Takeyama Ladies Clinic), Takeshi Taniguchi (Taniguchi Hospital), Keiichi Tasaka (Tasaka Clinic), Toshiaki Tatsumi (Tatsumi Ladies Clinic), Atsushi Tokuhira (Department of Obstetrics and Gynecology, Toyonaka Municipal Hospital), Shogo Tsubokura (Tsubokura Women's Clinic), Kayoko Ueda (Ueda Ladies Clinic), Yukiko Uenae (Uenae Ladies Clinic), Takahiko Unno (Unno Maternity Clinic), Hiroshi Yabuki (Yabuki Maternity Clinic), Tokihiro Yanamoto (Yanamoto Maternity Clinic), Yoshihiko Yamada (Department of Obstetrics and Gynecology, Yao Municipal Hospital), Nobuyuki Maruo (Department of Obstetrics and Gynecology, Yodogawa Christian Hospital), and Yoshitsugu Takada (Department of Obstetrics and Gynecology, Yoshikawa Hospital).

Notes

Financial support. This work was supported by the Ministry of Health, Labor, and Welfare, Japan (Research on Emerging and Reemerging Infectious Diseases, Health, and Labor Sciences research grants H23-SHINKO-IPPAN-017 and H26-SHINKOGYOSEI-SHITEI-003); and JSPS KAKENHI, Japan (grant in aid for scientific research [B] JP25293152).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2013–14. MMWR Recomm Rep **2013**; 62:1–43.
2. World Health Organization. Vaccines against influenza WHO position paper–November 2012. Weekly Epidemiol Rec **2012**; 87:461–76.
3. Steinhoff MC, Omer SB, Roy E, et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. CMAJ **2012**; 184:645–53.
4. Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. Clin Infect Dis **2010**; 51:1355–61.
5. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med **2008**; 359:1555–64.
6. Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D; Vaccine Safety Datalink Workgroup. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. Am J Perinatol **2004**; 21:333–9.
7. Reuman PD, Ayoub EM, Small PA. Effect of passive maternal antibody on influenza illness in children: a prospective study of influenza A in mother-infant pairs. Pediatr Infect Dis J **1987**; 6:398–403.
8. Sumaya CV, Gibbs RS. Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: reactogenicity and immunogenicity in mother and infant. J Infect Dis **1979**; 140:141–6.
9. Englund JA, Mbawuike IN, Hammill H, Holleman MC, Baxter BD, Glezen WP. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. J Infect Dis **1993**; 168:647–56.
10. Puck JM, Glezen WP, Frank AL, Six HR. Protection of infants from infection with influenza A virus by transplacentally acquired antibody. J Infect Dis **1980**; 142:844–9.
11. Steinhoff MC, Omer SB, Roy E, et al. Influenza immunization in pregnancy–antibody responses in mothers and infants. N Engl J Med **2010**; 362:1644–6.
12. France EK, Smith-Ray R, McClure D, et al. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. Arch Pediatr Adolesc Med **2006**; 160:1277–83.
13. Eick AA, Uyeki TM, Klimov A, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. Arch Pediatr Adolesc Med **2011**; 165:104–11.

Vaccine 37 (2019) 3588–3597

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness of Recombinant Zoster Vaccine (RZV) and Varicella Vaccine Live (VVL) against herpes zoster and post-herpetic neuralgia among adults aged 65 and over in Japan

Shu-ling Hoshi [a,*], Xerxes Seposo [b], Aiko Shono [c], Ichiro Okubo [d], Masahide Kondo [a]

[a] Department of Health Care Policy and Health Economics, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennoudai, Tsukuba, Ibaraki 3058577, Japan
[b] Department of Environmental Engineering, Environmental Health Division, Kyoto University, Nishikyo-ku, Kyoto 6158246, Japan
[c] Department of Public Health and Epidemiology, Faculty of Pharmaceutical Sciences, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 2048588, Japan
[d] Yokohama City Institute of Public Health, 7-1, Tomiokahigashi 2-chom, Kanazawa-ku, Yokohama City 236-0051 Japan

ARTICLE INFO

Article history:
Received 24 October 2018
Received in revised form 1 May 2019
Accepted 2 May 2019
Available online 29 May 2019

Keywords:
Cost-effectiveness
Economic evaluation
Herpes zoster
Varicella vaccine
Vaccination
Quality-adjusted life year

ABSTRACT

Background: The approval of the extended use of 1-dose varicella vaccine (VVL) in adults aged 50 and older against herpes zoster (HZ) in 2016 and the 2-dose recombinant zoster vaccine (RZV) in 2018 raised the need to evaluate the value for money between these two vaccines.
Methods: We conducted a cost-effectiveness analysis with Markov modelling to evaluate the efficiency of the immunisation programmes from payer's perspective. Eight strategies with different ages to receive VVL or RZV were set, namely: 65–84 year old (y.o.), 70–84 y.o., 75–84 y.o., and 80–84 y.o. VVL- or RZV-strategy. Incremental cost-effectiveness ratios (ICERs) compared with curative care scenario were calculated. The health statuses following the target cohort were as follows: acute HZ followed by recovery, post-herpetic neuralgia followed by recovery, post HZ/PHN, recurrence of HZ, and general death.
Results: At the vaccination cost ¥8000 (US$73) for 1-dose ZVL and ¥30,000 (US$273) for 2-dose RZV, ICERs ranged from ¥2,633,587/US$23,942 (age 80–84 y.o.) to ¥3,434,267 or US$31,221 (age 65–84 y.o.)/QALY gained for VVL-strategies; from ¥5,262,227 or US$47,838 (age 80–84 y.o.) to ¥6,278,557 or US$57,078/QALY gained (age 65–84 y.o.) for RZV-strategies. Cost-effectiveness acceptability curves derived from probabilistic sensitivity analyses showed that if the cost-effective threshold was at ¥3,000,000 or US$27,273/QALY, the acceptability was 90.7% and 8.8% for 65–84 VVL-strategy and 65–84 RZV-strategy, respectively; if at ¥5,000,000 or US$45,455/QALY, 56.2% and 43.8%, and if at ¥10,000,000 or US$90,909/QALY 11.9% and 88.1%, respectively.
Conclusion: Vaccinating individuals aged 65–84 y.o., 70–84 y.o., 75–84 y.o., 80–84 y.o. with VVL or RZV to prevent HZ-associated disease in Japan can be cost-effective from payer's perspective, with vaccination costs at ¥8,000 per shot for VVL, ¥30,000 for 2-dose RZV. While the results suggesting that only 65–84 VVL-strategy and 65–84 RZV strategy should be considered when introducing HZ immunisation programme. The optimal strategy varies depending on the willingness-to-pay threshold.

1. Introduction

Herpes zoster (HZ) results from the reactivation of varicella-zoster virus (VZV) in sensory ganglia after a long latency period following primary infection from varicella [1,2]. In high-income settings, age-adjusted HZ incidence in the total population ranged from 3.4 to 5.0 per 1000 person-years, with particularly higher incidence (8.0–11.0 per 1000 person-years) for those aged 65 and over [3]. Post-herpectic neuralgia (PHN) is the most common serious complication of HZ, which is characterised by persistent pain beyond the acute phase of vesicular rash [3]. Common treatment for HZ complications include antiviral chemotherapy, which shortens the length and severity of acute HZ, provided that the therapy must be started as soon as the rash appears [3]. Although healthcare in Japan is easily accessible, percentage of HZ patients visiting within the ideal period for antiviral chemotherapy, 0–2 days, is still low at 37% [4].

There are two kinds of HZ vaccine currently available in some countries for the immunisation of adults with HZ, who are aged 50 and over, namely single-dose Zoster Vaccine Live (ZVL, Zostavax®) and two-dose Recombinant Zoster Vaccine (RZV, Shingrix®).

* Corresponding author.
E-mail address: hoshi@hcs.tsukuba.ac.jp (S.-l. Hoshi).

https://doi.org/10.1016/j.vaccine.2019.05.006
0264-410X/

ZVL has been licensed for use among immunocompetent adults ≥50 years old (y.o.) since 2006 in over 60 countries [3]. On the other hand, RZV has been approved and used in the USA, Canada, and EU for HZ prevention in adults aged ≥50 y.o. from 2017 to 2018 [5].

In Japan, HZ incidence ranged from 3.0 to 8.0 per 1000 person-years, with particularly higher incidence (8.0 per 1000 person-years) for those 70 and over, according to a large-scale epidemiological study [6,7]. Though ZVL is not available, there are two kinds of vaccine available for the immunisation of HZ among adults aged 50 y.o. and over, namely: (1) 1-dose Varicella Vaccine Live (VVL), which has similar annual mean titer (42,000–67,000 plaque-forming unit (PFU) per dose) with ZVL [8] and has been approved in March 2016 for the extended use in adults aged 50 y.o. and over against HZ, and (2) 2-dose RZV, which was approved in March 2018. In Japan, Pharmaceuticals and Medical Devices Agency (PMDA) approves vaccines based on quality, safety and efficacy. There are two categories for approved vaccine immunisation, namely: routine immunisations and voluntary immunisations. Routine immunisations are defined by the Preventive Vaccination Law and scheduled in the National Immunisation Programme (NIP). These vaccinations included several childhood vaccinations and two vaccinations (seasonal influenza and pneumococcal diseases) for adults aged 65 and over. Childhood vaccinations are fully funded by public fund, while influenza and pneumococcal vaccinations are fully or partially funded depending on the municipalities, which are responsible for the implementation of the immunisation programme. Voluntary immunisations are not covered by the NIP, while individuals can uptake the vaccine with their own pocket money if only the vaccine is approved and is marketed. RZV utilisation was considered to be zero, since it was not included in the routine immunisation, given that the vaccine was just approved one years ago, and it is yet to be available in the market. On June 22, 2016, the Health Science Council in charge of Immunisation and Vaccine started to discuss issues related to VVL against HZ among elderly, on the premise of defining VVL into the routine immunisation [9]. This has raised the need to evaluate its value for money particularly taking into consideration the matters related to or arising from disease burden, effectiveness and safety of vaccine, and its cost-effectiveness. Based on the progress of these events, we have published a cost-effectiveness analysis in 2017, which estimated the value for money of VVL immunisation programme against HZ and PHN for adults aged 65 and over in Japan. We found that VVL immunisation programme is highly cost-effective compared to no immunisation programme, i.e., curative care scenario, (from ¥2,670,000 or US$24,273/QALY gained for adult age 65–84 to ¥3,650,000 or US$33,182/QALY for age 80–84) from payer's perspective (1US$ = ¥110, average of 2017) [10]. Amidst the increasing number of available HZ vaccines, a public immunisation programme (against HZ) is yet to be implemented. If ever the HZ immunisation programme were to be implemented, this raises the need to compare the value for money between the currently available vaccines (VVL and RZV).

Two cost-effectiveness studies from USA reported that RZV dominated ZVL from both payer's and societal perspectives [11,12]. The vaccination costs (including administration cost) of RZV/ZVL in these studies were at US$332/US$238.7 [11] and US$320/US$217 [12], respectively. In Japan, VVL vaccination cost ranges from ¥6,000 (US$55) to ¥10,000 (US$91), which is much lower than that of ZVL in previous studies, and may therefore provide varying yet insightful results if compared to that of other studies.

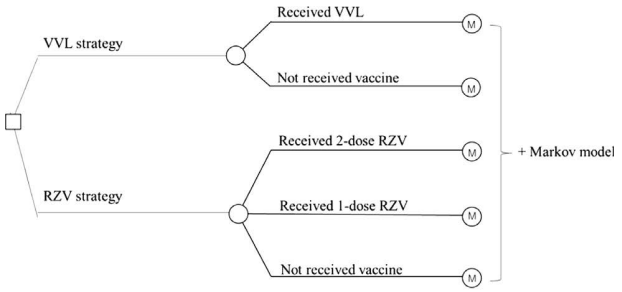
2. Method

We conducted a cost-effectiveness analysis with a decision tree and Markov modelling to evaluate the efficiency of 1-dose VVL immunisation programmes and 2-dose (administered 2–6 months apart) RZV immunisation programmes among Japanese elderly from payer's perspective, in which costs included both vaccination costs and disease treatment costs borne by all payers (including government, municipalities, vaccinees, patients and third-party payers), following the Research guidelines on the evaluation of the cost-effectiveness of vaccination in Japan [13,14]. Incremental cost-effectiveness ratios (ICERs) were calculated to determine resource use efficiency. In reference to the research guidelines on the evaluation of the cost-effectiveness of vaccination in Japan, the ICERs compared to curative care scenario (i.e., status quo in Japan) were reported as the base-case results. While ICERs compared to the next best alternative were also reported. The software used in this study was TreeAgePro 2018 [15]. In defining immunisation programmes and constructing the model, we conducted a literature survey to find out the best available evidence.

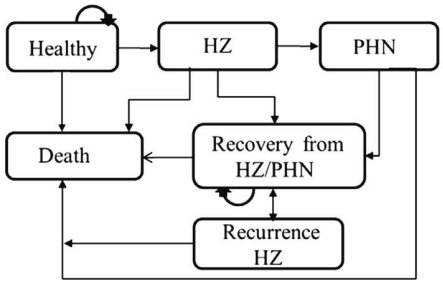
2.1. Programme and model

While both VVL and RZV were approved for adults aged 50 and over in Japan, we defined the study target population of the immunisation programmes to be evaluated as immunocompetent adults aged 65–84 [16]. We set the lower age of vaccination at 65 because: (1) in Japan, inoculated subjects' age of a routine immunisation programme was specified by a Cabinet Order; the target population of the currently being implemented immunisation programmes for adults (against seasonal influenza and pneumococcal disease) were those aged 65 and over, regardless that influenza vaccine and pneumococcal vaccination were also approved for adults under 65, and (2) the sub-committee, infections committee for national immunisation policy established by MHLW, is currently working on establishing the baseline data of herpes zoster of the "elderly" (defined to be aged 65 and over in Japan) [17,18]. We applied eight different preventive strategies with different ages to receive VVL or RZV, namely: 65–84 y.o. VVL- or RZV-strategy, 70–84 y.o. VVL- or RZV-strategy, 75–84 y.o. VVL- or RZV-strategy, and 80–84 y.o. VVL- or RZV-strategy. Because VVL and RZV were approved recently and since vaccination is voluntary, no data is available for the uptake rates. Instead, we adopted the vaccine uptake rate of the routine 23-valent pneumococcal polysaccharide vaccination in 2016, 40.8%, for the VVL-strategies and of the first dose of RZV-strategies [19]. As for the uptake rate of the second dose of RZV-strategies, we assumed it at 80% of 1st dose of RZV in base-case, in reference to those in previous cost-effectiveness studies [11,12,20]. Sensitivity analyses for the uptake rate were also performed.

The decision tree started from a decision node (Fig. 1a). For those under the VVL or RZV strategies, two/three kinds of decisions were considered for VVL/ZVL. For VVL strategies it is either they receive vaccine or not, while for ZVL strategies, decisions included: "to receive 1-dose", "to receive 2-dose", or "not to receive". The vaccinated and not vaccinated then followed the Markov model (Fig. 1b). Static Markov model with one-year cycle was updated from our previous study by including one time recurrence of HZ into the model based on recently published Miyazaki study by Shiraki et al. [6]. Six mutually exclusive health states considered, namely: healthy (being without the diseases defined by the model under consideration), HZ, PHN, recovery from HZ/PHN, recurrent HZ and death. Transitions between states were indicated with arrows. The model followed up the individuals in the cohort until they reach 100 y.o. Our model did not include, however, VZV-related complications (ophthalmic, neurological, or ocular) due to insufficient data in Japan. To accurately assess the value of an intervention, the benefits for the treated individual as well as for others must be considered, thus, a dynamic model should be considered initially. However, there were certain conditions which



(a) Decision tree model



(b) Markov Model

Fig. 1. Decision tree mocel (a) and Markov model (b). □: Decision node, ○: Chance node, M with circle: Markov node. Six mutually exclusive health states considered, namely: healthy (being without the diseases defined by the model under consideration), HZ, PHN, recovery from HZ/PHN recurrent HZ and death. Transitions between states were indicated with arrows. A Markov cycle for each stage was set at one year, the model continued until the surviving individual/s reached 100 y.o. Only one-time recurrence was assumed.

favoured more the use of a static Markov model, than of a dynamic model. In our case, these were due to: (1) HZ results from reactivation of the varicella-zoster virus (VZV) in sensory ganglia after a long latency period following primary infection from varicella [1,2], and (2) the groups we targeted were individuals aged ≥65, among them very few individual were susceptible to the transmission of varicella [21]. These conditions ignored the potential protective effect of vaccination for preventing varicella, both in the vaccinated individual as well as in the remainder of the community, which most of the previous studies did (Table S1, Supplementary 1), thus, we also used static Markov models to conduct the analysis.

2.2. Outcome estimation

Outcomes in terms of QALY were estimated by assigning transition

probabilities and utility weights from literature. There were four epidemiological studies [6,7,22,23], which reported age- and sex-specific HZ incidence rates in Japan (supplementary 2, Fig. S1). The incidence rates were from the Miyazaki study, which we also utilised in our previous study [10], but were updated by using the latest data (1996–2006 data [7] vs. 2009–2015 data [6]). The Miyazaki study was a large-scale epidemiological study, which included 36 dermatology clinics and the dermatology departments of seven flagship general hospitals belonging to the Miyazaki Dermatologist Society. Age- and sex-specific proportion of recurrence were also estimated from the latest Miyazaki study, while only one-time recurrence was assumed, based on the low proportion of patients experiencing three to four episodes (0.3%). Since data related to PHN was not available in the Miyazaki study, we used the proportion of PHN cases among HZ cases from the SHEZ study [22], which were at 19.4%, 12.5%, 34.8% for men and 10.8%, 24.7%, 32.0% for women aged 60–69, 70–79 and 80, respectively. SHEZ study was a prospective cohort study, which recruited participants aged ≥50 y.o. from 19,058 residents between Dec 2008 and Nov 2009. Rates of general death were from vital statistics [24].

Health-related quality of life utility weights of HZ and PHN were also updated from our previous study. They were calculated from the recent studies of Mizukami et al [25] and Kawashima et al [26]. The former was a prospective observational cohort study, which recruited 412 adult age ≥60 y.o. diagnosed with HZ and demonstrated the first EuroQol-5 Dimension (EQ-5D) utility scores in HZ with/without PHN by age group over time (from day 0 to day 360, Supplementary 3, Table S3-1) as well as the median duration and quartile (134 days, 185 days, and 274 days for Q1, median, and Q3, respectively) (Supplementary 3, Table S3-2) in Japan. The latter, which was the first randomized double-blind study in Japan to evaluate the efficacy and safety of amenamevir (for treatment of HZ), reported pain resolution duration as 5 days, 10 days, and 19 days for Q1, median, and Q3, respectively (Supplementary 3, Table S3-2). Using these EQ-5D scores and durations of pain release, we estimated the utility weights of HZ/PHN of each age group. Data and process to estimate the figures were shown in Table S3-3 (Supplementary 3).

2.3. Vaccine effectiveness (VE)

Although VVL was developed in Japan, not until October 2014 when the routine vaccination for children started, the vaccination has been used primarily for voluntary vaccination [8]. Most of the evidence related to the efficacy against varicella of Oka strain varicella vaccine for children were largely based on studies conducted in the United States, since they have adopted early the vaccine as part of the universal immunisation in 1996 [27]. Same situation happened with the evidence related to efficacy against HZ and PHN. An application, submitted on the pretense that overseas usage of drug and medical literature published both in Japan and other countries were sufficient to prove that the drug's safety and efficiency based on the common scientific knowledge within the medical and pharmacological communities, and does not require additional clinical studies to be conducted, either in whole or in part, was used to approve the extended use of VVL in adults ≥50 years old against HZ in Japan. We used instead the vaccine effectiveness (VE) of VVL in reducing HP/PHN incidence rates from overseas' studies on ZVL. Table S4 (Supplementary 4) indicated the similarities and differences between these two vaccines.

Since the first clinical trial, comparing RZV and ZVL directly, is expected to be completed on December 2019 [28], we decided to adopt the VEs from different studies which compared each vaccine with placebo, respectively. VEs of VVL for prevention of HZ were adopted from VEs of ZVL. In our study, they were 70.6%/64.5%/63.7% during the first year after vaccination for age 65–69/70–79/80+, waned to 48.8%/45.2%/41.8% during the second year after vaccination, then waned to zero until the 9th year in our study as shown in Table 1. These data were from a recently published long-term cohort study (5.8million person-years of follow-up, from 2007 to 2014) in USA by Baxter et al [29].

VEs of 2-dose/1-dose RZV, and waning duration (the duration that VE declines linearly from the initial VE to 0%) of 2-dose/1-dose RZV were based on the Advisory Committee on Immunization Practices (ACIP) presentation document on Oct. 25th, 2017 by Dr. Prosser [30]. In the document, VEs of initial year of 2-dose RZV's were cited from study of Lal et al. [31] (ZOE 50/70 study) and study of Cunningham et al. [32], which were two pivotal studies related to VEs of RZV. VEs of initial year of 1-dose RZV's, duration of 2-dose RZV was based from Cummingham et al. with an additional assumption; while waning duration of 1-dose RZV was thoroughly

Table 1
Variables.

Base case				One-way sensitivity analyses				PSA[b]	Reference
				Low		High			
Target Population of alternative strategies (×1000)									[16]
Age 65–84 strategy		29,389							
Age 70–84 strategy		19,115							
Age 75–84 strategy		11,707							
Age 80–84 strategy		5,181							
Male and female population in different age strata (×1000)									
Age	Male	Female							
65–59	4,971	5,303							
70–74	3,452	3,956							
75–79	2,906	3,620							
80–84	2,096	3,085							
Age-specific incidence rates of HZ (per 1000 persons)								ß	[6]
Age	Male	Female		Male	Female	Male	Female		
60–69	6.25	8.08		5.0	6.46	7.5	9.70	Male:(500; 80,000)[a] Female (690; 85,000)	
70–79	8.44	8.89		6.75	7.11	10.13	1.067	Male:(440; 58,000) Female (630; 76,000)	
80–89	8.45	8.30		6.76	6.64	10.14	9.96	Male:(250; 30,000) Female (420; 55,000)	
90+	6.78	6.51		5.42	5.21	8.14	7.81	Male:(20; 5000) Female (110; 17,000)	
Percentage of PHN cases among HZ cases								ß	[22]
Age	Male	Female		Male	Female	Male	Female		
60–69	19.4%	10.8%		15.5%	8.6%	23.3%	8.6%	Male: (7; 29)[a]; Female (8; 66)	
70–79	12.5%	24.7%		10.0%	19.8%	15.0%	19.8%	Male: (6; 42); Female (20; 61)	
80+	34.8%	32.0%		27.8%	25.6%	41.8%	25.6%	Male: (8; 15); Female (16; 34)	
Percentage of HZ recurrence; %									[6]
Age	Male	Female		Male	Female	Male	Female		
60–69	4.32	10.77		3.46	8.62	5.18	12.92		
70–79	6.87	9.56		5.50	7.65	8.24	11.47		
80–89	6.27	9.04		5.02	7.23	7.52	10.85		
90+	5.60	5.84		4.48	4.67	6.72	7.01		
General death (per 100,000 persons)									[24]
Age	Male	Female							
65	1315.6	538.8							
70	2111.2	896.4							
75	3354.6	1550.6							
80	6124.0	3114.3							
85	11144.9	6326.7							
90	18771.1	12624.0							
95	31750.7	23627.2							
100	44611.1	39319.3							
Vaccine effectiveness for VVL (%)									[29]
Base-case				Sensitivity analyses (Low, High)			Uniform		
Age	65–69	70–79	≥80	65–69	70–79	≥80	95(CI)		
Year 1	70.6	64.5	63.7	67.9, 73.2	60.5, 68.1	57.3, 69.1	95(CI)		
Year 2	44.8	45.2	41.8	44.5, 52.7	39.5, 50.3	31.9, 50.3	95(CI)		
Year 3	40.5	36.8	35.4	35.1, 45.5	29.9, 43.0	22.3, 46.3	95(CI)		
Year 4	40.5	44.2	34.7	33.8, 45.6	36.9, 50.7	18.8, 47.5	95(CI)		
Year 5	39.9	32.6	39.8	32.8, 46.2	23.6, 40.5	21.8, 53.7	95(CI)		
Year 6	34.3	29.1	35.8	25.3, 42.2	18.3, 38.4	12.0, 53.2	95(CI)		
Year 7	34.7	26.9	0	22.7, 44.7	12.3, 39.0	–	95(CI)		
Year 8	32.1	0	0	8.1, 49.9	–	–	95(CI)		
Year 9	0	0	0	–	–	–			
Vaccine effectiveness for 2-dose RZV (%)[b]							Uniform		[30–32]
		65–69	≥70	65–69	≥70				
Initial year		100	97.0	95.0, 1	92.0, 1				
Waning duration		19.4 years	18.8 years	10, 30	10, 30				
Vaccine effectiveness for 1-dose RZV (%)							Uniform		[30–32]
Initial year		90.0	69.0	0.85, 0.95	0.64, 0.74				
Waning duration		11.0 years	4.0 years	1, 17.5	1, 13.4				
Grade 3 solicited systemic events (myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms)									[33]
VLV		2%							
RZV		10.8%							
Utility weights									
Age	HZ	PHN	HZ (Low)	HZ (High)	PHN (Low)	PHN (High)			[25,26]
65–69	0.99098	0.87983	0.95480	–	0.79000	0.89400			

(*continued on next page*)

Table 1 (*continued*)

Base case				One-way sensitivity analyses			PSA[b]	Reference
				Low		High		
70–79	0.98633	0.82631	0.95440	–	0.76000	0.84400		
80+	0.98363	0.76661	0.95440	–	0.76000	0.84400		
Costs per vaccination			VZV (1-dose ¥8000; RZV (2-doses) ¥30,000					Assumed
Treatment costs							Normal	[36]
Age	HZ	PHN	SD (HZ)	SD (PHN)				
65–69	36,615	123,988	35,418	147,992				
70–79	38,414	82,502	25,151	74,362				
80+	33,853	113,304	20,418	60,806				

[a] First and second values in parentheses correspond to α and ß in ß distribution, or α and λ in γ distribution.

[b] VE of year1 to year4 for age 70+ (both in base-case and in sensitivity analysis were based on study of ZOE-70 by Cunningham et al [32] except year3, which is estimated by 0.5 * (year2 + year4), in order to make VE to decrease yearly. Waning duration of 2-dose was 19.4 year (range 10–30)/18.8 year (range 10–30) for age 65–69/age 70+ (Cunningham et al 2016, assumption made by Prosser [30]. Waning duration of 1-dose was 11.0 year (range 1–17.5)/4.0 year (range 1–13.4) for age 65–69/age 70 +) [30].

based on assumption. We conservatively assumed no additional VE against PHN and burden of illness for both vaccines.

Serious adverse events (SAE) associated with vaccination were not considered because no serious adverse events related to both vaccination was found, while Grade 3 solicited systemic events (myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms) were included in sensitivity analyses (10.8% for RZV vs. 2% for VVL [33].

2.4. Costing

In reference to the "Research guidelines on the evaluation of the cost-effectiveness of vaccination in Japan" [13,14], this study defined costs in terms of those (costs) borne by the government, municipalities, vaccinees, patients and third-party payers, while direct non-medical costs and productivity costs were not included. Direct non-medical costs related to the immunisation programme were not included because the vaccination programme was built within the public health services routine. Likewise, productivity costs were not included in accordance with the guidelines (only when the target population aged less than 65, will the productivity loss be incorporated). Amount of direct payments to healthcare providers by these entities was estimated as costs, whereby cost items were identified along the decision tree and Markov model. All cost data were shown in Table 1.

The vaccination costs (including vaccine price, doctor fee and technical fee) of 1-dose VVL, ¥8000 (US$73; US$1 = ¥110, average of 2017) (¥6,000–¥10,000), was based on an ad hoc internet survey from about 60 clinics. In Japan, regardless of voluntary or routine vaccination, only physicians can administer a vaccine, and the vaccination costs (including administration fee) for one shot is decided by the private or public facilities (clinics or hospitals). If the vaccination is defined as routine vaccination, then public subsidy (full or partial subsidy will depend on the municipality where the vaccinee inhabits) will pay directly to the private or public facilities and the facility will request the payment difference from the vaccinee. VVL is currently in the category of voluntary vaccination in Japan, therefore, the use of the vaccination costs at ¥8,000 or US$73, based on an ad hoc internet survey is considered to be sufficiently adequate. With reference to the CDC cost/private sector cost, US$ 102.19/US$140 per dose and average wholesale price, US$336 for 2-dose series [34,35], we assumed that the 2-dose RZV cost was at ¥300,000 or US$273. In Japan, in determining the vaccination costs for a newly vaccinated, costs in other high-income countries are usually used as a reference.

Disease treatment costs were updated from our previous study based on a recently published prospective physician practice-based cohort study, which reported age-specific treatment costs collected from 412 aged ≥60 y.o. patients diagnosed with herpes zoster: ¥33,853–¥38,414 (US$308–US$349) for HZ without PHN, ¥82,502–¥123,988 (US$750–US$1127) for HZ with PHN [36]. We incorporated the costs reported before 2016 with no adjustment because the variation of consumer price index of services related to medical care was less than 0.1% during these 10 years. On the other hand, sensitivity analyses were conducted on cost-related data.

2.5. Discounting

Outcomes and costs were discounted at a rate of 3% [37].

2.6. Sensitivity analyses

To appraise the ICERs' stability with the assumptions made in our economic model, and to explore the impact of each variable relative to each other, we performed one-way sensitivity and probabilistic sensitivity analyses (PSA). The probability density functions and the ranges for sensitivity analyses were shown in Table 1.

3. Cost-effectiveness threshold and net monetary benefit (NMB)

Although the MHLW of Japan has not yet set a willingness-to-pay (WTP) threshold for judging the cost-effectiveness of public health programmes in the country [38], local studies have initially begun citing the WTP threshold, at ¥5,000,000 (US$45,455) per QALYgained, from Shiroiwa et al. [39] to facilitate the analysis. In this study, we also used net monetary benefits (NMB) to express cost-effectiveness. NMB is another way of presenting the results of cost-effectiveness, especially when multiple alternatives are compared [37,40,41]. It is a summary statistic that represents the value of an intervention in monetary terms when a WTP threshold for a unit of benefit (QALY in this study) is known. NMB was calculated as "(incremental benefit × threshold) – incremental cost". A positive incremental NMB indicates that the intervention was cost-effective compared with the alternative at the given WTP threshold. Which means the cost to derive the benefit is less than the maximum amount that the decision-maker would be willing to pay for this benefit [41].

4. Results

Table 2(a) showed the expected costs per person and expected QALYs per person associated with curative care scenario and eight preventive alternatives. We have observed that compared to curative care scenario, all eight preventive strategies reduced disease treatment costs, however, these reduced costs did not offset vacci-

Table 2
Result of cost-effectiveness analysis.

(a). Costs, effectiveness, incremental costs, incremental effectiveness, and incremental cost-effectiveness ratio (compared to curative care scenario) in Japanese context

Scenario/ Strategies	Vaccination costs (¥)	Disease treatment costs (¥)	Total costs (¥)	Effectiveness (QALY)	Incremental costs (¥)	Incremental effectiveness (QALY)	Incremental cost-effectiveness ratio (¥/QALY)	NMB at certain WTP threshold (¥/QALY) 5,000,000	10,000,000
Curative care scenario	0	6,520	6,520	11.81693378	–	–	–	–	–
VVL 80–84	782	6,343	7,125	11.81716358	605	0.000230	2,633,587	544	1,693
VVL 75–84	2,071	6,035	8,106	11.81748032	1,586	0.000547	2,902,059	1,147	3,879
VVL 70–84	2,250	5,992	8,242	11.8175153	1,722	0.000582	2,961,041	1,186	4,093
VVL 65–84	3,200	5,750	8,950	11.81764131	2,430	0.000708	3,434,267	1,108	4,645
RZV 80–84	2,640	6,189	8,826	11.81737193	2,306	0.000438	5,262,227	−115	2,076
RZV 75–84	6,991	5,589	12,580	11.81802341	6,060	0.001090	5,561,451	−612	4,836
RZV 70–84	7,592	5,503	13,096	11.81810179	6,575	0.001168	5,629,590	−735	5,105
RZV 65–84	10,800	5,004	15,804	11.81841243	9,284	0.001479	6,278,557	−1,891	5,503

(b). Costs, effectiveness, incremental costs, incremental effectiveness, and incremental cost-effectiveness ratios (compared with the next best alternative)

Scenario/Strategies	Total costs (¥)	Incremental cost (¥)	Effectiveness (QALY)	Incremental effectiveness (QALY)		ICER (excluding dominated)
Curative care scenario	6,520	–	11.81693	–		–
VZV 80–84	7,125	605	11.81716	0.00023		2,633,587
VZV 75–84	8,106	981	11.81748	0.00032		3,096,832
VZV 70–84	8,242	136	11.81752	0.00003		3,882,797
RZV 80–84	8,826		11.81737		abs. dominated	–
VZV 65–84	8,950	708	11.81764	0.00013		4,540,425
RZV 75–84	12,580		11.81802		ext. dominated	–
RZV 70–84	13,096		11.81810		ext. dominated	–
RZV 65–84	15,804	6,854	11.81841	0.00077		8,888,295

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; NMB: net monetary benefits; WTP: willingness-to-pay.

nation costs, which means all the strategies gained more QALYs but cost more. Incremental costs per person ranged from ¥605–¥2430 or US$76–US$22 for VVL-strategies; from ¥2306–¥9284 or US$21–US$84 for RZV-strategies. Incremental effectiveness per person ranged from 0.000230 to 0.000708 QALYs for VVL-strategies; from 0.000438 to 0.001479 QALYs for RZV-strategies. Both incremental costs and incremental effectiveness increased with increasing target age in both VZV- and RZV-strategies. ICERs of strategies using the same vaccine were nearly similar, such as ¥2,633,587 or US $23,942 (age 80–84 y.o.) – ¥3,434,267 or US$31,221 (age 65–84 y.o.) per QALY gained for VVL-strategies; ¥5,262,227 or US $47,838 (age80-84 y.o.) – ¥6,278,557 or US$57,078 (age 65–84 y. o.) per QALY gained for RZV-strategies. VVL-strategy gained less QALY and cost less than their corresponding RZV-strategy, the ICER of VVL-strategy was around half of their corresponding RZV-strategy. Table 2(b) showed ICERs compared to the next best alternative. Among all the eight vaccination strategies, three RZV-strategies, namely 70–84 RZV-strategy, 75–84 RZV-strategy and 80–84 RZV-strategy, were dominated (absolute or extended, as shown in Table 2(b) and Fig. 2). The NMBs on Table 2(a) showed that all the strategies have positive values if the cost-effectiveness threshold was at ¥10,000,000 or US$90,909/QALY, with 65–84 RZV-strategy having the highest NMB. On the other hand, when WTP threshold was at ¥5,000,000 or US45,455/QALY, all four RZV strategies have negative values.

One-way sensitivity analyses showed that among four VVL-strategies, costs of vaccination, utility weight (HZ without PHN, only for 65–84 strategy), VE of VVL (only for 80–84 strategy) were variables which made the ICERs to change over ±¥1,000,000 or US $9,091 per QALY from the base-case ICERs. While among four RZV-strategies, vaccination cost, waning duration of 2-dose RZV and utility weight (HZ with/without PHN), made the ICERs change over ±¥1,000,000 or US$9,091 per QALY from the base-case ICERs. Other variables have less impact to the ICERs (Fig. 3).

The cost-effectiveness acceptability curves (CEACs) derived from PSA (Fig. 4) showed that if the cost-effective threshold was at ¥2,000,000 or US$18,182/QALY, the acceptability for 65–84 VVL-strategy was 97.1% (ie., the uncertainty for 65–84 VVL-strategy not to be accepted was only 2.9%), 0.24% for 70–84 VVL-strategy, 0.5% for 80–84 VVL-strategy. Whereas, if the threshold increased to ¥3,000,000 or US$27,273/QALY, the acceptability for 65–84 VVL-strategy decreased to 90.7% and 65–84 RZV-strategy increased from 0% to 8.8%. If the threshold increased to ¥5,000,000 or US$45,455/QALY, the acceptability for 65–84 VVL-strategy further decreased to 56.2% and 65–84 RZV-strategy increased to 43.8%. While if the threshold increased to ¥10,000,000 or US$90,909/QALY, the acceptability for 65–84 VVL-strategy decreased to 11.9% while for 65–84 RZV-strategy increase to 88.1%. For the other 6 strategies (70–84 y.o., 75–84 y.o., 80–84 y. o. VVL- or RZV-strategy) the acceptability were either 0% or less than 0.1%.

5. Discussion

With the approval of RZV in March 2018, two kinds of vaccines, against HZ (VVL and RZV) became available for adults aged 50 and over in Japan, which has raised the need to compare the value for money of immunisation programmes using VVL and RZV. We conducted cost-effectiveness analyses using age and sex-specific- incidence rates, VEs, utility weights, and disease treatment costs to estimate ICERs of four VVL-immunisation programmes and four RZV-immunisation programmes targeting different age stratum: 65–84 y.o, 70–84 y.o., 75–84 y.o., and 80–84 y.o. All the strategies were compared to curative care scenario (i.e., status quo). Results showed that, at the vaccination cost of ¥8,000 (US$73) for 1-dose VVL and ¥30,000 (US$273) for 2-dose RZV, all the fourVVL strategies' ICERs were less than, while all the four RZV strategies' ICERs were higher than, the frequently cited WTP threshold of ¥5,000,000 or US$45,455 per QALY gained [39]. On the other hand, cost-effectiveness results using NMB varied depending on the WTP threshold being utilised. At ¥5,000,000 or US$45,455/QALY, four VVL-strategies were considered to be cost-effective. All eight strategies were cost-effective at WTP threshold of ¥10,000,000 or US$90,909/QALY. The 70–84 and 65–84 VVL-strategy (at WTP threshold of ¥5,000,000 or US$45,455/QALY) and the 70–84 and

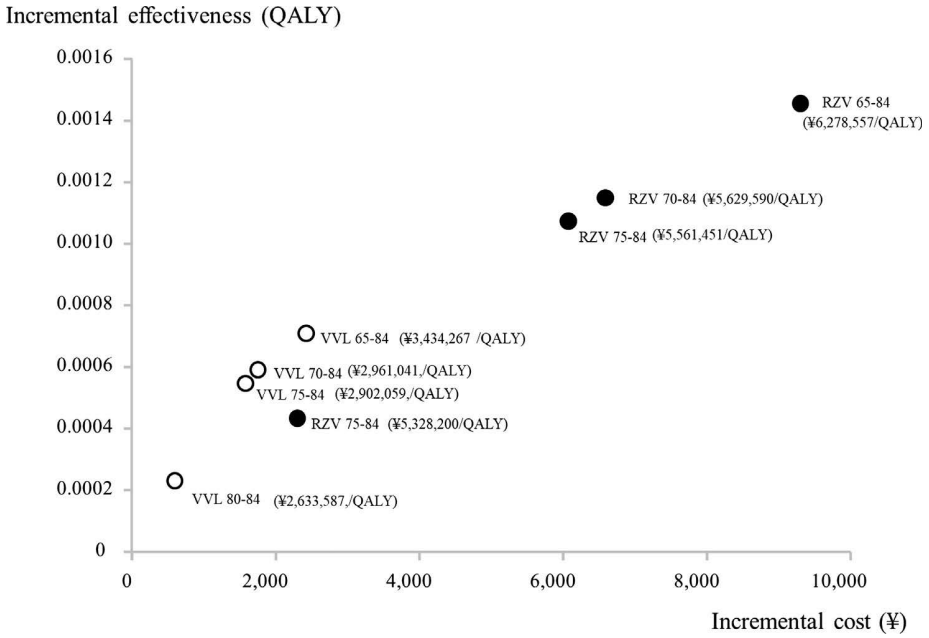


Fig. 2. Results of base-case analyses. Among strategies which used same vaccine (VVL or RZV), ICERs are very similar.

65–84 RZV-strategy (at WTP threshold of ¥10,000,000 or US $90,909/QALY) were considered to be optimal alternatives, since they have higher NMBs in the respective WTP threshold groups. One-way sensitivity analyses revealed that for VVL-strategy, vaccination costs, utility weight (HZ without PHN, only for 65–84 strategy), VE of VVL (only for 80–84 strategy) were the variables which made the ICERs increase or decrease over ¥1,000,000 or US$9,091 per QALY from base-case ICER, while for RZV-strategy, vaccination cost, RZV waning duration, and the utility weight (HZ with/without PHN) made the ICER increase or decrease over ¥1,000,000 or US $9,091 per QALY from the base-case ICER. CEACs derived from PSA showed that among the eight strategies, only 65–84 y.o. VVL-strategy and 65–84 y.o. RZV-strategy should be considered when introducing HZ immunisation programme, the other six strategies should be excluded because their acceptabilities were either 0% or less than 0.1%. The acceptability of 65–84 VVL-strategy reached 97.1% at ¥2,000,000 or US$18,182/QALY WTP threshold, decreased to 56.2% at ¥5,000,000 or US$45,455/QALY, further decreased to11.9% at ¥10,000,000 or US$90,909/QALY. On the other hand, the acceptability of 65–84 RZV-strategy increased from 0% at ¥2,000,000 or US$18,182/QALY to 43.8% at ¥5,000,000 or US$45,455/QALY and to 88.1% at ¥10,000,000 or US$90,909/QALY. This means that the optimal strategy change between these two strategies depend on the WTP threshold.

Since our study is the first study which estimated the value for money of VVL-immunisation programme and RZV-immunisation programme against HZ in Japan's healthcare setting, no comparison can be done within same healthcare setting. A study which evaluated the potential public health impact but not cost-effectiveness of HZ vaccination (VVL vs. RZV) among adults conducted by Watanabe et al [20], reported that RZV demonstrated a superior public health impact compared with VVL. Though our study presented the same results (RZV-strategy gained more QALYs than VVL-strategy), there are apparent differences between our study and that of Watanabe et al's study. Firstly, the incidence rates in Watanabe et al.'s were from the SHEZ study [22], while our data were adopted from the Miyazaki study [6]. As we have mentioned in Section 2, there are four epidemiological studies which reported age- and sex-specific HZ incidence rates in Japan, namely SHEZ study [22], Kushiro Study [23] and two Miyazaki studies (1997–2006 study and 2009–2015 study) [6,7] (supplementary 2, Fig. S1). Among them, SHEZ study reported the highest HZ incidence rates. The population, ageing rates, demographic composition of adult ≥65, and number of medical facilities of the site where the SHEZ study was conducted were significantly different to that of Miyazaki studies (supplementary 2, Table S2). Secondly, study of Watanabe et al. adopted lower vaccine waning rates than our study. Thirdly, the Markov model of Watanabe et al's study included ocular, neurologic and cutaneous complications, while we only used a simple model without including these complications.

We were able to identify two previously published studies which compared RZV- and ZVL- (similar to VVL in our study) vaccination programmes, namely; by Le et al. [11] and by Curran et al. [12], both from USA. Markov Model and data used in these two studies are not completely the same, therefore caution is warranted when comparing these two studies. We found that though both studies reported that RZV-programme dominated (gained more QALYs with less costs) ZVL-programme for adults aged ≥60 y.o., however, the ICERs (compared to no programme, including indirect costs) in the two studies were significantly different. Firstly, the ratio of ICER (vaccination adult aged ≥60) of ZVL to that of RZV in Curran et al. was 10.1:1, while in Le et al. were at 2.2:1 (vaccination at age 60), 1.7:1 (at age 70), 1.9:1 (at age 80). Secondly, Curran et al. reported lower ICERs of RZV-strategies and higher ICERs of ZVL-strategy than those reported by Le et al. In Curran et al, ICERs of RZV-programmes were about 0.5 time of those in Le et al., while ICERs of ZVL-programmes were around 1.5 time of those in Le et al. Higher HZ incidence rates, higher RZV's VEs, lower RZV's VE waning rates, higher RZV's second dose uptake rate, and lower RZV's vaccination costs were considered to contribute to the lower ICERs of RZV-programme in Curran et al. Curran et al. was an industry-funded study, while Le et al. reported no conflict of interest. Our study showed that, in Japan ICERs of VVL-programmes were lower than RZV-programmes, which is inconsistent with the results of the above mentioned two studies. Reasons for the inconsistency may be due to (1) the low vaccination costs of VVL (US$73) compared to ZVL (US$217 or US$239) in previous

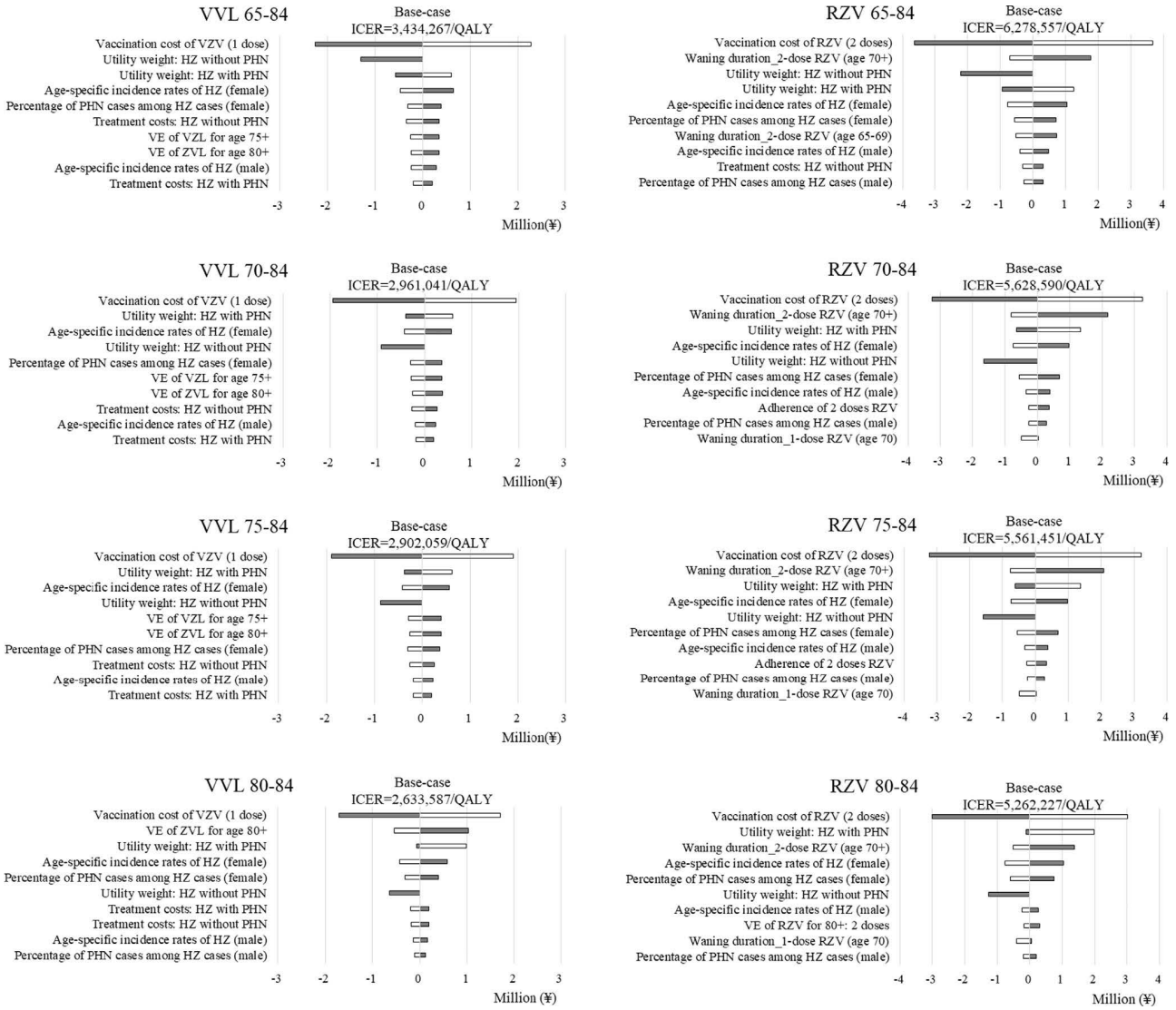


Fig. 3. Results of one-way sensitivity analyses. One-way sensitivity analyses were performed by varying one input at a time while holding others constant at their base-case estimates.

studies, and (2) the higher VEs of VVL in our study than in previous studies, especially VEs of the first 3 years after vaccination. Curran et al. and Le et al. adopted VEs of VZL from the initial RCT, while our study utilised VEs from a recently published large-scale cohort study presented by Baxter et al [29]. Baxter et al. reported higher VEs of time since vaccination and age at vaccination than those reported in previous studies. Baxter et al. highlighted that their overall VE estimate (49.1%) was consistent with the 51.3% VE estimate from the initial report on the pivotal trial [42], the 48.7% estimate based on longer follow-up from the trial [43], the 55% estimate from the initial report on the Kaiser Permanente Southern California population [44], and the 51% estimate from longer follow-up on the same population [45]. The 2-dose VEs of RZV in our study were not all that different from those in the two previous studies, while the 1-dose VEs of RZV in our study were more conservative than those in the two previous studies. VEs of both 2-dose and 1-dose RZV in our study were based on the ACIP presentation document by Prosser [30]

This study also updated our previous study, which evaluated the value for money of VVL immunisation programmes for adult aged ≥65 [10]. Regardless of the adoption of higher utility weights, the ICERs in the current study were slightly lower than those in our previous study. This was due to the higher incidence rates, the lower vaccination costs, the inclusion of one HZ recurrence into the model, and the adoption of VEs from Baxter et al. [29].

Our study faced certain limitations, such as: (1) in the absence of long-term effectiveness data, we modeled RZV effectiveness, in adults aged 65–69 years or ≥70 years, in such a way that it would wane to zero by 19 years following vaccination based on the rate of waning observed during the first four years of clinical trials as well as expert opinion, (2) Markov model used in the study is simple compared to previous studies from overseas. For example, we did not model the reduction in HZ pain in patients who have HZ despite vaccination, nor did we incorporate ophthalmic zoster cases due to the insufficient of data. Exclusion of these aspects of HZ infection could underestimate health benefits of all the strategies, (3) our incidence rates of HZ were from the Miyazaki study, the authors discussed that a proportion of participants with HZ likely received prompt antiviral therapy in Japan, which may have reduced the rate of complications and hospitalisation, (4) adverse

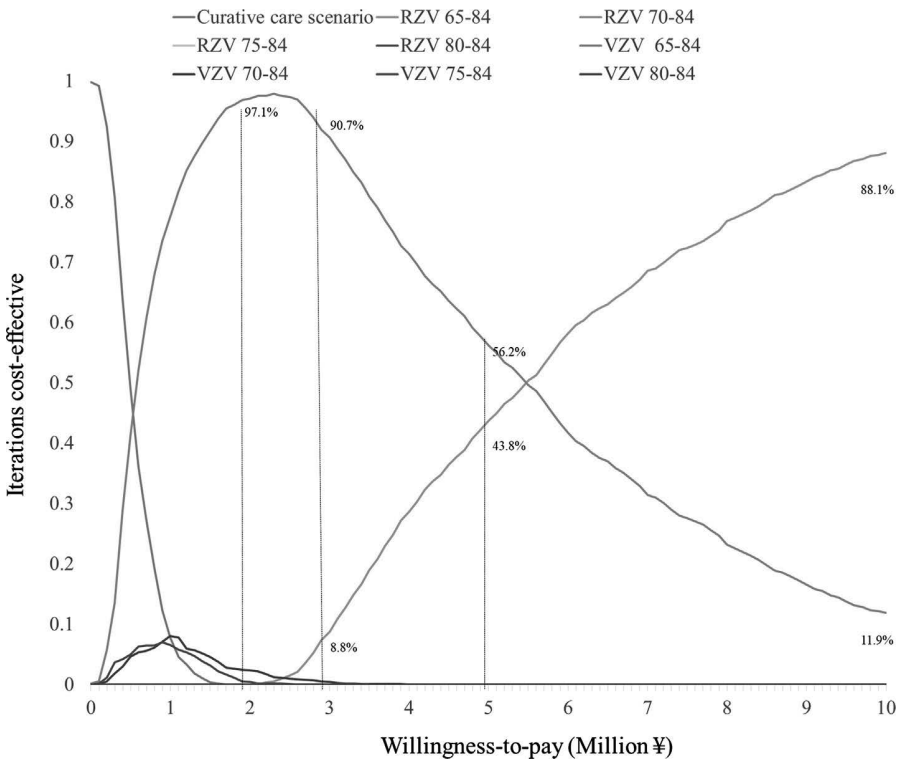


Fig. 4. Probabilistic sensitivity analyses (PSA). In PSA, all the inputs simultaneously varied according to pre-specified distributions of 1000 iterations. Acceptability curves indicate that at ¥2,000,000 (US$ 18,182)/QALY WTP threshold, the acceptability is at 97.1% for 65–84 VVL-strategy and 0% for 65–84 RZV-strategy. For ¥3,000,000 (US $27,273)/QALY, 65–84 VVL-strategy acceptability is at 90.7%, while 8.8% for 65–84 RZV-strategy. On the other hand, at ¥5,000,000 (US$45,455)/QALY, 65–84 VVL-strategy acceptability is at 56.2% and 43.8% for 65–84 RZV-strategy. While at 10,000,000/per QALY, 65–84 VVL-strategy is at 11.9% and 88.1% for RZV-strategy.

reaction was not incorporated into the model, while one-way sensitivity analysis has shown that the impact of Grade 3 reaction was small because it only lasts for 1–3 days, and (5) Japan started to give childhood varicella vaccination programme from October 2014. It has been hypothesised that varicella vaccine introduction might increase HZ incidence in the population because of VZV reduction circulating in the community, which can result to a decrease in the opportunity for boosting immunity against VZV [2]. On the other hand, some recent studies reported that there is no conclusive evidence in whether varicella vaccination programmes have been associated with an HZ incidence increase [46]. While the influence of the childhood varicella vaccination in our results remains to be unknown, we believe that the incorporation of robust, locally-published epidemiologic data, utility weights and costs, may have reduced this uncertainty to a certain level. We acknowledge that the study is limited to the Japanese setting. Nevertheless, we believe that the results of this study are fundamental components for policy-relevant strategies.

6. Conclusion

From our analyses, we found that vaccinating individuals aged 65–84 y.o., 70–84 y.o., 75–84 y.o., 80–84 y.o. with VVL or RZV to prevent HZ-associated disease in Japan can be cost-effective from payer's perspective, with vaccination costs at ¥8,000 (US$73) per shot for VVL, ¥30,000 (US$280) for 2-dose RZV, while the results of PSA suggest that only 65–84 VVL-strategy and 65–84 RZV strategy should be considered when introducing HZ immunisation programme. The optimal strategy varies depending on the WTP threshold. When the WTP threshold ≥¥5,000,000 or US$45,455/QALY, RZV-strategy is preferred, whereas, when WTP <¥5,000,000 or US$45,455, VVL-strategy is preferred. Our results are partially consistent with the results of two previous cost-effectiveness studies and recommendation of CDC, which preferred RZV than ZVL (VVL in Japan). The main factor affecting these results is the cost of VVL in Japan, which is much lower than cost of VZL in USA. Further analysis is warranted when costs per shot of RZV become apparent as well as when long-term VEs of RZV is reported, because waning duration of RZV is a key variable which has a large impact in the results.

Sponsors role

None.

Author's contributions

Shu-Ling Hoshi participated in the concept and design of the study, performed the literature searches, acquired the data, participated in the analysis and interpretation of the data, and wrote the manuscript. Xerxes Seposo participated in the writing of the manuscript. Aiko Shono participated in collecting data. Ichiro Okubo and Masahide Kondo participated in the concept and design of the study, and in the interpretation of the data.

Declaration of Competing Interest

None.

Acknowledgements

This study was supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour

Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan (H29-SHINKOGYOSEI-SHITEI-003). The authors declare no conflict of interest associated with this manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.05.006.

References

[1] Whitley RJ. Varicella zoster virus. In: Mandell GC, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia, PA: Churchill Livingstone; 2015. p. 1731–7.

[2] Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Med 1965;58(1):9–20.

[3] Varicella and Herpes Zoster vaccines. WHO position paper position paper, June 2014. Wkly Epidemiol Rec 2014 20;89(25):265–87.

[4] Miyachi M, Imafuku S. Relationship between prior knowledge about herpes zoster and the period from onset of the eruption to consultation in patients with herpes zoster. J Dermatol 2016;43(10):1184–7.

[5] GSK press release. Shingrix approved in Europe and Japan for the prevention of shingles in adults aged 50 and over. London, UK. 23 March 2018. <https://www.gsk.com/en-gb/media/press-releases/shingrix-approved-in-europe-and-japan-for-the-prevention-of-shingles-in-adults-aged-50-and-over/> [last accessed 2018 Oct 15].

[6] Shiraki K, Toyama N, Daikoku T, Yajima M. Miyazaki Dermatologist Society. Herpes zoster and recurrent herpes zoster. Open Forum Infect Dis 2017;4(1):ofx007.

[7] Toyama N, Shiraki K. Society of the Miyazaki Prefecture Dermatologists. Epidemiology of herpes zoster and its relationship to varicella in Japan: A 10-year survey of 48,388 herpes zoster cases in Miyazaki prefecture. J Med Virol 2009;81(12):2053–8.

[8] Kamiya H, Asano Y, Ozaki T, Baba K, Kumagai T, Nagai T, et al. Varicella vaccine potency and stability during transport and delivery. Kansenshogaku Zasshi 2011;85:161–5 [Japanese].

[9] Record of proceedings of the committee of Immunisation and Vaccine, Health Science Council, Ministry of Health, Welfare and Labour of Japan; 2016. June 22. [Japanese] <http://www.mhlw.go.jp/stf/shingi2/0000130809.html> [last accessed 2019 Feb 28].

[10] Hoshi S, Kondo M, Okubo I. Cost-effectiveness of varicella vaccine against herpes zoster and post-herpetic neuralgia for elderly in Japan. Vaccine 2017;35(24):3264–71.

[11] Le P, Rothberg MB. Cost-effectiveness of the adjuvanted herpes zoster subunit vaccine in older adults. JAMA Intern Med 2018;178(2):248–58.

[12] Curran D, Patterson B, Varghese L, Van Oorschot D, Buck P, Carrico J, et al. Cost-effectiveness of an adjuvanted recombinant zoster vaccine in older adults in the United States. Vaccine 2018;36(33):5037–45.

[13] Ikeda S. [Research guidelines on the evaluation of the cost-effectiveness of vaccination of Japan (Seshyu no Hiyoutaikouka no Hyouka ni Kansuru Kenkyu Gaidorain)]. Report of Research Grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan. March 2017. [Japanese] <https://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000184902_1.pdf> [last accessed 2019 Feb 28].

[14] Igarashi A, Ikeda S. Dealing with productivity losses in cost-effectiveness evaluations of vaccination. J Natl Inst Public Health 2017;66:41–6 [Japanese].

[15] TreeAge Pro 2015, R1.0. TreeAge Software, Williamstown, MA; software available at <https://www.treeage.com>.

[16] Ministry of Internal Affairs and Communications. Population estimates of Japan. Statistics Bureau, Tokyo; 2002.

[17] Watanabe D. [Sinki Taijouhousin Sabu Unito Wakutin (New shingles subunit vaccine)] Infectious Agents Surveillance Report (IASR). 2018;142-4. [Japanese] <https://www.niid.go.jp/niid/ja/allarticles/surveillance/2433-iasr/related-articles/related-articles-462/8237-462r09.html> [last accessed 2019, March 1].

[18] Record of proceedings of the committee of Immunisation and Vaccine, Health Science Council, Ministry of Health, Welfare and Labour of Japan; 2017. Feburary 10. [Japanese] <http://www.mhlw.go.jp/stf/shingi2/0000130809.html> [last accessed 2019 Feb 28].

[19] Murakami Y, Nishiwaki Y, Kanazu S, Oba M, Watanabe A. [A nationwide survey of PPSV23 vaccine coverage rates and their related factors among the elderly in Japan, 2016]. Nihon Koshu Eisei Zasshi 2018;65(1):20–4 [Japanese].

[20] Watanabe D, Mizukami A, Holl K, Curran D, Van Oorschot D, Varghese L, et al. The potential public health impact of herpes zoster vaccination of people aged ≥ 50 years in Japan: results of a markov model analysis. Dermatol Ther (Heidelb) 2018;8(2):269–84.

[21] Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine 2001;19(23–24):3076–90.

[22] Takao Y, Miyazaki Y, Okeda M, Onishi F, Yano S, Gomi Y, et al. Incidences of herpes zoster and postherpetic neuralgia in Japanese adults aged 50 years and older from a community-based prospective cohort study: the SHEZ study. J Epidemiol 2015;25(10):617–25.

[23] Sato K, Adachi K, Nakamura H, Asano K, Watanabe A, Adachi R, et al. Burden of herpes zoster and post-herpetic neuralgia in Japanese adults 60 years of age or older: results from an observational, prospective, physician practice-based cohort study. J Dermatol 2017;44:414–22.

[24] Ministry of Health, Labour and Welfare. Vital statistics of Japan 2015. Health and Welfare Statistics Association, Tokyo. [Japanese] <http://www.e-stat.go.jp/SG1/estat/List.do?lid=000001158448> [last accessed 2018 Oct 15].

[25] Mizukami A, Sato K, Adachi K, Matthews S, Holl K, Matsuki T, et al. Impact of herpes zoster and post-herpetic neuralgia on health-related quality of life in japanese adults aged 60 years or older: results from a prospective, observational cohort study. Clin Drug Investig 2018;38(1):29–37.

[26] Kawashima M, Nemoto O, Honda M, Watanabe D, Nakayama J, Imafuku S, et al. Amenamevir, a novel helicase-primase inhibitor, for treatment of herpes zoster: a randomized, double-blind, valaciclovir-controlled phase 3 study. J Dermatol 2017;44(11):1219–27.

[27] Yoshikawa T, Kawamura Y, Ohashi M. Universal varicella vaccine immunization in Japan. Vaccine 2016;34(16):1965–70.

[28] Clinical Trial gov Identifier: NCT02114333)], official title: A Comparison of the Immunogenicity and Descriptive Safety of a Live Attenuated Herpes Zoster Vaccine and the Glaxo Smith Kline (GSK) Herpes Zoster Recombinant HZ/su Candidate Vaccine in 50-59 Year Old and 70-85 Year Old Vaccine Recipients.

[29] Baxter R, Bartlett J, Fireman B, Marks M, Hansen J, Lewis E, et al. Long-term effectiveness of the live zoster vaccine in preventing shingles: a cohort study. Am J Epidemiol 2018;187(1):161–9.

[30] Prosser LA. Economic evaluation of vaccination for prevention of herpes zoster and related complications. Presentation to the advisory committee on immunization practices october 25th, 2017. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2017-10/zoster-03-prosser.pdf> [last accessed 2018 Oct 15].

[31] Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. ZOE-50 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med 2015;372(22):2087–96.

[32] Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Díez-Domingo J, et al. ZOE-70 Study Group. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. N Engl J Med 2016;375(11):1019–32.

[33] Dooling KL, Guo A, Patel M, Lee GM, Moore K, Edward A, et al. Recommendations of the advisory committee on immunization practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep 2018;67:103–8 [last accessed 2018 Oct 15].

[34] National pharmaceutical services. Drug update: April 2018. <https://www.pti-nps.com/nps/index.php/drug-update-november-2017/> [last accessed 2019 Feb 27].

[35] CDC vaccine price list. <https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html> [last accessed 2019 Feb 27].

[36] Nakamura H, Mizukami A, Adachi K, Matthews S, Holl K, Asano K, et al. Economic burden of herpes zoster and post-herpetic neuralgia in adults 60 years of age or older: results from a prospective, physician practice-based cohort study in Kushiro, Japan. Drugs Real World Outcomes 2017;4(4):187–98.

[37] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW, editors. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2015.

[38] Record of proceedings of the committee of cost-effectiveness, Central Social Insurance Medical Council, Ministry of Health, Welfare and Labour of Japan; 2017. March 15. [Japanese] <http://www.mhlw.go.jp/stf/shingi/shingi-chuo.html?tid=128159> [last accessed 2018 Oct 15].

[39] Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Econ 2010;19(4):422–37.

[40] National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. NICE: London; 2013.

[41] Net Monetary Benefit [online]. York; York Health Economics Consortium; 2016. <http://www.yhec.co.uk/glossary/net-monetary-benefit/> [last accessed 2018 Oct 15].

[42] Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352(22):2271–84.

[43] Schmader KE, Oxman MN, Levin MJ, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. Clin Infect Dis 2012;55(10):1320–8.

[44] Tseng HF, Smith N, Harpaz R, et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. JAMA 2011;305(2):160–6.

[45] Tseng HF, Harpaz R, Luo Y, et al. Declining effectiveness of herpes zoster vaccine in adults aged ≥60 years. J Infect Dis 2016;213(12):1872–5.

[46] Ogunjimi B, Van Damme P, Beutels P. Herpes zoster risk reduction through exposure to chickenpox patients: a systematic multidisciplinary review. PLoS One 2013;8(6):e66485.

Vaccine 36 (2018) 5109

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Letter to the Editor

Role of rotavirus vaccination on an emerging G8P[8] rotavirus strain causing an outbreak in central Japan

The manuscript by Hoque et al. reports the role of rotavirus vaccination on the emerging G8P[8] rotavirus A strains that caused a local outbreak in Shizuoka, Japan, during the 2017 rotavirus season [1]. Apart from whether or not a favorable result was due to the sharing of the P[8] VP7 genes between the vaccine strains and the outbreak strains, we welcome their findings, which lend strong assurance to current global recommendations of the use of rotavirus vaccines for the prevention of severe rotavirus gastroenteritis (RVGE) and encourage public health authorities to expedite the introduction of the rotavirus vaccine to infant immunization schedules in countries where the introduction has been delayed, such as Japan.

Regrettably, however, we noticed an apparent methodological inconsistency in the calculation of vaccine effectiveness (VE), which we wish to draw to the authors' attention for clarification. According to the authors, they designed a case-controlled study using rotavirus-negative patients as controls, which itself is being increasingly used and has gained acceptance [2]. This test-negative design aimed to estimate the VE by comparing the frequency of vaccination exposure of RVGE case-patients with the background frequency of control-patients who were free of rotavirus. Testing of all surveillance specimens indicates that these "test-negative controls" have similar healthcare-seeking behaviors for diarrheal illness to cases with confirmed rotavirus [3]. In Fig. 2 and Table 2, however, the authors divided the patients into vaccinated and unvaccinated groups [1], which suggests that they conducted a cohort study similar to those typically used in randomized clinical trials [4]. Moreover, they calculated attack rates of G8P[8] in vaccinated and unvaccinated patients instead of vaccine coverage among case and control patients.

According to the values and categorization of patients described in Fig. 2 and Table 2 [1], we understand that there were 41 G8P[8] -RVGE cases of which 22 were vaccinated and 19 were unvaccinated, and 20 test-negative controls of which 14 were vaccinated and 6 were unvaccinated. Therefore, a simple chi-squared test produces a crude odds ratio of 0.50 with lower and upper limits of the 95% confidence interval (CI) of 0.16 and 1.55. This indicates that the estimated VE against RVGE by emerging G8P[8] strains was 50% (95%CI: −55% to 84%). The small sample size and low statistical power (23%) would have made it difficult to detect statistical significance for a VE of 50% against G8P[8] -RVGE. When stratified by severity of RVGE, the authors estimated a VE by using G8P[8] -RVGE cases only, without including test-negative controls. Therefore, in the strict sense of the term, what the authors calculated does not represent the VE.

While the issues raised here do not change the overall results of the study, the methodological inappropriateness, if present as we suspect, needs to be clarified. Moreover, despite the methodological inconsistencies, we share the authors' view that currently-licensed vaccines play a pivotal role in preventing children from developing severe disease, including those with G8P[8] -RVGE.

References

[1] Hoque SA et al. Role of rotavirus vaccination on an emerging G8P[8] rotavirus strain causing an outbreak in central Japan. Vaccine 2018;36(1):43–9.
[2] WHO. Generic protocol for monitoring impact of rotavirus vaccination on gastroeneteroritis disease burden and viral strain; 2008.
[3] Tate JE et al. Use of patients with diarrhea who test negative for rotavirus as controls to estimate rotavirus vaccine effectiveness through case-control studies. Clin Infect Dis 2016;62(Suppl 2):S106–14.
[4] Schulz KF et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Med 2010;8:18.

Megumi Hara *
Department of Preventive Medicine, Faculty of Medicine, Saga University Saga, 5-1-1 Nabeshima, Saga 849-8501, Japan
* Corresponding author.
E-mail address: harameg@cc.saga-u.ac.jp

Osamu Nakagomi
Department of Molecular Epidemiology, Graduate School of Biomedical Sciences, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan
E-mail addresses: onakagom@nagasaki-u.ac.jp

DOI of original article: https://doi.org/10.1016/j.vaccine.2018.05.004

https://doi.org/10.1016/j.vaccine.2018.05.002

Vaccine 36 (2018) 5133–5140

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness analysis of pertussis vaccination during pregnancy in Japan

Shu-ling Hoshi [a,*], Xerxes Seposo [b], Ichiro Okubo [c], Masahide Kondo [a]

[a] Department of Health Care Policy and Health Economics, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennoudai, Tsukuba, Ibaraki 3058577, Japan
[b] Department of Environmental Engineering, Environmental Health Division, Kyoto University, Nishikyo-ku, Kyoto 6158246, Japan
[c] Yokohama City Institute of Public Health, 7-1, Tomiokahigashi 2-chom, Kanazawa-ku, Yokohama City 236-0051, Japan

ARTICLE INFO

Article history:
Received 8 February 2018
Received in revised form 12 July 2018
Accepted 13 July 2018
Available online 21 July 2018

Keywords:
Cost-effectiveness
Economic evaluation
Pertussis
Tdap
DTaP
Vaccination
Quality-adjusted life year

ABSTRACT

Background: Both re-emergence of pertussis outbreak among adolescents/adults and recent approval of the extended use of DTaP vaccine for boosting adolescents/adults against pertussis in Japan, have raised the possibility of using aP-containing vaccine in pregnant women to protect neonates and unvaccinated infants. There is a need, therefore, to evaluate the value for money of such possibility.
Methods: We evaluated the cost-effectiveness of conducting antepartum maternal vaccination (AMV) strategy in Japan. Considering the duration of vaccine effectiveness for infant (single year) and for mother (multiple years), the decision tree model and Markov model was adapted for infant and mother, respectively. Incremental cost-effectiveness ratio (ICER) compared with current no AMV strategy from societal perspective were calculated. The transition probabilities, utility weights to estimate quality-adjusted life year (QALY), and disease treatment costs were either calculated or extracted from literature. Costs per vaccination was assumed at ¥6000/US$54.5. Markov model for mothers with one-year cycle runs up to year four after vaccination, based on the waning of vaccine effectiveness. Infant who survived from pertussis was assumed to live until to his/her life expectancy.
Results: AMV strategy reduces disease treatment costs, while the reduction cannot offset the vaccination cost. Incremental QALYs were at 0.0002802, among them 79.5% were from infants, and others from mothers. ICER was ¥9,149,317/US$83,176 per QALY gained. One-way sensitivity analyses identified that the incidence rate and costs per shot were the two main key variables to impact the ICER.
Conclusion: We found that vaccinating pregnant women with aP-containing vaccine to prevent neonatal and unvaccinated infants from pertussis-associated disease in Japan can be cost-effective from societal perspective, under the WHO-suggested "cost-effective" criteria (1 to 3 times of GDP). Pertussis is expected be designated as a notifiable disease in 2018, re-analysis should be conducted when straightforward incidence data is available.

1. Introduction

Pertussis is an acute respiratory disease caused by the bacterium *Bordetella pertussis*. It is a highly contagious disease transmitted through respiratory droplets and is usually difficult to be differentiated from similar pathological conditions such as prolonged cough or common cold [1]. These similar pathological manifestations lead to underdiagnoses, thus leaving a pool of patients harboring the infection, which can serve as a source of future infections [1,2]. Pertussis can affect people of all ages, but with particularly severe complications among neonates and unvaccinated infants, thus making the prevention of such infection among the said vulnerable population of prime importance [1,2]. Even after the introduction of vaccination programmes and the achievement of high vaccination coverage, pertussis, which is endemic to all countries, have epidemic cycles occurring every 2–5 years [1].

Strategies for preventing pertussis among young infants before they commence their vaccinations at 2 or 3 months of age include: (1) booster doses in adolescents or adults (though there is yet have a substantial evidence that these programmes have significant impact) [1]; (2) cocooning strategy, i.e., vaccinating the infant's close contacts (beneficial effects of this strategy are inconsistent) [1]; (3) antepartum maternal vaccination (AMV) strategy, i.e., giving aP-containing vaccine in the third trimester in every pregnancy to prevent severe infant morbidity and mortality from pertussis during the narrow window before receiving their first dose of

* Corresponding author.
E-mail address: hoshi@hcs.tsukuba.ac.jp (S.-l. Hoshi).

https://doi.org/10.1016/j.vaccine.2018.07.026
0264-410X/

vaccine. Though AMV is relatively new [3], convincing and robust evidences have consistently indicated that it will not only reduce the infection among mothers, but also protect infants through the transfer of maternal antibody [1,4,5]. High-income countries, such as United States, the United Kingdom, Belgium, Ireland, Italy, Portugal, and New Zealand, where pertussis immunisation programmes have existed for a long time have already been implementing AMV [4,6].

In Japan, DTaP vaccine was introduced in 1981 and pertussis has been controlled by means of a vaccination schedule of three primary doses (at 3, 4, 5 months) and a single booster dose (18–23 months). Vaccine coverage of three primary doses of DPT-IPV in 2014 were at 99.2%, 99.1%, and 99.1%, in the first, second and third doses, respectively [7]. Similar to other countries, there is a re-emergence of pertussis outbreak in adolescents and adults, raising topics about pertussis control through various strategies. Currently, national initiatives have paved way in addressing pertussis control. In February 2016, the Ministry of Health, Labour and Welfare (MHLW) approved the extended use of DTaP as a booster for both adolescents and adults. This has then led to the possibility of using DTaP in pregnant women [8]. Taking into account the current progress in pertussis control, our study aims to estimate the value for money of AMV strategy by using aP-containing vaccine in Japan, assuming that in the future, there may be a need to consider its implementation.

2. Method

We conducted a cost-effectiveness analysis to evaluate the cost-effectiveness of the vaccination programme. The model was constructed by using TreeAge Pro, 2017, TreeAge Software.

2.1. Literature search

We searched the various databases for the parameters which were included in the modeling. Studies pertaining to epidemiology and prognosis of pertussis-relevant disease in Japan's setting were accessed from Medline database, Igaku Chuo Zasshi database (a Japanese medical bibliographic database which contains over 10 million citations originating from Japan), MHLW Grant System, and annual statistical reports published by the government. Due to insufficient evidences from Japan, overseas' reports from Medline, The Cochrane Database of Systematic Reviews, Health Technology Assessment database, and National Health Service, Economic Evaluation Database regarding vaccine effectiveness and utility weights to estimate QALY were used instead. Though we didn't limit the literature search to recently published journal articles, we selected, as much as possible, the robust ones suitable to our model, particularly data relevant to the epidemiology and prognosis of the disease, together with the vaccine effectiveness and the related utilities.

2.2. Programme

Our study estimated the value for money of AMV strategy in Japan by comparing AMV strategy with current no AMV strategy.

2.3. Models and variables

Two cohorts were followed via a decision tree and Markov model; one for the pregnant women and the other for their new born babies (given that maternal pertussis antibodies protect the newborn in the first 3 months of life). The decision tree model describing the courses for individuals started from a decision node, which were consequently followed by chance nodes with regard to the following circumstances (Fig. 1): (1) vaccinated/not vaccinated, (2) perinatal mortality/live birth, (3) pertussis contraction/no pertussis contraction, and (4) clinical courses after the contraction. Adverse effects of vaccination were not incorporated based on reports from large clinical trials and from post-marketing surveys [9,10].

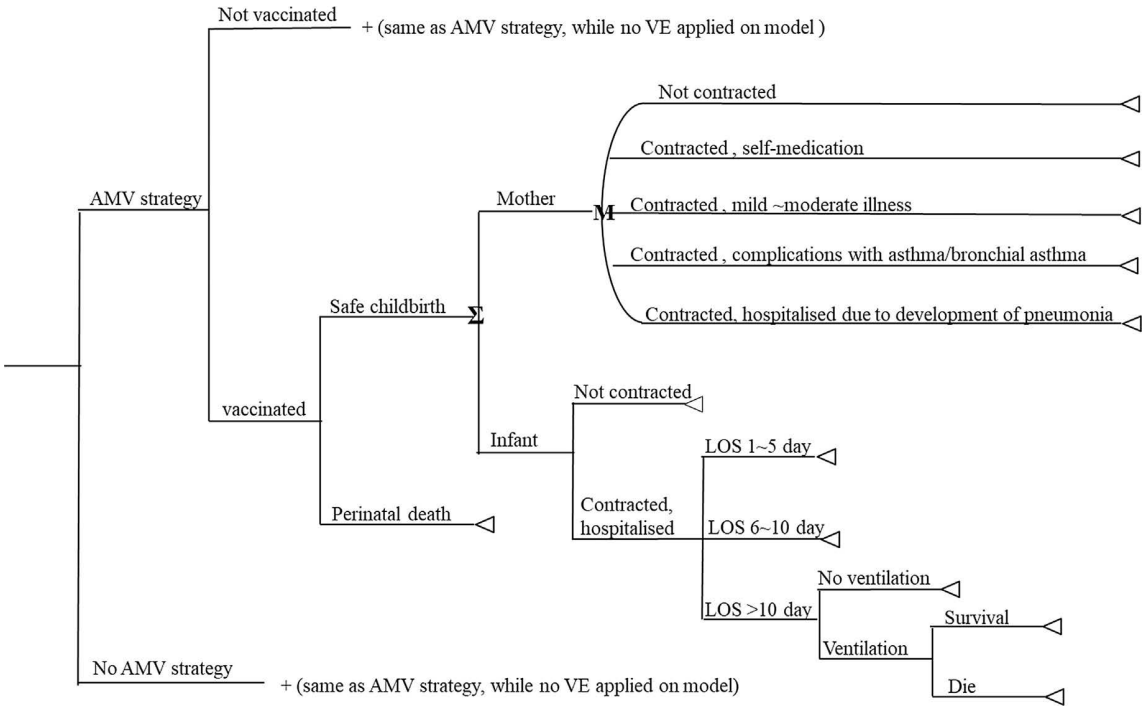


Fig. 1. Model. M: Markov model; Σ: Sum of both mother's and infant's results; LOS: Length of stay (in hospital).

Probability that a pregnant woman decided whether to uptake the vaccine or not, at 0.50, was based on influenza vaccine coverage among pregnant women in Japan in 2009 [11]. The probability that a baby was not safely delivered, at 0.0026, was based on the perinatal mortality in Japan in 2017 [12]. When perinatal mortality occurred, the benefit of vaccination will only go to the mothers.

The decision tree model continued for the infant's branch, because as the infant reaches the vaccination age, vaccine effectiveness (VE) from AMV strategy will no longer be considered, and the probability of being infected by pertussis will not be different between children born to vaccinated or non-vaccinated mothers. An infant who survived from pertussis was assumed to live until to his/her life expectancy [13]. In Japan, since pertussis incidence rate among infants aged < 3 m.o. is not available, we estimated the incidence rate from Suge et al. [14], at 139.6/100000 person-year (as seen in Table 1), instead.

We assumed that the pertussis cases aged <3 m.o. were all hospitalised [15]. The hospitalised infants were further divided into three groups by length of stay (LOS): (a) short-LOS group (probability of belonging to the group at 20.9%), (b) medium-LOS group (at 49.5%), and (c) long-LOS group (at 29.7%) [14]. LOS of each group is shown in Table 2. Among long-LOS group, 20.6% needed mechanical ventilation [14,16,17]. The fatality rate for those who required ventilation was assumed at 7.14% [17].

For mother's branch, a Markov model with one-year cycle was applied, since VE was expected to continue to the fourth year after vaccination [18]. Incidence rate of pertussis for the mother was assumed to be the same with that of the infant's [19]. Five mutually exclusive health states were used to describe the courses that a mother may follow (shown in Fig. 1). We assumed that 0.50% of mothers were hospitalised due to development of pneumonia based on a study by Miyashita et al. [20]. Miyashita et al. reported that among the 183 patients with laboratory-confirmed pertussis (by serology and polymerase chain reaction), only 0.50% was hospitalised, whereas percentage of hospitalisation among 1132 non-laboratory confirmed pertussis was at 0.80%; the study was conducted in a medical university hospital from 2005 to 2012 (with participants aged 16–77). There is a possibility that proportion of hospitalisation was underestimated because the authors excluded patients with underlying diseases that caused persistent cough. Taking all of these into consideration, we conservatively assumed the 0.50% hospitalisation rate in base-case analysis and used 0.80% for sensitivity analysis. Furthermore, we also assumed that 35.7% had complications with asthma/bronchial asthma and other mild-moderate illnesses based on study by Nogami et al. [21]. Nogami et al. reported that 5 of 14 loop-mediated isothermal amplification (LAMP) method and pertussis toxin antibody test of confirmed pertussis adult cases developed asthma/bronchial asthma, while only 5.3% (1/19) of non-confirmed cases developed asthma/bronchial asthma. We adopted the 35.7% in our base-case analysis and used 18.1% (6/33) in sensitivity analyses. Due to the data unavailability, we assumed that among patients who had mild-moderate illnesses, 80% seek medical treatment from a physician, while 20% treated themselves by purchasing over-the-counter (OTC) medication.

2.4. Vaccine effectiveness

VE in reducing contract pertussis for infants born to vaccinated mothers was assumed at 91% (86.5–94.4%) [4,5], preventing infants with pertussis from hospitalisation was at 58% (15–80%) [22], and preventing infant from death was at 95% [23]. Since there is no straightforward data related to the VE of preventing a vaccinated mother from contracting the disease, we adopted the VE estimates from two studies, which reported efficacy of aP-containing vaccine among adolescents/adults; namely, (1) Ward et al.'s RCT (reported a VE at 92% (32–99%) for a 22-month median follow-up duration among 18 wards), and (2) Koepke et al.'s comparison of VE between different Tdap brands (indicated that by the 4th year of Tdap receipt, no significant VE can be observed) [18]. In our study, VE in preventing a vaccinated mother from contracting pertussis was assumed to be at 92% (32–99%) in the 1st year and was assumed to linearly decrease to 0% within four years [18,24].

2.5. Health outcomes and end point

Incremental cost-effectiveness ratio (ICER) of AMV programme compared with no immunisation programme was calculated. ICER is defined as difference in cost between immunisation programme and no immunisation programme, divided by the difference in their effectiveness in terms of quality-adjusted life year (QALY). QALY, which takes into account the utility weights and the duration of illness, was estimated by assigning transition probabilities and utility weights from literature to the Markov model. The utility

Table 1
Estimation of infant pertussis hospitalisation incidence rate.

	Prefectures						
	Mie	Fukuoka	Chiba	Okinawa	Kouchi	Fukusima	Total
Original data from study of Suge et al.[a] (January 2009–December 2013)							
(a) Number of pertussis hospitalised patients age < 15 y.o.	22	249	57	78	24	35	465
(b) Percentage of hospitalised patient age < 3 m.o.	59%	57%	61%	49%	54%	57%	56%
(c) Number of pertussis hospitalised patients age < 3 m.o. (=a × b)	13	142	35	38	13	20	260
Number of birth from vital statistic							
2009	15,614	46,084	51,839	16,744	5415	16,326	152,022
2010	15,262	46,818	51,633	17,098	5518	16,216	152,545
2011	15,080	46,220	50,379	16,918	5244	15,072	148,913
2012	14,729	45,815	48,881	17,074	5266	13,770	145,535
2013	14,514	45,897	48,343	17,209	5266	14,546	145,775
(d) Total number of birth (2009 ~ 2013)	75,199	230,834	251,075	85,043	26,709	75,930	744,790
Person-year (<3m.o.) =(3/12) * (d)	18,800	57,709	62,769	21,261	6677	18,983	186,198
Incidence rate/10000 person-year							139.9 (=100000 × 260/186198)
Incidence rate/100000 person-month							11.66

[a] Suge et al.' study [14] is a complete enumeration retrospective survey from all the hospitals located in six prefectures of Japan, which reported 465 pertussis patients aged < 15 years old, who were hospitalised during January 2009 to December 2013, among them 56% (260 patients) were aged < 3 months.

Table 2
Variables.

Probability used at each chance node	Maternal	Infant	Distribution used in PSA	Reference
Probability for a pregnant woman to uptake the vaccine; %	50	–	constant	[11]
Probability that a baby was safely delivered (perinatal mortality); %	0.26	–	constant	[12]
Probabilities of a non-vaccinated mother or her infant to contract pertussis; per 100,000	139.6 (119.0–519.6)		Uniformed	[14,19,27]
Probabilities of a non-vaccinated mother/infant to be hospitalised after contracting pertussis;%	0.50	100		[15]
Probabilities of a hospitalised infant who's LOS* was 1–5 days (mean: 3 days); %	–	20.9	[c]	[14]
Probabilities of a hospitalised infant who's LOS was 6–10 days (mean: 8 days); %	–	49.5 (39.6–59.4)	Uniformed	[14]
Probabilities of a hospitalised infant who's LOS was >10 days (mean: 15 days); %	–	29.7 (23.8–35.6)	Uniformed	[14]
Probability of an infant pertussis patient with LOS >10 days, require mechanical ventilation treatment; %	–	20.6 (16.8–25.1)	Uniformed	[14,16,17]
Probability of an infant pertussis patient dying in NICU; %		7.14 (3.10–8.60)	Uniformed	[17]
Probabilities of a non-vaccinated mother developed pneumonia after contracting pertussis; %	0.5			[20]
Probabilities of a non-vaccinated mother developed asthma/bronchial asthma after contracting pertussis; %	35.7	–		[21]
Probabilities of a non-vaccinated mother ill mild ∼ moderate visted a doctor after contracting pertussis; %	80.0	–		assumed
Probabilities of a non-vaccinated mother ill mild ∼ moderate treated herself by purchasing OTCs; %	20.0	–		assumed
Life expectancy for new born (before discounting[a])	–	Mlae:79.58 Female: 86.32	constant	[13]
Percentage of male new born		0.513	constant	[12]
Vaccine effectiveness				
Protecting from contracting pertussis;%	92.0 (waning to 0 by 4 years)	91 (32–99)	uniform	[18,24,4,5]
Protecting infant with pertussis from hospitalisation;%	–	58.0 (15–80)	uniform	[22]
Protecting hospitalised infant from death;%	–	95.0 (76–100)	uniform	[23]
Reducing LOS; days	–	3 (2–4)	uniform	[22]
Reducing cough days	5 (4–6)		uniform	[26]
Utility weights				
Infant: hospitalised	–	0.58 (SD 0.37)	Normal	[25]
Infant: mechanical ventilation	–	0.29 (0.23–0.35)	uniform	[25]
Mother: mild ∼ moderate illness	0.85 (0.696–0.99)	–		[25]
Mother: hospitalised	0.82 (SD 0.3)	–	Normal	[25]
Mother: asthma	0.81 (SD 0.30)	–	Normal	[25]
LOS for short-LOS group; days	–	5 (4–6)	Triangle	assumed
LOS for median-LOS group;days	–	8 (7–9)	Triangle	assumed
LOS for long-LOS group; need not ventilation; days	–	9.5 (SD 4.4)	Normal	[16]
LOS for long-LOS group; need ventilation; days	–	26 (SD 9.6)	Normal	[16]
Average duration of assisted ventilation; days	–	12.5 (SD 7.4)	Normal	[16]
Mean cough days for none vaccinated mother/their infant; days	55 (45–120)	60 (45–120)	Triangle	[20.21]
Mean cough days for vaccinated mother/their infant; days	Half of mean cough days for none vaccinated mother/their infant			
*Costs**				
Vaccination	¥6,000 (¥2000-¥10000)	–	constant	assumed
Treatment costs				
Infant: per hospitalised day	–	¥46,010(±20%)	Gamma[b]	[36]
Infant: per NICU/PICU day	–	¥147,800(±20%)	Gamma[b]	[37]
Mother: OTC	¥10,000 (±20%)	–	Gamma[b]	assumed
Mother: outpatient	¥33,901	–	Gamma[b]	[36]
Mother: asthma/bronchial asthma	¥100,000	–	Gamma[b]	[36]
Mother hospitalised due to develop of pneumonia	¥116,304	–	Gamma[b]	[36]

LOS: Length of stay (in hospital); OTC: Over the counter medicine; NICU: Neonatal intensive care unit; PICU: Perinatal intensive care unit; PSA: probabilistic sensitivity analysis.
Numerical values shown in parentheses are, lower- and upper- values, Stand Deviation (SD) used for sensitivity analyses.
[a] Future cost and health benefit occurred after fist year were discounted (3% yearly) by using $P = F_0 + F_1/1.03 + F_2/1.03^2 + F_3/1.03^3 + \ldots$ Where P = present value, Fn = future cost or health benefit at year n.
[b] Probability density plots of gamma distributions: $\alpha = 1$, $\beta = \text{cost}/\text{cost}^2$.
[c] This variable are set as (1− Probabilities of a hospitalised infant whose LOS was 6–10 days – Probabilities of a hospitalised infant who's LOS was >10 days.

weights for mother/infant in different health states were from Lee et al. [25], which were frequently cited in previous studies. The literature search did not identify any study reporting the utility of patients who were in need of assisted ventilation, so it was assumed to be half of that of hospitalised infants. LOS for infant born to vaccinated mother was assumed to be 3 days shorter than those born to unvaccinated mothers [22]. The mean cough days for unvaccinated mothers and infants were assumed to be 55 (45–120 days) [20,21] and 60 days, respectively, while those for vaccinated mothers and their infants were assumed to be half of the unvaccinated and their infants [26].

We estimated ICER from societal perspective, which in this case is also payer's perspective because maternity leave (six weeks ahead of expected date of birth to eight weeks after delivery for all the female employees) and child-care leave (one year for male/female employee) are provided under Japanese law, therefore, there is no need to consider productivity loss due to vaccination or disease treatment.

2.6. Costs

The amount of direct payments to health care providers by government, municipalities, vaccinees, patients and third party payers was estimated as costs, while non-direct medical costs related to the immunisation programme were not included, because we assumed that the vaccination programme will be built within the public health services routine.

Vaccination costs per aP-containing shot (included doctor's fee for medical advice and technical fee for administering) was assumed at ¥6000 (US$54.5) based on: (1) costs per Tdap shot, though not available in Japan, ranged from US$14.6∼$57.6 according to previous studies [19,27–34] and (2) cost per DTaP in Japan is around ¥5500 (US$50.0) [35]. Treatment costs for hospitalised infant were estimated as cost per diem multiplied by hospital days. For infants, cost per diem of acute upper respiratory tract infection for patients aged 0–4 year old was assumed at ¥46,014 (US$418.3) based on the data published by MHLW in 2015 [36]. Cost per diem for patient who needs ventilation was assumed at ¥147,600 (US $1341.8; including NICU/PICU fee) based on medical fee schedule published in 2015 [37]. Cost for those who died after treatment, assumed as cost per diem for patient who needed ventilation multiplied by assisted ventilation days (12.5 ± 7.4 days), was from Kishimoto et al., which reported the treatment process of 46 severe infantile pertussis cases [16]. For mothers, ¥10,000 (US$90.9) per case for patients who purchased OTC, ¥30,000 (US$272.7) per case (¥4843/visit × 7 visits)for those who sought a doctor, and ¥100,000 (US$909.1) per case for those who developed bronchial asthma. For those who were hospitalised due to the development of pneumonia, cost was estimated as costs per diem multiplied by hospital days (¥38,768/US$352.4 × 3 days) based on data published by MHLW in 2015 [36]. Costs per diem used in this study were all reported at 2015, which were the most recently available data.

In this study, we used the average currency ratio from 2017 January to 2018 January, at 1US$ = ¥110.

2.7. Discounting

Costs and outcomes occurring over 1 year were discounted at an annual rate of 3% [38].

2.8. Sensitivity analyses

To appraise the ICERs' stability with the assumptions made in our economic model, and to explore the impact of each variable relative to each other, we performed one-way sensitivity analyses with all the variables utilised in this study. We also performed a two-way sensitivity analyses using the top two variables which changed the ICER the most. Probabilistic sensitivity analyses (PSA) [38,39], i.e., 1000 Monte Carlo simulations, were also conducted. Results of the upper- and lower- limits as well as distributions for PSA are reported in Table 3.

2.9. Cost-effectiveness threshold

Since there is no established threshold in judging the cost-effectiveness of public health programmes in Japan, a willingness-to-pay threshold at ¥5,000,000 (US$45,455) per QALY gained was utilised; a suggested threshold for evaluating healthcare interventions [40]. Also, WHO suggests a "cost-effective" criterion at 1 to 3 times of GDP [41]. These criteria were used in determining whether the immunisation programme was cost-effective or not.

3. Results

3.1. Results of base-case analysis

Table 3 shows the results of base-case analyses. When comparing AMV strategy with current no AMV strategy, estimated average incremental QALYs were at 0.0002802, among them 79.5% (0.0002227 QALYs) were from infant, and remaining 20.5% were from mother. Though AMV strategy reduces disease treatment costs, the reduction cannot offset the vaccination costs. Estimated incremental cost-effectiveness ratio (ICER) were at ¥9,149,317 (US $83,176)/QALY gained.

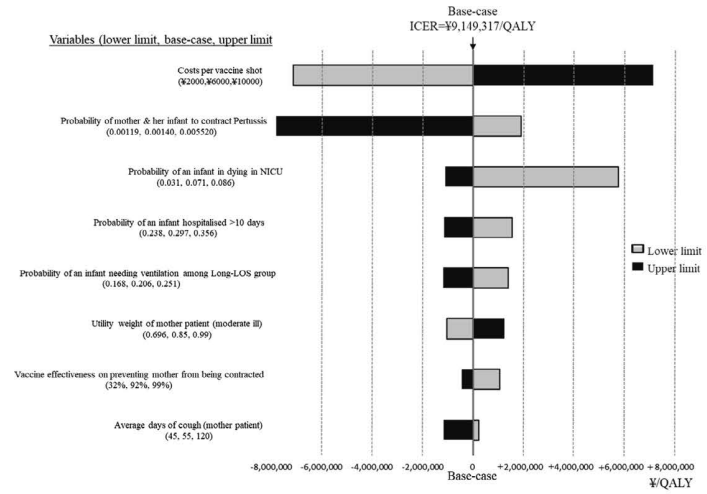
3.2. Results of sensitivity analyses

In Fig. 2-1, we can observe the eight variables which changed the ICER to be greater than ¥1,000,000 (US$9091)/QALY. Two-way sensitivity analyses on two key variables (Table 4, Fig. 2-2), i.e., costs per shot and probabilities of an infant aged < 3 m.o. from a non-vaccinated mother to contract pertussis, showed that if we adopt a ¥10,000,000 (US$90,909)/QALY as a criterion for cost-effectiveness, AMV strategy will be cost-effective regardless of the incidence rate of infant pertussis when cost per shot ≤¥5,500 (US$50.0). While if we adopt ¥5,000,000 (US$45,454.5)/QALY as a criterion, AMV strategy will only be cost-effective when cost per shot is ≤¥3,000 (US$27.3). Fig. 2-3 shows the cost-effectiveness acceptability curve (CEAC) of AMV strategy compared to current no AMV strategy. Among 1000 ICERs produced by Monte Carlo simulations, the probabilities that ICER is under ¥5,000,000 (US $45454.5) and ¥10,000,000 (US$90909.1) per QALY gained was at 65.4% and 92.3%, respectively. Mean ICER was ¥4,595,055 (SD = ¥3,563,788) or US$41,773 (SD = US$32,398) per QALY.

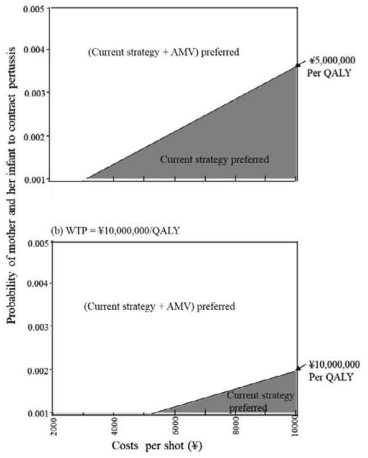
Table 3
Results: cost, incremental cost effectiveness and incremental effectiveness per mother and/or per infant, and ICER of base-case analysis.

	Cost		Incremental cost		Effectiveness	Incremental effectiveness	ICER	
Strategy	(¥)	(US$)	(¥)	(US$)	(QALYs)	(QALYs)	(¥/QALY)	(US$/QALY)
Total (mother and infant)								
current strategy	981	8.9			35.341758			–
current strategy + AMV	3545	32.2	2564	23.3	35.342038	0.0002802	9,149,317	83175.6
Mother								
current strategy	305	2.8			3.9825251			
current strategy + AMV	3188	29	2883	26.2	3.9825846	0.0000575		
Infant								
current strategy	675	6.1	319	2.9	31.35923			
current strategy + AMV	356	3.2	0	0	31.35946	0.0002227		

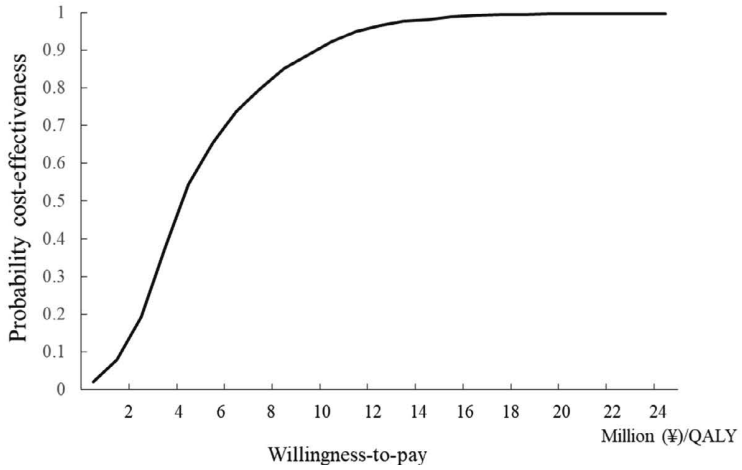
AMV: Antepartum Maternal Vaccination.
QALY: Quality Adjusted Life Year.
ICER: Incremental cost-effectiveness ratio.



(1) One-way sensitivity analysis (Tornado diagram showing the eight variables which changed the ICER to be larger than ¥1,000,000/QALY)



(2) Two-way sensitivity analyses (cost per shot vs. probability to contract pertussis)



(2) PSA: cost-effectiveness acceptability curve (CEAC).
Among 1,000 ICERs produced by Monte Carlo simulations, the probabilities that ICER is under ¥5,000,000 (US$45,454.5)/ ¥10,000,000 (US$90,909.1) per QALY gained was at 65.4%/92.3% when the costs of per course of vaccination were at¥60,000 (US$54.5).

Fig. 2. Sensitivity analyses (Current strategy + AMV vs. current strategy): (2-1) One-way sensitivity analyses, (2-2) Two-way sensitivity analyses, and (2-3) Probabilistic sensitivity analyses (PSA) QALY: quality adjusted life year. ICER: incremental cost-effectiveness ratio (¥/QALY). WTP: willingness-to-pay.

Table 4
Results (ICERs) of two-way sensitivity analyses (ICER = ¥/QALY).

	Incidence rate of pertussis in infant and mother, respectively				
Costs per shot	0.001	0.002	0.003	0.004	0.005
¥2000	3,438,545	941,905	109,841	Dominant*	Dominant
¥3000	5,936,300	2,191,228	943,019	319,026	Dominant
¥4000	8,434,056	3,440,551	1,776,198	944,132	444,982
¥5000	10,931,811	4,689,874	2,609,376	1,569,239	945,245
¥6000	13,429,566	5,939,196	3,442,555	2,194,345	1,445,508
¥7000	15,927,321	7,188,519	4,275,733	2,819,451	1,945,770
¥8000	18,425,076	8,437,842	5,108,912	3,444,557	2,446,033
¥9000	20,922,831	9,687,165	5,942,090	4,069,664	2,946,296
¥10,000	23,420,586	10,936,488	6,775,269	4,694,770	3,446,559

* Dominant: When comparing AMV strategy with current no AMV strategy, AMV strategy gained more QALYs with less cost.

4. Discussion

We conducted the first cost-effectiveness analysis in Japan comparing AMV strategy (with aP-containing vaccine) to current no vaccination for pregnant women. The purpose of AMV is mainly to prevent infant < 3 m.o. from contracting pertussis. Results showed that ICER of AMV strategy was under the WHO-suggested "cost-effective" criterion at 1 to 3 times of GDP (¥11,000,000 or US$100,000 in Japan) [41]. One-way sensitivity analyses showed that costs per shot and incidence rate of infant

pertussis were the two key variables which have large impacts on the results. Two-way sensitivity analyses indicated that the upper limit of the cost per shot to gain one QALY under ¥5,000,000 (US $45,455) and ¥10,000,000 (US$9091), regardless of the incidence rate of infant pertussis, were at ¥3000 (US$27.3) and ¥5500 (US $50.0), respectively. PSA show that the probabilities of AMV strategy to be under ¥5,000,000 (US$45454.5) and ¥10,000,000 (US $90909.1) per QALY are 65.4% and 92.3%, respectively. Mean ICER (¥4,595,055 or US$41773.2 per QALY) derived from PSA was favoured than that of deterministic analysis (¥9,149,317 or US $83175.6 per QALY) due to the usage of a relatively high upper limit of incidence rate of pertussis, i.e., 519.6/100,000 person-year; adopted from van Hoek et al. [19].

Since our study is the first study which evaluated the value for money of AMV strategy with aP-containing vaccine in Japan, no comparison can be done within same healthcare setting, hence, we compared our study with seven previous studies from overseas [19,27,30–34]. Reports by Atkins et al. (USA), Sartori at al. (Brazil) and Westra et al. (Netherland) concluded that AMV strategy was cost-effective [30–32]. While, van Hoek et al. (England) reported that AMV strategy gained one QALY at £16,856∼£42,070 depending on the incidence [19]. Lunger et al. (Netherland) reported an ICER of €126,000/QALY and discussed that the high ICER may partly be due to the assumption about the lower disease burden. Terranella et al. (USA) reported an ICER at US$414,523/QALY; the resulting high ICER may partly be due to the high vaccine cost US$57.6/shot (the highest one among the previous studies). Fernández-Cano et al. (Spain) reported a benefit-to-cost ratio of 0.15 and mentioned that additional CEA studies are needed. Analytic time horizon for mother in previous studies as well as in our study was more than 1 year, while this variable in study of Fernández-Cano et al. was set at 1 year only; this assumption may contribute to the low benefit-to-cost ratio. Our results suggested that AMV strategy in Japan can be potentially cost-effective, while the result is largely depending on the incidence. The incidence rates (per 100,000 person-month) of infant pertussis from previous studies were: 10.8 (age < 5 m.o.) in Lugner et al.'s study, 7–43.3 (age < 3 m.o.) in Van Hoek et al.' study; 5.54 (age < 12 m.o.) in Satori et al.'s study, 9.9 (age < 2 m.o.) in Fernandez-Cano et al.'s study; 12.4 (age < 1 m.o.), 18.9 (age 1 m.o.), 15.3 (age 2 m.o.) in Terranella et al.'s study; 9.0 (age < 1 m.o.), 17.7 (age 1 m.o.), and 23.4 (age 2 m.o.) in Westra et al.'s study. While in our study we observed that it was at 11.7 (<3 m.o.), which is comparatively low when compared to those used in previous studies. Incidence rates in all the seven previous studies were from the notifiable diseases' surveillance system of each country. Underreporting related to incidence in infants has been discussed in all the previous studies, most studies concluded that there were minor underreporting in infants' incidence because pertussis usually leads to disease severe enough to be recognise among infants [19,27,30–34]. Pertussis in Japan is defined as a sentinel-reported disease, therefore, at this point we have no way of finding whether our estimated results are under-reported or not. Costs per vaccination is another key variable which impacts the results largely. Among previous studies, cost per vaccination is between ¥1606∼¥6336 (US$14.6–57.6), which, in our study, was set at ¥6000 (US$54.5).

Our study has certain limitations, namely: (1) One-way sensitivity analyses revealed that pertussis incidence rate is a variable which has strong impact on ICER. In Japan, pertussis is not a notifiable disease, therefore we estimated the incidence rate based on a complete enumeration retrospective survey from all the hospitals located in six prefectures in the country. As discussed above, our estimated incidence rate is comparatively low when compared to those used in previous studies. Until the disease is assigned as a notifiable disease, there is no way to know whether the figure is overestimated or under estimated. From January 2018, pertussis is expected to be assigned as a notifiable disease, re-analysis should be conducted when incidence data is available. (2) Since we are not able to further characterise infant health outcome according to pneumonia or other pertussis-related complications, we used the costs of upper respiratory infection to estimate the hospitalised instead; this might result to the underestimation of pertussis cost. (3) We didn't define other strategies, which also aims at reducing the incidence among infant as alternative strategies. There are three previous studies which compared AMV with cocooning/neonatal strategy. Among them, two reported that AMV strategy is favourable than cocooning/neonatal strategy [31,34], while Lugner et al. reported that cocooning strategy is favourable than AMV strategy [33]. Lugne et al. assumed that in cocooning, all new mothers would be vaccinated only if they had not received the vaccine in the previous 5 years, while in AMV strategy all pregnant women had to be vaccinated during each pregnancy, this assumption makes the cocooning strategy to have lower vaccination cost than AMV strategy, which led to the result of cocooning being favourable than AMV. (4) The utility weights were cited from overseas which would cause uncertainty to the result, however, sensitivity analyses revealed that the impact of these utility weights were not significantly large. (5) Though vaccine coverage are high in Japan with three primary doses reaching 90%, the delays of vaccination, which happened in some cases would leave infants at a longer vulnerable age with less protection than anticipated [42]. It is possible that transplacental maternal antibodies or the antibody through breastfeeding could protect those infants [43]. (6) We only took into account the benefits of the protection of pertussis without considering additional benefits, which can be expected if combination vaccine was to be used. (7) An ecological study reported that increased DTaP immunisation coverage is associated with decreased sudden infant death syndrome (SIDS) mortality [44]. Another study reported that among SIDS mortality, 5.1% was caused by pertussis [45]. If these additional benefits were to be included, ICERs may be improved.

In February 2016, the MHLW approved the extended use of DTaP for boosting adolescents and adults [6]; a DTaP-IPV dose to replace current one Td dose for adolescents ageing 11–12 y.o. is now under consideration. Several countries have implemented booster dose for adolescents to control the transmission, however, vaccinating adolescents might increase the average age of re-infection resulting to more susceptible young mother due to the waning of the VE of the acellular vaccine to protect against the transmission of pertussis [19]. Taking into account the current circumstances in pertussis control, in the near further, Japan may need to consider the implementation of AMV strategy to protect infants from pertussis during the narrow window before receiving their first dose of vaccine. Our study suggests that in Japan using aP-containing vaccine in pregnant women has the potential to be cost-effective.

5. Author's contributions

Shu-Ling Hoshi participated in the concept and design of the study, performed the literature searches, acquired the data, participated in the analysis and interpretation of the data, and wrote the manuscript. Xerxes Seposo participated in the writing of the manuscript. Ichiro Okubo and Masahide Kondo participated in the concept and design of the study, and in the interpretation of the data.

Conflict of interest

None.

Sponsors role

None.

Acknowledgements

This study was supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan.

References

[1] World Health Organization. Pertussis vaccines: WHO position paper - September 2015. Wkly Epidemiol Rec. 2015;90:433–58.
[2] Nakano T, Watanabe M, Saitoh A, Suga S, Oishi K, Nishimura N. Symposium report of the 17th annual meeting of the Japanese Society for Vaccinology, 2013: bacterial vaccines: Effectiveness and issues. Vaccine 2016;34:1956–7.
[3] Raya BA, Edwards KM, Scheifele DW, Halperin SA. Pertussis and influenza immunisation during pregnancy: a landscape review. Lancet Infect Dis 2017;17(7):e209–22.
[4] Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014;384(9953):1521–8.
[5] Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of vaccination during pregnancy to prevent infant pertussis. Pediatrics 2017;139(5).
[6] European Center for Disease and Control. Recommended immunisations for pertussis <https://ecdc.europa.eu/en/pertussis> [accessed 2017.11.12].
[7] Ministry of Health, Labour and Welfare [Implementation of Routine Immunizations, 1994–2015]. Tokyo <http://www.mhlw.go.jp/topics/bcg/other/5.html> [In Japanese].
[8] Okada K. [Sekai to Nihon no Hyakunitizeki Taisaku] (Measures for world and Japan's pertussis). Radio Nikkei: Monthly Vaccine Info. 17, February 2014 [accessed 2017.11.12] <http://medical.radionikkei.jp/vaccine/vaccine_pdf/vaccine-140217.pdf> [In Japanese].
[9] Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway A, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. JAMA 2014;312:1897–904.
[10] Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. BMJ 2014;349:g4219.
[11] Nakai A, Saito S, Unno N, Kubo T, Minakami H. Review of the pandemic (H1N1) 2009 among pregnant Japanese women. J Obstet Gynaecol Res 2012;38:757–62.
[12] Ministry of Health, Labour and Welfare. Vital statistics of Japan 2015. Health and Welfare Statistics Association, Tokyo. Available from: <http://www.e-stat.go.jp/SG1/estat/List.do?lid=000001158448> [In Japanese].
[13] Ministry of Health, Labour and Welfare. The 21th life tables. Tokyo: Health and Welfare Statistics Association; 2015[In Japanese].
[14] Suga S, Nakamura H, Ihara T, Suyama K, Hosoya M, Ishiwada N, et al. [Hyakunitizeki syouni nyuuinnrei no kouhousiteki Tyousa (Retrospective investigation of hospitalized child pertussis cases). MHLW GRANTS 2014 [In Japanese].
[15] Ouchi K. [Syouni Kokyuuki Kannsen Shinnryou Gaidorainn 2017: Hyakunichizeki no Shinryou Kijunn to Kennsa jisshi furo-tya-to ga Minaoshita (Guidelines for the management of respiratory infectious diseases in children in Japan 2017: The diagnostic criteria of pertussis and the examination execution flowchart were revised. Medical Technology 2017;45(7):686–8 [in Japanese].
[16] Kishimoto K, Tamura T, Haruta T. The risk factors for severe infantile pertussis: report of 46 infants hospitalized with pertussis. Japanese J Pediatr Pulm 2008;19(2):122–9 [In Japanese].
[17] Takeuchi M, Yasunaga H, Horiguchi H, Matsuda S. The incidence of pertussis hospitalizations among Japanese infants: excess hospitalizations and complications? Epidemiol Infect 2012;140(8):1497–502.
[18] Koepke R, Eickhoff JC, Ayele RA, Petit AB, Schauer SL, Hopfensperger DJ, et al. Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand. J Infect Dis 2014;210:942–53.
[19] van Hoek AJ, Campbell H, Amirthalingam G, Andrews N, Miller E. Cost-effectiveness and programmatic benefits of maternal vaccination against pertussis in England. J Infect 2016;73:28–37.
[20] Miyashita N, Akaike H, Teranishi H, Kawai Y, Ouchi K, Kato T, et al. Diagnostic value of symptoms and laboratory data for pertussis in adolescent and adult patients. BMC Infect Dis 2013;13:129.
[21] Nogami H, Okada K, Honjo S, Kamachi K, Iwanaga T. Clinical features of pertussis in adult. Ann Japanese Resp Soc 2014;3:665–70 [In Japanese].
[22] Winter K, Cherry JD, Harriman K. Effectiveness of prenatal tetanus, diphtheria, and acellular pertussis vaccination on pertussis severity in infants. Clin Infect Dis. 2017;64:9–14.
[23] Amirthalingam G, Campbell H, Ribeiro S, Fry NK, Ramsay M, Miller E, et al. Sustained effectiveness of the maternal pertussis immunisation program in England 3 years following introduction. Clin Infect Dis 2016;63(suppl 4): S236–43.
[24] Ward JI, Cherry JD, Chang SJ, Partridge S, Lee H, Treanor J, et al. APERT Study Group. Efficacy of an acellular pertussis vaccine among adolescents and adults. N Engl J Med. 2005;353(15):1555–63.
[25] Lee GM, Salomon JA, LeBaron CW, Lieu TA. Health-state valuations for pertussis: methods for valuing short-term health states. Health Qual Life Outcomes 2005;3:17.
[26] Tozzi AE, Ravà L, Ciofi degli Atti ML, Salmaso Progetto Pertosse Working Group. Clinical presentation of pertussis in unvaccinated and vaccinated children in the first six years of life. Pediatrics 2003;112(5):1069–75.
[27] Fernández-Cano MI, Armadans Gil L, Campins Martí M. Cost-benefit of the introduction of new strategies for vaccination against pertussis in Spain: cocooning and pregnant vaccination strategies. Vaccine 2015;33(19):2213–20.
[28] Healy CM, Rench MA, Wootton SH, Castagnini LA. Evaluation of the impact of a pertussis cocooning program on infant pertussis infection. Pediatr Infect Dis J 2015;34(1):22–6.
[29] Amirthalingam G1. Strategies to control pertussis in infants. Arch Dis Child 2013;98(7):552–5.
[30] Atkins KE, Fitzpatrick MC, Galvani AP, Townsend JP. Cost-effectiveness of pertussis vaccination during pregnancy in the United States. Am J Epidemiol 2016;183:1159–70.
[31] Sartori AMC, de Soárez PC, Fernandes EG, Gryninger LCF, Viscondi JYK, Novaes HMD. Cost-effectiveness analysis of universal maternal immunisation with tetanus-diphtheria-acellular pertussis (Tdap) vaccine in Brazil. Vaccine 2016;34:1531–9.
[32] Westra TA, de Vries R, Tamminga JJ, Sauboin CJ, Postma MJ. Cost-effectiveness analysis of various pertussis vaccination strategies primarily aimed at protecting infants in the Netherlands. Clin Ther 2010;32:1479–95.
[33] Lugnér AK, van der Maas N, van Boven M, Mooi FR, de Melker HE. Cost-effectiveness of targeted vaccination to protect new-borns against pertussis: comparing neonatal, maternal, and cocooning vaccination strategies. Vaccine 2013;31:5392–7.
[34] Terranella A, Asay GR, Messonnier ML, Clark TA, Liang JL. Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: a decision analysis. Pediatrics 2013;131:e1748–56.
[35] Itatani T, Shimizu S, Iwasa M, Ohkusa Y, Hayakawa K. Cost-effectiveness analysis of a pertussis vaccination programme for Japan considering intergenerational infection. Vaccine 2013;31(27):2891–7.
[36] Medical Economics Division, Health Insurance Bureau, 2013. Iryou kyuhu jitai tyousa, 2015. Tokyo: Ministry of Health, Labour and Welfare 2015 [In Japanese].
[37] Medical fee schedule, Health Insurance Bureau, 2014. Sinnryou Houshyu, 2014. Tokyo: Ministry of Health, Labour and Welfare 2015 [In Japanese].
[38] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 4th ed. Oxford: Oxford University Press; 2015.
[39] Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. Med Decis Making 2012;32(5):722–32.
[40] Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Econ 2010;19(4):422–37.
[41] World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. Geneva, Switzerland: WHO Document Production Services; 2008.
[42] Curran D, Terlinden A, Poirrier JE, Masseria C, Krishnarajah G. Vaccine timeliness: a cost analysis of the potential implications of delayed pertussis vaccination in the US. Pediatr Infect Dis J 2016;35(5):542–7.
[43] Abu Raya B, Srugo I, Kessel A, Peterman M, Bader D, Peri R, et al. The induction of breast milk pertussis specific antibodies following gestational tetanus-diphtheria-acellular pertussis vaccination. Vaccine 2014;32(43):5632–7.
[44] Müller-Nordhorn J, Hettler-Chen CM, Keil T, Muckelbauer R. Association between sudden infant death syndrome and diphtheria-tetanus-pertussis immunisation: an ecological study. BMC Pediatr 2015;15:1.
[45] Heininger U, Kleemann WJ, Cherry JD, Sudden Infant Death Syndrome Study Group. A controlled study of the relationship between Bordetella pertussis infections and sudden unexpected deaths among German infants. Pediatrics 2004;114(1):e9–e15.

Vaccine 36 (2018) 5187–5193

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effectiveness of monovalent and pentavalent rotavirus vaccines in Japanese children

Kaoru Araki [a,b,*], Megumi Hara [a], Takeshi Tsugawa [c], Chisato Shimanoe [a], Yuichiro Nishida [a], Muneaki Matsuo [b], Keitaro Tanaka [a]

[a] Department of Preventive Medicine, Faculty of Medicine, Saga University Saga, Japan
[b] Department of Pediatrics, Faculty of Medicine, Saga University Saga, Japan
[c] Department of Pediatrics, Sapporo Medical University School of Medicine Hokkaido, Japan

ARTICLE INFO

Article history:
Received 26 March 2018
Received in revised form 26 June 2018
Accepted 3 July 2018
Available online 20 July 2018

Keywords:
Rotavirus
Vaccine effectiveness
Genotype
Severity

ABSTRACT

Background: Rotavirus (RV) vaccination has been available in Japan since November 2011, but is not yet part of Japan's national immunisation programs. There are insufficient data on vaccine effectiveness (VE) among Japanese children.

Methods: Between the months of January and May in 2014 and 2015, we conducted active surveillance of gastroenteritis among children at 14 medical facilities. Rectal swabs from all patients with diarrhoea or vomiting were tested for RV by immunochromatography, and positive specimens were genotyped. Demographic data and immunisation records were obtained from a questionnaire completed by their parents/guardians or medical records. A test-negative case-control design was used to examine vaccine effectiveness (VE) using unconditional logistic regression analysis adjusted for possible confounding factors.

Results: Among the 1519 eligible subjects (children with acute gastroenteritis symptoms aged ≥2 months to <3 y visiting medical facilities) recruited, 487 cases and 925 controls were enrolled. Cases had more severe symptoms than controls, requiring more intensive treatment, including intravenous rehydration or hospitalisation. VE against all rotavirus gastroenteritis (RVGE) was 80.0% (95% confidence interval [CI], 72.8–85.5%), and VEs against RV1 and RV5 were similar, at 80.6% (95%CI, 70.7–87.1%) for RV1 and 80.4% (95% CI, 69.1–87.6%) for RV5. Although VEs of both vaccines decreased with age, VEs against all RVGE were >70% up to 2 years after vaccination. VEs increased with severity of RVGE, and VE against severe RVGE, requiring intravenous rehydration or hospitalisation, was 97.3% (95% CI, 88.8–99.3%). VEs of RV1 and RV5 against G1P[8] and G2P[4] were comparable, at RV1, 89.8% (95% CI, 78.2–95.5%) and 78.3% (95% CI, 23.6–93.8%); and RV5, 85.8% (95% CI, 72.8–92.6%) and 88.1% (95% CI, 10.1–98.4%), respectively.

Conclusions: Rotavirus vaccines were effective in preventing mild to severe RVGE, irrespective of vaccine type, time since vaccination, or RV genotype.

1. Introduction

Rotavirus (RV) is a common cause of severe gastroenteritis among infants and young children aged <5 years. It causes diarrhoea and vomiting, and can cause fatal dehydration, especially in developing countries [1]. Since 2006, two live oral vaccines, a monovalent human rotavirus vaccine (RV1, Rotarix®, GlaxoSmithKline Biologicals, Rixansart, Belgium) and a pentavalent bovine-human reassortant vaccine (RV5, RotaTeq®, Merck & Co., Inc., Rahway NJ, USA) have been licensed in >100 countries [2,3]. The World Health Organization (WHO) recommends these vaccines for national immunisation programs (NIP) [4]. Globally, 86 countries had developed NIPs by September 2016 [5].

Despite the WHO recommendations [4], and the effectiveness [6,7], safety [8], and impact of the RV vaccines against RV-related death [9,10] or hospitalisation [10], many countries in Asia, including Japan, have not yet introduced RV1 or RV5 into their NIPs [5]. The disease burden, severity of disease, vaccine efficacy or vaccine effectiveness (VE), and vaccine safety are generally addressed in the decision-making process of introducing a vaccine into an NIP [11]. Following clinical trials in Japan [12,13], RV1 and RV5 became available on the private market in November 2011 and July 2012,

* Corresponding author at: Department of Preventive Medicine, Faculty of Medicine, Saga University Saga, Japan.
E-mail address: e5814@cc.saga-u.ac.jp (K. Araki).

https://doi.org/10.1016/j.vaccine.2018.07.007
0264-410X/

respectively. Before the introduction of RV vaccines in Japan, RVGE-related hospitalisation among children aged <5 y was estimated to be 7.9–17.6 hospitalisations/1000 person-years, 2–5 times higher than that in other developed countries (before the advent of the vaccine), although fatal cases were rare [14]. Recently, substantial declines in RVGE incidence [15] and RVGE hospitalisation cases were reported in the post-licensure period [16]. A case-control study using a test-negative design showed that vaccine effectiveness (VE) against hospitalisation due to RVGE among children <5 y was 70.4% in Japan [17]. However, VE against RVGE according to disease severity, virus genotype, vaccine type, and duration after vaccination have not been fully evaluated in Japan. Because the disease burden, epidemic virus type, and vaccination coverage are different in different countries, evaluation of VE by each country is needed. Without such evidence it is difficult for health decision makers to decide upon introduction of RV vaccine into their country's NIP.

The present study was conducted to evaluate the VE of RV against RVGE according to vaccine type, duration of protection, RVGE severity, and RV genotype among children aged <3 y in Japan.

2. Materials and methods

2.1. Study design and setting

We evaluated the VE of rotavirus vaccines using a WHO test-negative design, which is commonly used for assessing VE against rotavirus [18]. We conducted active surveillance of gastroenteritis among children ≥2 months to <3 years. All patients presenting to a medical facility for acute gastroenteritis were enrolled. The study was conducted between 1st January and 31 May in both 2014 and 2015. According to the National Epidemiological Surveillance of Infectious Diseases, Japan, this period correlates with the peak rotavirus epidemic data reported by a national infection research institute [19]. The investigation areas were Saga and Fukuoka prefectures. In most of these areas, rotavirus vaccination is voluntary, costing ¥13000–15000 (€96.7–111.6) per inoculation. We requested the cooperation of 14 medical facilities (12 clinics and 2 hospitals). Clinics were paediatric outpatient departments with weekday hours, and hospitals included paediatric outpatient, inpatient, and emergency departments. The survey protocol was approved by the Ethical Committees of Saga University Faculty of Medicine and Saga-ken Medical Centre Koseikan. Other facilities were approved as cooperating institutions of the Saga University Faculty of Medicine.

2.2. Patient recruitment and case/control definition

Children, ≥2 months to <3 y, visiting the target medical facilities for acute gastroenteritis, whose parents or guardian gave consent according to the rules of the Declaration of Helsinki to this study, were eligible for recruitment. Acute gastroenteritis was defined as two or more diarrhoea (looser-than-usual stool or liquid stools or frequent stools) during the preceding 24 h or vomiting (excluding coughing with vomiting). Children were excluded if their symptom onset occurred within 14 days of rotavirus vaccination (immunization status was available from records in 98% of patients; 2% were from parent/guardian verbal report) or they had a history of previous rotavirus infection before presentation. Stool samples were collected by rectal swabs from all eligible children and tested initially for rotavirus via an immunochromatographic assay (ICA, ImmunoCard® SD Rota/Adeno, Standard Diagnostics, Inc., Yongin-si, South Korea) at each facility. The sensitivity and specificity of ICA were 100% and 99.7%, respectively [20]. Even if the initial symptom was vomiting only and diarrhoea appeared after the visit, all rectal swabs were tested for rotavirus. Stool samples obtained at study recruitment were stored at −20 °C after testing in each medical facility, and positive samples were sent to Sapporo Medical University for genotyping.

2.3. Data collection

The following data were obtained by means of a self-administered questionnaire completed by each child's parents or guardian during the visit: sex, date of birth, birth weight, current breastfeeding (yes/no), receipt of day care service, number of family members in the home, number of siblings in the home, parents/guardian age(s), underlying illnesses (food allergy, asthma, atopic dermatitis, epilepsy, otolaryngologic disease, digestive disease, heart disease, Kawasaki disease, febrile convulsions, immunodeficiency, and congenital deformity), history of RVGE, history of rotavirus vaccination, number of doses, date of the last dose and type of vaccine (if vaccinated), clinical symptoms (diarrhoea, vomiting, fever, seizures), and date of symptom onset. In Japan, vaccination history is usually recorded in a maternal and child health handbook maintained by individuals. Thus, the information collected about vaccination status was verified using the record. When missing answers or illogical data were detected, accurate data were obtained by telephone interview with the parent/-guardian. In addition, we also obtained the following clinical findings from medical records in the medical facilities in cooperation with paediatricians: detailed clinical symptoms, date at diagnosis, and treatment (oral medication, intravenous rehydration to correct dehydration, hospitalisation). Unless there was a second visit for the acute illness, within 1–2 months after the subjects' outpatient visit we telephoned their parents/guardians to assess when their symptoms had resolved, and whether they had taken the child to a different facility for further treatment.

2.4. Severity classification

To assess the severity of disease in the outpatient setting, we adopted three of seven variables in the modified Vesikari score [21] (MVS) (severity score): (1) maximal number of diarrhoeal stools per 24 h period (0 points: none, 1 point: 1–3, 2 points: 4–5, 3 points: ≥6), (2) maximal number of vomiting episodes per 24 h period (0 points: none, 1 point: 1, 2 points: 2–4, 3 points: ≥5), and (3) maximal fever (recorded at the facility or at home) (0 points: <37.0 °C, 1 point: 37.1–38.4 °C, 2 points: 38.5–38.9 °C, 3 points: ≥39.0 °C). The symptoms of all enrolled patients were scored, and disease severity was classified into three categories (mild severe: 1–4, moderate severe: 5–6, and severe: 7–9 in total score).

2.5. Rotavirus genotypes

Double-stranded RNA was extracted from stool suspensions of cases in assay diluent using a QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany). Reverse transcription-polymerase chain reaction (RT-PCR) was performed as previously described [22] using conventional G and P genotyping primers [23,24]. Briefly, reverse transcription was performed using reverse transcriptase (SuperScript II®, Invitrogen, Carlsbad CA, USA) at 45 °C for 45 min followed by 94 °C for 3 min. Polymerase chain reaction (PCR) was performed using a DNA polymerase (GoTaq Flexi DNA polymerase®, Promega, Madison WI, USA) in a thermal cycler (SimpliAmp®, Applied Biosystems, Foster City CA, USA) under the following conditions: initial denaturation at 95 °C for 15 min; 40 cycles at 94 °C for 45 s, 50 °C for 45 s, and 70 °C for 2.5 min; and

a final extension at 70 °C for 7 min. The G and P genotypes were determined by the size of the second PCR products.

2.6. Statistical analysis

Primary analysis assessed the effectiveness against any severity of RVGE of at least one dose of either vaccine, full doses of RV1 (two doses) or RV5 (three doses), or partial vaccination (one dose of RV1 and one or two doses of RV5), compared with no vaccination. Subgroup analyses were performed to estimate (1) the duration of protection after vaccination by measuring effectiveness among children 6–11 months, 1 y, and 2 y of age, (2) potential differences in protection against RVGE according to severity and treatment, and (3) strain-specific protection.

We first performed bivariate analyses to assess differences in indicators of the background characteristics, clinical symptoms, and treatment between cases and controls using the chi-squared test or Wilcoxon rank sum test. Background characteristic variables that exhibited a $P < .05$ or appeared to be medically related to the disease were considered potential confounders for adjustment. Unconditional logistic regression models were constructed to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). We employed the following continuous and categorical variables for adjustment: age (months), use of day care (yes/no), having siblings (yes/no), current breastfeeding (yes/no), facility (12 clinics/2 hospitals), onset year (2014/2015), and severity score (1–4, 5–6, and 7–9). For sensitivity analysis, we further adjusted for year and month of birth, creating six categories: January–June 2012, July–December 2012, January–June 2013, July–December 2013, January–June 2014, and July 2014–February 2015. We included this as a possible confounding factor. VE was calculated as $(1 - \mathrm{OR}) \times 100$ (%). Commercial software (Ver. 9.3 for Windows; SAS Institute, Cary, NC, USA) was used for statistical analysis.

3. Results

Of a total of 1516 patients, the parents/guardians of 1488 (98.1%) consented to participate in this study and responded to the questionnaire. Of these, we excluded 76 patients (5.1%) who did not meet the inclusion criteria, leaving a final group of 1412, including 487 cases and 925 test-negative controls (Fig. 1).

Table 1 shows the characteristics, clinical symptoms, and treatment of cases and controls. The mean severity score of all 1412 patients was 3.42, and the scores in the top 10% and 25% of all patients were ≥7 and ≥5, respectively. Based on this result, we defined the severity of disease according to the following severity score: 1–4 mild, 5–6 moderate, and 7–9 severe. The proportion of subjects with severe symptoms was significantly higher in cases than in controls. In total, progress following outpatient visits could be confirmed for 1010 patients (395 cases and 615 controls). Cases more commonly required extensive treatment, including intravenous rehydration and hospitalisation, than controls.

After adjustment for potential confounders, the VE against any severity of RVGE was calculated at 80.0% (95% CI, 72.8–85.5). The VE was similar for full doses of the two vaccines; partial vaccination provided lower protection than full vaccination (Table 2).

Table 3 shows VE according to age by vaccine type. Because only seven cases were fully vaccinated by 6–11 months of age, we considered the VE of the two vaccines together. Although the VE declined over time following vaccination, the effect persisted at 24–35 months of age.

Table 4 shows VE by symptom severity or clinical treatment. The VE against RVGE with a severity score of 5–6 was 85.9% (95% CI, 76.2–91.6) and that for a severity score of 7–9 was 91.4% (95% CI, 78.1–96.6). Among children with complete clinical information

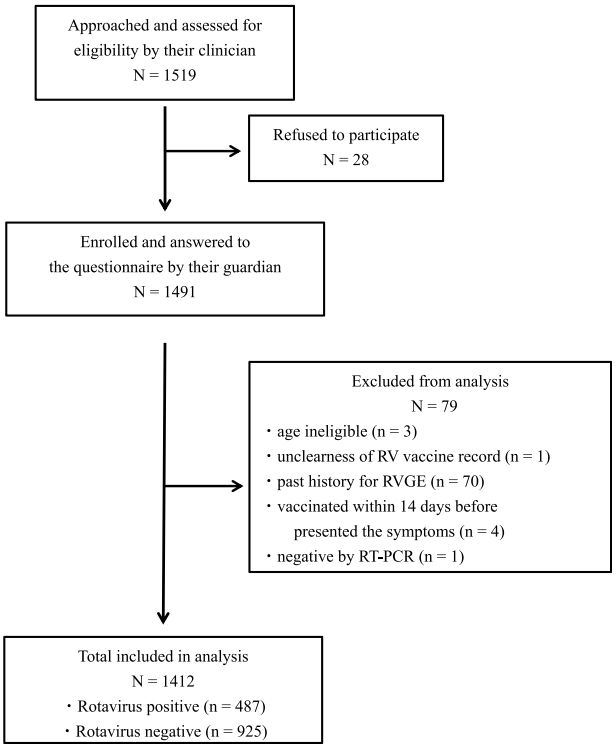


Fig. 1. Flow diagram for the enrollment of cases and controls (January to May 2014 and 2015).

for treatment, only two vaccinated cases (0.5%) required intravenous rehydration, and none needed hospitalisation. The VE for patients needing intravenous rehydration or hospitalisation due to RVGE was 97.3% (95% CI, 88.8–99.3).

The rotavirus genotype was identified in 99.8% (487/488) of rotavirus-positive specimens. The most common rotavirus GP genotype was G1P[8], which was detected in 235 strains (48.2%), followed by G9P[8] (175; 35.9%) and G2P[4] (35; 7.2%) (Supplemental Table 1). The VEs of RV1 and RV5 against G1P[8] were 89.8% (95% CI, 78.2–95.5) and 85.8% (95% CI, 72.8–92.6), and those against G2P[4] were 78.3% (95% CI, 23.6–93.8) and 88.1% (95% CI: 10.1–98.4), respectively. The VE against G9P[8] was lower for both vaccines compared to that against G1P[8] and G2P[4] (Table 5). Results from sensitivity analyses, including adjustments for year and month of birth, were comparable to the above VEs (Supplemental Tables 2–5).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.07.007.

4. Discussion

We demonstrated the effectiveness of RV vaccines according to vaccine type, time interval after vaccination, disease severity, and virus genotype in Japan, using a case test-negative control design. RV vaccines were highly effective against severe RVGE needing intravenous rehydration or hospitalization (VE was 97.3% [95% CI: 88.8–99.3]) and mild-to-moderate RVGE (VE was 78.7% [68.9–85.4] for mild RVGE and 85.9% [76.2–91.6] for moderate RVGE). The VEs of RV1 and RV5 against any genotype of RVGE were comparable. These levels of effectiveness were similar to those reported by previous clinical trials [12,13], confirming the effectiveness of rotavirus vaccines in the real-world setting in Japan. In addition, although it waned somewhat with age, VE was >70%

Table 1
Baseline characteristics, clinical symptoms, and treatment of cases and controls.

Variables	Cases, n = 487 Rotavirus-positive		Controls, n = 925 Rotavirus-negative		*P* value[a]
Demographics					
Age at onset, median months [range]	19	[2–35]	15	[2–35]	<.01
Sex: males, n (%)	269	(55.2)	503	(54.4)	0.76
Location of hospital, n (%)					0.14
Saga	347	(71.2)	693	(74.9)	
Fukuoka	140	(28.8)	232	(25.1)	
Onset year, n (%)					<.01
2014 season	64	(13.1)	262	(28.3)	
2015 season	423	(86.9)	663	(71.7)	
Additional history					
Underlying condition: Yes, n (%)	83	(17.0)	146	(15.8)	0.54
Premature (BW > 2500 g) [b], n (%)	438	(90.7)	811	88.3	0.18
Use of day care : Yes, n (%)	320	(66.4)	482	(52.5)	<.01
Siblings: Yes, n (%)	319	(65.5)	554	(59.7)	0.03
No. of siblings, median [range]	1	[1–7]	1	[1–6]	0.18
Age of parents, median years [range]					
Mother[c]	32	[19–46]	32	[18–48]	0.35
Father[d]	34	[20–57]	34	[20–62]	0.67
Breastfed[e]: Yes, n (%)	143	(29.6)	405	(44.1)	<.01
Systemic symptoms before receiving the medical examination					
Diarrhea, n (%)	460	(94.5)	805	(87.0)	<.01
No. of diarrheal stools, median [IQR]	4	[2–6]	3	[2–6]	0.15
Vomiting, n (%)	368	(75.6)	412	(44.5)	<.01
No. of vomiting episodes, median [IQR]	3	[2–5]	2	[1–4]	<.01
Fever, n (%)	340	(69.8)	364	(39.4)	<.01
Max recorded fever, median [IQR]	38.5	[37.9–39.0]	38.0	[37.6–38.9]	0.02
Seizure[f] (in the course of disease), n (%)	8	(2.0)	4	(0.7)	0.07
Severity of disease[g], n (%)					<.01
Mild severe	256	(52.6)	80.1	(86.6)	
Moderate severe	162	(32.3)	103	(11.1)	
Severe	69	(14.1)	21	(2.3)	
Treatment[h], n (%)					<.01
Outpatient (oral treatment)	320	(81.0)	594	(96.6)	
Outpatient (intravenous rehydration)	64	(16.2)	16	(2.6)	
Hospitalisation	11	(2.8)	5	(0.8)	

Abbreviations: SD, standard deviation; IQR, Interquartile Range.
[a] Chi-squared test or Wilcoxon's rank-sum test was used as appropriate.
[b] Analyses were based on data from 483 cases and 919 controls.
[c] Analyses were based on data from 482 cases and 919 controls.
[d] Analyses were based on data from 485 cases and 919 controls.
[e] Analyses were based on data from 459 cases and 909 controls.
[f] Analyses were based on data for children younger than 12 months old (n = 383).
[g] Severity of disease was assessed using the severity score (see the Methods section) "mild severe" corresponds to a total score of 1–4, "moderate severe" corresponds to 5–6, and "severe" corresponds to 7–9.
[h] Analyses were based on data from patients for whom confirmation of the outcome was possible (cases/control = 395/615).

Table 2
Vaccine effectiveness against rotavirus disease.

	Cases		Controls		Crude OR	Adjusted OR[b]	VE(%)	95% CI(%)
	n	(%)	n	(%)				
Unvaccinated	420	(86.2)	498	(53.8)	1[c]	1[c]		
Vaccinated (≥1 dose)	67	(13.8)	427	(46.2)	0.19	0.20	80.0	72.8–85.5
Partial vaccination[a]	4	(0.8)	22	(2.4)	0.30	0.33	67.2	−3.7–89.6
Full dose vaccination								
RV1 2 doses	36	(7.4)	226	(24.4)	0.19	0.19	80.6	70.7–87.1
RV5 3 doses	27	(5.5)	179	(19.4)	0.18	0.20	80.4	69.1–87.6

Abbreviations: OR, odds ratio; VE, vaccine effectiveness; CI, confidence interval; RV1, monovalent; RV5, pentavalent.
[a] Received one or two doses of RV5 or one dose of RV1.
[b] Adjusted for age in months, use of day care, having siblings, breastfeeding, severity score, facility, and onset year.
[c] Reference category.

2 y after vaccination. These results are pivotal evidence in favour of the introduction of RV vaccine into the Japanese NIP.

The strength of this study was that VE was evaluated according to the vaccine type and RV genotype. The effectiveness of RV1 against RVGE of G2P[4] strains has been a concern because genotypes of all 11 genes of G2P[4] are typically different from those of G1P[8] strains [25]. However, despite being slightly less effective than the 88.1% of VE of RV5, the 78.3% VE of RV1 proves its worth against G2P[4] in our study. These data are compatible with previous reviews in other developed countries. The pooled VEs of RV1 and RV5 against severe RVGE attributed to G2P[4] were 87% (95% CI, 76–93) and 82% (95% CI, 70–89), respectively [26]. In

Table 3
Vaccine effectiveness against rotavirus disease in Japan according to age.

		Cases		Controls		Crude OR	Adjusted OR[b]	VE	95% CI (%)
Age		n	(%)	n	(%)				
6–11 months	Unvaccinated	53	(88.3)	141	(52.6)	1[c]	1[c]		
	Full-dose vaccination[a]	7	(11.7)	123	(45.9)	0.15	0.14	85.8	64.3–94.3
12–23 months	Unvaccinated	233	(87.9)	240	(54.7)	1[c]	1[c]		
	RV1 2 doses	14	(5.3)	103	(23.5)	0.14	0.16	84.5	70.6–91.8
	RV5 3 doses	17	(6.4)	90	(20.5)	0.20	0.17	83.0	68.7–90.7
24–35 months	Unvaccinated	129	(82.2)	88	(54.0)	1[c]	1[c]		
	RV1 2 doses	15	(9.6)	50	(30.7)	0.21	0.24	75.7	51.4–87.8
	RV5 3 doses	10	(6.4)	25	(15.3)	0.27	0.29	70.8	32.2–87.4

Abbreviations: OR, odds ratio; VE, vaccine effectiveness; CI, confidence interval; RV1, monovalent; RV5, pentavalent.
[a] Received two doses of RV1 or three doses of RV5.
[b] Adjusted for use of day care, having siblings, breastfeeding, severity score, facility, and onset year.
[c] Reference category.

Table 4
Vaccine effectiveness against rotavirus disease in Japan by severity of symptoms or clinical treatment.

	Cases		Controls		Crude OR	Adjusted OR[c]	VE(%)	95% CI(%)
	n	(%)	n	(%)				
	Mild severe[b]							
Unvaccinated	213	(83.2)	498	(53.8)	1[d]	1[d]		
Full-dose vaccination[a]	40	(15.6)	405	(43.8)	0.23	0.21	78.7	68.9–85.4
	Moderate severe[b]							
Unvaccinated	143	(88.3)	498	(53.8)	1[d]	1[d]		
Full-dose vaccination[a]	18	(11.1)	405	(43.8)	0.16	0.14	85.9	76.2–91.6
	Severe[b]							
Unvaccinated	64	(71.1)	498	(53.8)	1[d]	1[d]		
Full-dose vaccination[a]	5	(5.6)	405	(43.8)	0.10	0.09	91.4	78.1–96.6
	Requiring intravenous Rehydration							
Unvaccinated	61	(15.4)	295	(48.0)	1[d]	1[d]		
Full-dose vaccination[a]	2	(0.5)	302	(49.1)	0.03	0.03	96.8	86.8–99.2
	Requiring hospitalisation							
Unvaccinated	11	(1.8)	295	(48.0)	1[d]	1[d]		
Full-dose vaccination[a]	0	(0.0)	302	(49.1)	0	0	100	Not estimated

Abbreviations: OR, odds ratio; VE, vaccine effectiveness; CI, confidence interval; RV1,monovalent; RV5, pentavalent.
[a] Received two doses of RV1 or three doses of RV5.
[b] Severity of disease was assessed with severity score (see the Methods section).''mild severe" corresponds to a total score of 1–4, ''moderate severe" corresponds to 5–6, and ''severe" corresponds to 7–9.
[c] Adjusted for age in months, use of day care, having siblings, breastfeeding, facility, and onset year.
[d] Reference category.

Table 5
Vaccine effectiveness against rotavirus disease in Japan by genotype.

	Cases		Controls		Crude OR	Adjusted OR[a]	VE(%)	95% CI(%)
	n	(%)	n	(%)				
	With G1P[8] strains							
Unvaccinated	212	(18.3)	498	(53.8)	1[b]	1[b]		
RV1 2 doses	8	(0.7)	226	(24.4)	0.08	0.10	89.8	78.2–95.5
RV5 3 doses	12	(1.0)	179	(19.4)	0.16	0.14	85.8	72.8–92.6
	With G9P[8] strains							
Unvaccinated	138	(12.5)	498	(53.8)	1[b]	1[b]		
RV1 2 doses	22	(2.0)	226	(24.4)	0.35	0.32	67.8	45.7–80.9
RV5 3 doses	13	(1.2)	179	(19.4)	0.26	0.33	67.5	39–82.7
	With G2P[4] strains							
Unvaccinated	31	(3.2)	498	(53.8)	1[b]	1[b]		
RV1 2 doses	3	(0.3)	226	(24.4)	0.21	0.22	78.3	23.6–93.8
RV5 3 doses	1	(0.1)	179	(19.4)	0.09	0.12	88.1	10.1–98.4

Abbreviations: OR, odds ratio; VE, vaccine effectiveness; CI, confidence interval; RV1, monovalent; RV5, pentavalent.
[a] Adjusted for use of day care, having siblings, breastfeeding, severity score, facility, and onset year.
[b] Reference category.

contrast, the effectiveness of both vaccines against G9P[8] was low. In addition to temporal and regional differences in rotavirus genotype [27], the improvement of vaccine coverage may induce changes in the dominant genotype and the appearance of reassortant mutant strains. Therefore, long-term observation of the rotavirus genotype distribution will be necessary.

In general, the VEs for RVGE are higher in developed countries than in developing countries, irrespective of disease severity [28]. For example, VE against RVGE not requiring hospitalisation in Spain was 83.5% (95% CI, 25.4–96.3) [29] compared to 64% (95% CI, 24–83) in Malawi [30]. The VE for RVGE may also be affected by whether vaccination is provided as part of a country's NIP or not, because vaccination under NIP can attain higher vaccine coverage than vaccination paid for out-of-pocket. However, the VEs against severe RVGE in countries where RV vaccination is paid for out-of-pocket [29,31–33] have been similar to those in countries where RV vaccination is under NIP [34]. Our findings are analogous to those in developed countries where RV vaccination is paid for out-of-pocket.

In relation to the duration of protection after vaccination, Immergluck et al. [34–36] reported no evidence of waning of protection from RV1 and RV5 beyond 24 months of age. Conversely, Correia et al. [37] found that VE declined among children aged ≥12 months. Although the VE decreased over time, VE against RVGE was >70% in children aged 24–35 months in our study. In Japan, before the introduction of rotavirus vaccines, 70% of cases of RVGE requiring hospitalisation in children <5 y were <2 y [14]. This result indicates that rotavirus vaccination is particularly protective against severe RVGE in children aged <2 y in this country.

Several reports have evaluated the disease burden for RVGE hospitalisation [14,38], and a recent study has examined the impact of RV vaccine introduction on RVGE hospitalisation in Japan [16]; however, disease burden data for RVGE outpatient visits are still lacking. Only one study reported the age-specific annual incidence of RVGE outpatient visits before 2000, before RV vaccine was introduced [38]. According to Yokoo et al., the age-specific annual incidence of RVGE outpatient visits before RV vaccine was introduced were 151.3 per 1000 infants of 6–11 months and 270.7 per 1000 children of 12–23 months [38]. Given the results of our study, with 85.8% VE among infants 6–11 months old and the 83.0%–84.5% VE among children 12–23 months old, the rate of RVGE cases would be expected to decrease to 21.2 per 1000 infants 6–11 months, and 43.3–46.0 per 1000 children aged 12–23 months, if all infants received the RV vaccines. In fact, a substantial reduction in the disease burden of RVGE incidence after RV vaccine introduction was observed in national surveillance data of Infectious Agents Surveillance Reports (laboratory-confirmed RV pathogen) [15,19,39]. During the 2010/2011 to 2012/2013 seasons (from October to September), before RV vaccine had been introduced, the number of laboratory-confirmed RV infections was 908–940, while it was 435 in the 2013/2014 season (from October to September) after its introduction.

This study has some limitations. First, we used our original independent score to compare severity. MVS is useful for assessing the severity of acute gastroenteritis, and it is also used in clinical trials [12]. However, it is difficult to compare severity using MVS, which incorporates the durations of diarrhoea and vomiting [21], because many target children visit medical facilities and receive treatment during the early disease stage. We adopted parts of the MVS and scored each symptom at the time of the outpatient visit. Severity was determined by the score distribution of all patients, and this was considered sufficiently valid. Second, most of the target medical facilities were limited to primary care facilities. If symptoms are severe, patients tend to visit not a clinic but a hospital to receive more aggressive treatment. In the 2012/13 season, we targeted higher-order medical institutions and evaluated the VE of rotavirus vaccines retrospectively [40]. The effectiveness for hospitalised patients was 88.8% (95% CI, 34.3–100.0). That finding coincides with our present results in that the VE of rotavirus vaccines was higher among cases of severe illness. Finally, this study targeted medical facilities in Saga and Fukuoka prefecture in the 2015 and 2016 seasons, and it is a concern whether the same results would be obtained in other seasons or areas, because vaccination coverage and endemic virus genotype might vary. The Ministry of Health, Labour and Welfare published rotavirus vaccine coverage data by prefecture in April 2013. Vaccine coverage in Saga and Fukuoka prefectures totalled 28% and 40%, respectively, which were lower than those in other prefectures. However, our findings are similar to those in developed countries, and confirm the efficacy of rotavirus vaccines in Japan.

5. Conclusions

Rotavirus vaccines were effective in preventing not only severe RVGE, but also mild and moderate RGVE, irrespective of vaccine type or RV genotype. The highly protective effect lasted well over 2 y.

Conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

Funding

This study was supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Science Research Grants from the Ministry of Health, Labour and Welfare, Japan [H26-Shinko-Shitei-003, H27-Shinko-Shitei-003, H28-Shinko-Shitei-003, H29-Shinko-Shitei-003, H30-Shinko-Shitei-003].

Acknowledgements

We thank Masanori Egashira (Egashira Kid's Clinic), Kanoko Hashino (Hashino Children's Clinic), Kazuya Sasaki (Sasaki Children's Clinic), Masuko Koga (Koga Internal Medicine Child Clinic), Eriko Muro (Takashima Hospital), Kaoru Shida (Shida Hospital), Syuichi Yamamoto (Higashisaga Hospital), Shinji Nishimura (Saga-Ken Medical Centre Koseikan), Noriko Rikitake (Saga Chubu Hospital), Kosei Takasaki (Takasaki Pediatric Clinic), Shizuo Shindo (Shindo Children's Clinic), Yuji Yamashita (Yamashita Pediatric Clinic), Takato Yokoyama (Yokoyama Pediatric Clinic) and Yumi Kiyomathu (Kiyomathu Pediatric Clinic) for their assistance. We thank Libby Cone, MD, MA, from DMC Corp. (www.dmed.co.jp <http://www.dmed.co.jp/>) for editing drafts of this manuscript.

References

[1] Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD, et al. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12:136–41.
[2] Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006;354:23–33.
[3] Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006;354:11–22.
[4] Rotavirus vaccines. WHO position paper - January 2013. Wkly Epidemiol Rec. 2013;88:49-64.
[5] Loharikar A, Dumolard L, Chu S, Hyde T, Goodman T, Mantel C. Status of New Vaccine Introduction - Worldwide, September 2016. MMWR Morb Mortal Wkly Rep. 2016;65:1136–40.

[6] Schwartz LM, Halloran ME, Rowhani-Rahbar A, Neuzil KM, Victor JC. Rotavirus vaccine effectiveness in low-income settings: An evaluation of the test-negative design. Vaccine. 2017;35:184–90.
[7] de Oliveira LH, Camacho LA, Coutinho ES, Ruiz-Matus C, Leite JP. Rotavirus vaccine effectiveness in Latin American and Caribbean countries: A systematic review and meta-analysis. Vaccine. 2015;33(Suppl 1):A248–54.
[8] Velazquez RF, Linhares AC, Munoz S, Seron P, Lorca P, DeAntonio R, et al. Efficacy, safety and effectiveness of licensed rotavirus vaccines: a systematic review and meta-analysis for Latin America and the Caribbean. BMC Pediatr. 2017;17:14.
[9] Tate JE, Burton AH. Boschi-Pinto C, Parashar UD, World Health Organization-Coordinated Global Rotavirus Surveillance N. Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000–2013. Clin Infect Dis. 2016;62(Suppl 2):S96–S105.
[10] Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD. Global Impact of Rotavirus Vaccination on Childhood Hospitalizations and Mortality From Diarrhea. The Journal of infectious diseases. 2017;215:1666–72.
[11] Nohynek H, Wichmann O, F DA, Gatekeepers VN. National Advisory Groups and their role in immunization policy-making processes in European countries. Clin Microbiol Infect. 2013;19:1096-105.
[12] Kawamura N, Tokoeda Y, Oshima M, Okahata H, Tsutsumi H, Van Doorn LJ, et al. Efficacy, safety and immunogenicity of RIX4414 in Japanese infants during the first two years of life. Vaccine. 2011;29:6335–41.
[13] Iwata S, Nakata S, Ukae S, Koizumi Y, Morita Y, Kuroki H, et al. Efficacy and safety of pentavalent rotavirus vaccine in Japan: a randomized, double-blind, placebo-controlled, multicenter trial. Hum Vaccin Immunother. 2013;9:1626–33.
[14] Nakagomi T, Nakagomi O, Takahashi Y, Enoki M, Suzuki T, Kilgore PE. Incidence and burden of rotavirus gastroenteritis in Japan, as estimated from a prospective sentinel hospital study. The Journal of infectious diseases. 2005;192(Suppl 1):S106–10.
[15] Hashizume M, Nakagomi T, Nakagomi O. An Early Detection of Decline in Rotavirus Cases during the 2013/2014 Season in Japan as Revealed by Time-series Analysis of National Surveillance Data. Trop Med Health. 2015;43:177–81.
[16] Kobayashi M, Adachi N, Miyazaki M, Tatsumi M. Decline of rotavirus-coded hospitalizations in children under 5 years: A report from Japan where rotavirus vaccines are self-financed. Vaccine 2017.
[17] Fujii Y, Noguchi A, Miura S, Ishii H, Nakagomi T, Nakagomi O, et al. Effectiveness of rotavirus vaccines against hospitalisations in Japan. BMC Pediatr. 2017;17:156.
[18] WHO. Generic protocol for monitoring impact of rotavirus vaccination on gastroeneteroritis disease burden and viral strain. 2008.
[19] Disease. NIoI. Weekly reports of rotavirus detection 2012/13–2016/17.:2017.
[20] Hara M. Rapid diagnosis of rotavirus and intestinal adenovirus gastroenteritis (in Japanese). Japanaese Journal of Pediatrics. 2003;56:887–90.
[21] Freedman SB, Eltorky M, Gorelick M. Group PERCGS. Evaluation of a gastroenteritis severity score for use in outpatient settings. Pediatrics 2010;125:e1278–85.
[22] Tsugawa T, Hoshino Y. Whole genome sequence and phylogenetic analyses reveal human rotavirus G3P[3] strains Ro1845 and HCR3A are examples of direct virion transmission of canine/feline rotaviruses to humans. Virology 2008;380:344–53.
[23] Gouvea V, Glass RI, Woods P, Taniguchi K, Clark HF, Forrester B, et al. Polymerase chain reaction amplification and typing of rotavirus nucleic acid from stool specimens. J Clin Microbiol. 1990;28:276–82.
[24] Gentsch JR, Glass RI, Woods P, Gouvea V, Gorziglia M, Flores J, et al. Identification of group A rotavirus gene 4 types by polymerase chain reaction. Journal of clinical microbiology. 1992;30:1365–73.
[25] Matthijnssens J, Ciarlet M, Rahman M, Attoui H, Bányai K, Estes MK, et al. Recommendations for the classification of group A rotaviruses using all 11 genomic RNA segments. Arch Virol. 2008;153:1621–9.
[26] Leshem E, Lopman B, Glass R, Gentsch J, Bányai K, Parashar U, et al. Distribution of rotavirus strains and strain-specific effectiveness of the rotavirus vaccine after its introduction: a systematic review and meta-analysis. Lancet Infect Dis. 2014;14:847–56.
[27] Bányai K, László B, Duque J, Steele AD, Nelson EA, Gentsch JR, et al. Systematic review of regional and temporal trends in global rotavirus strain diversity in the pre rotavirus vaccine era: insights for understanding the impact of rotavirus vaccination programs. Vaccine. 2012;30(Suppl 1):A122–30.
[28] Cortese MM, Parashar UD, (CDC) CfDCaP. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2009;58:1-25.
[29] Bellido-Blasco JB, Sabater-Vidal S, MeM Salvador-Ribera, Arnedo-Pena A, Tirado-Balaguer MD, Meseguer-Ferrer N, et al. Rotavirus vaccination effectiveness: a case-case study in the EDICS project, Castellón (Spain). Vaccine. 2012;30:7536–40.
[30] Bar-Zeev N, Kapanda L, Tate JE, Jere KC, Iturriza-Gomara M, Nakagomi O, et al. Effectiveness of a monovalent rotavirus vaccine in infants in Malawi after programmatic roll-out: an observational and case-control study. Lancet Infect Dis. 2015;15:422–8.
[31] Castilla J, Beristain X, Martínez-Artola V, Navascués A, García Cenoz M, Alvarez N, et al. Effectiveness of rotavirus vaccines in preventing cases and hospitalizations due to rotavirus gastroenteritis in Navarre. Spain. Vaccine. 2012;30:539–43.
[32] Yeung KH, Tate JE, Chan CC, Chan MC, Chan PK, Poon KH, et al. Rotavirus vaccine effectiveness in Hong Kong children. Vaccine. 2016;34:4935–42.
[33] Marlow R, Ferreira M, Cordeiro E, Trotter C, Januário L, Finn A, et al. Case control study of rotavirus vaccine effectiveness in Portugal during 6 years of private market use. Pediatr Infect Dis J. 2015;34:509–12.
[34] Cortese MM, Immergluck LC, Held M, Jain S, Chan T, Grizas AP, et al. Effectiveness of monovalent and pentavalent rotavirus vaccine. Pediatrics 2013;132:e25–33.
[35] Immergluck LC, Parker TC, Jain S, Laghaie E, Spandorfer P, Jerris RC, et al. Sustained Effectiveness of Monovalent and Pentavalent Rotavirus Vaccines in Children. J Pediatr. 2016;172(116–20):e1.
[36] Phua KB, Lim FS, Lau YL, Nelson EA, Huang LM, Quak SH, et al. Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomized clinical trial in an Asian population. Vaccine. 2012;30:4552–7.
[37] Correia JB, Patel MM, Nakagomi O, Montenegro FM, Germano EM, Correia NB, et al. Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P[4] strains in Brazil. J Infect Dis. 2010;201:363–9.
[38] Yokoo M, Arisawa K, Nakagomi O. Estimation of annual incidence, age-specific incidence rate, and cumulative risk of rotavirus gastroenteritis among children in Japan. Jpn J Infect Dis. 2004;57:166–71.
[39] Disease. NIoI. Weekly reports of rotavirus detection 2009/10–2013/14. 2014..
[40] Araki K, Hara M, Sakanishi Y, Shimanoe C, Nishida Y, Matsuo M, et al. Estimating rotavirus vaccine effectiveness in Japan using a screening method. Hum Vaccin Immunother. 2016;12:1244–9.

Vaccine 36 (2018) 5886–5890

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The impact on vaccination coverage following introduction of a routine pneumococcal vaccination programme for the elderly in Japan

Aiko Shono [a,*], Shu-ling Hoshi [b], Masahide Kondo [b]

[a] Department of Public Health and Epidemiology, Faculty of Pharmaceutical Sciences, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan
[b] Department of Health Care Policy and Health Economics, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8577, Japan

ARTICLE INFO

Article history:
Received 26 December 2017
Received in revised form 7 June 2018
Accepted 9 August 2018
Available online 22 August 2018

Keywords:
Elderly
Pneumococcal
Vaccination
Routine programme

ABSTRACT

In October 2014, a routine pneumococcal vaccination programme in the elderly aged 65–100 years old was initiated in Japan. Currently, this programme is within a transitional period. Eligibility for subsidy under the programme is granted for target ages in 5-year increments, over a 5-year roll-out period. We assessed the impact of the routine vaccination programme on vaccination coverage and explored the factors relating to pneumococcal vaccine uptake. We conducted a cross-sectional web-based survey in 2015 for respondents aged 65–79 years. A total of 3889 respondents answered the survey. The vaccination coverage in this study was estimated as 33.5%. Of the total respondents, 3327 were not vaccinated at initiation of the routine vaccination programme. The uptake of vaccination after implementation of the programme among them was 22.3%. There was a significant relationship between vaccination and eligibility for subsidy under the routine vaccination programme (adjusted odds ratio: 16.7). While there are some limitations to this study, introduction of the routine vaccination programme might affect pneumococcal vaccination coverage in the elderly.

1. Introduction

Pneumococcal infection carries the risk of serious infection, hospitalisation and even death, especially in older people [1,2]. Pneumococcal vaccines are effective in prevention of invasive pneumococcal disease (IPD) in healthy adults [3,4]. Pneumococcal polysaccharide vaccine (PPSV) 23 and/or pneumococcal conjugate vaccine (PCV) 13 are recommended for vaccination of older people in many countries, including the USA [5], UK [6], Germany [6], Canada [7], Singapore [8], and Taiwan [9].

In Japan, pneumonia is the third leading cause of death (96.5 per 100,000 population in 2015), and this type of death is particularly high in the older population (death caused by pneumococcal disease among those aged ≥65 years comprised 97% of the total deaths in 2015) [10]. In October 2014, a routine vaccination programme for the older people, targeting individuals aged 65–100 years, aimed to prevent IPD was initiated by an amendment of the Immunisation Act [11]. During the five-year from 2014 to 2019, this programme has been in a transitional period; eligibility for subsidy under the programme is granted for those newly of ages 65, 70, 75, 80, 85, 90, 95 or 100 in the fiscal year [11]. Individuals falling within these age criteria are eligible for a subsidised single vaccination per person. The routine vaccination programme is nationwide, but its implementation is decentralised to municipalities which set differing payment amounts, with some municipalities adding their own subsidy schemes such as granting subsidy without age criteria from the first year. While both PCV13 and PPSV23 pneumococcal vaccines are available in Japan, only PPSV23 is subsidised for use in the routine vaccination programme [11].

The national vaccination coverage of pneumococcal vaccines in older people (≥65 years) was reported as 38.3% in 2014 (vaccination counts under the national programme divided by eligibility for subsidy for the fiscal year) after the programme started [12]. Vaccination coverage under the new programme was low compared with the influenza vaccine in 2014 (50.6%) [12], and was also lower than the USA (63.6%) [13], UK (69.8%) [14], and Australia (56.0%) [15]. The vaccination coverage in Japan is higher than that in other Asian countries that introduced it as a recommendation, including Taiwan (20.7%, ≥75 years) [16] and Singapore (6.1%) [17].

Currently in Japan, the routine pneumococcal vaccination programme represents an ongoing nationwide experiment during

Abbreviations: PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; IPD, invasive pneumococcal disease.

* Corresponding author.
E-mail address: shono@my-pharm.ac.jp (A. Shono).

https://doi.org/10.1016/j.vaccine.2018.08.023
0264-410X/

the five-year transitional period. In this study, therefore, we assessed the effect of this programme on vaccination coverage in older people. We have also explored the factors relating to pneumococcal vaccine uptake.

2. Methods

We conducted a cross-sectional web-based survey in December 2015. The target population involved those who were registered throughout Japan with a private web survey company because there is no official behavioural surveillance system in Japan. Therefore, this was a closed survey that was only open to individuals that were registered and invited by the survey company [18].

Respondents were aged 65–79 years at the time of this research. This target age was chosen for feasibility of collecting data. For the recruitment process, an invitation was provided to the registered target population through personal websites and e-mail, and people could access the research website. Those who answered the question could obtain some incentives from the survey company, such as points that are exchangeable for gift cards once they reach a certain value.

The respondents were within the target population for the routine vaccination programme, both already eligible for subsidy (i.e. aged 65, 70, 75, 80, 85, 90, 95 or 100 at the end of fiscal year 2014/2015) and not yet eligible for subsidy (all other ages from 65 to 100 years).

The questionnaire mainly comprised 15 queries and was categorized into two parts involving a general part and a health-specific part, including vaccination status. The general part of the questionnaire assessed the following: age (birth month, year), gender, marital status, household income, education background as the final level of education completed, employment status, and children living in the same household. The health-specific part assessed smoking status, pneumococcal and seasonal influenza vaccination status, and any disease under treatment. The queries regarding pneumococcal vaccination also included the timing of vaccination (calendar year and month of vaccination) and the reason for seeking this vaccination. The reason for vaccination was queried to obtain information on the influence of the media and other resources. We did not differentiate between PPSV23 and PCV13 in this study because we aimed to focus on the vaccination trend and ease of response.

Firstly, we estimated the vaccination coverage (vaccinated population divided by target population) to investigate the effect of the routine vaccination programme. Second, we analysed the relationship between pneumococcal vaccination after programme implementation and the factors affecting vaccination uptake using a logistic regression model. These factors were as follows: eligibility for subsidy, age, gender, marital status, education, employment status, smoking status, seasonal influenza vaccination status, any disease under treatment, children within the same household, and household income. In addition, the main reason for vaccination was analysed as summary statistics.

Only respondents who provided informed consent were included in this study. This study was approved by the ethical committee at Meiji Pharmaceutical University.

3. Results

The total number of valid responses was 3889 (total respondents). The median amount of time to complete the questionnaire was 2 min and 23 s. Summary statistics are shown in Table 1. The average age of respondents was 70.8 years old at the time of survey, with males accounting for 1830 (47.1%). The proportion of respondents with a marital status was 77.1%, high school graduate was the most common educational background, and the proportion of employed respondents was 24.4%. The proportion answering "never smoked" was 60.6% and "ever smoked but currently do not smoke" was 29.6%. Influenza vaccination status was as follows: 44.3% for "annual vaccination", 36.0% for "never vaccinated". The proportion of respondents with any disease under treatment was 59.2% and that for having children within the same household was 2.7%. Household income data was available for 3090 respondents (79.5%), with a mode and median of 3–4 million yen (27,000–36,000 USD, 1USD = 110JPY) and 4.2 million yen (38,000 USD), respectively.

We estimated the vaccination coverage in this study from the total respondents and from those who were not vaccinated at introduction of the routine vaccination programme. A total of 1304 (33.5% of the total respondents, 1304/3889) respondents answered that they had been vaccinated with the pneumococcal vaccine at the time of the survey (vaccinated respondents) (Table 1). The vaccination coverage of the total respondents by age is shown in Fig. 1.

Of the total respondents, 3327 (85.5%, 3327/3889) were not vaccinated at initiation of the routine vaccination programme. During the second fiscal year after introduction, a total of 1368 respondents aged 65, 66, 70, 71, 75, 76 or 80 comprised the eligible population within our survey (41.1%, 1368/3327). Seven hundred and forty-two respondents (22.3%, 742/3327) were vaccinated after implementation of the programme. While 619 of 742 (83.4%) vaccinated respondents were eligible for subsidy under the programme, 123 (16.6%, 123/742) vaccinated respondents were not.

The effect of programme implementation was explored as a regression model based on the 3327 respondents who were not vaccinated at programme initiation (Table 2). There was a significant relationship between vaccination and eligibility for subsidy under the routine vaccination programme in the unadjusted and adjusted models (odds ratio: 12.3; 95% confidence interval: 10.0–15.2 for unadjusted and 16.7; 12.6–22.0 for adjusted). There were also relationships between vaccination and the following factors: age, employment status, influenza vaccination status, any disease under treatment, and household income in the adjusted model.

The main reason for vaccination after introduction of the routine vaccination programme was notification by post from municipalities (49.7%), followed by recommendation by a family doctor (16.7%), and commercial information from pharmaceutical companies through television (12.9%) (Table 1). Those who were already eligible for the routine vaccination programme answered that notification by post from municipalities was the main reason for vaccination. The main reason for vaccination in those who were not eligible was the family doctor, followed by notification by post.

4. Discussion

Currently in Japan, the routine pneumococcal vaccination programme for older people (≥65 years old) is within a transitional period. At the time this survey was performed, the programme was in its second year of a 5-year roll-out and 41.1% of respondents in this study were eligible for subsidised vaccination. Eligibility for subsidy under the routine vaccination programme was found to have an effect on coverage (Fig. 1), and it had the largest odds ratio (adjusted odds ratio:16.7) among the factors affecting vaccination uptake. Therefore, introduction of the routine vaccination programme has had an effect on pneumococcal vaccination coverage in older people, similar to the effect observed in Australia following introduction of universal funding [15].

In this study, vaccine uptake differed according to the respondents' factors, such as any disease under treatment, household

Table 1
Summary statistics.

Attributes		Total respondents N = 3889		Respondents who were not vaccinated at the point of introduction of the routine vaccination programme N = 3327	
		Count	%	Count	%
Age					
65–69		1665	42.8	1542	46.3
70–74		1364	35.1	1139	34.2
75–79		860	22.1	646	19.4
Gender (male)		1830	47.1	1566	47.1
Marital status (yes)		3000	77.1	2560	76.9
Education background					
Junior high school		212	5.5	188	5.7
High school		1868	48.0	1601	48.1
College		593	15.3	509	15.3
University		1139	29.3	970	29.2
Graduate school		71	1.8	54	1.6
Others or no answer		6	0.2	5	0.2
Employment (yes)		948	24.4	850	25.5
Smoking					
Yes		382	9.8	345	10.4
Never		2355	60.6	1991	59.8
Ever smoked		1152	29.6	991	29.8
Influenza vaccination					
Never		1401	36.0	1338	40.2
Annually		1723	44.3	1317	39.6
Sometimes		765	19.7	672	20.2
Any disease under the treatment (yes)		2302	59.2	1892	56.9
Children within the same household (yes)		105	2.7	91	2.7
Eligible for subsidy[1]		–	–	1368	41.1
Pneumococcal vaccination (yes)		1304	33.5	742	22.3
Main reason for vaccination				Respondents who were vaccinated after implementation of the programme N = 742	
				Count	%
Postal information from municipalities				369	49.7
Recommendation by a doctor				124	16.7
Commercial information via television[2]				96	12.9
Recommendation by family member				50	6.7
Public information from municipalities				35	4.7
Commercial information at clinic or hospital				21	2.8
Information from friends				20	2.7
Commercial information via newspaper				18	2.4
Others				6	0.8
None				3	0.4
Income per yr (million yen)[3]	(Thousand USD)	N	%	N	%
<1	<9	101	2.6	85	2.6
1–2	9–18	332	8.5	289	8.7
2–3	18–27	631	16.2	547	16.4
3–4	27–36	753	19.4	636	19.1
4–5	36–45	505	13.0	424	12.7
5–6	45–55	272	7.0	238	7.2
6–7	55–64	137	3.5	115	3.5
7–8	64–73	89	2.3	75	2.3
8–9	73–82	70	1.8	60	1.8
9–10	82–91	69	1.8	60	1.8
10–15	91–136	89	2.3	79	2.4
15≤	136≤	42	1.1	29	0.9
no answer	–	799	20.6	690	20.7

[1] For the routine vaccination programme. Individuals who were already vaccinated at the time of programme introduction were not eligible for subsidy under the routine vaccination programme.
[2] From pharmaceutical companies through television.
[3] Respondents could answer from one million yen (9000 USD) to 15 million yen or more (136,000 USD) and they could also select "do not know/do not want to answer". 1USD = 110JPY.

income, age, and employment. Respondents undergoing any treatment were likely to be vaccinated, which was also found in other countries [19]. Recipients in Japan are required to pay about 3000 JPY (27 USD) as the median copayment for vaccination under the routine vaccination programme [20]. Therefore, income could be a factor influencing vaccine uptake [21]. This was also shown for seasonal influenza vaccination for adults and children in Japan [22–24]. However, some studies on vaccination in other countries showed no associations with income [21,25]. Influenza vaccine uptake is also related to that of the pneumococcal vaccine, and risk perception is further considered to be a factor [19,26]. Furthermore, in our study, a higher age of the respondents, especially

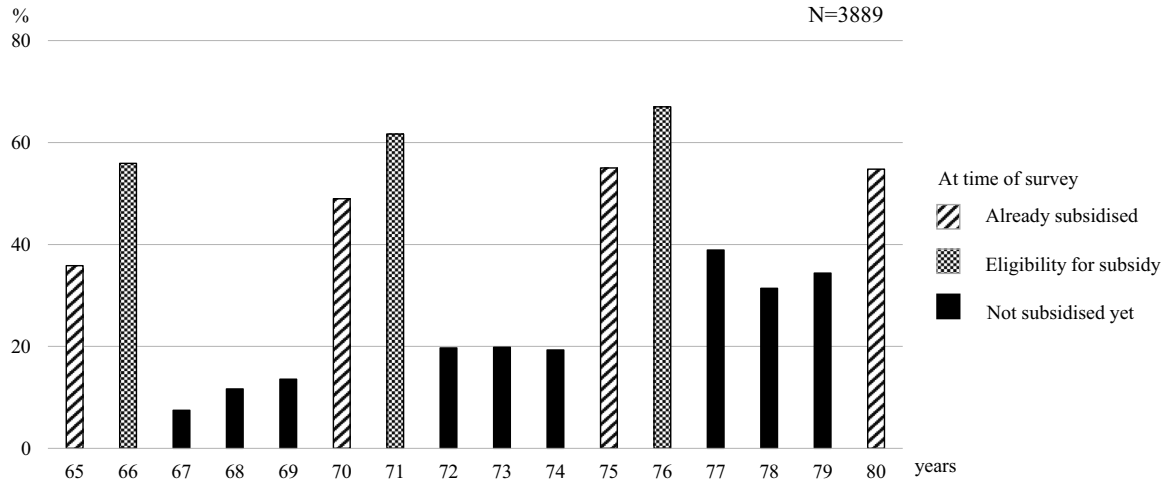


Fig. 1. Vaccination coverage by age*. *Age at the end of fiscal year.

Table 2
Logistic regression model for vaccine uptake under the routine pneumococcal vaccination programme.

	Unadjusted odds ratio	95%CI		Adjusted odds ratio	95%CI	
Age	0.99	0.97	1.01	1.04	1.01	1.07
Gender (male; 1)	0.98	0.84	1.16	1.23	0.91	1.66
Marital Status (yes; 1)	1.24	1.01	1.51	1.24	0.80	1.94
Education (year)	1.01	0.98	1.05	1.00	0.95	1.07
Employment (yes; 1)	0.92	0.76	1.11	0.64	0.48	0.86
Smoking status						
Smoking	–					
Never	1.34	1.00	1.80	1.28	0.82	1.98
Ever smoked	1.27	0.93	1.73	1.24	0.79	1.93
Influenza vaccination						
Never	–					
Annually	3.55	2.91	4.34	4.86	3.63	6.50
Sometimes	1.90	1.48	2.43	2.00	1.42	2.82
Any disease under treatment (yes; 1)	1.62	1.36	1.92	1.37	1.07	1.77
Children within the same household (yes; 1)	0.96	0.58	1.58	0.72	0.35	1.49
Eligibility for subsidy* (yes; 1)	12.34	9.99	15.24	16.67	12.65	21.96
Income (million yen)	1.0036	1.0003	1.0069	1.0062	1.0018	1.0107

In the unadjusted model, 3327 cases were included, and 2172 were included in the adjusted model. Missing data were excluded in both models.
* For the routine vaccination programme.

older than 75 years, resulted in a tendency to be vaccinated, even though they were not eligible for the subsidy. Other research conducted before introduction of the routine pneumococcal vaccination programme in Japan has also shown that vaccine coverage for those older than 75 years was relatively higher than that for older people aged younger than 74 years [27]. There could be two possible reasons for these findings. Older people may have protective behaviour [28] and they may have more chances to visit doctors who recommend vaccination [29]. With regard to the factor of employment, people who are employed might miss the opportunity to be vaccinated because they have limited time [30].

The municipalities' strategy of posting information directly to those eligible for subsidy was the main trigger for seeking the vaccine in our study. However, the effort spent in promotion of vaccination differed between municipalities. In 2016, 85% of municipalities informed individuals about the vaccination by posted mail [20]. This approach may affect the vaccination behaviour of older people in a similar manner to that seen for human papillomavirus vaccination in the younger generation in Japan [31]. The encouragement by a family doctor could also be effective for the ineligible group because older people may have a higher chance of visiting the family doctor [29].

There are some limitations to this study. First, currently, only PPSV 23 is covered by the subsidy programme, but we did not differentiate between PPSV23 and PCV13. Because we focussed on the vaccination coverage trend for pneumococcal infection by introduction of the subsidy program, we consider that our main conclusions are legitimate. Second, we should consider selection bias. This study was a web-based survey of the spontaneous registered population of a private web survey service. Therefore, respondents in this survey were not selected by random sampling. While the respondents were collected from overall Japan, there was self-selected bias. The age structure ($\geq$65 years old) in the target population in this survey and that in Japan is different. Additionally, internet access in Japan is only available for 71.4% of the population aged 65–69 years and in 53.5% of those aged 70–79 years [32]. Therefore, this study might not be representative of Japan. Third, self-reporting bias could also have occurred because we did not confirm the respondents' certificate of their vaccination. Fourth, we did not specifically investigate the effect of any original municipality-instigated programmes before and after introduction of the routine pneumococcal vaccination programme [33]. Fifth, we only included 15 questions. Therefore, we did not examine other factors, such as social factors of the area residence, living

conditions, private insurance, and knowledge on pneumococcal infection that affects vaccination behaviour [21]. Finally, this survey was conducted in the middle of the fiscal year. Therefore, some respondents might not have been vaccinated yet, but intended to be vaccinated. While there are some limitations to our study, we attempted to determine the current situation throughout Japan.

Currently in Japan, the routine pneumococcal vaccination programme is ongoing under the 5-year transitional period, until fiscal year 2018; eligibility for subsidy under the programme is granted for those newly aged 65, 70, 75, 80, 85, 90, 95 or 100 years in the fiscal year. As this is a new trial of vaccine policy by the Japanese government, the process will be finished in fiscal year 2018. After that, the ongoing program of subsidizing vaccination for those newly aged 65 years is assumed to maintain the vaccine coverage among older populations. The study findings may also imply that decentralised efforts by municipalities aimed at new target populations are also required, for example, through use of mass communication, like regular newsletters and through personal communication intended to achieve higher coverage. This implication would be also valid for decentralised local governments in other countries.

In conclusion, under the routine vaccination programme, eligibility for subsidy appears to have a relation to higher coverage (adjusted odds ratio: 16.7). Therefore, introduction of the routine vaccination programme might affect pneumococcal vaccination coverage in older people.

Conflict of interests

None.

Acknowledgements

This study was supported by JSPS KAKENHI Grant Number (25460817) and a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan.

References

[1] Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalisation among U.S. adults. NEJM 2015;373:415–27.
[2] Centers for disease control and prevention. Pneumococcal vaccination: what everyone should know. <https://www.cdc.gov/vaccines/vpd/pneumo/public/index.html> [accessed 28 November 2017].
[3] Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database of Systematic Reviews 2013;1:CD000422.
[4] Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. NEJM 2015;372:1114–25.
[5] Centers for disease control and prevention. Pneumococcal vaccine recommendations. <https://www.cdc.gov/vaccines/vpd/pneumo/hcp/recommendations.html> [accessed 6 December 2017].
[6] European centre for disease prevention and control. Pneumococcal disease: recommended vaccinations. <https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=25&SelectedCountryIdByDisease=-1> [accessed 15 March 2018].
[7] Government of Canada. Pneumococcal vaccine. <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-16-pneumococcal-vaccine.html> [accessed 8 March 2018].
[8] Ministry of Health. MOH establishes national adult immunisation schedule: extends use of Medisave for vaccines under the schedule. <https://www.moh.gov.sg/content/moh_web/home/pressRoom/pressRoomItemRelease/2017/moh-establishes-national-adult-immunisation-schedule–extends-us.html> [accessed 6 March 2018].
[9] Centers for disease control, R.O.C. (Taiwan). Invasive pneumococcal disease. <http://www.cdc.gov.tw/english/info.aspx?treeid=e79c7a9e1e9b1cdf&nowtreeid=e02c24f0dacdd729&tid=00B8C8D154EEAE73> [accessed 6 March 2018].
[10] Health, Labour and Welfare Statistics Association. J Health Welfare Statistics 2017/2018. [in Japanese].
[11] National Institute of Infectious Disease. Koreisha no haien kyukin vaccine no teikisesshu ni tuite. 2014 IASR;35:240–1. <https://www.niid.go.jp/niid/ja/iasr-sp/2300-related-articles/related-articles-416/5030-dj4168.html> [accessed 4 July 2017]. [in Japanese].
[12] Ministry of Health, Labour and Welfare. Teiki no yobo sesshu jisshishasuu. <http://www.mhlw.go.jp/topics/bcg/other/5.html> [accessed 7 July 2017]. [in Japanese].
[13] Williams WW, Lu P, O'Halloran A, Kim DK, Grohskopf LA, Pilishvili T, et al. Surveillance of vaccination coverage among adult populations—United States, 2015. MMWR Surveill Summ 2017;66:1–28.
[14] Public Health England. Health protection report: pneumococcal polysaccharide vaccine (PPV) coverage report, England, April 2016 to March 2017. <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/448406/hpr2615_ppv.pdf> [accessed 5 December 2017].
[15] Dyda A, Karki S, Hayen A, MacIntyre CR, Menzies R, Banks E, et al. Influenza and pneumococcal vaccination in Australian adults: a systematic review of coverage and factors associated with uptake. BMC Infect Dis 2016;16:515.
[16] Chen CH, Wu MS, Wu IC. Vaccination coverage and associated factors for receipt of the 23-valent pneumococcal polysaccharide vaccine in Taiwan: a nation-wide community-based study. Medicine (Baltimore) 2018;97:e9773.
[17] Ho HJ, Chan YY, Ibrahim MAB, Wagle AA, Wong CM, Chow A. A formative research-guided educational intervention to improve the knowledge and attitudes of seniors towards influenza and pneumococcal vaccinations. Vaccine 2017;35. 6367–74.18.
[18] Eysenbach G. Improving the quality of web surveys: the checklist for reporting results of internet E-surveys (CHERRIES). J Med Internet Res 2004;6(3):e34.
[19] Dower J, Donald M, Begum N, Vlack S, Ozolins I. Patterns and determinants of influenza and pneumococcal immunisation among adults with chronic disease living in Queensland, Australia. Vaccine 2011;29:3031–7.
[20] Murakami Y, Nishiwaki Y, Kanazu S, Oba M, Watanabe A. A nationwide survey of PPSV23 vaccine coverage rates and their related factors among the elderly in Japan, 2016. Nihon Koshu Eisei Zasshi 2018;65:20–4 [in Japanese].
[21] Jain A, van Hoek AJ, Boccia D, Thomas SL. Lower vaccine uptake amongst older individuals living alone: a systematic review and meta-analysis of social determinants of vaccine uptake. Vaccine 2017;35:2315–28.
[22] Kondo M, Hoshi SL, Okubo I. Does subsidy work? Price elasticity of demand for influenza vaccination among the elderly in Japan. Health Policy 2009;91:269–76.
[23] Shono A, Kondo M. Factors that affect voluntary vaccination of children in Japan. Vaccine 2015;33:1406–11.
[24] Wada K, Smith DR. Influenza vaccination uptake among the working age population of Japan: results from a national cross-sectional survey. PLoS One 2013;8:e59272.
[25] Ganczak M, Gil K, Korzeń M, Bażydło M. Coverage and influencing determinants of influenza vaccination in elderly patients in a country with a poor vaccination implementation. Int J Environ Res Public Health 2017;14.
[26] Brewer NT, Chapman GB, Gibbons FX, Gerrard M, McCaul KD, Weinstein ND. Meta-analysis of the relationship between risk perception and health behaviour: the example of vaccination. Health Psychol 2007;26:136–45.
[27] Washio S, Kondo R, Fujisawa N, Matsumoto N, Harada E, Tashiro H, et al. Haienkyukin wakutin sesshu koureisya to hi-sesshu koureisya no tokucho. Jpn J Clin Exp Med 2016;93:1109–12 [in Japanese].
[28] Tsai YY, Lee JJ, Hsieh WH. Determinants of the public intent to receive the seasonal influenza vaccine and protective behaviors: a population-based study in Taiwan. Vaccine 2014;32:6667–75.
[29] Szucs TD, Müller D. Influenza vaccination coverage rates in five European countries-a population-based cross-sectional analysis of two consecutive influenza seasons. Vaccine 2005;23:5055–63.
[30] Iwasa T, Wada K. Reasons for and against receiving influenza vaccination in a working age population in Japan: a national cross-sectional study. BMC Public Health 2013;13:647.
[31] Kobayashi H, Nakajima Y, Akasaki M. Factors influencing coverage of human papillomavirus (HPV) vaccination: questionnaire survey of local government in Nara Prefecture about the HPV vaccination program and communication campaigns to promote the program. Prog Med 2012;32:753–9 [in Japanese].
[32] Ministry of Internal Affairs and Communications. White paper information and communications in Japan. <http://www.soumu.go.jp/johotsusintokei/whitepaper/ja/h28/html/nc252110.html> [accessed 13 July 2017].
[33] Kondo M, Yamamura M, Hoshi SL, Okubo I. Demand for pneumococcal vaccination under subsidy program for the elderly in Japan. BMC Health Serv Res 2012;12:313.

Vaccine 35 (2017) 7080

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Letter to the Editor

Response to Curran and Mrkvan, Letter to the Editor: Response to publication by Hoshi SL et al.: Cost-effectiveness of varicella vaccine against herpes zoster and post-herpetic neuralgia for elderly in Japan

We thank Curran and Mrkvan for their interest in and comments to our paper "Cost-effectiveness of varicella vaccine against herpes zoster and post-herpetic neuralgia for elderly in Japan" in Vaccine [1].

We would like to respond to their insightful comments. Firstly, vaccine efficacy (VE) reported by Long term Persistence Sub-study (LTPS) [2] was our first choice, due to its feasibility in application with our model. However, we found that LTPS was not able to demonstrate how VE changed with chronological age, thus we adopted VE estimates from Li et al. [3], and conducted sensitivity analyses on these data to understand how it impacted the results. Our sensitivity analysis showed that the uncertainty of VE didn't change the ICER largely as expected.

Secondly, in order to consider the alternative VE and waning scenario, we conducted additional threshold analyses to find out the VE duration, which could lead the ICERs of the four strategies beyond the cost-effective criteria, which is ¥5,000,000/QALY in our study. Results showed that ICERs would be beyond 5,000,000/QALY for each strategy when the duration is <6 years.

Lastly, we also conducted an additional scenario analysis, which adopted the VE reported in LTPS [2]. We assumed VE estimates from 1st to 8th year: 0.620, 0.489, 0.468, 0.446, 0.431, 0.306, 0.460, and 0.311 over every age stratum, respectively, with no VE set from 9th year and onwards. Results showed that ICERs for all four strategies were less than ¥5,000,000/QALY (Table 1).

Table 1
Results of Scenario analysis (adopted VE reported by Morrison et al. [3] for all the four strategies.

Strategies	ICERs
No programme	–
Age 80–84	¥3,725,947/QALY
Age 75–84	¥4,068,345/QALY
Age 70–84	¥4,302,749/QALY
Age 65–84	¥4,773,467/QALY

We think that the results of the additional threshold analyses, of 6 years, suggest the stability of the conclusion of our paper. Results of this additional scenario analysis using VE estimates based on LTPS though produced less favourable ICERs, can still be judged as cost-effective. Although the VE and waning scenario adopted in our paper might be opportunistic, the vaccination programmes could still be concluded as cost-effective.

References

[1] Hoshi SL, Kondo M, Okubo I. Cost-effectiveness of varicella vaccine against herpes zoster and post-herpetic neuralgia for elderly in Japan. Vaccine 2017;35 (24):3264–71.
[2] Morrison VA, Johnson GR, Schmader KE, Levin MJ, Zhang JH, Looney DJ, et al. Shingles Prevention Study Group. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis 2015;60(6):900–9.
[3] Li X, Zhang JH, Betts RF, Morrison VA, Xu R, Itzler RF, et al. Modeling the durability of ZOSTAVAX® vaccine efficacy in people ≥60 years of age. Vaccine 2015;33(12):1499–505.

Shu-ling Hoshi *
Masahide Kondo
Department of Health Care Policy and Health Economics, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennoudai, Tsukuba, Ibaraki 3058577, Japan
* Corresponding author.
E-mail address: hoshi@hcs.tsukuba.ac.jp (S.-l. Hoshi)

Ichiro Okubo
Yokohama City Institute of Public Health, 7-1, Tomiokahigashi 2-chome, Kanazawa-ku, Yokohama City 236-0051, Japan

https://doi.org/10.1016/j.vaccine.2017.10.046

Vaccine 35 (2017) 5303–5308

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Key points in evaluating immunogenicity of pandemic influenza vaccines: A lesson from immunogenicity studies of influenza A(H1N1) pdm09 vaccine

Satoko Ohfuji [a,b,*], Masayuki Kobayashi [c], Yuichiro Ide [d], Yumi Egawa [e], Tomoko Saito [f], Kyoko Kondo [a], Kazuya Ito [a,b], Tetsuo Kase [a,b], Akiko Maeda [a], Wakaba Fukushima [a,b], Yoshio Hirota [a,g,h]

[a] Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan
[b] Research Center for Infectious Disease Sciences, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan
[c] Medical Affairs, MSD K.K., 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo 102-0073, Japan
[d] Graduate School of Nursing Science, St. Mary's College, 422 Tsubukuhon-machi, Kurume-city, Fukuoka 830-8558, Japan
[e] Senrichuo Yumi Skin Clinic, 1-3-412 Shinsenri-higashi-machi, Toyonaka-city, Osaka 560-0082, Japan
[f] Department of Neurology, National Hospital Organization Toneyama National Hospital, 5-1-1 Toneyama, Toyonaka-city, Osaka 560-8552, Japan
[g] College of Healthcare Management, 960-4 Takayanagi, Setaka-machi, Miyama-shi, Fukuoka 835-0018, Japan
[h] Clinical Epidemiology Research Center, Medical Co. LTA, 3-5-1 Kashii-Teriha, Higashi-ku, Fukuoka 813-0017, Japan

ARTICLE INFO

Article history:
Received 27 April 2017
Received in revised form 28 June 2017
Accepted 7 July 2017
Available online 4 August 2017

Keywords:
Associated factors
Influenza vaccine
Immunogenicity
Pandemic

ABSTRACT

Introduction: Immunogenicity studies on pandemic influenza vaccine are necessary to inform rapid development and implementation of a vaccine during a pandemic. Thus, strategies for immunogenicity assessment are required.
Objective: To identify essential factors to consider when evaluating the immunogenicity of pandemic influenza vaccines using the experience in Japan with the influenza A(H1N1)pdm09 vaccine.
Methods: We conducted a search of observational studies using PubMed and IchushiWeb. Search terms included "influenza vaccine AND (immunogenicity OR immune response) AND Japan AND (2009 OR pdm09) NOT review," and was limited to studies conducted in humans.
Results: A total of 33 articles were identified, of which 16 articles met the inclusion criteria. Immunogenicity of the commercially available influenza A(H1N1)pdm09 vaccine satisfied the international criteria for influenza vaccine immunogenicity in all study populations. The most remarkable immune response was observed in junior high school students, while the lowest immune response was observed in hematological malignancy patients. Similar to immunogenicity studies on seasonal influenza vaccines, factors such as patient background (e.g., age, underlying condition, pre-vaccination titer, body mass index, etc.) and study procedure (e.g., concurrent measurement of pre- and post-vaccination antibody titer, effects of infection during the study period) may have affected the assessment of immunogenicity to the influenza A(H1N1)pdm09 vaccine. In addition, prior vaccination with the seasonal influenza vaccine may inhibit antibody induction by the influenza A(H1N1)pdm09 vaccine.
Conclusions: This review discusses factors and strategies that must be considered and addressed during immunogenicity assessments of pandemic influenza vaccines, which may provide useful information for future influenza pandemics.

1. Introduction

In the Northern Hemisphere, seasonal influenza viruses typically circulate from late fall through early spring. Such characteristics of seasonal influenza enable us to prepare influenza vaccines in advance to prevent influenza illnesses. In addition, we can advise populations at high risk for severe influenza to receive influenza vaccination early [1].

Abbreviations: CI, confidence interval; GMT, geometric mean titer; HI, hemagglutination inhibition; MFR, mean fold rise; OR, odds ratio; SCR, seroconversion proportion; SRP, seroresponse proportion; SPP, seroprotection proportion.

* Corresponding author at: Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan.
E-mail address: satop@med.osaka-cu.ac.jp (S. Ohfuji).

http://dx.doi.org/10.1016/j.vaccine.2017.07.092
0264-410X/

However, the situation is quite different for pandemic influenza. In April 2009, swine-origin influenza A(H1N1) virus was first identified in the United States; it rapidly spread throughout the world, resulting in the first influenza pandemic of the 21st century [2]. Since this was a new strain of influenza, no vaccine was available at the early stage of this pandemic. In addition, there was no data on high-risk populations of this virus. To control this influenza pandemic, various information regarding the epidemiology of influenza A(H1N1)pdm09 virus was necessary, and an effective influenza vaccine had to be produced as soon as possible.

The general procedure for an immunogenicity study of influenza vaccines includes the following processes: (1) measure the antibody titer for paired serum samples (i.e., before and several weeks after vaccination), and (2) analyze data of antibody titers. In these analyses, most studies calculate the following markers as outcome indices: (1) the geometric mean titer (GMT), (2) mean fold rise (MFR), (3) seroconversion proportion (SCR), (4) seroresponse proportion (SRP), and (5) seroprotection proportion (SPP) in all study subjects. The immunogenicity of influenza vaccines in the target population is also assessed according to the international licensing criteria of the European Medicines Evaluation Agency and the United States Food and Drug Administration (Table 1) [3,4]. However, several factors can affect vaccine immunogenicity.

Here, we present a summary of the results from immunogenicity studies of influenza A(H1N1)pdm09 vaccine conducted in Japan. The main objective was to discuss key points to consider when evaluating the immunogenicity of pandemic influenza vaccines.

2. Immunogenicity studies of influenza A(H1N1)pdm09 vaccine in Japan

We conducted a comprehensive search using PubMed and IchushiWeb provided by Japan Medical Abstracts Society with the search terms "influenza vaccine AND (immunogenicity OR immune response) AND Japan AND (2009 OR pdm09) NOT review." Only studies conducted in humans were included. The literature search was conducted on June 7, 2017 and yielded a total of 33 articles, of which 17 articles were excluded. Reasons for exclusion included investigation of immune responses after influenza A (H1N1)pdm09 virus infection (n = 2), investigation of viral characteristics of influenza A(H1N1)pdm09 virus (n = 1), investigation of immunogenicity of influenza vaccine in another season (n = 6), experimental studies conducted in mice (n = 2), and clinical trials for a non-commercial vaccine (n = 6). Finally, the results from 16 articles [5–20] are summarized in Table 2.

When the results of these 16 studies were evaluated against the international criteria for influenza vaccine immunogenicity as shown in Table 1, the immunogenicity of the commercially available influenza A(H1N1)pdm09 vaccine satisfied to meet the criteria in all study populations. However, GMT after 1 dose of vaccination (S1) ranged from 13 to 162, whereas SPP at S1 ranged from 25% to 92% (Table 2). Therefore, specific factors may be involved which affected immune responses to influenza A(H1N1)pdm09 vaccine. We reviewed these studies, paying careful attention to the study procedure and the effect of subject background characteristics.

Table 1
International criteria for influenza vaccine immunogenicity.

EMEA criteria (satisfies 1 or more of the following 3 items)		
	Age: 18–60 years	Age: ≥61 years
(1) SCP*	>40%	>30%
(2) MFR	>2.5	>2.0
(3) SPP†	>70%	>60%
FDA criteria		
	Age: ≤64 years	Age: ≥65 years
(1) Lower limit of 95% CI of SCP*	>40%	>30%
(2) Lower limit of 95% CI of SPP†	>70%	>60%

Cited and reconstructed from Refs. [3,4].
Abbreviations: EMA, European Medicines Evaluation Agency; SCP, seroconversion proportion; MFR, mean fold rise; SPP, seroprotection proportion; FDA, Food and Drug Administration.
* SCP: the proportion of persons with pre-vaccination HI antibody titer of <1:10 and post-vaccination titer of ≥1:40 or ≥4-fold post-vaccination rise in antibody titer.
† SPP: the proportion of persons satisfying the protective level of antibody titer (HI antibody titer of ≥1:40).

3. Factors to consider in immunogenicity studies of pandemic influenza vaccines

3.1. At the study procedure

In general, the first key point to consider in the study procedure is existed in the measurement of pre- and post-vaccination antibody titers. These measurements should be performed concurrently. Even if test accuracy has recently improved, a 1-tube (i.e., 2-fold) difference in an influenza hemagglutination inhibition (HI) antibody titer could occur as a result of measurement error. For example, if pre- and post-vaccination antibody titers are measured at separate time points, the pre-vaccination antibody titer could be 1-tube lower than the true value, whereas the post-vaccination antibody titer could be 1-tube higher than the true value due to measurement error. This measurement error would result in a 4-fold increase from pre- to post-vaccination titers although the patient's antibody titer did not actually increase. Therefore, to minimize the effects of measurement errors, the test environment must be standardized as much as possible.

According to the descriptions in the papers we reviewed, approximately 60% of studies on influenza A(H1N1)pdm09 vaccine in Japan performed concurrent measurement of pre- and post-vaccination antibody titers [5,8,10–16,18]. Thus, in these studies, the study procedure for the measurement of antibody titer did not seem to explain the variation in antibody response. To provide proper interpretation of vaccine immunogenicity, concurrent measurement of paired serum samples would be needed, and the description would help readers to interpret the results appropriately.

The second key point to consider in the study procedure concerns analysis and interpretation of results. During the study period, some subjects may develop influenza. If the effects of subjects who develop influenza (including subclinical infection) during the study period are included, then post-vaccination antibody titers will be increased because of influenza infection, which can lead to an overestimation of the immunogenicity of the influenza vaccine. Thus, in immunogenicity studies of influenza vaccines, we should collect information regarding the development of influenza during the study period, and infected subjects should be excluded from the analyses.

Among published papers from Japan, approximately 60% of papers disclosed the inclusion/exclusion of subjects who developed influenza during the study period and the management methods of such infected subjects [5,7,8,11–14,16,18,19]. Especially in the case of the pandemic influenza vaccine, the spread of influenza preceded the development of the vaccine. Thus, even in the relatively short study period of an immunogenicity study (generally 3–4 weeks), subjects can develop pandemic influenza. In fact, in our study of influenza A(H1N1)pdm09 vaccine, 9 of 111 study subjects experienced a confirmed influenza A virus infection (as determined by the rapid test) between the first dose

Table 2
Immunogenicity of influenza A(H1N1)pdm09 vaccine in Japan.

Ref.	Study subjects	N	Age (years)	No. of doses	GMT			MFR		SCP* (95%CI) at S1	SPP† (95%CI) at S1
					S0‡	S1‡	S2‡	S1/S0	S2/S0		
[5]	Junior high school	60	12–15	2	10	162	158	15.6	15.4	83% (73–93%)	92% (84–106%)
	High school	46	15–18	2	15	126	136	8.3	8.3	72% (58–85%)	89% (80–98%)
[6]	Health-care workers	389	20–65	1	6	22	–	3.5	–	35% (30–40%)	38% (33–43%)
[7]	Pediatricians	16	27–49	1	10	27	–	5.4	–	44% (17–71%)	44% (16–71%)
[8]	Pregnant women	149	17–41	2	8	139	114	17.1	14.1	91% (86–96%)	89% (84–94%)
[9]	Pregnant women	128	34.8 ± 4.1	2	Not applicable					Not applicable	90% at S2
[10]	Hematological malignancy patients	50	21–83	2	6	13	22	2.3	3.9	32% (19–45%)	27% (14–40%)
[11]	Subjects with severe motor and intellectual disability	104	40.1 ± 12.9	2	7	39	41	5.4	5.6	54% (44–64%)	56% (46–66%)
[12]	Diabetes mellitus patients	48	26–75	1	6	53	–	9.0	–	73% (60–86%)	73% (60–86%)
[13]	Diabetes mellitus patients	48	28–78	2	6	33	34	5.3	5.6	46% (32–60%)	25% (38–66%)
[14]	Hepatitis C patients	79	64.5 ± 10.6	1	8	82	–	10.3	–	72% (62–82%)	71% (61–81%)
[15]	Duchenne muscular dystrophy patients	44	17–47	1	7	75	–	10.5	–	SRP§: 84% (73–95%)	70% (57–83%)
[16]	HIV-infected patients	104	34.3–53.0	2	8	31	39	Not applicable		44% (31–58%)	52% (38–66%)
[17]	HIV-infected patients	182	46.6 ± 12.7	1	10	35	–	Not applicable		39% (32–46%)	50% (43–57%)
[18]	Children with renal diseases under immunosuppressive therapy	15	11.8 ± 4.0	2	6	104	50	16.9	9.0	69% (39–91%)	77% (46–95%)
[19]	Pediatric liver transplant recipients	13	1–18	2: <13 years; 1: ≥13 years	6	32		5.2		46% (19–75%)	54% (25–81%)
[20]	Healthy adults with prior seasonal influenza vaccination	51	22–61	2	8	45	41	6.4	5.9	59% (44–72%)	61% (46–74%)
	Healthy adults without prior seasonal influenza vaccination	59	23–62	2	8	100	107	14.6	15.6	80% (67–89%)	80% (67–89%)

Abbreviations: CI, confidence interval; GMT, geometric mean titer; MFR, mean fold rise; SCP, seroconversion proportion; SPP, seroprotection proportion, SRP, seroresponse proportion.
* SCP: the proportion of persons with pre-vaccination HI antibody titer of <1:10 and post-vaccination titer of ≥1:40 or ≥4-fold post-vaccination rise in antibody titer.
† SPP: the proportion of persons satisfying the protective level of antibody titer (HI antibody titer of ≥1:40).
‡ S0, before vaccination; S1, 3–4 weeks after 1st dose of vaccination; S2, 4 weeks after 2nd dose of vaccination.
§ SRP: the proportion of persons with ≥4-fold post-vaccination rise in antibody titer.

and serum sampling after the second dose and thus were excluded from the analyses [5]. Therefore, to accurately determine vaccine immunogenicity, it is essential to compile data on the presence/absence of disease development during the study period, and infected individuals must be rigorously excluded from the analysis.

3.2. The effect of subject background characteristics

When we reviewed immunogenicity studies on influenza A (H1N1)pdm09 vaccine in Japan (Table 2), the most remarkable immune response was observed in junior high school students [5], while the lowest immune response was observed in hematological malignancy patients [10]. This difference is likely due to differences in patient characteristics, as patients with underlying illnesses and/or receiving immunosuppressive therapy are known to demonstrate lower immune responses to vaccines [1].

Age is another important factor that can affect immune responses to vaccines. In general, elderly subjects are likely to exhibit lower immune responses to vaccines, whereas young children require two doses of influenza vaccine to achieve a sufficient immune response [1]. In fact, the international criteria of vaccine immunogenicity take into consideration the effect of age (Table 1) [3,4]. According to these criteria, most studies about influenza A (H1N1)pdm09 vaccine conducted in Japan also considered the effect of age by using stratified or multivariate analyses [5–8,10–14,16,17]. In the study of hematological malignancy patients, half of the subjects were ≥60 years of age, which might explain the observed lower immune responses to the vaccine [10]. In addition, other studies also indicated that higher aged subjects had lower GMT and lower SPP after vaccination among diabetes mellitus patients [12,13] and hepatitis C patients [14]. It is therefore considered that higher age also affects the immunogenicity of influenza A(H1N1)pdm09 vaccine.

As for other subject characteristics which potentially affect to vaccine immunogenicity, some studies showed that subjects with a lower body mass index exhibited lower immune responses to the vaccine, regardless of the effect of age, disease condition, medication and pre-vaccination titer [12,13]. Another study indicated that a lower serum protein level was associated with a lower immune response, after adjusting for potential confounders including body mass index [14]. Although the precise mechanisms remain unclear, these results suggest that malnutrition might account for the decreased immune response, since malnutrition is related to a lower body mass index.

3.3. The effect of pre-vaccination titer

An inverse association between the pre-vaccination titer and MFR and SRP has been shown, referred to as the "law of initial value" or "negative feedback," in an immunogenicity study of seasonal influenza vaccine [21]. In general, persons with high pre-vaccination titers (i.e., an influenza HI antibody titer of ≥1:40) are likely to show lower MFR or lower SRP values. Inclusion of these immunized subjects may lead to underestimation of vaccine immunogenicity unless the effect of these immunized subjects is appropriately considered in the analyses and interpretation of results. The pre-vaccination titer is a significant concern in immunogenicity assessment of seasonal influenza vaccines because many people have some level of antibody due to a previous infection or vaccination with a similar strain as the relevant vaccine. On the other hand, for pandemic influenza vaccines, clinicians may presume few subjects have antibody to pandemic influenza before vaccination and thus consider the effect of pre-

vaccination titer negligible. However, our review of immunogenicity studies of influenza A(H1N1)pdm09 vaccine demonstrated some subjects had pre-vaccination titers of ≥1:40, despite that all studies excluded subjects with a history of confirmed or suspected infection of influenza A(H1N1)pdm09 at the study recruitment. As one example, we present below the results of an immunogenicity study of the influenza A(H1N1)pdm09 vaccine in adolescents [5].

We conducted a study to provide information for a national decision regarding the recommended number of doses of influenza A(H1N1)pdm09 vaccine for adolescents. We recruited 106 subjects without any history of influenza A(H1N1)pdm09 infection. In the analysis, however, approximately 28% of high school students demonstrated pre-vaccination titers [5], which may have resulted from asymptomatic infection of influenza A(H1N1)pdm09 because the influenza A(H1N1)pdm09 pandemic in Japan started among high school students. In addition, immunogenicity markers as the study outcome (i.e., GMT, MFR, SCR, and SPP after 1 dose of vaccination) were lower in high school students than junior high school students (Table 2) [5]. Unless we considered the effect of subjects with pre-vaccination titer, the results could suggest that the immune response to this influenza vaccine was lower in high school students than junior high school students, which would mislead the decision about the number of doses for adolescents. To avoid such misinformation, we conducted additional analyses using stratified or multivariate analyses.

As shown in Table 3, a lower SRP value was also observed among high school students compared with junior high school students, which resulted in a lower (approximately half) odds ratio for SRP in high school students compared to junior high school students in the univariate analysis. However, subjects with higher pre-vaccination titers also had lower SRP values, so-called "law of initial value." Thus, when we considered the effect of pre-vaccination titer in the multivariate analysis, the odds ratio of high school students approached the null value, indicating no difference in the antibody response to this vaccine observed between junior high school students and high school students. It became clear that the results obtained from Table 2 (i.e., high school students had a lower MFR in antibody titer and a lower SCP than junior high school students) were merely due to the effect of pre-vaccination antibody titer. The results of this study emphasize the importance of considering the effect of pre-vaccination titer even in the study of pandemic influenza vaccines.

The effect of the pre-vaccination antibody titer on vaccine immunogenicity has been recognized in immunogenicity studies of seasonal influenza vaccines [22]. Moreover, factors suggested from immunogenicity studies of seasonal influenza vaccines (e.g., age, pre-vaccination antibody titer, underlying illness, use of an immunosuppressant) should similarly be considered in the assessment of vaccine immunogenicity of pandemic influenza vaccines. Taking these factors into consideration by adjusting for subject characteristics and pre-vaccination titer in stratified and multivariate analyses or by using strict inclusion criteria will lead to proper assessment of vaccine immunogenicity.

3.4. Time interval between seasonal influenza vaccination and vaccination with a relevant pandemic influenza vaccine

In the assessment of pandemic influenza vaccine immunogenicity, effects resulting from the time interval between seasonal influenza vaccination and pandemic influenza vaccination should be considered. As one example, we present the results of an immunogenicity study of the influenza A(H1N1)pdm09 vaccine in pregnant women [8]. Single vaccination of influenza A(H1N1)pdm09 vaccine led to a sufficient antibody response in pregnant women, which satisfied the international criteria for the immunogenicity of the pandemic influenza vaccine (Tables 2 and 4). However, the antibody response to influenza A(H1N1)pdm09 vaccination was lower in pregnant women who had received seasonal influenza vaccination prior to the influenza A(H1N1)pdm09 vaccine (Table 4). The lower antibody response was particularly remarkable in subjects who had a vaccination interval of <20 days. Moreover, when an additional analysis was performed by changing the cut-off value for the vaccination interval from 20 days to 14 days, subjects who had been vaccinated with the seasonal vaccine within 14 days demonstrated even lower antibody responses to the influenza A (H1N1)pdm09 vaccine (post-vaccination GMT = 49, MFR = 4.9, SCP = 60%, and SPP = 50%) [8]. Similar observations were also reported in patients with hepatitis C [13] and healthy children [23]. Lower immune responses were also observed in the study of health-care workers, in which 85% of study subjects had received the seasonal influenza vaccine 7–10 days before influenza A(H1N1)pdm09 vaccine [6]. In addition, one randomized controlled trial among healthy adults also showed that subjects with prior vaccination with the seasonal influenza vaccine had lower SPP and SCP to influenza A(H1N1)pdm09 vaccine than those without prior vaccination with seasonal influenza vaccine, as shown in Table 2 [20]. These findings suggest the possibility that, when the interval after vaccination with the seasonal vaccine is short, interference between the two vaccines can occur, and the antibody response to the influenza A(H1N1)pdm09 vaccine might decrease.

For pandemic influenza, two main influenza vaccines (monovalent influenza vaccine against the pandemic influenza strain and seasonal influenza vaccine) would be available. However, supply

Table 3
Effects of pre-vaccination titer on seroresponse proportion.

Category	N	SRP* (95%CI)	Univariate		Multivariate†	
			OR (95%CI)	P	OR (95%CI)	P
School type						
Junior high school	60	87% (78–96%)	1.00		1.00	
High school	46	78% (66–90%)	0.55 (0.20–1.54)	0.26	0.86 (0.25–3.03)	0.82
Pre-vaccination titer						
<1:10	48	93% (86–100%)	1.00		1.00	
1:10–1:20	36	94% (86–102%)	1.13 (0.18–7.16)	0.89	1.14 (0.18–7.22)	0.89
≥1:40	22	41% (20–62%)	0.05 (0.01–0.20)	<0.01	0.05 (0.01–0.21)	<0.01
			Trend P < 0.01		Trend P < 0.01	

Cited and reconstructed from Ref. [5].
Abbreviations: OR, odds ratio; CI, confidence interval; SRP, seroresponse proportion.
* SRP: the proportion of persons with ≥4-fold post-vaccination rise in antibody titer.
† Model includes school type and pre-vaccination titer.

Table 4
Immunogenicity in pregnant women after 1 dose of vaccination with influenza A(HIN1)pdm09 vaccine.

Category	N	GMT		MFR	SCP* (95%CI) at S1	SPP† (95%CI) at S1
		S0‡	S1‡			
All subjects	149	8	139	17.1	91% (86–96%)	89% (84–94%)
Vaccination with current seasonal vaccine						
Not vaccinated	114	8	159	20.3	95% (91–99%)	92% (87–97%)
Vaccinated	35	9	90	9.8	80% (67–93%)	77% (63–91%)
		P = 0.41	P = 0.03	P = 0.008	P = 0.007	P = 0.02
Vaccination interval from seasonal vaccine						
Not vaccinated	114	8	159	20.3	95% (91–99%)	92% (87–97%)
≥20 days	17	8	120	15.4	100% (100%)	88% (73–100%)
<20 days	17	10	68	6.8	65% (42–88%)	65% (42–88%)
		P = 0.69	P = 0.08	P = 0.02	Trend P < 0.01	Trend P < 0.01

Cited and reconstructed from Ref. [8].
Abbreviations: CI, confidence interval; GMT, geometric mean titer; MFR, mean fold rise; SCP, seroconversion proportion; SPP, seroprotection proportion.
* SCP: the proportion of persons with pre-vaccination HI antibody titer of <1:10 and post-vaccination titer of ≥1:40 or ≥4-fold post-vaccination rise in antibody titer.
† SPP: the proportion of persons satisfying the protective level of antibody titer (HI antibody titer of ≥1:40).
‡ S0, before vaccination; S1, 3–4 weeks after 1st dose of vaccination.

of the pandemic influenza vaccine is limited, rendering it difficult to obtain the pandemic vaccine. In this situation, many people may choose to receive seasonal influenza vaccination first, and there is no clear standard concerning the duration between seasonal influenza vaccination and pandemic influenza vaccination. In general, a vaccination interval of 4 weeks after vaccination with a live vaccine and an interval of 1 week after vaccination with an inactivated vaccine are recommended to avoid mutual interference between vaccines. Moreover, findings concerning the influenza A(H1N1) pdm09 vaccine suggest that a vaccination interval of at least 3 weeks may be necessary. However, this vaccination interval may only be applicable to the influenza A(H1N1)pdm09 vaccine, since vaccines greatly differ from each other. Therefore, for future pandemic influenza vaccines, the effect of the vaccination interval between seasonal influenza vaccine and the newly developed pandemic influenza vaccine should be considered in the immunogenicity assessment of the pandemic vaccine. This can be performed using similar methods described for other factors, such as adjusting for the vaccination interval in stratified and multivariate analyses.

4. Conclusion

We encountered an influenza pandemic in 2009, which gave us an opportunity to study the immunogenicity of the influenza A (H1N1)pdm09 vaccine. This review describes the lessons our experiences have taught us, which may provide useful information for future influenza pandemics. However, studies on pandemic influenza will most certainly succeed studies on seasonal influenza. Therefore, appropriate procedures suggested by seasonal influenza studies and factors affecting the immunogenicity of seasonal influenza vaccines may be applied to similar studies on pandemic influenza vaccines. In addition, factors and strategies described herein might be applicable to immunogenicity studies of vaccines for other infectious diseases, as they share the basic principles of immunogenicity assessments.

Conflict of interest

None.

References

[1] Recommendations of the Advisory Committee on Immunization Practices (ACIP). Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practice (ACIP) — United States, 2016–2017 Influenza Season. MMWR 2016; 65 (5): 1–52.
[2] World Health Organization. New influenza A/H1N1 virus: global epidemiological situation, June 2009. Wkly Epidemiol Rec 2009;84:249–57.
[3] European Committee for Proprietary Medical Products. Note for guidance on harmonisation of requirements for influenza vaccines (CPMP/BWP/214/96). London: European Agency for the Evaluation of Medical Products; 1997.
[4] Center for Biologics Evaluation and Research. Guidance for industry: clinical data needed to support the licensure of pandemic influenza vaccines. Bethesda, MD: Food and Drug Administration; May 2007.
[5] Kobayashi M, Ohfuji S, Fukushima W, Maeda A, Maeda K, Fujioka M, et al. Immunogenicity and reactogenicity of a monovalent inactivated 2009 Influenza a vaccine in adolescents: with special reference to pre-existing antibody. J Pediatr 2012;160:632–7.
[6] Igari H, Segawa S, Watanabe A, Suzuki A, Watanabe M, Sakurai T, et al. Immunogenicity of a monovalent pandemic influenza A H1N1 vaccine in health-care workers of a university hospital in Japan. Microbiol Immunol 2010;54:618–24.
[7] Hata A, Mano C, Nakamura Y, Nishida H, Kumakura A, Mizumoto H, et al. Low response to a monovalent inactivated unadjuvanted influenza A (H1N1) pdm09 vaccine in pediatricians of a general hospital in Japan. Hum Vaccin Immunother 2012;8:587–91.
[8] Ohfuji S, Fukushima W, Deguchi M, Kawabata K, Yoshida H, Hatayama H, et al. Immunogenicity of a monovalent 2009 influenza A (H1N1) vaccine among pregnant women: lowered antibody response by prior seasonal vaccination. J Infect Dis 2011;203:1301–8.
[9] Horiya M, Hisano M, Iwasaki Y, Hanaoka M, Watanabe N, Ito Y, et al. Efficacy of double vaccination with the 2009 pandemic influenza A (H1N1) vaccine during pregnancy. Obstet Gynecol 2011;118:887–94.
[10] Ide Y, Imamura Y, Ohfuji S, Fukushima W, Ide S, Tsutsumi C, et al. Immunogenicity of a monovalent influenza A(H1N1)pdm09 vaccine in patients with hematological malignancies. Hum Vaccin Immunother 2014;10:2387–94.
[11] Hara M, Hanaoka T, Mizushima T, Honma J, Maeda K, Ohfuji S, et al. Diminished immunogenicity to pandemic H1N1 2009 influenza vaccine in subjects with severe motor and intellectual disability. Vaccine 2011;29:8323–9.
[12] Egawa Y, Ohfuji S, Fukushima W, Yamazaki Y, Morioka T, Emoto M, et al. Immunogenicity of influenza A(H1N1)pdm09 vaccine in patients with diabetes mellitus: with special reference to age, body mass index, and HbA1c. Hum Vaccin Immunother 2014;10:1187–94.
[13] Eto T, Matsubara M, Nagamizu M, Ishibashi M, Tsuru T, Ito K, et al. Immunogenicity of an inactivated vaccine against influenza A(H1N1)pdm09 virus in diabetic patients. J Japan Diab Soc 2013;56:219–26.
[14] Ohfuji S, Fukushima W, Tamori A, Maeda K, Maeda A, Hirota Y. Immunogenicity of influenza A(H1N1)pdm09 vaccine and the associated factors on lowered immune response in patients with hepatitis C. Influenza Other Respir Viruses 2013;7:456–65.
[15] Saito T, Ohfuji S, Matsumura T, Saito T, Maeda K, Maeda A, et al. Safety of a pandemic influenza vaccine and the immune response in patients with duchenne muscular dystrophy. Intern Med 2015;54:1199–205.
[16] Hatakeyama S, Iwatsuki-Horimoto K, Okamoto K, Nukui Y, Yata N, Fujita A, et al. Unadjuvanted pandemic H1N1 influenza vaccine in HIV-1-infected adults. Vaccine 2011;29:9224–8.
[17] Yanagisawa N, Maeda K, Ajisawa A, Imamura A, Suganuma A, Ando M, et al. Reduced immune response to influenza A (H1N1) 2009 monovalent vaccine in HIV-infected Japanese subjects. Vaccine 2011;29:5694–8.
[18] Tanaka S, Saikusa T, Katafuchi Y, Ushijima K, Ohtsu Y, Tsumura N, et al. Serologic response after vaccination against influenza (A/H1N1)pdm09 in

children with renal disease receiving oral immunosuppressive drugs. Vaccine 2015;33:5000–4.
[19] Torii Y, Kimura H, Ochi N, Kaneko K, Ando H, Kiuchi T, et al. Immunogenicity of inactivated 2009 H1N1 influenza vaccine in pediatric liver transplant recipients. Vaccine 2011;29:4187–9.
[20] Uno S, Kimachi K, Kei J, Miyazaki K, Oohama A, Nishimura T, et al. Effect of prior vaccination with a seasonal trivalent influenza vaccine on the antibody response to the influenza pandemic H1N1 2009 vaccine: randomized controlled trial. Microbiol Immunol 2011;55:783–9.
[21] Hobson D, Baker FA, Curry RL. Effects of influenza vaccines in stimulating antibody in volunteers with prior immunity. Lancet 1973;2:155–6.
[22] Hirota Y, Kaji M, Goto S, Oka T. The hemagglutination inhibition antibody responses to an inactivated influenza vaccine among healthy adults: with special reference to the prevaccination antibody and its interaction with age. Vaccine 1996;14:1597–602.
[23] Nolan T, McVernon J, Skeljo M, et al. Immunogenicity of a monovalent 2009 influenza A (H1N1) vaccine in infants and children. JAMA 2010;303:37–46.

Vaccine 35 (2017) 4787–4790

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Vaccine epidemiology: Its role in promoting sound immunization programs in Japan

Yoshio Hirota [a,b,*], Kotaro Ozasa [c], Takashi Nakano [d]

[a] College of Healthcare Management, 960-4, Takayanagi, Setaka-machi, Miyama-shi, Fukuoka 835-0018, Japan
[b] Clinical Epidemiology Research Center, Medical Co. LTA, 3-5-1, Kashii-Teriha, Higashi-ku, Fukuoka 813-0017, Japan
[c] Department of Epidemiology, Radiation Effects Research Foundation, 5-2, Hijiyama-koen, Minami-ku, Hiroshima 732-0815, Japan
[d] Department of Pediatrics, Kawasaki Medical School, 2-1-80, Nakasange, Kita-ku, Okayama 700-8505, Japan

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 5 October 2016
Accepted 24 November 2016

Keywords:
Vaccine
Epidemiology
Influenza
Antibody efficacy
Immunogenicity
Pregnant women
Test-negative design

ABSTRACT

In Japan, the Vaccine Epidemiology Research Group created by the Ministry of Health, Labour and Welfare has played an important role in demonstrating the solid scientific basis for vaccine efficacy and safety since 2002. Members of the group, including epidemiologists, clinicians and microbiologists, have been conducting collaborative studies on vaccines for influenza, pertussis, rotavirus gastroenteritis, polio and pneumonia. So far, the group has achieved several works and contributed to the national vaccination program, including research on the immunogenicity of low doses of influenza vaccine among young children, the immunogenicity and effectiveness of the 2009 influenza pandemic vaccine among various risk groups, the interchangeability of live/inactivated polio vaccines, the health impact of influenza on pregnant women, and the monitoring of influenza vaccine effectiveness using case-control studies with a test-negative design. As part of the 18th Annual Meeting of the Japanese Society of Vaccinology, these accomplishments were featured in the Vaccine Epidemiology Symposium. This report summarizes the recent epidemiological studies on vaccine in Japan as a prologue to the next six papers collected from the symposium.

1. Introduction

After over 20 years of chaos with the influenza vaccination policy and debate over the effectiveness of the influenza vaccine in Japan, an influenza vaccination program targeting elderly people (≥65 years of age) was started in 2001 [1]. Currently, the vaccine coverage is estimated to remain constant at 50% or more in this age group. The total amount of influenza vaccine manufactured exceeded 33 kL (approximately 66 million doses) in 2013, as compared to 0.3 kL (approximately 0.6 million doses) in 1994 when the anti-vaccination campaign against the influenza vaccine was the most intense. During the influenza pandemic in 2009, 27 kL (approximately 54 million doses) of the pandemic vaccine was manufactured in addition to the already produced 23.13 kL (approximately 46.26 million doses) of the seasonal vaccine for that season. Thus, the importance of influenza vaccination against influenza infection appears to have become well understood, and the influenza vaccine production capacity has sufficiently recovered despite the anti-vaccination campaigns that still remain active to some extent. Over the course of these events, there is no doubt that the Vaccine Epidemiology Research Group created by the Ministry of Health, Labour and Welfare (MHLW) in 2002 has played an important role in demonstrating the solid scientific basis for influenza vaccination [1].

Recently, Japan has made major progress in conquering the vaccine gap by amending or promulgating the law and ordinances for general immunization programs. As such, five diseases have been newly listed as target diseases of the Preventive Vaccination Law since 2009. However, to achieve sound immunization programs, it is essential to promote mutual understanding between both the vaccine-providing and vaccine-receiving sides through the sharing of accurate information on vaccine efficacy and safety. Regrettably, however, poor-quality studies on vaccine effectiveness are still being reported, and their results are often being referred to without adequate scientific review.

Abbreviations: MHLW, Ministry of Health, Labour and Welfare of Japan; JSV, the Japanese Society of Vaccinology; ILI, influenza-like illness; HI, hemagglutination inhibition.

* Corresponding author at: College of Healthcare Management, 960-4, Takayanagi, Setaka-machi, Miyama-shi, Fukuoka 835-0018, Japan.
E-mail address: yos-hirota@healthcare-m.ac.jp (Y. Hirota).

http://dx.doi.org/10.1016/j.vaccine.2017.07.001
0264-410X/

Based upon this history, the 18th Annual Meeting of the Japanese Society of Vaccinology (JSV) adopted the theme "To promote sound immunization programs: providing safe and effective vaccines and obtaining public understanding" and organized a symposium titled "Vaccine Epidemiology: Principles and Methods" [2]. Here, as a prologue to the next six papers collected from among the presentations in the symposium that focused on the methodology for vaccine effectiveness and related research, this report summarizes the current situation of vaccine effectiveness and safety studies in Japan from an epidemiological viewpoint.

2. Vaccine Epidemiology Research Group

2.1. Outline and framework

The Vaccine Epidemiology Research Group was established by the MHLW in 2002, immediately after the start of the influenza vaccination program targeting elderly persons in 2001, to assess the effectiveness of the influenza vaccine [1]. Following the success of its first research group, the group has remained active by modifying the study theme every 3 years (Table 1), expanding the objectives to several kinds of vaccines and involving more researchers from various fields. Presently, there is a total of 172 members, including epidemiologists, pediatricians, physicians, obstetricians, microbiologists, clinical pharmacologists and public health specialists, who are conducting collaborative studies on vaccines for influenza, pertussis [3,4], rotavirus gastroenteritis, polio and pneumonia [5].

2.2. Coordination

In addition to the routine studies performed by the individual members in their own research areas, there are research projects that are closely related to the national vaccination program, such as studies on the target groups of vaccinations, interchangeability among different vaccines for the same disease, and vaccination schedules. These studies generally require investigators with various specialties or from particular research institutes or organizations, and participants in large numbers or with certain characteristics, such as high-risk conditions.

Thus, the group has worked in close cooperation with institutes specialized in phase-1 trials from which experts in clinical pharmacology were invited. Their expertise as individual scientists and as a pillar of the institute is quite beneficial for the group, since vaccine research almost always requires the participation of otherwise healthy subjects. The group has also created a network of pediatric practitioners in the community who have a strong interest in vaccines and are therefore helpful in achieving studies by interacting with children and their parents for vaccinations, collecting blood samples, and conducting attack surveys, etc.

2.3. Development of two research methodologies

So far, two noteworthy methods of vaccine research have been developed by the group. One is the assessment of influenza vaccine efficacy based on "antibody efficacy" [6,7]. In this method, the frequency of influenza-like illness (ILI) or other clinical outcomes is compared between those who achieved a protective level of hemagglutination inhibition antibody (HI $\geq$ 1:40) and those who did not (HI < 1:40) after vaccination; this is in contrast to the typical comparison made between vaccinees and non-vaccinees. The product of the antibody efficacy and the achievement proportion which is the percentage of those who achieved a protective level of HI titer after vaccination among those with an HI < 1:40 before vaccination, is theoretically equivalent to the vaccine efficacy. Multivariate analysis for computing antibody efficacy, which includes variables representing HI titers against vaccine antigens together with potential confounders, makes it possible to estimate the clinical effectiveness of vaccine-induced antibodies by virus type or subtype without confirming strain-specific diseases. This method has two major strengths: first, vaccine efficacy can be calculated from the data of vaccinees alone, which is advantageous as the growing vaccine coverage among high-risk individuals makes it difficult to create an unvaccinated comparison group; second, the observation of clinical outcomes can be conducted in a double-blind manner, i.e., information on the HI titers is not known by the investigators or the study subjects, since antibody measurements are usually performed in the post-season.

The other method is the detailed analysis of antibody responses in immunogenicity studies. The generally used indices to illustrate immunogenicity, such as the geometric mean titer, sero-response proportion and the sero-protection proportion, are obtained through rather simple calculations as long as they are carried out for all of the subjects. However, studies for elucidating predictors of immunogenicity require substantially redundant and iterative calculations since the indices have to be computed separately for the different groups of individuals with or without specific characteristics, e.g., the age group, body mass index and severity among diabetes mellitus patients [8]. Such laborious work has discouraged researchers from exploring antibody responses in detail, and as a result, clinicians are obliged to provide and repeat explanations based on inferences and not on evidence when asked questions such as "Which was responsible for the lowered immune response: the underlying illness per se or the medicine for the treatment?" The group has made it possible to perform such iterative calculations more easily by developing a computational program that can be used to demonstrate whether some factors are actually associated with immunogenicity. Some outstanding studies have shown that prior seasonal influenza vaccination weakened the antibody responses to the 2009 pandemic vaccine [9], and that rituximab, a biological immune suppressant, rather than the disease per se, was the causal factor for lowered immunogenicity to the influenza vaccine in those with a hematological malignancy [10].

2.4. Accomplishments

The group has contributed to the national vaccination program by providing data obtained from epidemiological studies. Several examples are provided below.

Table 1
Chronology of the Vaccine Epidemiology Research Group organized by the Ministry of Health, Labour and Welfare, Japan.

Fiscal year	Title of research	Grant amount (Japanese yen)
2002–2004	Appraisal of influenza vaccine effectiveness and vaccination policy in conformity with evidence-based medicine	103,950,000
2005–2007	Analytical epidemiologic study on the effectiveness of influenza and other vaccines and vaccination policy	124,600,000
2008–2010	Analytical epidemiologic study on influenza and other respiratory infections of concern in recent years	216,837,000
2011–2013	Analytical epidemiologic study on the effectiveness and safety of vaccines	256,478,000
2014–2016	Analytical epidemiologic study on vaccine effectiveness and safety and on vaccine-preventable disease control	113,944,000

Compared to Western standards, the standard influenza vaccine dose for children in Japan had long been low (0.1 mL if <1 year old; 0.2 mL if 1–5 years old; 0.3 mL if 6–12 years old; and 0.5 mL if ≥13 years old). The group demonstrated the immunogenicity and safety of the vaccine doses according to Japanese and Western standards, and Japan subsequently switched to the same doses as those used in the Western standard in 2011 [11].

During the 2009 influenza pandemic, the group investigated the immunogenicity, effectiveness, and safety of the pandemic vaccine in study subjects with various characteristics, including young children and adolescents [12], the elderly and pregnant women [9], persons with motor and intellectual disability [13], those under hemodialysis, and patients with diabetes mellitus [8], chronic liver disease [14,15], hematological malignancies [10], or neuromuscular disorders [16]. The clinical effectiveness among pregnant women which was studied using the "antibody efficacy" method is worthy of note [17] as it would have been difficult to create an unvaccinated comparison group due to the prioritized use of vaccines for this group.

Besides the influenza vaccine, the group also played a decisive role in replacing the oral polio vaccine (OPV) with an inactivated polio vaccine (IPV). In Japan, OPV had been used until 2013 despite the strong calls to change to IPV because of the possibility of vaccine-associated paralytic polio (VAPP). The group investigated the interchangeability of OPV, DPT-IPV (Sabin) and IPV (Salk) by comparing the immunogenicities among four arms, i.e., one dose of OPV followed by three doses of DPT-IPV, one dose of OPV followed by three doses of IPV, two doses of DPT-IPV followed by two doses of IPV, and two doses of IPV followed by two doses of DPT-IPV. This study was successfully achieved after overcoming administrative and practical difficulties, i.e., the two test vaccines (DPT-IPV and IPV) were products from different manufacturers and neither had been licensed in Japan, and DPT-IPV had to be given in conformity with the vaccination schedule for DPT since many children had already received the dose(s) for the primary series of DPT in the general vaccination program.

Presently, the group is making great efforts in conducting two studies. The first study is the investigation of the health impact of influenza on pregnant women. In Japan, there has been no evidence on the extent of the effect of influenza on the health condition of pregnant women even though the World Health Organization recommended annual influenza vaccination for this group in its position paper in 2012 [18]. In fact, the proportion of hospitalized cases of pregnant women with influenza was quite low during the 2009 pandemic in Japan as compared to other countries [19]. A study adopting the "self-control method" has been completed with the cooperation of the Osaka Association of Obstetricians and Gynecologists involving more than 10,000 pregnant women; this represents a first since no large-scale database on pregnant women, such as the health maintenance organization, had been available in Japan. The final decision on whether routine influenza vaccination for pregnant women should be stipulated in the Preventive Vaccination Law will be made based on the findings of this study.

The second is the establishment of a monitoring system of influenza vaccine effectiveness; this is required as the level of detection of vaccine effectiveness varies depending on the time, place, and population. In a case-control study with a "test-negative (RT-PCR) control design", as are already being performed in the United States, Canada, Europe, Australia and New Zealand [20–24], vaccine effectiveness is being assessed among children aged <6 years who were recruited from five pediatric clinics in Osaka in the 2013–2014 season, and from 10 clinics in Osaka and Fukuoka in the 2014–2015 season. This study is expected to provide an abstract statement on influenza vaccine effectiveness and to enable comparisons with the data from other monitoring systems outside of Japan.

3. Frustrations of epidemiologists

When the fallacy that the influenza vaccine has no efficacy took over Japanese society, those who could theoretically explain why the influenza vaccine is so ineffective were regarded as influenza vaccine specialists. Their negative views were founded upon experimental findings, e.g., the nature of influenza virus to easily change its antigenic characteristics, the presence of antigenic differences between vaccines and circulating strains, and little or no antibody induction by inactivated vaccines on the surface of the respiratory tract mucosa. However, it is the principle that the efficacy and safety of any pharmaceutical products must be described based on data obtained solely from the human population. Thus, skepticism about vaccine efficacy resulting from the clinicians' low-quality studies that contained substantial disease misclassifications [25] was reinforced by the inference led from the experiments. In addition, the recent reports describing that seed viruses for the influenza vaccine are liable to mutations during incubation in eggs provided virologists with further speculative bases to negate influenza vaccine effectiveness. It is not easy for epidemiologists to overcome such negative inference generated from experimental findings. Epidemiological verification requires a large number of subjects and a long period of observation, while the results from those studies are generally regarded as the "gold standard" in evaluating medical intervention among human populations.

Although they are decreasing in number, low-quality studies containing substantial faults in the study design, conduct and analysis, that consequently suffer from serious validity problems, such as confounding and bias, are still being reported by clinicians. Furthermore, there are not many reviewers who can adequately judge those studies. In one clinic-based study that analyzed nearly 9000 vaccinees and non-vaccinees to investigate vaccine effectiveness against clinical influenza using a positive rapid diagnostic test, only the influenza attacks among the clinic visitors were taken into account, and those in non-visitors were not considered [26]. Thus, this study does not satisfy the principle that all study participants should be observed with equal intensity. A recent case-control study with a test-negative design using rapid diagnostic test results indicated no effectiveness for the influenza vaccine among infants aged 6–11 months [27]. However, this study suffered from selection bias due to a poor sampling scheme and a negative bias that originated from false-negative test results. It is regrettable that there are clinicians without even rudimentary knowledge of epidemiology who attempt to conduct case-control studies by themselves. Fortunately, however, a growing number of clinicians are trying to gain insight into the weaknesses of such attempts at epidemiological studies by consulting with epidemiologists.

Adverse events observed after vaccination, especially serious ones that are seen as a cluster, are also the concern of epidemiologists from the view of causality. In Japan, serious adverse events (SAEs) associated with vaccinations are usually explored by clinicians, as is the case for ordinal medicines, and presence or absence of causal relation is apt to be judged based on the interpretation of whether the connection between vaccination and SAEs can or cannot be explained by existing medical knowledge; unfortunately, vaccine-caused side effects are often unexplainable by current scientific information. An epidemiological approach seems to be crucial when examining whether an association is present or not, and if present, whether it is causal or not. Relatively new methods, such as case-crossover (CCO) studies and self-controlled case series (SCCS) studies, may bring about further clues to illuminate such

relationships [28,29]. However, the officials who are in charge of pharmaceutical affairs and clinicians who are in the position to remark on the SAEs often consider the judgment of causality to be their exclusive responsibility, and are unlikely to understand and apply epidemiological methods to their investigations.

4. Perspectives

When the symposium on influenza vaccine effectiveness was first held at the 9th Annual Meeting of the JSV in 2005 [1], a group of anti-vaccination activists took photographs point-by-point of slides projected in the conference hall to scrutinize potential faults in the presentation. Afterwards, they sent open letters addressed to the organizer of the symposium and the chairperson of the meeting to accuse them of the "faults" that they believed to have found. In contrast, at the symposium in 2014, we were able to enjoy fruitful discussions in an academic atmosphere. The public understanding of and attitude toward vaccines and vaccination has actually changed, but difficulty in establishing adequate scientific evidence that is firm enough to convince the general public remains a major obstacle in promoting the vaccination program in Japan.

The difficulties we have so far experienced with respect to the influenza vaccine and vaccination are considered to represent the general challenges faced with any vaccine. The maintenance and expansion of the present framework of the Vaccine Epidemiology Research Group will contribute to the creation of solid vaccination programs at the national level. The following six articles related to the subjects of the symposium will undoubtedly convey to the readers not only information on the present research activities of the group, but also insight into the obstacles related to the national vaccination program in Japan.

Conflict of interest

The author declare that there is no conflict of interest.

Acknowledgements

This study was supported by Health and Labour Science Research Grants from the Ministry of Health, Labour and Welfare of Japan in 2002-2016.

References

[1] Hirota Y, Kaji M. History of influenza vaccination programs in Japan. Vaccine 2008;26:6451–4.
[2] Hirota Y. Announcement for and invitation to the 18th annual meeting of Japanese Society of Vaccinology (JSV). Vaccine 2014;32:5888.
[3] Hara M, Okada K, Yamaguchi Y, Uno S, Otsuka Y, Shimanoe C, et al. Immunogenicity and safety after booster vaccination of diphtheria, tetanus, and acellular pertussis in young adults: an open randomized controlled trial in Japan. Clin Vaccine Immunol 2013;20:1799–804.
[4] Ohfuji S, Okada K, Nakano T, Ito H, Hara M, Kuroki H, Hirota Y. Effectiveness of acellular pertussis vaccine in a routine immunization program: a multicenter, case-control study in Japan. Vaccine 2015;33:1027–32.
[5] Kondo K, Suzuki K, Washio M, Ohfuji S, Fukushima W, Maeda A, et al. Association between monovalent influenza A (H1N1) pdm09 vaccine and pneumonia among the elderly in the 2009-2010 season in Japan: a case-control study. Hum Vaccin Immunother 2015;11:1088–93.
[6] Hirota Y, Kaji M, Ide S, Kajiwara J, Kataoka K, Goto S, Oka T. Antibody efficacy as a keen index to evaluate influenza vaccine effectiveness. Vaccine 1997;15:962–7.
[7] Hara M, Tanaka K, Kase T, Maeda A, Hirota Y. Evaluation of seasonal influenza vaccination effectiveness based on antibody efficacy among the institutionalized elderly in Japan. Vaccine 2010;35:5664–8.
[8] Egawa Y, Ohfuji S, Fukushima W, Yamazaki Y, Morioka T, Emoto M, et al. Immunogenicity of influenza A(H1N1)pdm09 vaccine in patients with diabetes mellitus: with special reference to age, body mass index and HbA1c. Hum Vaccin Immunother 2014;10:1187–94.
[9] Ohfuji S, Fukushima W, Deguchi M, Kawabata K, Yoshida H, Hatayama H, et al. Immunogenicity of a monovalent 2009 influenza A(H1N1) vaccine among pregnant women: lowered antibody response by prior seasonal vaccination. J Infect Dis 2011;203:1301–8.
[10] Ide Y, Imamura Y, Ohfuji S, Fukushima W, Ide S, Tsutsumi C, Koga M, Maeda K, Hirota Y. Immunogenicity of a monovalent influenza A(H1N1)pdm09 vaccine in patients with hematological malignancies. Hum Vaccines Immunother 2014;10:1–8.
[11] Mugitani A, Ito K, Irie S, Eto T, Ishibashi M, Ohfuji S, et al. Immunogenicity of the trivalent inactivated influenza vaccine in young children less than 4 years of age, with a focus on age and baseline antibodies. Clin Vaccine Immunol 2014;21:1253–60.
[12] Kobayashi M, Ohfuji S, Fukushima W, Maeda A, Maeda K, Fujioka M, et al. Immunogenicity and reactogenicity of a monovalent inactivated 2009 influenza A vaccine in adolescents: with special reference to pre-existing antibody. J Pediatr 2012;160:632–7.
[13] Hara M, Hanaoka T, Mizushima T, Honma J, Maeda K, Ohfuji S, et al. Diminished immunogenicity to pandemic H1N1 2009 influenza vaccine in subjects with severe motor and intellectual disability. Vaccine 2011;29:8323–9.
[14] Ohfuji S, Fukushima W, Tamori A, Maeda K, Maeda A, Hirota Y. Immunogenicity of influenza A(H1N1)pdm09 vaccine and the associated factors on lowered immune response in patients with hepatitis C. Influenza Other Respi Viruses 2013;7:456–65.
[15] Ohfuji S, Fukushima W, Sasaki Y, Tamori A, Kurai O, Kioka K, et al. Influenza A (H1N1)pdm09 vaccine effectiveness and other characteristics associated with hospitalization in chronic liver disease patients. Liver Int 2014;34:700–6.
[16] Saito T, Ohfuji S, Matsumura T, Saito T, Maeda K, Maeda A, et al. Safety of a pandemic influenza vaccine and immune response in patients with Duchenne muscular dystrophy. Intern Med 2015;54:1199–205.
[17] Fukushima W, Ohfuji S, Deguchi M, Kawabata K, Hatayama H, Yoshida H, et al. Effectiveness of an influenza A (H1N1) 2009 monovalent vaccine among Japanese pregnant women: a prospective observational study assessing antibody efficacy. Vaccine 2012;30:7630–6.
[18] WHO. Vaccines against influenza WHO position paper – November 2012. Wkly Epidemiol Record 2012;87:461–76.
[19] WHO. Transmission dynamics and impact of pandemic influenza A(H1N1) 2009 virus. Wkly Epidemiol Record 2009;84:481–4.
[20] Treanor JJ, Talbot HK, Ohmit SE, Coleman LA, Thompson MG, Cheng PY, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. Clin Infect Dis 2012;55:951–9.
[21] Skowronski DM, Janjua NZ, De Serres G, Dickinson JA, Winter AL, Mahmud SM, et al. Interim estimates of influenza vaccine effectiveness in 2012/13 from Canada's sentinel surveillance network, January 2013. Euro Surveill 2013;18 (5).
[22] Kissling E, Valenciano M, Falcao J, Larrauri A, Widgren K, Pitigoi D, et al. "I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in Europe, 2008-9. Euro Surveill 2009;14(44).
[23] Carville KS, Grant KA, Sullivan SG, Fielding JE, Lane CR, Franklin L, et al. Understanding influenza vaccine protection in the community: an assessment of the 2013 influenza season in Victoria, Australia. Vaccine 2015;33:341–5.
[24] Turner N, Pierse N, Huang QS, Radke S, Bissielo A, Thompson MG, et al. Interim estimates of the effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2014. Euro Surveill 2014;19(42).
[25] Hirota Y, Kaji M. Scepticism about influenza vaccine efficacy in Japan. Lancet 1994;344:408–9.
[26] Kawai N, Ikematsu H, Iwaki N, Satoh I, Kawashima T, Tsuchimoto T, et al. A prospective, Internet-based study of the effectiveness and safety of influenza vaccination in the 2001–2002 influenza season. Vaccine 2003;21:4507–13.
[27] Shinjoh M, Sugaya N, Yamaguchi Y, Tomidokoro Y, Sekiguchi S, Mitamura K, et al., Keio Pediatric Influenza Research Group. Effectiveness of trivalent inactivated influenza vaccine in children estimated by a test-negative case-control design study based on influenza rapid diagnostic test results. PLoS ONE 10(8): e0136539. doi: 10.1371/journal.pone.0136539.
[28] Ki M, Park T, Yi SG, Oh JK, Choi BY. Risk analysis of aseptic meningitis after measles-mumps-rubella vaccination in Korean children by using a case-crossover design. Am J Epidemiol 2003;157:158–65.
[29] Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. VSD rapid cycle analysis influenza working group. signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011. Vaccine 2012;30:2024–31.

Vaccine 35 (2017) 4791–4795

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Basic principle of population-based cohort study to evaluate influenza vaccine effectiveness among elderly Japanese

Megumi Hara [a,*], Yoshio Hirota [b,c]

[a] Department of Preventive Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan
[b] College of Healthcare Management, 960-4, Takayanagi, Setaka-machi, Miyama-shi, Fukuoka 835-0018, Japan
[c] Clinical Epidemiology Research Center, Medical Co. LTA, 3-5-1 Kashii-Teriha, Higashi-ku, Fukuoka 813-0017, Japan

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 27 December 2016
Accepted 18 January 2017

Keywords:
Influenza vaccine
Vaccine effectiveness
Cohort study

ABSTRACT

Influenza vaccines minimize the risk of influenza-related morbidity, complication, and death in elderly people. Although evaluating vaccine effectiveness (VE) is important for promoting immunization programs and coping with influenza epidemics, it is difficult to evaluate its effectiveness in Japan, where no frameworks to use large databases, such as a vaccination registry and health maintenance organization datasets, are available. Therefore, another analytic epidemiological investigations to evaluate VE in Japan are required. Herein, we describe the basic principles of a cohort study, which might be the most comprehensive, but expensive, study design. It is particularly important to be aware of the potential bias and confounding factors that should be minimized in the study design and analysis. We focus on "laboratory-confirmed influenza" and "influenza-like illness", and discuss why it is important to follow up with equal intensity, and how to control for bias; problems that often arise in population-based observational cohort studies.

1. Introduction

Influenza is an infectious disease, and vaccination is available; however, epidemiological evidence of vaccine effectiveness (VE) of influenza vaccine among elderly people is insufficient in Japan. In 1994, influenza was excluded from target disease list in the Japan's Preventive Vaccination Law. This owed to governmental and medical distrust of the vaccine's VE. Suspicions about VE caused a reduced vaccination coverage in Japan around 2001, when the Preventive Vaccination Law was amended to include influenza for those aged 65 years or above and for those aged 60–64 years at high-risk again [1]. To promote vaccination and to cope with a potential influenza epidemic, evidence for VE among elderly people in Japan is needed. In 2002, the Ministry of Health, Labour and Welfare organized a research group on VE in Japan.

Among the epidemiological study designs, randomized controlled trials that measure laboratory-confirmed influenza virus infections as the outcome are the most persuasive for obtaining reliable evidence of VE. However, such trials cannot be conducted ethically among groups recommended to receive vaccination annually, because those assigned to control groups will thereby miss their opportunity for vaccination. Longitudinal cohort studies provide clear information about the vaccination and outcome. Most cohort studies among community-dwelling older people were reported in Western countries [2–9]. They were conducted by record linkage studies, using large existing administrative datasets, such as health maintenance organizations, Medicare, Medicaid, national health insurance schemes, general practice research databases, population and mortality registries, as well as a vaccination registry database. The VE against serious outcome measures such as influenza-related pneumonia, hospitalization, and death were usually evaluated in those studies, but the VE against clinically diagnosed influenza was rarely detected. Because clinically diagnosed influenza was detected only among patients who had visited medical institutions, this was considered an inappropriate indicator. Additionally, most linkage studies did not control adequately for differences in the propensity for healthier persons to be more likely to receive vaccination than less healthy persons.

In Japan, there is no vaccination registry and it is difficult to use health maintenance organization datasets, owing to the Privacy Protection Law and the nature of the Japanese health care system. In principal, the Japanese health insurance system guarantees a

Abbreviations: VE, vaccine effectiveness; ILI, influenza-like illness.

* Corresponding author.
E-mail addresses: harameg@cc.saga-u.ac.jp (M. Hara), yos-hirota@healthcare-m.ac.jp, hiro8yoshi@lta-med.com (Y. Hirota).

http://dx.doi.org/10.1016/j.vaccine.2017.07.002
0264-410X/

patient's freedom to choose a medical institution; thus the seriousness of influenza symptoms is not necessarily related with visiting medical institutions. Therefore, special epidemiological investigations to evaluate VE in Japan are needed. In this article, we describe the basic principles and several potential pitfalls of population-base cohort studies, which are the most comprehensible study design, with reference to our previous report [10].

2. Basic principle of cohort studies for VE

Vaccine efficacy and VE were first described by Greenwood and Yule in 1915 [11]. In observational studies, VE is the percent reduction in the incidence of disease in vaccinated subjects (I_{vac}) compared with the incidence of disease in unvaccinated subjects (I_{unv}): $VE = \{(I_{unv} - I_{vac})/I_{unv}\} \times 100 = \{1 - (I_{vac}/I_{unv})\} \times 100 = \{1 - \text{risk ratio (RR)}\} \times 100$. For ease of understanding, Fig. 1 shows the concept and an example of VE. A reduction in the incidence of disease in I_{vac} was "20%–6%", which accounts for "{(20%–6%)/20%} × 100 (%) = 70 (%)" of I_{unv}. Therefore, a VE of 70% does not mean that 70% of vaccinated subjects will not develop influenza. The concept of RR might make it easy to understand VE. Assuming I_{unv} to be 1, then I_{vac} will be 0.3, the ratio of the incidence of vaccinated subjects compared with unvaccinated subjects.

It is an essential point that all cohort studies for evaluating VE need to observe the target outcome in both vaccinated and unvaccinated subjects over time with "equal intensity". "Laboratory-confirmed influenza" virus infections as the outcome are the most persuasive evidence of VE, because this reduces the risk of misclassification of outcome for infection. However, laboratory-confirmed influenza virus infections are not always ideal outcomes for population based cohort studies. In general, they are diagnosed only when subjects' specimens are collected at medical institutions. Because the likelihood of visits to medical institutions when patients present symptoms depends not only on symptom severity, but also on patient characteristics, laboratory-confirmed influenza may induce ascertainment bias in population-based cohort studies. Unvaccinated subjects might visit medical institutions more frequently when they have influenza-related symptoms as compared with vaccinated subjects, because they might worry about influenza. Thus, unvaccinated subjects tend to be diagnosed as having laboratory-confirmed influenza by passive surveillance in clinical settings, causing VE to be overestimated. To avoid such bias by using laboratory-confirmed influenza as an outcome, active surveillance with a weekly survey for symptom and specimen collection should be performed. To the best of our knowledge, only one randomized controlled trial among children demonstrated VE using laboratory-confirmed influenza [12]. The researchers contacted all study participants every week to obtain information regarding the onset of influenza-like illness (ILI) during an epidemic period, and once they ascertained ILI, they collected respiratory specimens from every participant within a few days, and identified influenza virus infection. However, because such a study requires huge effort and cost, it is not easy to adopt for the study on evaluation of VE. The case definition, which can collect all outcomes from both vaccinated and unvaccinated subjects with an "equal intensity", should be made.

3. Case definition and standardized active surveillance

As already mentioned, the case definition is an essential element for studies. A case definition that poorly represents the disease might cause a differential misclassification of the outcome, leading to imprecise estimates of VE. Additionally, if infection or disease is differently diagnosed in vaccinated and unvaccinated subjects, potential bias may occur. Thus, the case detection must be made independent of vaccination history, and can be adopted within the scope of the budget and logistics of the study. To ascertain influenza onset with equal intensity in a population-based study, active surveillance requires contact with all study participants at regular intervals via mail [13] or telephone [10,12]. In this situation, ILI during an influenza epidemic can be available for the outcome. Although using ILI is likely to lead to underestimating VE because of the non-differential misclassification of true influenza, it is more favorable than using biased outcomes.

In our previous study of the 2003–2004 influenza season [10], we asked participants to measure their body temperature prospectively and record all sudden onset fever ≥37.0 °C with any symptoms onto a special diary sheet, that we provided before follow-up. The diary sheets included a checklist of symptoms, such as cough, sore throat, nasal congestion, muscle ache and arthralgia, hospital visit, and medication. Active surveillance through monthly phone calls by nurses was conducted to ascertain outcomes with equal intensity throughout the influenza season. The subjects or their family members reported their outcomes with reference to the records on their diary sheet. The collected information was as follows: all acute febrile illness ≥37.8 °C with any symptoms in the list, visits to medical institutions owing to these symptoms, hospitalization for all causes, hospitalization for influenza or

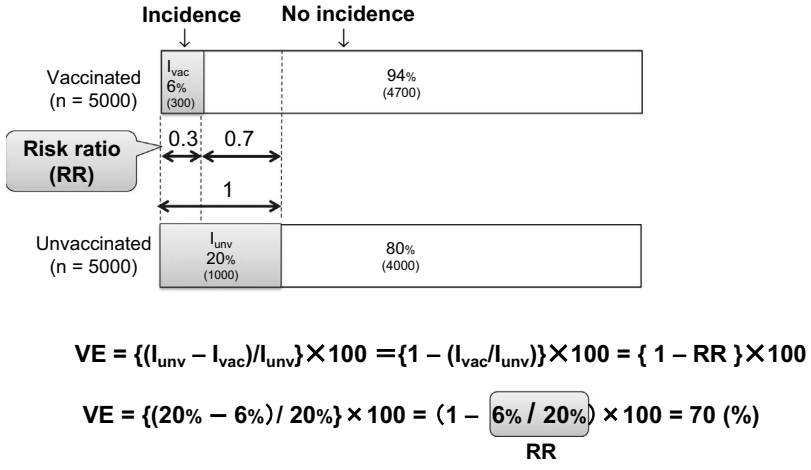


Fig. 1. Concept of vaccine effectiveness (VE). VE refers to the percent reduction in the incidence of disease in vaccinated individuals (I_{vac}) compared with the incidence of disease in unvaccinated individuals (I_{unv}). RR, risk ratio.

pneumonia, and total deaths. After the follow-up, the ILI was defined by limiting the acute febrile illness to cases occurring during the influenza epidemic in the study field. To increase the specificity of ILI, we analyzed the RR of vaccination according to fever degree and defined the ILI with high fever. Self-reported medical institution visits and hospitalization were identified by review with physicians to verify clinically diagnosed influenza and hospitalization for all causes and those for influenza or pneumonia. Death was certificated using the population registry.

4. Study setting and eligibility criteria for participation

Based on the characteristics of influenza, a VE study needs to specify the season, place, and population, because epidemic strains of influenza differ by season and place; the proportion of susceptible individuals differs by the season, place, and population; and vaccine strains differ by season. In our previous study of the 2003–2004 influenza season, we set a fixed cohort of older persons aged 65–79 years in the southern Japanese city of Saga [10]. In addition to explaining the study purpose and receiving written consent to study participation, we set the eligibility criteria for study participation to complete follow-up with equal intensity as follows: possible to contact by telephone at least once a month, living with family, not being hospitalized, not being institutionalized, and not having any long-term absence. We were also permitted to inquire about their information at Basic Resident Register city offices, when we failed to contact them during the follow-up period.

5. Sample size calculation and making a list to enroll older subjects

The parameters we used for sample size calculation were vaccination coverage (40–60%), VE (30–50%), and proportion of primary outcome onset among unvaccinated subjects (3–7%). If we set α-error and β-error as 0.05 (for a two-sided test) and 0.10, respectively, the total numbers of participants were estimated to be 5000–6000. When we take into account a participation proportion of 50% to 60%, then almost 10,000 older persons must be enrolled.

Because Japan has a Privacy Protection Law, we could not obtain electronic datasets from the population registry of the city office, even though the study protocol was approved by an institutional ethical committee. We selected 10,000 community-dwelling older persons randomly from the Basic Resident Register, and traced their name, sex, address, and birth date to form the study list.

6. Confounding and misclassification of vaccination status

Because VE can be determined by comparing the incidence of disease among vaccinated and unvaccinated individuals, potential bias may occur if any of the following conditions occur: there is unequal opportunity for exposure to people with influenza that encourages individuals to self-select for vaccination, and taking action to receive vaccination systematically differs between healthy and diseased persons. Confounding factors by indication induce a bias in the comparison. For example, older persons with any disease might be diagnosed as influenza, as well as be vaccinated, more frequently than a person without any disease, because they visit to a medical institution regularly (Fig. 2). Therefore, confounding factors might lead to the reduction of VE. Factors such as age, sex, race, socioeconomic status, residence, comorbid conditions, day care use, health-conscious behavior, and vaccination history of influenza may be independently related to both risk of influenza and vaccination status. Therefore, we asked subjects

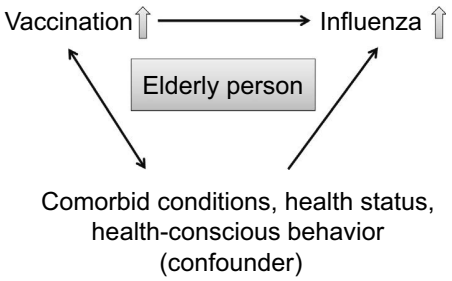


Fig. 2. Confounding factors on vaccine effectiveness in elderly persons.

about these factors using a self-administered questionnaire at the beginning of the study, and adjusted them by multivariate analysis.

Misclassification of vaccination status by self-reporting may also influence VE. Non-differential misclassification of vaccination status can dilute the VE, which can be acceptable. In contrast, differential misclassification may lead to either overestimation or underestimation, which might cause more complicated or serious consequences [14]. To avoid misclassification of vaccination status, we verified self-reported vaccination status with the individual records of the city vaccination subsidy.

7. Results and interpretation of the results

In our study of the 2003–2004 influenza season [10], a total of 4748 community-dwelling older persons were observed during the 2003–2004 influenza season with "equal intensity" via a monthly telephone survey based on a diary with a symptom checklist. After limiting subjects to those with a fever $\geq$37.8 °C during the influenza epidemic period, 115 cases were defined as ILI. The higher the threshold of the fever, the greater the degree of VE (Fig. 3). VE reached a plateau when fever was $\geq$38.5 °C, indicating that limiting ILI to those with a fever $\geq$38.5 °C adequately minimized the misclassification of influenza. We therefore defined this threshold as "high fever" and set "ILI with high fever" as the primary outcome. Because female sex, vaccination history of influenza, comorbid conditions, day care use, health conscious behavior,

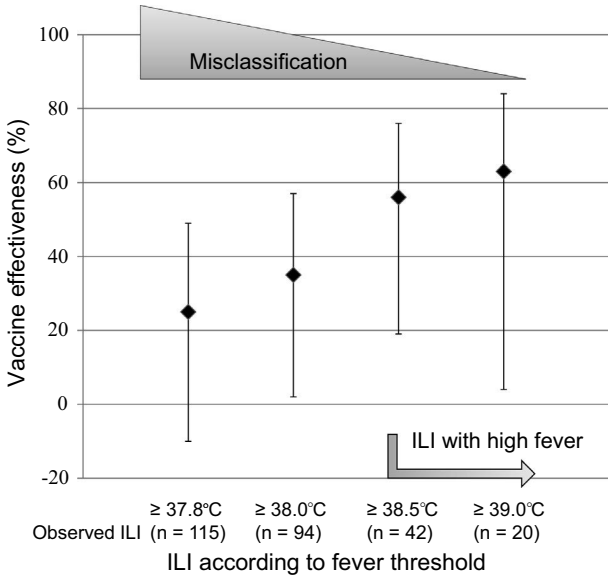


Fig. 3. Minimizing misclassification of influenza by fever threshold. ILI, influenza-like illness.

Table 1
Vaccine effectiveness (VE) according to outcomes and their interpretations.

Outcomes	Influence on VE	Adjusted* RR	95% CI	VE (%)
ILI with high fever		**0.38**	**(0.17–0.85)**	**62**
Clinically diagnosed influenza	Bias	0.76	(0.28–2.06)	24
Hospitalization for all causes	Misclassification	0.72	(0.46–1.13)	28
Hospitalization for IP	Sample size	0.37	(0.09–1.47)	63
Deaths from all causes	Confounding, Misclassification, Sample size	3.68	(0.75–18.12)	−268

CI: confidence interval, ILI: influenza-like illness, IP: influenza or pneumonia, RR: relative risk, VE: vaccine effectiveness.
* Adjusted for age and sex plus the potential confounders at baseline, which were significantly associated with the vaccine uptake. Marked the statistical significance in bold.

and living with children were positively associated with both vaccination status and ILI, these confounding factors were adjusted by multivariate analysis when estimating VE. After follow-up, 42 cases of ILI with high fever, 28 clinically diagnosed influenza, 137 hospitalizations for all causes, 17 hospitalizations for influenza or pneumonia, and 18 deaths were recorded. The VE after adjustment for possible confounding factors, ILI with high fever, clinically diagnosed influenza, hospitalizations for all causes, hospitalizations for influenza or pneumonia, and death were estimated as 62%, 24%, 28%, 63%, and −268%, respectively (Table 1).

Determining which season is suitable for evaluating VE should consider the following points: circulating virus strain and vaccine strain are antigenically well matched or not, and the scale of epidemic is large or not, and the attack rate of influenza is high or not. This season (2003–2004) was not advantageous for evaluating VE, because the influenza epidemic was mild in comparison with the previous 10 seasons, and antigenic similarity between vaccine strain and circulating strain was low. However, we detected VE for ILI with high fever, owing to several reasons as follows: completeness of follow-up (>98%) by setting eligible criteria for participation, sufficient sample size to detect VE for ILI with high fever, ascertainment of all outcomes in equal intensity throughout the epidemic period via telephone interview based on a symptom diary sheet, minimized misclassification of outcomes by setting a fever threshold, minimized misclassification of vaccination status by verification with list of recipients of partially funded vaccination, and controlling confounding factors by multivariate analysis.

In contrast to VE for ILI with high fever, VE against other outcomes were not detected (Table 1). Regarding clinically diagnosed influenza, biased outcome detection at clinical settings might have occurred. Clinically diagnosed influenza was only detected among ILI patients who visited medical institutions. Misclassification might occur, because hospitalization for all causes might include non-influenza virus diseases. Although the specificity of hospitalization for influenza and pneumonia was high and its evaluation was not biased, the sample size was not large enough to detect statistically significant values of VE for this outcome. Regarding death from all causes, several factors, such as confounding by indication, residual confounding, misclassification of outcome, and a small sample size for VE against death, had an influence on the inconclusive result.

As I already mentioned, influenza epidemics differ by season, population, and place; thus, we conducted a study for evaluating VE in the following season in the same people and place. VE against ILI with high fever was estimated at 45% (95% CI: 7–67%) in the 2004–2005 season. Therefore, VE against ILI with high fever in community-dwelling older persons ranged from 45% to 62%, which was consistent with a recent meta-analysis [15,16].

8. Conclusion

The main strategy to evaluate VE is to perform an observational study, because influenza vaccination is recommended worldwide to prevent suffering influenza. This article summarized the basic principles and several potential pitfalls of population-based cohort studies with reference to our previous report [10]. Several points should be emphasized. First, unbiased active surveillance by "equal intensity" for both vaccinated and unvaccinated is essential for cohort studies. Second, minimizing the misclassification of both vaccination status and outcome should be made. Last, careful consideration should be made for confounding factors.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

This study was supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Science Research Grants from the Ministry of Health, Labour and Welfare, Japan. We also thank Prof. Tanaka for his contribution and active discussion. Additionally, we presented this study at the 18th annual meeting of the Japanese Society for Vaccination, and wish to express our gratitude toward the attendees for their active discussion.

References

[1] Hirota Y, Kaji M. History of influenza vaccination programs in Japan. Vaccine 2008;26(50):6451–4.
[2] Mullooly JP, Bennett MD, Hornbrook MC, Barker WH, Williams WW, Patriarca PA, et al. Influenza vaccination programs for elderly persons: cost-effectiveness in a health maintenance organization. Ann Intern Med 1994;121(12):947–52.
[3] Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. N Engl J Med 1994;331(12):778–84.
[4] Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. Arch Intern Med 1998;158 (16):1769–76.
[5] Nordin J, Mullooly J, Poblete S, Strikas R, Petrucci R, Wei F, et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. J Infect Dis 2001;184(6):665–70.
[6] Hak E, Nordin J, Wei F, Mullooly J, Poblete S, Strikas R, et al. Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. Clin Infect Dis 2002;35(4):370–7.
[7] Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. N Engl J Med 2003;348(14):1322–32.
[8] Jefferson T, Rivetti D, Rivetti A, Rudin M, Di Pietrantonj C, Demicheli V. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet 2005;366(9492):1165–74.
[9] Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med 2007;357 (14):1373–81.
[10] Hara M, Sakamoto T, Tanaka K. Effectiveness of influenza vaccination in preventing influenza-like illness among community-dwelling elderly: population-based cohort study in Japan. Vaccine 2006;24(27–28):5546–51.
[11] Greenwood M, Yule GU. The Statistics of Anti-typhoid and Anti-cholera Inoculations, and the Interpretation of such Statistics in general. Proceedings of the Royal Society of Medicine 1915;8(Sect Epidemiol State Med):113-94.

[12] Belshe RB, Mendelman PM, Treanor J, King J, Gruber WC, Piedra P, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med 1998;338(20):1405–12.
[13] Fujieda M, Maeda A, Kondo K, Kaji M, Hirota Y. Inactivated influenza vaccine effectiveness in children under 6 years of age during the 2002–2003 season. Vaccine 2006;24(7):957–63.
[14] Hirota Y, Fukushima W, Fujieda M, Ohfuji S, Maeda A. Essential tools for assessing influenza vaccine efficacy in improperly conducted studies: a Japanese perspective. Vaccine 2008;26(50):6455–8.
[15] Darvishian M, Bijlsma MJ, Hak E, van den Heuvel ER. Effectiveness of seasonal influenza vaccine in community-dwelling elderly people: a meta-analysis of test-negative design case-control studies. Lancet Infect Dis 2014;14(12):1228–39.
[16] Darvishian M, Gefenaite G, Turner RM, Pechlivanoglou P, Van der Hoek W, Van den Heuvel ER, et al. After adjusting for bias in meta-analysis seasonal influenza vaccine remains effective in community-dwelling elderly. J Clin Epidemiol 2014;67(7):734–44.

Vaccine 35 (2017) 4796–4800

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Basic principles of test-negative design in evaluating influenza vaccine effectiveness

Wakaba Fukushima [a,b,*], Yoshio Hirota [c,d]

[a] Department of Public Health, Osaka City University, Graduate School of Medicine, Osaka, Japan
[b] Research Center for Infectious Disease Sciences, Osaka City University, Graduate School of Medicine, Osaka, Japan
[c] College of Healthcare Management, Miyama, Japan
[d] Clinical Epidemiology Research Center, Medical Co. LTA, Fukuoka, Japan

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 20 April 2017
Accepted 31 May 2017

Keywords:
Influenza vaccine
Effectiveness
Test-negative design
Control selection
Rapid diagnostic testing
Selection bias

ABSTRACT

Based on the unique characteristics of influenza, the concept of "monitoring" influenza vaccine effectiveness (VE) across the seasons using the same observational study design has been developed. In recent years, there has been a growing number of influenza VE reports using the test-negative design, which can minimize both misclassification of diseases and confounding by health care-seeking behavior. Although the test-negative designs offer considerable advantages, there are some concerns that widespread use of the test-negative design without knowledge of the basic principles of epidemiology could produce invalid findings. In this article, we briefly review the basic concepts of the test-negative design with respect to classic study design such as cohort studies or case-control studies. We also mention selection bias, which may be of concern in some countries where rapid diagnostic testing is frequently used in routine clinical practices, as in Japan.

1. Introduction

It is widely accepted that the best study design for obtaining conclusive findings on prophylactic or therapeutic effects in human population is the randomized controlled trial (RCT). Such a concept can be also applied in assessing efficacy/effectiveness for almost all vaccines. With regard to the influenza vaccines, however, even a large and well-conducted RCT would simply provide a time-, place-, and subject-specific observation because: (1) epidemic strains of influenza differ by time and place; (2) the proportion of those having pre-existing antibody titers differ by time, place and age group; (3) vaccine strains differ by time (i.e., season) [1]. Together with the ethical consideration that influenza vaccination is recommended for wide-ranging high risk groups [2], the concept of "monitoring" the influenza vaccine effectiveness (VE) across the seasons using the same observational study design has been developed.

During the last decade, a test-negative design, which is a modified case-control study, has been introduced to assess VE against influenza. The design enables us to estimate VE in the early, mid, and end of the influenza season in a timely manner. Several countries including the US [3], Canada [4], Europe [5], Australia [6] and New Zealand [7] have applied the method for monitoring the annual VE. Because the test-negative design is practically easier to conduct than other study designs, a growing number of reports have been recently published. However, there are some concerns that widespread use of the test-negative design without knowledge of the basic principles of epidemiology would introduce invalid findings. In this article, we briefly review the basic concepts of the test-negative design with respect to classic study design such as cohort studies or case-control studies. We also discuss selection bias, which may be introduced when results from clinician-ordered laboratory testing is used as an outcome measure. This may be particularly of concern in some countries, including Japan, where rapid diagnostic testing for influenza is frequently used in routine clinical practice.

2. Rationale for applying the test-negative design in evaluating influenza VE

At present, the test-negative design seems to be very useful in evaluating VE against influenza. Using laboratory-confirmed influenza as an outcome measure, we can reduce disease misclassification. Furthermore, the design enable us to minimize confounding due to health care-seeking behavior. For a better understanding

* Corresponding author at: Department of Public Health, Osaka City University, Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka 545-8585, Japan.
E-mail address: wakaba@med.osaka-cu.ac.jp (W. Fukushima).

http://dx.doi.org/10.1016/j.vaccine.2017.07.003
0264-410X/

of the latter advantage, the basic principles in cohort studies should be referred.

In cohort studies, both vaccinees and non-vaccinees should be followed-up with "equal intensity" to identify the occurrence of the outcome [8,9]. If influenza-like illness (ILI) is used as an outcome measure, equal intensity of follow-up would be achieved via telephone or questionnaire survey for all subjects on a weekly or monthly basis to obtain information on onset of the disease (i.e., active surveillance) [10–12]. In contrast, when using outcome of laboratory-confirmed influenza, a more strictly defined outcome, there is a concern that bias due to health care-seeking behavior becomes an issue because: (1) the outcome is usually confirmed only after the subjects visit medical institutions due to symptoms (i.e., passive surveillance); (2) vaccinees and non-vaccinees are inherently different in the likelihood of a medical visit (Fig. 1). Given these issues relating to health care-seeking behavior, the basic principle of following the vaccinees and non-vaccinees with equal intensity is difficult to satisfy when laboratory-confirmed influenza is used as an outcome measure in cohort studies. It is still possible to comply with the principle, as noted in a previous RCT among children [13]. In that study, the investigators contacted all subjects on a weekly basis to obtain the information on ILI onset, and once they confirmed that a subject had developed ILI, they attempted to collect his/her respiratory specimens within a couple of days. Obviously, such procedures require significant efforts and costs. Other exceptions may include a VE study based on antibody efficacy, in which all subjects received vaccine and medical visits for respiratory illnesses were compared between those with and without protective level of hemagglutination inhibition titer [14]. As subjects were not aware of their post-vaccination antibody level, the distortion due to health care-seeking behavior would be non-differential. Although antibody efficacy is expected to be an accurate index of VE [15], the estimates are strain-specific and interpretation of the results is sometimes complicated. Thus, it is considered a reasonable alternative for researchers to accept ILI as an outcome measure in cohort studies, which ensures achievement of equal intensity of follow-up resulting in higher feasibility and validity [10–12].

The test-negative design has a notable strength in controlling for afore-mentioned health care-seeking behavior (Fig. 2). Typically, study subjects are patients who visit medical institutions due to ILI during the influenza season. Subjects with positive test results for influenza are classified into cases, while subjects with negative results are classified as controls, and then vaccination status during the season can be compared between cases and controls. As the subjects are likely to visit a medical institution soon after ILI onset, both cases and controls are considered to be similar in their health care-seeking behavior. Therefore, the test-negative design can minimize confounding by health care-seeking behavior in evaluating influenza VE even though the outcome measure is laboratory-confirmed influenza, which is expected to resolve the dilemma in cohort studies.

Some articles have discussed the theoretical issues of the test-negative design [16–19]. VE against influenza is supposed to be the same in those who do seek care for ILI and who do not [17], although the test-negative design is limited by visitor attendance at the medical institution. An important factor relating to seeking of care may be the disease severity because disease severity is also expected to be associated with vaccination status. For example, it is possible that non-vaccinees are likely to develop severe ILI once

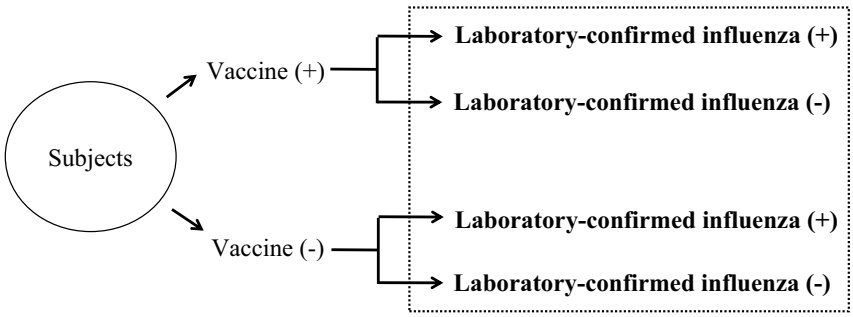


Fig. 1. Design of a cohort study to evaluate influenza vaccine effectiveness against laboratory-confirmed influenza. "Health care-seeking behavior" can introduce bias because (1) the outcome is usually confirmed only after the subjects visit medical institutions and (2) vaccinees and non-vaccinees are inherently different in the likelihood of their medical visit.

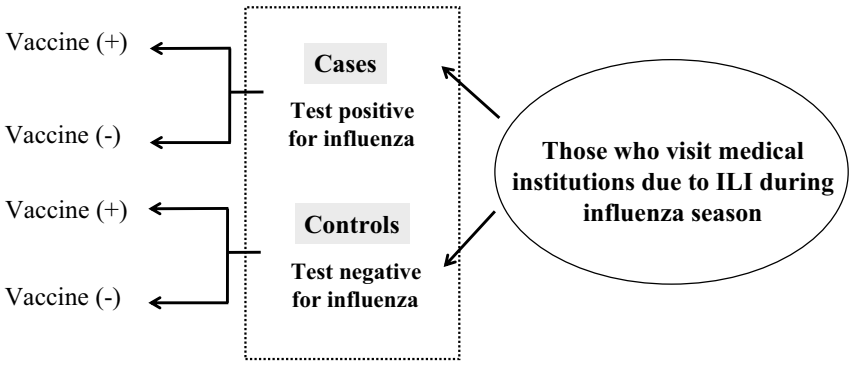


Fig. 2. A test-negative design to evaluate influenza vaccine effectiveness against laboratory-confirmed influenza. ILI denotes influenza-like illness. The test-negative design can minimize confounding by health care-seeking behavior even though the outcome measure is laboratory-confirmed influenza because "health care-seeking behavior" is likely to be similar between cases and controls.

they get infected by influenza, and those with severe ILI are likely to seek care. Thus, an appropriate adjustment for disease severity in analyses will be required to obtain a valid VE estimate [18].

3. Several principles must be satisfied in controls in the test-negative design

In the test-negative design, researchers are not aware of subjects' case/control status at recruitment, but later classify the subjects into cases or controls according to the test results. However, they should satisfy the same basic principles as for the classic case-control studies.

First, controls should be drawn from a source population, which generates the cases (i.e., study base principle). This condition may be inherently met in the test-negative design because both cases and controls are subjects who visited the same institution due to ILI.

The second principle is that both cases and controls are likely to have the same extent of experience in their exposure to influenza virus (i.e., a necessary cause in disease etiology). Recruitment of cases and controls when influenza is not circulating should be avoided, which translates to avoiding recruitment of the subjects who were not at risk of the disease in cohort studies. This is straightforward because case-control studies provide findings that mirror what could be learned from cohort studies [20].

Finally, controls should be selected independently of the exposure status. In test-negative design assessing influenza VE, the risk of non-influenza ILI that places the subjects into controls should be independent of influenza vaccination status. Controls in the test-negative design potentially consist of two types of ILI patients: negative for influenza *per se* but positive for other respiratory virus (other respiratory virus [ORV] positive controls), and negative for all respiratory virus tested (pan-negative controls). Recently, an argument regarding "appropriate controls" has been discussed.

The issue was pointed out for the first time in a study from Australia, in which VE against trivalent inactivated influenza vaccine (IIV3) was evaluated among young children aged $\leq$5 years in 2008 [21]. The study unexpectedly found that the proportion of vaccination was higher among ORV positive controls than pan-negative controls, resulting in higher VE using ORV positive controls. Nasal swabs were used as respiratory specimens, which were logistically difficult to obtain from young children. As pan-negative controls would include some false negatives for influenza, they interpreted that ORV positive controls were more appropriate in ensuring adequate sample collection.

The phenomenon of higher vaccination rates in ORV positive controls compared with pan-negative controls was further discussed. A viral interference known as "temporary non-specific immunity" has been suggested [22]. This is a biological mechanism that involves a respiratory virus infection, which induces immunity not only against the same viruses but also for other viruses over a short time. Those who receive influenza vaccine would miss two opportunities: to be infected with influenza and to acquire temporary non-specific immunity to other respiratory viruses through natural infection of influenza. In the test-negative design, such vaccinated subjects would be classified into ORV positive controls, and contribute to higher vaccination rates among all controls. Control selection irrespective of vaccine status may be violated, and VE using all controls or ORV positive controls would be greater in comparison to that using pan-negative controls.

Some test-negative studies of IIV3 using different controls showed inconsistent results. Reports from Japan [23] and Portugal [24] found considerable VE variation, whereas no difference was observed in studies in the US [25] or Australia [26]. One small RCT in Hong Kong children reported that those who received IIV3 had an increased risk of non-influenza infections during the pre-pandemic period in 2009 [27]. On the other hand, a validation study using datasets from 4 published, double-blind RCTs found no meaningful association between live attenuated influenza vaccine and increased risk for non-influenza respiratory episodes [28]. A recent simulation study indicated that the effect of temporary non-specific immunity was significant when the attack rate of influenza was elevated to pandemic levels (>50%) but just marginal in typical influenza seasons (<20%) [29]. This simulation also suggested that combined data across the multiple influenza seasons may conceal the variation in attack rate, which may partly account for the inconsistency in the previous findings. To date, no recommendation regarding the most appropriate controls has been provided. Further discussion including what is meant by ORV positive controls or pan-negative controls is required.

4. Cautions for applying the test-negative design in routine clinical practice

Practically, test-negative designs would be easier to conduct by clinicians in comparison to classic case-control studies. Although real-time reverse transcription polymerase chain reaction (RT-RCR) or viral culture are desirable in defining case/control status in test-negative studies, results based on rapid diagnostic testing for influenza can be used as an outcome measure. In some countries where rapid diagnostic testing is widely available in routine clinical practice, such as Japan, test-negative studies can be readily employed using clinician-ordered testing results. The dataset would be huge if the information from many institutions is combined. However, such careless use of the test-negative design would result in some repercussions.

First, using rapid diagnostic testing results as an outcome measure has been demonstrated to underestimate VE due to imperfect sensitivity and specificity in comparison to RT-PCR or viral culture. A simulation study examined the extent of underestimation, in which the sensitivity and specificity of the rapid test was set at 80% and 90%, respectively. When rapid testing results were used in the test-negative design, the true VE of 90%, 70% and 50% was decreased to approximately 72.6%, 57.0% and 41.1%, respectively [16]. Another simulation also showed that when true VE was set at 70% for young children and 50% for all ages, use of a rapid test with the same sensitivity and specificity (i.e., 80% and 90%, respectively) in test-negative studies resulted in a VE estimate of 53% for children and 37% for all ages, respectively [30]. It is notable that lower specificity of the laboratory test for influenza was expected to contribute more to underestimation of VE than a lowering of sensitivity, if one value (e.g., sensitivity) was fixed at 1.0 and the other value (e.g., specificity) was changed from 0.8 to 1.0 [30]. Since specificity of rapid diagnostic tests is usually high, the influence of applying a rapid test for estimation of VE in test-negative studies might not be meaningful. However, as previously mentioned, the combination of imperfect sensitivity and specificity would greatly affect the VE even if rapid test misclassification was compensated by its high specificity. An approximate 20% reduction in effect estimates are considerable in influenza VE studies.

Second, enrolling the study subjects within a routine clinical setting can introduce selection bias. As shown in Fig. 3, the source population for the study is the patients with ILI who visit medical institutions. A certain proportion is then sampled as study subjects from the source population. The study subjects should have their test results for influenza because they have to be classified into either cases or controls thereafter. If the study subjects are limited to those who received the clinician-ordered test in a routine clinical setting, application of the test would depend on the likelihood

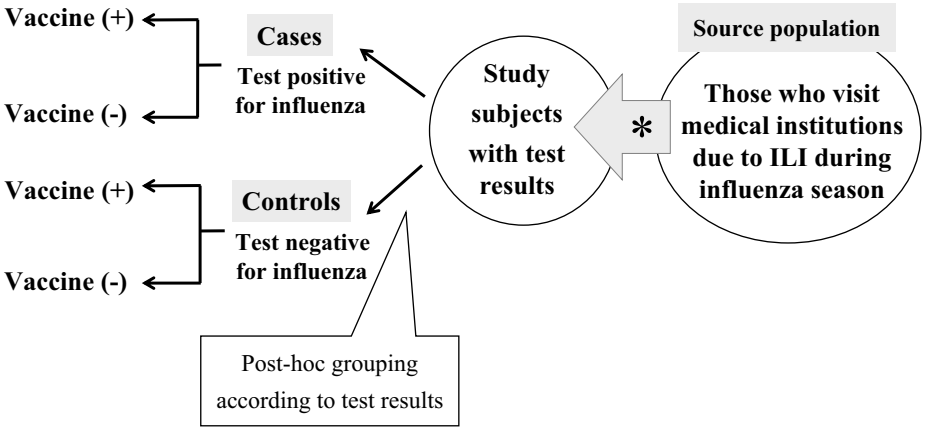


Fig. 3. A test-negative design to evaluate influenza vaccine effectiveness against laboratory-confirmed influenza. ILI denotes influenza-like illness. Asterisk (*) indicates a point where selection bias may occur. If the study subjects are limited to those who received the clinician-ordered test in the routine clinical setting, the application of the test would be related to (1) the likelihood of having influenza (outcome) or (2) influenza vaccination status (exposure), resulting in biased sampling (non-representativeness) of the study subjects from the source population.

of having influenza (outcome) or influenza vaccination status (exposure), resulting in biased sampling (non-representativeness) of the study subjects from the source population. For example, if clinicians order the diagnostic test for those with severe ILI and those who did not receive the vaccine, the proportion of non-vaccinees among cases is likely to increase, resulting in overestimation of VE. This translates to selection bias and it is impossible to estimate its extent or direction once such a bias is introduced. A report from the US pointed out that clinician-ordered rapid diagnostic testing could be a potential source of bias in influenza VE studies using the test-negative design [31]. The study showed that VE estimates based on rapid diagnostic testing results in the routine clinical setting were considerably underestimated and significant VE would have been missed. This study emphasized the importance of active recruitment of ILI patients according to the pre-defined standardized criteria.

With respect to possible selection bias in recruitment of the subjects, some researchers claim that during the influenza epidemic, clinicians would be too busy to develop their idea regarding application of the test. However, we cannot completely deny the possibilities that selection bias arise unconsciously. In order to avoid selection bias as far as possible, it is essential to recruit study subjects systematically from the source population according to pre-defined criteria. In effect, research on test-negative designs should be employed separately from routine clinical practice.

5. Conclusion

The methodology of VE studies is evolving. The test-negative design, a modified case-control study, has notable advantages in estimating influenza VE. Given that principles of case-control studies are more complicated than that of cohort studies or RCTs, collaboration, or consultation with epidemiologists would be useful. It should also be noted that reflecting on the basic concepts of epidemiology is always worthwhile. Accumulation of evidence from appropriately conducted test-negative designs will provide valid and universal estimates of VE against influenza.

Conflict of interest

None declared.

Acknowledgement

This study was supported by Health and Labour Science Research Grants from the Ministry of Health, Labour and Welfare of Japan in 2014–2016.

References

[1] Hirota Y, Kaji M. Principles and methods of influenza epidemiology: with special reference to field evaluation of vaccine efficacy. Kansenshogaku Zasshi 1994;68(11):1293–305 [in Japanese].
[2] World Health Organization. Vaccines against influenza: WHO position paper – November 2012. Weekly Epidemiol Rec 2012;87(47):461–6.
[3] Treanor JJ, Talbot HK, Ohmit SE, Coleman LA, Thompson MG, Cheng PY, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. Clin Infect Dis 2012;55(7):951–9.
[4] Skowronski DM, Janjua NZ, De Serres G, Dickinson JA, Winter AL, Mahmud SM, et al. Interim estimates of influenza vaccine effectiveness in 2012/13 from Canada's sentinel surveillance network, January 2013. Euro Surveill 2013;18(5).
[5] Kissling E, Valenciano M, Falcao J, Larrauri A, Widgren K, Pitigoi D, et al. "I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in Europe, 2008–9. Euro Surveill 2009;14(44).
[6] Carville KS, Grant KA, Sullivan SG, Fielding JE, Lane CR, Franklin L, et al. Understanding influenza vaccine protection in the community: an assessment of the 2013 influenza season in Victoria Australia. Vaccine 2015;33(2):341–5.
[7] Turner N, Pierse N, Huang QS, Radke S, Bissielo A, Thompson MG, et al. Interim estimates of the effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2014. Euro Surveill 2014;19(42).
[8] Hirota Y, Fukushima W, Fujieda M, Ohfuji S, Maeda A. Essential tools for assessing influenza vaccine efficacy in improperly conducted studies: a Japanese perspective. Vaccine 2008;26(50):6455–8.
[9] Ozasa K. The effect of misclassification on evaluating the effectiveness of influenza vaccines. Vaccine 2008;26(50):6462–5.
[10] Fujieda M, Maeda A, Kondo K, Kaji M, Hirota Y. Inactivated influenza vaccine effectiveness in children under 6 years of age during the 2002–2003 season. Vaccine 2006;24(7):957–63.
[11] Hara M, Sakamoto T, Tanaka K. Effectiveness of influenza vaccination in preventing influenza-like illness among community-dwelling elderly: population-based cohort study in Japan. Vaccine 2006;24(27–28):5546–51.
[12] Ochiai H, Fujieda M, Ohfuji S, Fukushima W, Kondo K, Maeda A, et al. Inactivated influenza vaccine effectiveness against influenza-like illness among young children in Japan–with special reference to minimizing outcome misclassification. Vaccine 2009;27(50):7031–5.
[13] Belshe RB, Mendelman PM, Treanor J, King J, Gruber WC, Piedra P, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med 1998;338(20):1405–12.
[14] Fukushima W, Ohfuji S, Deguchi M, Kawabata K, Hatayama H, Yoshida H, et al. Effectiveness of an influenza A (H1N1) 2009 monovalent vaccine among Japanese pregnant women: a prospective observational study assessing antibody efficacy. Vaccine 2012;30(52):7630–6.

[15] Hirota Y, Kaji M, Ide S, Kajiwara J, Kataoka K, Goto S, et al. Antibody efficacy as a keen index to evaluate influenza vaccine effectiveness. Vaccine 1997;15 (9):962–7.
[16] Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. Int J Epidemiol 2007;36(3):623–31.
[17] Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine 2013;31(17):2165–8.
[18] Foppa IM, Haber M, Ferdinands JM, Shay DK. The case test-negative design for studies of the effectiveness of influenza vaccine. Vaccine 2013;31(30):3104–9.
[19] Haber M, An Q, Foppa IM, Shay DK, Ferdinands JM, Orenstein WA. A probability model for evaluating the bias and precision of influenza vaccine effectiveness estimates from case-control studies. Epidemiol Infect 2015;143(7):1417–26.
[20] Rothman KJ. Epidemiology: an introduction. New York: Oxford University Press; 2002.
[21] Kelly H, Jacoby P, Dixon GA, Carcione D, Williams S, Moore HC, et al. Vaccine effectiveness against laboratory-confirmed influenza in healthy young children: a case-control study. Pediatr Infect Dis J 2011;30(2):107–11.
[22] Cowling BJ, Nishiura H. Virus interference and estimates of influenza vaccine effectiveness from test-negative studies. Epidemiology 2012;23(6):930–1.
[23] Suzuki M, Minh le N, Yoshimine H, Inoue K, Yoshida LM, Morimoto K, et al. Vaccine effectiveness against medically attended laboratory-confirmed influenza in Japan, 2011–2012 Season. PLoS One 2014;9(2):e88813.
[24] Nunes B, Machado A, Guiomar R, Pechirra P, Conde P, Cristovão P, et al. Estimates of 2012/13 influenza vaccine effectiveness using the case test-negative control design with different influenza negative control groups. Vaccine 2014;32(35):4443–9.
[25] Sundaram ME, McClure DL, VanWormer JJ, Friedrich TC, Meece JK, Belongia EA. Influenza vaccination is not associated with detection of noninfluenza respiratory viruses in seasonal studies of influenza vaccine effectiveness. Clin Infect Dis 2013;57(6):789–93.
[26] Blyth CC, Jacoby P, Effler PV, Kelly H, Smith DW, Robins C, et al. Effectiveness of trivalent flu vaccine in healthy young children. Pediatrics 2014;133(5): e1218–25.
[27] Cowling BJ, Fang VJ, Nishiura H, Chan KH, Ng S, Ip DK, et al. Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine. Clin Infect Dis 2012;54(12):1778–83.
[28] De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. Euro Surveill 2013;18(37).
[29] Suzuki M, Camacho A, Ariyoshi K. Potential effect of virus interference on influenza vaccine effectiveness estimates in test-negative designs. Epidemiol Infect 2014;142(12):2642–6.
[30] Jackson ML, Rothman KJ. Effects of imperfect test sensitivity and specificity on observational studies of influenza vaccine effectiveness. Vaccine 2015;33 (11):1313–6.
[31] Coleman LA, Kieke B, Irving S, Shay DK, Vandermause M, Lindstrom S, et al. Comparison of influenza vaccine effectiveness using different methods of case detection: clinician-ordered rapid antigen tests vs. active surveillance and testing with real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). Vaccine 2011;29(3):387–90.

Vaccine 35 (2017) 4801–4805

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Control selection and confounding factors: A lesson from a Japanese case-control study to examine acellular pertussis vaccine effectiveness

Satoko Ohfuji [a,*], Kenji Okada [b], Takashi Nakano [c], Hiroaki Ito [d], Megumi Hara [e], Haruo Kuroki [f], Yoshio Hirota [a,g,h]

[a] Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka 545-8585, Japan
[b] Section of Pediatrics, Department of Medicine, Fukuoka Dental College, 2-15-1, Tamura, Sawara-ku, Fukuoka 814-0193, Japan
[c] Department of Pediatrics, Kawasaki Medical School, 577, Matsushima, Kurashiki, Okayama 701-0192, Japan
[d] Field Epidemiology Training Program, National Institute of Infectious Diseases, 1-23-1, Toyama, Shinjuku-ku, Tokyo 162-8640, Japan
[e] Department of Preventive Medicine, Faculty of Medicine, Saga University, 5-1-1, Nabeshima, Saga 849-8501, Japan
[f] Sotobo Children's Clinic, Medical Corporation Shigyo-no-kai, 1880-4, Izumi, Misaki-cho, Isumi, Chiba 299-4503, Japan
[g] College of Healthcare Management, 960-4, Takayanagi, Setaka-machi, Miyama-shi, Fukuoka 835-0018, Japan
[h] Clinical Epidemiology Research Center, Medical Co. LTA, 3-5-1, Kashii-Teriha, Higashi-ku, Fukuoka 813-0017, Japan

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 2 September 2016
Accepted 4 October 2016

Keywords:
Effectiveness
DTaP vaccine
Pertussis
Friend control
Risk factors
Case-control study

ABSTRACT

When using a case-control study design to examine vaccine effectiveness, both the selection of control subjects and the consideration of potential confounders must be the important issues to ensure accurate results. In this report, we described our experience from a case-control study conducted to evaluate the effectiveness of acellular pertussis vaccine combined with diphtheria-tetanus toxoids (DTaP vaccine). Newly diagnosed pertussis cases and age- and sex-matched friend-controls were enrolled, and the history of DTaP vaccination was compared between groups. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of vaccination for development of pertussis.

After adjustment for potential confounders, four doses of DTaP vaccination showed a lower OR for pediatrician-diagnosed pertussis (OR = 0.11, 95% CI, 0.01–0.99). In addition, the decreasing OR of four doses vaccination was more pronounced for laboratory-confirmed pertussis (OR = 0.07, 95%CI, 0.01–0.82). Besides, positive association with pertussis was observed in subjects with a history of steroid treatment (OR = 5.67) and those with a recent contact with a lasting cough (OR = 4.12).

When using a case-control study to evaluate the effectiveness of vaccines, particularly those for uncommon infectious diseases such as pertussis, the use of friend-controls may be optimal due to the fact that they shared a similar experience for exposure to the pathogen as the cases. In addition, to assess vaccine effectiveness as accurately as possible, the effects of confounding should be adequately controlled with a matching or analysis technique.

1. Introduction

When using a case-control study to examine vaccine effectiveness, the selection of control subjects is a critical issue. If it failed to select adequate controls, the observed results will be biased, and lead to an erroneous conclusion. According to a description in "*Epidemiology: An Introduction*" edited by Rothman [1], "*a control group is sampled from the entire source population that gives rise to the cases. Because the control group is used to estimate the distribution of exposure in the source population, the cardinal requirement of control selection is that the controls be sampled independently of exposure status*". In other words, when considering the optimum controls, the first step is to define the source population from which the controls will be selected.

Based on the fact that all cases who develop an infectious disease must have been exposed to the pathogen, the ideal setting would one in which control subjects have a similar experience for exposure to the pathogen as the cases. More specifically, the "source population" should be defined as those who were exposed to the pathogen in question. Cases and controls should then be

Abbreviations: DTaP vaccines, acellular pertussis vaccine combined with diphtheria-tetanus toxoids; LAMP method, loop-mediated isothermal amplification method; OR, odds ratio; CI, confidence interval.

* Corresponding author.
E-mail address: satop@med.osaka-cu.ac.jp (S. Ohfuji).

http://dx.doi.org/10.1016/j.vaccine.2017.07.004
0264-410X/

recruited from among this predefined "source population", and differences in vaccination history between the groups were compared. However, in the case of uncommon sporadic infectious diseases such as pertussis, it is particularly difficult to define a "source population" with a similar experience of exposure to the pathogen. In this case, even if traditional hospital or community controls are selected, most of them might not have had the contact with the pathogen; this would result in an underestimation of vaccine effectiveness. Therefore, in order to evaluate vaccine effectiveness as accurately as possible, it is necessary to take into account the opportunity of exposure to the pathogen when selecting controls.

In addition, when performing observational studies such as case-control studies to evaluate vaccine effectiveness, the presence of confounders is another concern. In the field of vaccine epidemiology, a confounding factor is defined as a variable which relate to vaccination and to the outcome such as infection or infectious disease development, but which is not on the intermediate from vaccination to outcome [2]. For example, age and underlying illness are generally considered to be important potential confounders that may affect the evaluation of vaccine effectiveness. If potential confounders such as these are not adequately controlled or adjusted, they will inevitably introduce a bias in the results.

In this report, we present our experience from a case-control study conducted to evaluate the effectiveness of acellular pertussis vaccine combined with diphtheria-tetanus toxoids (DTaP vaccine). In our study, friend-controls were chosen because they would have shared a similar experience for exposure to pertussis as the cases. Besides, in our study, by conducting several multivariate analyses, we became aware of several confounding factors.

2. Materials and methods

The detail of the study methods and subjects have been described elsewhere [3]. In brief, we conducted a multicenter, case-control study at five collaborating hospitals in the following five prefectures of Japan (from north to south): Chiba, Saitama, Mie, Saga, and Fukuoka. Cases were patients newly pediatrician-diagnosed with pertussis between April 2009 and October 2012, whose age at diagnosis was less than 30 years and who satisfied the following clinical criteria for pertussis: persistent cough for more than 7 days with one or more additional symptoms (paroxysmal cough, whoop, or post-tussive vomiting) accompanied by positive results for *Bordetella pertussis* isolation, positive results by the loop-mediated isothermal amplification (LAMP) method, serodiagnosis or an epidemiological link to a confirmed pertussis case. The friend-control method was adopted for the recruitment of control subjects. Each case was asked to provide up to five friend-controls who had the same age (or school grade) and sex as the case. Exclusion criteria for friend-controls were: presence of lasting cough for more than 1 week during 1 month prior to the case diagnosis.

The following information was obtained by means of a self-administered questionnaire completed by each child's parent or guardian: sex, date of birth; history of pertussis; history of DTaP vaccination, number of vaccinations, vaccination dates, vaccine manufacturer and vaccine lot number if vaccinated; underlying illnesses (e.g., heart disease, renal disease, liver disease, diabetes mellitus, anemia, asthma, other respiratory diseases, tonsillitis, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, immunodeficiency, epilepsy), history of steroid treatment for more than one month; preschool or school attendance, frequency of going out (per week), hand washing habits or gargling habits at getting home, frequency of tooth brushing (per day); total room space in the house (m^2), number of family members, number of siblings; contact with a confirmed pertussis case during the recent one month; and contact with a person with a lasting cough during the recent one month. In Japan, vaccination history is usually recorded in individually maintained Mother-Child Health Records; these books were used to confirm the information collected on vaccination status. When missing answers or illogical data were detected by research technicians, research technicians conducted a telephone interview to complete the data.

In the analyses, continuous variables except for age and the number of family members were re-categorized into two levels according to the median value of the distribution of controls. Age was re-categorized into three levels, based on the age at which most children completed DTaP vaccination (i.e., 2 years) and the age when the effects of DTaP vaccination could be continued (i.e., 10 years) [4–10]. Regarding the number of family members, a three-level category was used when considering the family structure.

The background characteristics were compared between cases and controls using the chi-square test, Fisher's exact test, or the Wilcoxon rank-sum test. To calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs) of each variables for pertussis, a logistic regression model was employed. Because some cases had no corresponding pair as controls and vice versa, main analyses were conducted in all cases and controls who responded to the questionnaire using an unconditional logistic regression model. Trends for associations were assessed by assigning ordinal scores to the level of the independent variable. In constructing the multivariate model, matching variables (age and gender) and variables that showed a p-value less than 0.1 were considered potential confounders for adjustment. Since underlying illnesses, asthma, and history of steroid treatment were strongly correlated with one another, the variable most strongly associated with pertussis (i.e., history of steroid treatment) was considered to be a prior variable to the multivariate models. Adjustment for age was conducted by including variable of the three-level age category rather than continuous age, in order to increase the statistical power. Additional analyses were then conducted to assess the effectiveness of DTaP vaccination for laboratory-confirmed pertussis. All tests were two-sided. All analyses were performed using SAS version 9.1.3 software (SAS Institute, Cary, NC, USA).

The study protocol was approved by the ethics committees at the Osaka City University Faculty of Medicine and collaborating hospitals. Written, informed consent was obtained from all subjects (or their parents or guardians) prior to participation.

3. Results

Among the 72 pertussis cases and 75 controls enrolled, 63 cases and 73 controls responded to the questionnaire (response rate: 88% for cases, 97% for controls). However, two controls were subsequently found to be ineligible because they had a history of pertussis. A further eight cases and two controls failed to provide complete data and were thus excluded. Eventually, 55 cases and 69 controls were included as subjects in the analysis. The number of laboratory-confirmed cases (i.e., positive results for culture isolation, the LAMP method, or serological assessment) was 39 (71%).

Table 1 shows a comparison of background characteristics between the 55 cases and 69 controls. Age and gender were well-matched. However, cases were less likely to have received DTaP vaccine than controls. In addition, cases had more underlying illnesses (particularly asthma), more history of steroid treatment, less frequency of tooth brushing, smaller room space in the house, and more contact with a person with a lasting cough.

A logistic regression model was employed to evaluate vaccine effectiveness for pediatrician-diagnosed pertussis (Table 2). The

Table 1
Comparison of background characteristics between cases and controls.

Variables		Cases (N = 55) n (%)	Controls (N = 69) n (%)	P value[a]
Matching variables				
Age (years)	Median (range)	9.6 (0.5–27.5)	10.3 (0.5–25.1)	0.543
	<2.0	5 (9)	3 (4)	0.197
	2.0–9.9	25 (45)	28 (41)	
	10.0+	25 (45)	38 (55)	
Sex	Male	22 (40)	23 (33)	0.443
	Female	33 (60)	46 (67)	
Vaccination status				
Number of DTaP vaccinations	0	7 (13)	3 (4)	0.061
	1–3	3 (5)	2 (3)	
	4	45 (82)	64 (93)	
Health-related conditions				
Underlying illnesses	Present	21 (38)	15 (22)	0.045
Asthma	Present	10 (18)	4 (6)	0.030
History of steroid treatment	Present	10 (18)	3 (4)	0.013
Environmental characteristics				
Preschool or school attendance	Present	50 (91)	67 (97)	0.240
Frequency of going out (per week)	<4	22 (40)	33 (49)	0.344
	4+	33 (60)	35 (51)	
Hand washing habits at getting home	Present	44 (80)	52 (75)	0.540
Gargling habits at getting home	Present	27 (49)	29 (42)	0.432
Frequency of tooth brushing (per day)	≤2	42 (76)	39 (57)	0.021
	3+	13 (24)	30 (43)	
Total room space in the house (m^2)	<100	36 (65)	34 (49)	0.071
	100+	19 (35)	35 (51)	
Number of family members	<4	20 (36)	16 (23)	0.149
	4	11 (20)	23 (33)	
	5+	24 (44)	30 (43)	
Number of siblings	Present	35 (64)	51 (74)	0.218
Recent contact with a person with a lasting cough	Present	17 (31)	8 (12)	0.008

[a] Chi-square test, Fisher's exact test, or Wilcoxon rank-sum test, where apppropriate.

Table 2
Adjusted odds ratios of DTaP vaccination and selected variables for pediatrician-diagnosed pertussis.

Variables		Univariate		Multivariate[a]	
		OR (95%CI)	P value	OR (95%CI)	P value
Number of DTaP vaccinations	0	1.00		1.00	
	1–3	0.64 (0.07–6.06)	0.700	0.24 (0.02–2.93)	0.264
	4	0.30 (0.07–1.23)	0.094	0.11 (0.01–0.99)	0.049
		(Trend P = 0.071)		(Trend P = 0.050)	
History of steroid treatment	Absent	1.00		1.00	
	Present	4.89 (1.27–18.8)	0.021	4.66 (1.06–20.5)	0.042
Frequency of tooth brushing (per day)	≤2	1.00		1.00	
	3+	0.40 (0.18–0.88)	0.023	0.48 (0.19–1.19)	0.113
Total room space in the house (m^2)	<100	1.95 (0.94–4.04)	0.073	1.97 (0.85–4.58)	0.117
	100+	1.00		1.00	
Recent contact with a person with a lasting cough	Absent	1.00		1.00	
	Present	3.41 (1.34–8.67)	0.010	4.54 (1.55–13.2)	0.006

DTaP vaccination, acellular pertussis vaccine combined with diphtheria-tetanus toxoids; OR, odds ratio; CI, confidence interval.
[a] Model includes variables in this table and matching variables (three-level age category and sex).

crude OR of four doses vaccination was 0.30 (95%CI, 0.07–1.23) and that of 1–3 doses vaccination was 0.64 (0.07–6.06). After adjustment for the potential confounders, ORs of DTaP vaccination revealed to be lowered and the reduction in the OR of four doses vaccination was statistically significant (OR = 0.11, 95%CI, 0.01–0.99). Besides, a significant positive association with pertussis was observed in subjects with a history of steroid treatment (OR = 4.66) and those with a recent contact with a lasting cough (OR = 4.54).

When analyzed the association with laboratory-confirmed pertussis, these association were more pronounced than that with pediatrician-diagnosed pertussis (Table 3). The multivariate OR (95%CI) of four doses vaccination decreased to 0.07 (0.01–0.82), although decreasing OR of 1–3 doses vaccination did not reach to the significant association. In addition, the associations between other potential confounders and pertussis were also emphasized. Subjects with a history of steroid treatment (OR = 5.67) and those with a recent contact with a lasting cough (OR = 4.12) seemed to be a higher risk condition for development of pertussis. Since 72% of vaccinees provided the name of vaccine manufacture, we also examined ORs of DTaP vaccination according to the vaccine manufactures. However, no obvious difference of ORs among vaccine manufactures was observed (data not shown).

To confirm these results, conditional logistic regression models were also employed. However, since only 31 cases and 56 controls

Table 3
Odds ratios of DTaP vaccination and selected variables for laboratory-confirmed pertussis.

Variables		Univariate		Multivariate[a]	
		OR (95%CI)	P value	OR (95%CI)	P value
Number of DTaP vaccinations	0	1.00		1.00	
	1–3	0.90 (0.09–8.90)	0.928	0.33 (0.02–4.40)	0.398
	4	0.29 (0.07–1.30)	0.105	0.07 (0.01–0.82)	0.034
		(Trend P = 0.062)		(Trend P = 0.029)	
History of steroid treatment	Absent	1.00		1.00	
	Present	5.68 (1.41–22.9)	0.015	5.67 (1.15–27.9)	0.033
Frequency of tooth brushing (per day)	≤2	1.00		1.00	
	3+	0.45 (0.19–1.06)	0.068	0.58 (0.20–1.63)	0.297
Total room space in the house (m^2)	<100	1.65 (0.74–3.67)	0.221	1.84 (0.70–4.81)	0.213
	100+	1.00		1.00	
Recent contact with a person with a lasting cough	Absent	1.00		1.00	
	Present	3.00 (1.09–8.26)	0.034	4.12 (1.23–13.8)	0.022

DTaP vaccination, acellular pertussis vaccine combined with diphtheria-tetanus toxoids; OR, odds ratio; CI, confidence interval.
[a] Model includes variables in this table and matching variables (three-level age category and sex).

(i.e., 31 matched-set) maintained the initial matched combination and statistical power lowered, no meaningful result could be obtained. Therefore, a model was constructed in which age and sex (i.e., matching variables), instead of matched-set number, were included as stratified variables and other potential confounders were included as explanatory variables. As a result, the model, which included three-level age category and sex as stratified variables and other potential confounders as explanatory variables, showed that the decreasing ORs of four doses vaccinees were similarly observed for both pediatrician-diagnosed pertussis (OR = 0.12; 95%CI, 0.01–1.04) and laboratory-confirmed pertussis (OR = 0.08; 95%CI, 0.01–0.80). The ORs of other potential confounders were also similar to the results from the unconditional logistic regression model (data not shown).

4. Discussion

Although the present case-control study had a unique design that included friend controls, our results were comparable to those of previous studies [11–13]. In our study, the vaccine effectiveness of four doses vaccination was 89% (1–99%) for pediatrician-diagnosed pertussis and 93% (18–99%) for laboratory-confirmed pertussis. These results seemed to support the usefulness of DTaP vaccine in the Japanese routine immunization program.

Regarding the selection of controls, some might think that hospital controls would have been preferable, because our cases were selected from among hospital patients. However, for the uncommon sporadic infectious diseases such as pertussis, traditional hospital or general population controls might not have had contact with the pathogen. In this case, even if the controls had not been previously vaccinated, they did not develop pertussis because they had not been exposed to the pathogen. If this background characteristics had been ignored and controls selected among those subjects without exposure to pertussis, it could have resulted in an underestimation of vaccine effectiveness. Therefore, in evaluating vaccine effectiveness, particularly for uncommon infectious diseases, the use of friend-controls may be optimal due to the fact that they had shared a similar experience for exposure to the pathogen as the cases.

Besides, since this was an observational study, some background characteristics could have been unequally distributed between the comparison groups. Therefore, it is essential to consider potential confounders. In fact, although the crude ORs of vaccination did not show any significant effectiveness (vaccine effectiveness, 70%), the multivariate ORs revealed a vaccine effectiveness of 89% for pediatrician-diagnosed pertussis (Table 2), suggesting that the effectiveness would have been underestimated by about 19%, if the effect of potential confounders had not been considered. Previous studies on the effectiveness of pertussis vaccine also suggested the importance of considering potential confounders. In most of the previous case-control studies, controls matched with cases for age, sex, and residence were selected [13–17]. In addition, the effects of other confounders (e.g., the number of family members, age of sibling, vaccination status of siblings, etc.) were controlled by conducting multivariate analyses [15–17]. Therefore, confounding factors that may influence the effectiveness of pertussis vaccine should be adequately controlled using conventional methods such as matching or analysis technique.

When four potential confounders were simultaneously considered in our analysis of vaccine effectiveness, two factors mainly contributed to affect the results as the confounders. These confounding factors also affect as risk factors of pertussis. First, subjects with a history of steroid treatment were shown to have a higher risk for pertussis. To the best of our knowledge, no previous study has reported an association between a history of steroid treatment and pertussis. However, some studies have reported a higher risk for pertussis among patients with asthma [18,19], who often receive steroid treatment. In addition, several studies have reported that steroid treatment is a risk factor for respiratory infections such as pneumonia [20] and influenza [21]. Taken together, a history of steroid treatment might be a proxy variable for severe asthma, and thus have an effect of increasing the individual risk for pertussis infection.

Second, variables related to exposure to the pathogen (i.e., having recent contact with a person with a lasting cough) were associated with an increased risk of pertussis. In light of previous studies, pertussis outbreaks often occurred in crowded environments such as schools [12,22], within families [23], or among soldiers [24]. Furthermore, some studies have reported that subjects who had recent contact with a person with a pertussis-like cough had a higher risk for pertussis infection [23–25]. These results suggest that increased susceptibility to pertussis in a crowded situation or increased opportunities on contact with possible pertussis patients is related to pertussis infection.

However, our study had the following limitations. First, due to the small sample size, there was insufficient statistical power, which made the detection of significant vaccine effectiveness and potential confounders difficult. Particularly for younger pertussis cases, however, it was very difficult to find up to five friend-controls according to this study protocol, because they did not have many friends. Thus, we could enroll only 75 controls for 72

cases at the time of enrolment. Second, the possibility of residual confounding cannot be ruled out. For example, the effect of total room space in the house was adjusted in multivariate analyses, but the two-level categorization may not have been sufficient to control for all of the confounding by the room space. In addition, the effects of other potential confounders such as social economic status were not considered.

Despite the limitations, the results of our case-control study using friend-control method indicated the effectiveness of DTaP vaccination and the effects of several confounders. These results are expected to highlight the importance both of selecting adequate controls and of controlling for potential confounders when assessing vaccine effectiveness using case-control study design.

Conflict of interest

None.

Acknowledgments

This study was supported by Health and Labour Sciences Research Grants from the Ministry of Health, Labor and Welfare of Japan in 2008-2016.

References

[1] Rothman KJ. Epidemiology: an introduction. New York: Oxford University Press; 2002.
[2] Mori M, Oura A, Ohnishi H, Washio M. Confounding in evaluating the effectiveness of influenza vaccine. Vaccine 2008;26:6459–61.
[3] Ohfuji S, Okada K, Nakano T, Ito H, Hara M, Kuroki H, et al. Effectiveness of acellular pertussis vaccine in a routine immunization program: a multicenter, case-control study in Japan. Vaccine 2015;33:1027–32.
[4] Wendelboe AM, van Rie A, Salmaso S, Englund JA. Duration of immunity against pertussis after natural infection or vaccination. Pediatr Intfect Dis J 2005;24:S58–61.
[5] Tartof SY, Lewis M, Kenyon C, White K, Osborn A, Liko J, et al. Waning immunity to pertussis following 5 doses of DTaP. Pediatrics 2013;131:e1047.
[6] Tindberg Y, Blennow M, Granstrom M. A ten year follow-up after immunization with a two component acellular pertussis vaccine. Pediatr Infect Dis J 1999;18:361–5.
[7] Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med 2012;367:1012–9.
[8] Misegades LK, Winter K, Harriman K, Talarico J, Messonnier NE, Clark TA, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since laset vaccine dose, California, 2010. JAMA 2012;308:2126–32.
[9] Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a North American outbreak. Clin Infect Dis 2012;54:1730–5.
[10] Sin MA, Zenke R, Onckendorf R, Littmann M, Jorgensen P, Hellenbrand W. Pertussis outbeak in primary and secondary schools in Ludwigslust, Germany demonstrating the role of waning immunity. Pediatr Infect Dis J 2009;28:242–4.
[11] Aoyama T, Murase Y, Kato T, Iwata T. Efficacy of an acellular pertussis vaccine in Japan. J Pediatr 1985;107:180–3.
[12] Hara M, Fukuoka M, Tashiro K, Ozaki I, Ohfuji S, Okada K, et al. Pertussis outbreak in university students and evaluation of acellular pertussis vaccine effectiveness in Japan. BMC Infect Dis. 2015;15:45.
[13] Okada K, Ohashi Y, Matsuo F, Uno S, Soh M, Nishima S. Effectiveness of an acellular pertussis vaccine in Japanese children during a non-epidemic period: a matched case-control study. Epidemiol Infect 2008;137:124–30.
[14] De Serres G, Shadmani R, Boulianne N, Duval B, Rochette L, Douville Fradet M, et al. Effectiveness of a single dose of acellular pertussis vaccine to prevent pertussis in children primed with pertussis whole cell vaccine. Vaccine 2001;19:3004–8.
[15] Bisgard KM, Rhodes P, Connelly BL, Bi D, Hahn C, Patrick S, et al. Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA. Pertussis vaccine effectiveness among children 6 to 59 months of age in the United States, 1998–2001. Pediatrics 2005;116:e285–94.
[16] Liese JG, Meschievitz CK, Harzer E, Froeschle J, Hosbach P, Hoppe JE, et al. Efficacy of a two-component acellular pertussis vaccine in infants. Pediatr Infect Dis J 1997;16:1038–44.
[17] Bentsi-Enchill AD, Halperin SA, Scott J, MacIsaac K, Duclos P. Estimates of the effectiveness of a whole-cell pertussis vaccine from an outbreak in an immunized population. Vaccine 1997;15:301–6.
[18] Liu BC, McIntyre P, Kaldor JM, Quinn HE, Ridda I, Banks E. Pertussis in older adults: prospective study of risk factors and morbidity. Clin Infect Dis 2012;55:1450–6.
[19] Capili CR, Hettinger A, Rigelman-Hedberg N, Fink L, Boyce T, Lahr B, et al. Increased risk of pertussis in patients with asthma. J Allergy Clin Immunol 2012;129:957–63.
[20] Yawn BP, Li Y, Tian H, Zhang J, Arcona S, Kahler KH. Inhaled corticosteroid use in patients with chronic obstructive pulmonary disease and the risk of pneumonia: a retrospective claims data analysis. Int J Chron Obstruct Pulmon Dis 2013;8:295–304.
[21] Recommendations of the Advisory Committee on Immunization Practices (ACIP). Prevention and control of seasonal influenza with vaccines: recommendations of the ACIP-United States, 2013-14. MMWR, **62** (RR07) 2013;1–43.
[22] Berger F, Njamkepo E, Minaberry S, Mayet A, Haus-Cheymol R, Verret C, et al. Investigation on a pertussis outbreak in a military school: risk factors and approach to vaccine efficacy. Vaccine 2010;28:5147–52.
[23] Waters V, Jamieson F, Richardson SE, Fikelstein M, Wormsbecker A, Halperin SA. Outbreak of atypical pertussis detected by polymerase chain reaction in immunized preschool-aged children. Pediatr Infect Dis J 2009;28:582–7.
[24] Klement E, Uliel L, Engel I, Hasin T, Yavzori M, Orr N, et al. An outbreak of pertussis among young Israeli soldiers. Epidemiol Infect 2003;131:1049–54.
[25] Izurieta HS, Kenyon TA, Strebel PM, Baughman AL, Shulman ST, Wharton M. Risk factors for pertussis in young infants during an outbreak in Chicago in 1993. Clin Infect Dis 1996;22:503–7.

Vaccine 35 (2017) 4806–4810

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effectiveness of 23-valent pneumococcal polysaccharide vaccine and seasonal influenza vaccine for pneumonia among the elderly – Selection of controls in a case-control study

Kyoko Kondo [a,*], Kanzo Suzuki [b], Masakazu Washio [c], Satoko Ohfuji [a], Wakaba Fukushima [a], Akiko Maeda [a], Yoshio Hirota [a,d,e], The Study Group for Pneumonia in the Elderly Individuals[1]

[a] Department of Public Health, Osaka City University Graduate School of Medicine, Osaka, Japan
[b] Nagoya City University, School of Nursing, Nagoya, Japan
[c] Department of Community Health and Clinical Epidemiology, St. Mary's College, Kurume, Japan
[d] Clinical Epidemiology Research Center, Medical Co. LTA, Fukuoka, Japan
[e] College of Healthcare Management, Miyama, Japan

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 5 October 2016
Accepted 24 November 2016

Keywords:
Case-control study
Elderly people
Pneumonia
Effectiveness
23-valent pneumococcal polysaccharide vaccine
Seasonal influenza vaccine

ABSTRACT

We conducted a case-control study to elucidate associations between pneumonia in elderly individuals and 23-valent pneumococcal polysaccharide vaccine (PPSV23) and seasonal influenza vaccine (influenza vaccine). Here, we examined selection of controls in our study using an analytic epidemiology approach. The study period was from October 1, 2009 through September 30, 2014. Cases comprised ≥65-year-old patients newly diagnosed with pneumonia. For every case with pneumonia, two patients with other diseases (one respiratory medicine, one non-respiratory medicine) who were sex-, age-, visit date- and visit hospital-matched were selected as controls. Odds ratios (ORs) and 95% confidence intervals (CIs) of vaccination for pneumonia were calculated using conditional logistic regression model. Similar analyses were also conducted based on the clinical department of controls. Analysis was conducted in 234 cases and 438 controls. Effectiveness of pneumococcal vaccination or influenza vaccination against pneumonia was not detected. Proportions of either vaccination in controls were greater among respiratory medicine (pneumococcal vaccine, 38%; influenza vaccine, 55%) than among non-respiratory medicine (23%; 48%). Analysis using controls restricted to respiratory medicine showed marginally significant effectiveness of pneumococcal vaccination (OR, 0.59; 95%CI, 0.34–1.03; P = 0.064) and influenza vaccination (0.64; 0.40–1.04; 0.072). However, this effectiveness might have been overestimated by selection bias of controls, as pneumonia cases are not necessarily respiratory medicine patients. In the analysis using controls restricted to non-respiratory medicine, OR of pneumococcal vaccination for pneumonia was close to 1, presumably because the proportion of pneumococcal vaccination was higher in cases than in controls. Because pneumococcal vaccine was not routinely administered during the study period, differences in recommendations of vaccination by physician in different clinical departments might have greatly affected vaccination proportions. When we select controls, we should consider the background factors (underlying diseases, clinical department, etc.) which affect physicians' recommendation of vaccination.

1. Introduction

Pneumonia is the third leading cause of death in Japan, and the mortality rate by age group is high in the elderly, particularly among individuals ≥80 years old [1]. With Japanese society aging at an unprecedented rate not seen anywhere else in the world, prevention of pneumonia among the elderly is becoming a critical issue. In our country, both pneumococcal vaccine and seasonal influenza vaccine (influenza vaccine) have been recommended.

Abbreviations: PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; influenzavaccine, seasonal influenza vaccine; COPD, chronic obstructive pulmonary disease; ADL, activities of daily living; OR, odds ratio; CI, confidence interval.

* Corresponding author at: Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan.
E-mail address: kyou@med.osaka-cu.ac.jp (K. Kondo).

[1] Other members of the Study Group are listed in Appendix.

http://dx.doi.org/10.1016/j.vaccine.2017.07.005
0264-410X/

For adults aged 65 years or older, 23-valent pneumococcal polysaccharide vaccine (PPSV23) can be provided as a periodical inoculation (starting from October 1, 2014) through the national vaccination program and 13-valent pneumococcal conjugate vaccine (PCV13) can be inoculated as arbitrary vaccination [2]. On the other hand, the Advisory Committee on Immunization Practices (ACIP) in the United States recommended PPSV23 and PCV13 for adults 65 years old or older in September 2014 [3].

Large-scale observational studies from the United States, Sweden, and Hong Kong have investigated the association between pneumonia in the elderly and influenza and/or pneumococcal vaccinations, and have demonstrated that vaccinations have decreased hospitalizations and deaths caused by influenza or pneumonia [4–7]. A Japanese study of nursing home residents showed that PPSV23 prevented pneumococcal pneumonia and thus reduced mortality from pneumococcal pneumonia [8]. Kawakami et al. reported the effectiveness of the PPSV23 against pneumonia in elderly people 75 years old or older who received the influenza vaccine in Japan [9]. We conducted a case-control study from October 1, 2009 to September 30, 2014 to investigate the effects of pneumococcal and influenza vaccines on pneumonia prevention among elderly individuals in Japan. If our study covered four vaccination patterns (no inoculation with either vaccine, inoculation with influenza vaccine only, inoculation with PPSV23 only, inoculation with both vaccines), we thought that we might be able to clarify the effectiveness of each vaccination pattern.

Selecting appropriate controls is extremely important in a case-control study. Controls must be selected from the population to which the cases belong, but vaccine effectiveness studies must also consider whether both cases and controls have had the opportunity to be exposed to the pathogen (necessary cause). The present study considered the opportunity for exposure to the pathogen to be relatively uniform within an area, and therefore controls were defined as hospital controls. In addition, because pneumococcal vaccine was not routinely administered during our study period, the recommendation of vaccinations by physician may be different in various clinical departments. We therefore further selected controls from non-respiratory medicine.

Here, we examined the selection of controls in our case-control study on the basis of an analytical epidemiology approach, and discussed the methods for investigating vaccine effectiveness in the elderly.

2. Material and methods

2.1. Study subjects

A hospital-based matched case-control study at 24 hospitals in Tokyo, Chiba, Shizuoka, Aichi, Gifu, Kyoto, and Fukuoka was conducted between October 1, 2009 and September 30, 2014. Because the study outcome was community-acquired pneumonia (CAP), study subjects were limited to outpatients (i.e., those living in their own home or in a home for the elderly that resembled their own home). All study participants received an explanation of the study content and provided consent prior to participation. The study protocol was approved by the Ethics Committee at the Osaka City University Graduate School of Medicine and was conducted in accordance with the principles of the Helsinki Declaration.

Cases were ≥65-year-old patients who were newly diagnosed with pneumonia by a physician. Pneumonia was diagnosed based on increased white blood cell count or elevated levels of C-reactive protein (CRP), and the presence of an infiltrative shadow on chest X-rays in addition to clinical presentation (cough, sputum, fever).

Controls were sex-, age (grouped in 5-year increments)-, visit date- (within 2 months after visit by case)-, and visit hospital-matched patients without pneumonia. As much as possible, two controls (one respiratory medicine and one non-respiratory medicine) were selected for each case.

Exclusion criteria were: presence of aspiration pneumonia; presence of malignant tumor; current treatment with oral steroid or immunosuppressant; and history of splenectomy.

2.2. Data collection

The attending physicians of cases and controls completed a questionnaire that included the following clinical information: a) sex, age, presence or absence of underlying respiratory system disease (pulmonary emphysema, chronic bronchitis, diffuse panbronchiolitis, pulmonary fibrosis, bronchial asthma, pulmonary tuberculosis sequelae); and b) disease information related to pneumonia (cases only), comprising date of definitive diagnosis and test results concerning pathogenic diagnosis (influenza rapid diagnostic test, pneumococcal urinary antigen test, sputum Gram staining, sputum culture, blood culture).

Cases and controls completed a self-administered questionnaire that included the following information: presence or absence of underlying disease (respiratory system disease, hypertension, hypercholesterolemia, heart disease, cerebral hemorrhage, cerebral infarction, stroke, diabetes mellitus, kidney disease), activities of daily living (ADL) (bedridden, semi-bedridden, semi-self-supported, self-supported), and vaccination status (23-valent pneumococcal polysaccharide vaccine (PPSV23), monovalent influenza A (H1N1) pdm09, trivalent seasonal influenza vaccine (influenza vaccine)).

2.3. Statistical analysis

Subjects who had received the pneumococcal vaccine within the past 5 years were considered "vaccinated," while all others were considered "unvaccinated." Subjects who had received the influenza vaccine (monovalent influenza A (H1N1) pdm09 vaccine, trivalent seasonal influenza vaccine) within the past 6 months were considered "vaccinated," while all others were considered "unvaccinated." All underlying diseases were analyzed as "present vs. absent" and ADL were analyzed as "non-self-supported (bedridden, semi-bedridden, semi-self-supported) vs. self-supported." For medical institutions that did not have a respiratory medicine, clinical department was determined based on the condition of the subject at the time of the visit: visits for respiratory system diseases were considered "respiratory medicine," and visits for all other diseases were considered "non-respiratory medicine."

The Wilcoxon rank-sum test and the chi-square test were used where appropriate to compare characteristics between cases and controls.

The odds ratio (OR) and 95% confidence interval (CI) of vaccination for pneumonia were calculated using a conditional logistic regression model. Variables included in the multivariate analysis model were pneumococcal vaccination, influenza vaccination, respiratory system disease, hypertension, diabetes mellitus, and ADL.

Next, to investigate the effects by different clinical departments, similar analyses were conducted based on the clinical department (respiratory medicine or non-respiratory medicine) of the control subjects. Variables included in each multivariate model were similar to those of the overall multivariate model. However, respiratory system diseases were excluded in the model using controls restricted to respiratory medicine.

Values of $P < 0.05$ were considered statistically significant. SAS software (version 9.3, SAS Institute, Cary, NC) was used for analysis. Since the influenza A (H1N1) pandemic occurred and seasonal

influenza did not spread during the 2009–2010 season [10], monovalent influenza A (H1N1) pdm09 vaccine was considered as the influenza vaccine.

3. Results

A total of 234 cases and 438 controls were enrolled. Table 1 shows the comparison of characteristics between cases and controls. The proportion of pneumococcal vaccination was 27% in cases and 30% in controls, and the proportion of influenza vaccination was 44% in cases and 51% in controls. The prevalence of hypertension and diabetes mellitus in controls was significantly greater than cases. The proportion of self-supported participants in controls was significantly greater than cases. Significant differences between cases and controls were not observed in any other variables. Among our cases, 24% (56 of 234 cases) represented pneumococcal pneumonia. Test results concerning the pathogenic diagnosis of cases were as follows: 24% (46 of 190 cases) showed positive results to the pneumococcal urinary antigen test, *Streptococcus pneumoniae* was detected by sputum Gram staining in 23% (28 of 124 cases), *S. pneumoniae* was detected by sputum culture in 22% (33 of 147 cases), and *S. pneumoniae* was detected by blood culture in 57% (4 of 7 cases).

Table 2 shows the OR of vaccination for pneumonia in all study subjects. The crude OR of pneumococcal vaccination was 0.90 (95% CI: 0.60–1.35, $P = 0.603$), and the adjusted OR decreased to 0.84 (95%CI: 0.54–1.30, P = 0.437). The crude OR of influenza vaccination was 0.71 (95%CI: 0.50–1.03, $P = 0.070$), and the adjusted OR was 0.74 (95%CI: 0.51–1.08, $P = 0.119$).

Results of analysis by the clinical departments of controls are shown in Table 3. When controls were restricted to respiratory medicine, there were 188 cases and 208 respiratory medicine controls for analysis (155 sets of case: respiratory medicine control: non-respiratory medicine control = 1:1:1; 13 sets of case: respiratory medicine control: non-respiratory medicine control = 1:1:0; and 20 sets of case: respiratory medicine control: non-respiratory medicine control = 1:2:0). The adjusted OR of pneumococcal vaccination for pneumonia was 0.59 (95%CI: 0.34–1.03, P = 0.064) and the adjusted OR of influenza vaccination for pneumonia was 0.64 (95%CI: 0.40–1.04, P = 0.072), with both vaccines showing marginal significance. Among respiratory medicine controls, the pneumococcal vaccination proportion was 38% and the influenza vaccination proportion was 55%.

When controls were restricted to non-respiratory medicine, 201 cases and 230 non-respiratory medicine controls were analyzed (155 sets of case: respiratory medicine control: non-respiratory medicine control = 1:1:1; 17 sets of case: respiratory medicine control: non-respiratory medicine control = 1:0:1; and 29 sets of case: respiratory medicine control: non-respiratory medicine control = 1:0:2). The adjusted OR of pneumococcal vaccination for pneumonia was 0.98 (95%CI: 0.49–1.95, P = 0.949) and the adjusted OR of influenza vaccination for pneumonia was 0.68 (95%CI: 0.39–1.17, P = 0.163). In non-respiratory medicine controls, the pneumococcal vaccination proportion was 23% and the influenza vaccination proportion was 48%.

Table 1
Characteristics of cases and controls.

Characteristics	Cases (n = 234)	Controls (n = 438)	*P*
Age (mean years, range)	77.2 (65–99)	76.8 (65–100)	0.518[b]
Sex			
Male	148 (63)	279 (64)	0.908[c]
Female	86 (37)	159 (36)	
Pneumococcal vaccine			
Unvaccinated	170 (73)	307 (70)	0.486[c]
Vaccinated	64 (27)	131 (30)	
Influenza vaccine			
Unvaccinated	131 (56)	213 (49)	0.069[c]
Vaccinated	103 (44)	225 (51)	
Underlying disease			
Respiratory system disease[a]	96 (41)	176 (40)	0.832[c]
Hypertension	106 (45)	237 (54)	0.030[c]
Hypercholesterolemia	32 (14)	80 (18)	0.128[c]
Heart disease	40 (17)	88 (20)	0.346[c]
Cerebral hemorrhage, cerebral infarction, stroke	27 (12)	38 (9)	0.232[c]
Diabetes mellitus	32 (14)	105 (24)	0.002[c]
Kidney disease	7 (3)	18 (4)	0.466[c]
ADL			
Self-supported	179 (76)	378 (86)	0.001[c]
Semi-self-supported, semi-bedridden, or bedridden	55 (24)	60 (14)	

Variables are expressed as number (percent), unless otherwise specified.
[a] Pulmonary emphysema, chronic bronchitis, diffuse panbronchiolitis, pulmonary fibrosis, bronchial asthma, pulmonary tuberculosis sequelae.
[b] Wilcoxon rank-sum test.
[c] Chi-square test.

4. Discussion

In the present study, analysis using controls restricted to respiratory medicine showed marginal effectiveness of the pneumococcal vaccine. However, vaccine effectiveness in the examination using controls restricted to respiratory medicine might be overestimated by selection bias of controls, because pneumonia cases are not necessarily respiratory medicine patients. On the other hand, analysis using controls restricted to non-respiratory medicine showed that the OR of pneumococcal vaccination for pneumonia was approximately 1. This is because the proportion of pneumococcal vaccination among cases (27%) was higher than proportion of pneumococcal vaccination among non-respiratory medicine controls (23%).

The rate of pneumococcal vaccination in Japan during the study period has been estimated at around 20%, although this number is not absolute due to large differences based on region and clinical department. The proportion of pneumococcal vaccination in the present study differed greatly depending on the clinical department, and was significantly higher among respiratory medicine controls (38%) than among non-respiratory medicine controls (23%). We expected that the extent of recommendations of vaccination by physician would have been different depending on the clinical department because the pneumococcal vaccine was not routinely administered during the study period. According to the above-mentioned result, when we perform case-control study under the situation that pneumococcal vaccine is not routinely administered, we should select controls in consideration of the background factors (clinical section, underlying disease) which affect physicians' recommendation of pneumococcal vaccination.

The mean rate of influenza vaccination during the study period in Japan was 51% [11]. The proportion of influenza vaccination in the present study was 55% in respiratory medicine controls and 48% in non-respiratory medicine controls. Because the influenza vaccine was routinely administered, the influenza vaccination proportion among non-respiratory medicine patients resembled that in the general population. Therefore, in case-control studies of routinely administered influenza vaccine, selection of controls from non-respiratory medicine might also be necessary, on the basis of the theory that controls must be selected from the population to which the cases belong.

When we examine vaccine effectiveness in case-control studies in situations where a vaccine is not routinely administered, controls should be selected in consideration of the background factors

Table 2
Odds ratios of vaccination (pneumococcal vaccine and influenza vaccine) for pneumonia.

	Cases (n = 234) n (%)	Controls (n = 438) n (%)	Crude OR	95%CI	*P*	Adjusted OR[a]	95%CI	*P*
Pneumococcal vaccine								
Unvaccinated	170 (73)	307 (70)	1			1		
Vaccinated	64 (27)	131 (30)	0.90	0.60–1.35	0.603	0.84	0.54–1.30	0.437
Influenza vaccine								
Unvaccinated	131 (56)	213 (49)	1			1		
Vaccinated	103 (44)	225 (51)	0.71	0.50–1.03	0.070	0.74	0.51–1.08	0.119

[a] Model included pneumococcal vaccination, influenza vaccination, underlying respiratory system disease, hypertension, diabetes mellitus and ADL.

Table 3
Vaccination proportion of pneumococcal vaccine and influenza vaccine and odds ratios of vaccination for pneumonia (by clinical departments of Controls).

Object for analysis	n/n	Pneumococcal vaccination				Influenza vaccination			
		Proportion (%)	Adjusted OR[a]	95%CI	*P*	Proportion (%)	Adjusted OR[a]	95%CI	P
All cases/all controls	234/438	27/30	0.84	0.54–1.30	0.437	44/51	0.74	0.51–1.08	0.119
All cases/respiratory medicine controls	188/208	29/38	0.59	0.34–1.03	0.064	45/55	0.64	0.40–1.04	0.072
All cases/non-respiratory medicine controls	201/230	27/23	0.98	0.49–1.95	0.949	43/48	0.68	0.39–1.17	0.163

[a] Model included the same as Table 2, but underlying respiratory system disease was excluded in "All cases/respiratory medicine controls".

affecting physician recommendations for vaccination. On the other hand, in situations where a vaccine is routinely administered, selection of controls from various clinical departments appears desirable.

We discussed the selection of controls in this case-control study on the basis of an analytical epidemiological approach, but some limitations must be acknowledged in this study. We included aspiration pneumonia as an exclusion criterion. In the planning stages of the current study in 2008, aspiration pneumonia (i.e., pneumonia associated with physical factors such as aspiration at the time of eating) was excluded because we thought that its mechanism was different from "normal" pneumonia. However, it later became clear that the incidence of aspiration pneumonia determined according to swallowing function testing was high among hospitalized patients with CAP and HAP [12]. Therefore, use of aspiration pneumonia as an exclusion criterion might be inappropriate. A further limitation was that we obtained information about vaccination status from a patient questionnaire, but were unable to verify the validity of that information.

Conflict of interest statement

The authors have no competing interests to declare.

Acknowledgements

This study was supported by Health and Labour Science Research Grants from the Ministry of Health, Labour and Welfare of Japan in 2008-2016.

Appendix

The other members of the Pneumonia in Elderly People Study Group are listed with their affiliation: Noriko Kojimahara (Tokyo Women's Medical University); Sakae Kan (Kaisei Hospital); Chiharu Ota, Ikuji Usami, Munehiro Kato, Toshinobu Yamamoto (Asahi Rosai Hospital); Kazuhide Yamamoto (Kazu Clinic); Yoichi Nakanishi, Takanari Kitazono (Graduate School of Medical Sciences, Kyushu University); Nobumitsu Fujisawa, Takafumi Matsumoto, Hideki Tashiro (St. Mary's Hospital); Masahiko Taketomi (Doukai Clinic); Tomoaki Iwanaga, Hiroko Nogami (Fukuoka National Hospital); Koichi Takano (Nishifukuoka Hospital); Ken Tonegawa, (Nagoya City Koseiin Geriatric Hospital); Yoshimitsu Hayashi (Kasugai Municipal Hospital); Seiichiro Imai (Graduate School of Medicine, Kyoto University); Ikuo Ikeda (Ikeda Clinic); Shigeki Sugiyama (Sugiyama Clinic); Kunihiko Yoshimura (Mitsui Memorial Hospital), Masahiro Aoshima, Kei Nakashima (Kameda Medical Center), Yoshitaka Nakamori, Yasushi Seida, Yoshiko Kichikawa (Mishuku Hospital), Akira Adachi (Kasadera Hospital), Atsushi Nakamura (Graduate School of Medical Sciences, Nagoya City University), Yasuhito Iwashima (Iwashima Clinic), Yasuhiro Kojima (Kojima Clinic), Yasuo Yamada (Yama Clinic), Hidekazu Kawamura (Kawamura Clinic), Toshiaki Niwa (Hamada Asai Clinic), Atsuro Kawai (Kawai Clinic), Yuuji Ito, Emi Aoyama (Daiyukai Hospital), Noriko Kusada, Chizuko Sumida (Inazawa Municipal Hospital), Naoyuki Miyashita (Department of Internal Medicine 1, Kawasaki Medical School).

References

[1] Annual statistical report of national health conditions. Health and welfare statistics association 2014; 61: 49–82 [in Japanese].
[2] Pneumococcal infection (elderly person). Ministry of health, labour and welfare. http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou/haienkyukin/index_1.html
[3] Tomczyk S, Bennett NM, Stoecker C, Gierke R, Moore MR, Whitney CG, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the advisory committee on immunization practices (ACIP). MMWR Morb Mortal Wkly Rep 2014;63(37):822–5.
[4] Nichol KL. The additive benefits of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease. Vaccine 1999;17:S91–3.
[5] Christenson B, Lundbergh P, Hedlund J, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older; a prospective study. Lancet 2001;357:1008–11.
[6] Hung IFN, Leung AYM, Chu DWS, Leung D, Cheung T, Chan CK, et al. Prevention of acute myocardial infarction and stroke among elderly persons by dual pneumococcal and influenza vaccination: a prospective cohort study. CID 2010;51:1007–16.
[7] Grijalva CG, Zhu Y, Williams DJ, Self WH, Ampofo K, Pavia AT, et al. Association between hospitalization with community-acquired laboratory-confirmed influenza pneumonia and prior receipt of influenza vaccination. JAMA 2015;314(14):1488–97.
[8] Maruyama T, Taguchi O, Niederman MS, Morser J, Kobayashi H, Kobayashi T, et al. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomized and placebo controlled trial. BMJ 2010;340:c1004.
[9] Kawakami K, Ohkusa Y, Kuroki R, Tanaka T, Koyama K, Harada Y, et al. Effectiveness of pneumococcal polysaccharide vaccine against pneumonia and cost analysis for the elderly who receive seasonal influenza vaccine in Japan. Vaccine 2010;28:7063–9.

[10] National Institute of Infectious Diseases. Infectious disease surveillance center. Infectious agents surveillance report 2010;31:248–50 [in Japanese].
[11] The number of the periodical vaccination enforcers. Ministry of health, labour and welfare. http://www.mhlw.go.jp/topics/bcg/other/5.html [in Japanese]
[12] Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T, Japanese Study Group on Aspiration Pulmonary Disease. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc 2008;56 (3):577–9.

Vaccine 35 (2017) 4811–4816

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Estimating influenza disease burden among pregnant women: Application of self-control method

Satoko Ohfuji [a,*], Masaaki Deguchi [b], Daisuke Tachibana [c], Masayasu Koyama [c], Tetsu Takagi [d], Takayuki Yoshioka [e], Akinori Urae [f], Wakaba Fukushima [a], Yoshio Hirota [a,g,h], for the Osaka Pregnant Women Influenza Study Group [1]

[a] Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan
[b] Department of Obstetrics and Gynecology, Kishiwada City Hospital, 1001, Gakuhara-cho, Kishiwada-city, Osaka 596-8501, Japan
[c] Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan
[d] Takagi Ladies Clinic, 1-13-44, Kamihigashi, Hirano-ku, Osaka-city, Osaka 547-0002, Japan
[e] Osaka Branch, Mediscience Planning Inc., 3-6-1, Hiranomachi, Chuo-ku, Osaka-city, Osaka 541-0052, Japan
[f] Head Office, Mediscience Planning Inc., 1-11-44, Akasaka, Minato-ku, Tokyo 107-0052, Japan
[g] College of Healthcare Management, 960-4, Takayanagi, Setaka-machi, Miyama-shi, Fukuoka 835-0018, Japan
[h] Clinical Epidemiology Research Center, Medical Co. LTA, 3-5-1, Kashii-Teriha, Higashi-ku, Fukuoka 813-0017, Japan

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 2 September 2016
Accepted 4 October 2016

Keywords:
Influenza
Disease burden
Pregnant women
Self-control method

ABSTRACT

To evaluate influenza disease burden among pregnant women, an epidemiological study using the self-control method was conducted. Study subjects were 12,838 pregnant women who visited collaborating maternity hospitals and clinics in Osaka Prefecture, Japan, before the 2013/14 influenza season. As a study outcome, hospitalization due to respiratory illnesses between the 2010/11 and 2013/14 seasons was collected from each study subject through a baseline survey at the time of recruitment and a second survey after the 2013/14 season. The hospitalization rates during pregnancy and non-pregnancy periods was calculated separately. To compare the hospitalization rate during pregnancy with that during non-pregnancy within the same single study subject, Mantel-Haenzel rate ratios (RR_{MH}) were calculated.

During the four seasons examined in this study, nine and 17 subjects were hospitalized due to respiratory illnesses during pregnancy and non-pregnancy periods, respectively. The hospitalization rate was 2.54 per 10,000 woman-months during pregnancy and 1.08 per 10,000 woman-months during non-pregnancy. The RR_{MH} for the hospitalization rate during pregnancy compared with that during non-pregnancy was 4.30 (95% confidence interval, 1.96–9.41).

Our results suggest that during the influenza season, pregnant women have a higher risk than non-pregnant women for hospitalization due to respiratory illnesses. The self-control method appears to be an appropriate epidemiological method for evaluating the disease burden of influenza among pregnant women.

1. Introduction

In November 2012, the World Health Organization recommended that pregnant women should be the highest priority group for influenza vaccination. This recommendation was based on compelling evidence regarding the substantial risk of severe disease in pregnant women, the effectiveness of vaccines against severe disease, and the secondary protection of vaccination for infants under 6 months of age [1]. However, in Japan, during the influenza A(H1N1)pdm09 pandemic, influenza-related hospitalization reported among pregnant women was only 74 cases [2] (cf. the number of annual births was 1,070,035 in 2009) [3], which was lower than that in other countries. Besides, no specific data regarding seasonal influenza disease burden among pregnant women has been reported. Therefore, before the highest priority group for influenza vaccination in Japan can be identified, information on seasonal influenza disease burden among pregnant women must be obtained.

Abbreviations: OR, odds ratio; CI, confidence interval.

* Corresponding author.
E-mail address: satop@med.osaka-cu.ac.jp (S. Ohfuji).

[1] Other members of the study group are listed in the Appendix.

http://dx.doi.org/10.1016/j.vaccine.2017.07.006
0264-410X/

The objective of this study was to investigate whether pregnancy is a high risk condition for hospitalization due to severe influenza. To examine this hypothesis, some might firstly consider the feasibility of conventional epidemiological methods such as cohort or case-control studies. In the countries that have established databases capable of identifying cohorts and hospitalization of pregnant women, cohort and case-control studies can be used to examine our hypothesis. For example, Neuzil et al. conducted a case-control study using a database of women aged 15–44 years enrolled in the Tennessee Medicaid program. They found that compared with postpartum women, those at 14–42 weeks' gestation had increased odds ratios for influenza-related hospitalization [4]. However, under the situation that there is no available database for child-bearing aged women and their hospitalization, it is difficult to conduct such case-control study, and even more cohort study.

As an alternative, a new epidemiological method called the "self-control method" has been proposed. The self-control method is described as a variant of the cohort study; however, as opposed to a different comparison group, it comprises a comparison of the person-time experience between the exposed and the unexposed period within the same study subjects [5]. To date, this study design has primarily been used to investigate the association between vaccines and adverse events [6,7]; however, it has also been widely used to investigate several issues in relation to infectious diseases [8]. To apply the self-control method in an epidemiological study, the study hypothesis needs to satisfy in principle the following three points: (1) exposure status is changing according to the time experience of the subjects; (2) the effect of exposure is transient and only continues for a brief time; and (3) outcomes must be characterized by an abrupt onset [5]. In our study hypothesis, pregnancy status (i.e., exposure) varies from time to time within the subject, and its related effects only continue within a period of about 10 months. In addition, influenza-related hospitalization (i.e., outcome) occurs suddenly. Thus, the self-control method was considered appropriate for investigating our hypothesis.

Here, we present our experience using the self-control method to examine whether pregnancy is a high risk condition for influenza-related hospitalization.

2. Materials and methods

2.1. Study subjects

The Osaka Pregnant Women Influenza Study was conducted at 117 collaborating maternity hospitals and clinics in Osaka Prefecture, Japan. Between September 2013 and January 2014 (i.e., recruitment), pregnant women who had been under clinical follow-up for pregnancy at these hospitals and clinics were invited to participate in this study. Eligible subjects were women at any stage of pregnancy at the time of recruitment. A total of 20,420 subjects agreed to participate and were enrolled. All study subjects verbally provided their informed consent prior to participation.

The study protocol was approved by the Ethics Committees at the Osaka City University Faculty of Medicine and the collaborating hospitals, and was performed in accordance with the Declaration of Helsinki.

2.2. Information collection

To collect information on hospitalization during four influenza seasons from 2010/11 to 2013/14 as a study outcome, a baseline and a second survey were conducted on each study subject using self-administered questionnaires. The baseline survey was carried out at the time of recruitment. The baseline questionnaire was composed of items regarding history of influenza vaccination, physician-diagnosed influenza, and hospitalization (as a study outcome) since January 2011, as well as the following background characteristics: demographic factors such as age and date of birth; gestational week at the time of recruitment, expected delivery date; height and weight before pregnancy; influenza-related underlying illnesses before pregnancy (e.g., asthma, chronic respiratory disease, hypertension, heart disease, renal disease, liver disease, anemia, blood disease, diabetes mellitus, diseases of the thyroid gland, diseases of the nerve or muscle systems, immunodeficiency), underlying illnesses in obstetrics and gynecology (myoma uteri, endometriosis, ovarian disease, infertility, etc.), mental disorders, allergic disorders; smoking and alcohol drinking habits; and duration of residence in Osaka Prefecture. Next, after the 2013/14 influenza season ended in May 2014, a second survey was conducted on the study subjects each time they underwent a regular medical examination for their pregnancy. In the case that they had already delivered during the season and were not under clinical follow-up at the hospitals, a questionnaire was sent by mail to their residence. The questionnaire for the second survey was composed of items regarding influenza vaccination, physician-diagnosed influenza, and hospitalization (as a study outcome) since the time of the baseline survey, and the delivery date. In both surveys, subjects who answered "hospitalized" were also asked to provide the reason for hospitalization and the hospital name.

The self-reported information on hospitalization in these two surveys was confirmed by hospital records at the reported hospitals. Based on the reported hospital name, we sent the questionnaire to physicians in the hospitals, and collected information for confirmation, including date of admission, date of discharge, name of disease that led to hospitalization, and laboratory data at the time of hospitalization.

In addition, a structured questionnaire, completed by the obstetrician-in-charge after delivery, was used to collect information about the clinical course of pregnancy for each study subject. The questionnaire gathered information about: pregnancy-induced complications during pregnancy, pregnancy outcome (i.e., abortion, dead birth, or live birth) and date; and reproductive history (i.e., parity number, delivery date, and gestational week for older children).

2.3. Outcome definitions and epidemic

The study outcome was defined as hospitalization due to respiratory illnesses that occurred during an influenza epidemic. The period of the influenza epidemic was determined using surveillance data from Osaka Prefecture [9–12], and defined as the period in which the weekly number of influenza patients remained at $\geq$5 per sentinel. Based on the epidemic curve (Fig. 1), the epidemic periods were from the second week to the 17th week of 2011 in the 2010/11 season, from the second week to the 14th week of 2012 in the 2011/12 season, from the second week to the 12th week of 2013 in the 2013/14 season, and from the second week to the 13th week of 2014 in the 2013/14 season.

Hospitalization due to respiratory illnesses was extracted from all reported hospitalization during the epidemic period when the following disease names were noted in the hospital records or reported on the self-administered questionnaires: influenza, pneumonia, bronchitis, common cold, infectious disease, asthma, high fever, tonsillitis, otitis media, or sinusitis. The selected disease names were adapted from those used in the previous studies [4,8].

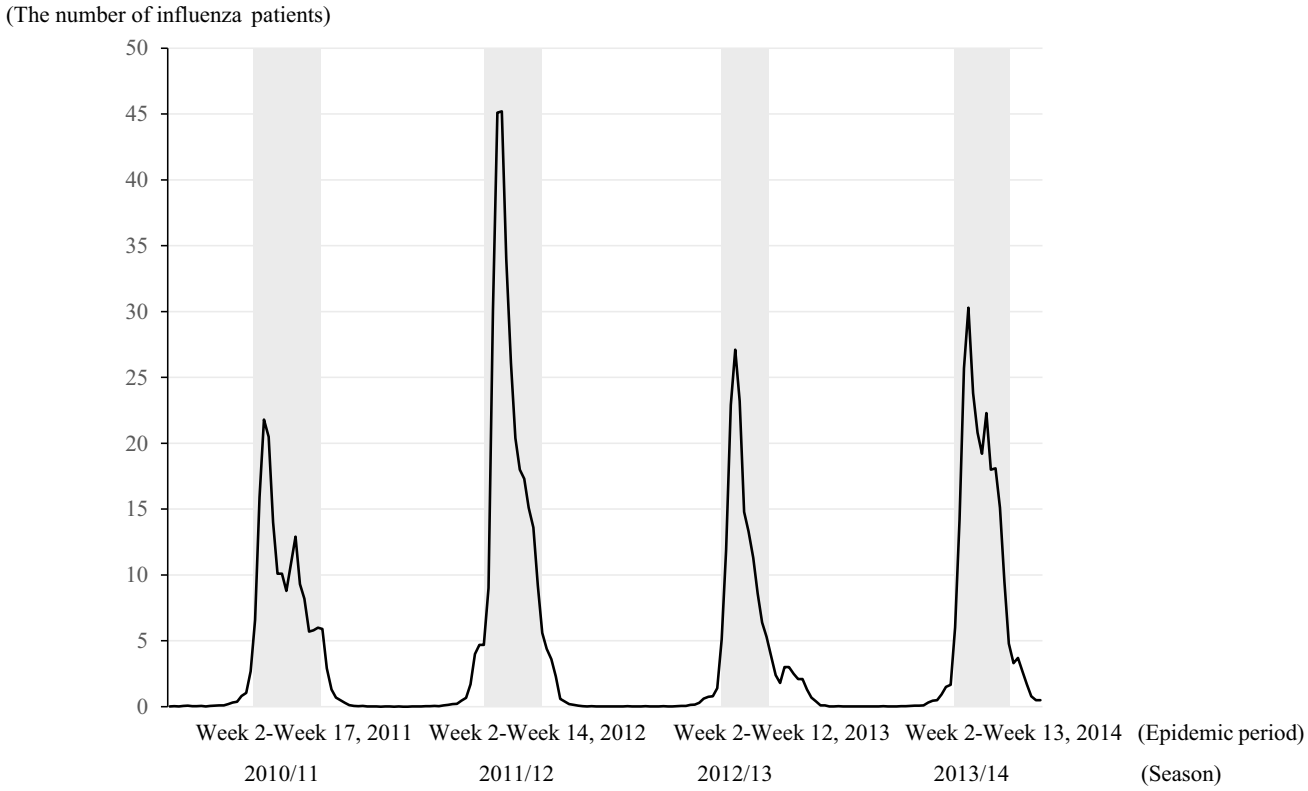


Fig. 1. Weekly number of influenza patients reported by sentinels in Osaka Prefecture during influenza seasons.

2.4. Statistical analysis

The number of woman-days for each influenza season was counted from the beginning of each epidemic period until the date of hospitalization due to respiratory illnesses or the end of the epidemic period, whichever came first. Next, based on the information regarding the date and gestational week of delivery experiences, the number of woman-days was divided into pregnancy and non-pregnancy period for each study subject.

To compare the hospitalization rate between the pregnancy and non-pregnancy periods within the same single study subject, Mantel-Haenzel rate ratio (RR_{MH}) and 95% confidence intervals (CI) were calculated [13,14]. Analyses were conducted using woman-days, but the results were translated to woman-months for ease of interpretation. All tests were two-sided. All analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

3. Results

Among the 20,420 study subjects enrolled, 12,838 subjects responded to both the baseline and the second surveys, and included in the analysis. The characteristics of the subjects are shown in Table 1. Median age was 32 years, and median gestational week at the time of recruitment was 23.0 weeks. One third of the subjects had any underlying illnesses, and the proportion of subjects with influenza-related underlying illnesses was 15%. Only a small number of subjects had pregnancy-induced complications such as hospitalization due to threatened abortion (5%), hypertension (3%), diabetes (3%), intrauterine growth restriction (3%) or multiple pregnancy (2%). Most of the subjects had lived in Osaka Prefecture since three years or more before, suggesting similar recent exposure to the influenza virus.

The weekly number of influenza patients reported from sentinels in Osaka Prefecture since January 2011 are shown in Fig. 1. The magnitude and length of the epidemic period in the 2013/14 season was similar to that in the 2012/13 season. The epidemic in the 2011/12 season was the largest of the 10 most recent seasons, and that in the 2010/11 season was smaller but longer continuing until May 2011.

Table 2 shows the number of hospitalizations and the hospitalization rate in each influenza season according to pregnancy status. In the 2013/14 season, eight subjects were admitted to hospital due to respiratory illnesses during pregnancy. The hospitalization rate was 4.04 per 10,000 woman-months, which was higher than that during the non-pregnancy period in any of the four influenza season examined in this study. During the four seasons, a total of nine subjects were admitted to hospital due to respiratory illness during pregnancy, whereas 17 were hospitalized during non-pregnancy. The hospitalization rate was 2.54 per 10,000 woman-months during pregnancy and 1.08 per 10,000 woman-months during non-pregnancy. The RR_{MH} for the hospitalization rate during pregnancy compared with that during non-pregnancy was 4.30 (95% CI, 1.96–9.41).

When limited to subjects who had lived in Osaka Prefecture since three years or more before, these results were almost unchanged. During the four seasons, the hospitalization rate was 2.59 per 10,000 woman-months during pregnancy and 1.04 per 10,000 woman-months during non-pregnancy. The RR_{MH} for hospitalization rate during pregnancy compared with that during non-pregnancy was 5.17 (95%CI, 2.14–12.5).

4. Discussion

In this study, which utilized a specific epidemiological technique called the “self-control method”, we found that the rate of

Table 1
Baseline characteristics among pregnant women.

Variables		N	n (%) or median (range)
Age at the time of recruitment (years)	Median (range)	12,838	32.0 (15–51)
Gestational age at the time of recruitment (weeks)	Median (range)	12,831	23.0 (4–42)
Body mass index before pregnancy (kg/m^2)	Median (range)	12,646	20.4 (9.1–62.5[a])
Underlying illnesses before pregnancy	Present	12,838	3978 (31)
Influenza-related	Present	12,838	1909 (15)
Obstetrics and gynecology-related	Present	12,838	2329 (18)
Mental disorders	Present	12,838	339 (3)
Allergic disorders	Present	12,838	53 (0.4)
Pregnancy-induced complications			
Hospitalization due to threatened abortion	Present	11,138	588 (5)
Pregnancy-induced hypertension	Present	11,127	375 (3)
Gestational diabetes	Present	11,152	310 (3)
Intrauterine growth restriction	Present	11,135	315 (3)
Multiple pregnancy	Present	11,186	168 (2)
Intrauterine infection	Present	11,128	98 (0.9)
Placenta previa	Present	9453	56 (0.5)
Placental abruption	Present	11,141	43 (0.4)
Smoking habit			
Before pregnancy	Present	12,618	2376 (19)
During pregnancy	Present	11,974	386 (3)
Drinking habit			
Before pregnancy	Present	12,613	4790 (38)
During pregnancy	Present	11,990	82 (0.7)
Duration of residence in Osaka Prefecture (years)	3 years or more	12,131	11,045 (91)

[a] Including 9 subjects whose body weight before pregnancy was less than 35.0 kg and 14 subjects whose body weight before pregnancy was more than 100.0 kg. When excluding these 23 subjects, body mass index before pregnancy ranged from 14.1 to 40.2 kg/m^2.

the hospitalization during pregnancy was 4.3 times higher than that during non-pregnancy. This suggests that pregnant women are at a higher risk than non-pregnant women for hospitalization due to respiratory illnesses during the influenza season. To the best of our knowledge, only one study has applied the self-control method to investigate hospitalization due to respiratory illnesses during the influenza season among pregnant women. That study, which examined data from pregnant women enrolled in the Nova Scotia Atlee Perinatal Database in Canada, reported that the hospitalization rate among pregnant women was 1.7 and 5.1 times higher during the first and third trimesters, respectively, than that of the same subjects' non-pregnancy periods [8]. Other cohort or case-control studies, as well as those using descriptive epidemiology, also found that pregnant women were at 3–22 times higher risk for influenza-related hospitalization [17–19] or ICU hospitalization [15–17] compared with non-pregnant women. Taken together, the self-control method seemed to provide comparable results to those using other study designs, and the results from all of these studies suggest that pregnancy is a risk factor for influenza-related hospitalization.

Regarding possible causal mechanisms, a previous study suggested that during pregnancy, the immune system adapts to tolerate a genetically foreign fetus, and this immunologic adaptation results in an increased risk for influenza-related complications. Another possible interpretation is that physiological changes during pregnancy, including increased heart rate, stroke volume, oxygen consumption, and decreased lung capacity might put women at an increased risk for severe influenza illness [20–22]. Therefore, our results seem reasonable in terms of the mechanisms.

However, in our study, the observed hospitalization rate during pregnancy was 2.54 per 10,000 woman-months, and that during non-pregnancy was 1.08 per 10,000 woman-months; these rates were lower than those reported in other countries [4,8]. For example, the Canadian study reported that the hospitalization rate (per 10,000 woman-months) among women without comorbidities was 2.4 during the first trimester, 3.0 during the second trimester, 7.4 during the third trimester, and 1.4 during non-pregnancy [8]. The discrepancy in the results between our study and the Canadian study might be partly explained by the estimated influenza vaccination coverage among the study subjects. In the Canadian study, only 2.6% of pregnant women and 6.7% of non-pregnant women were immunized [8], whereas vaccination coverage in our study subjects was estimated to be 45% in the 2013/14 season, 38% in the 2012/13 season, and 37% in the 2011/12 season. Therefore, the relatively higher vaccination coverage among our study subjects might have led to lower hospitalization rates, irrespective of pregnancy status.

Our study had several methodological advantages. First, in the self-control method, since hospitalization rates during pregnancy and non-pregnancy were compared in the same study subjects, the effect of confounding factors would be almost negligible. Second, the information on hospitalization rates was highly reliable, because the accuracy of the data on reported hospitalization was guaranteed by contacting the relevant hospital of admission. In fact, we were able to obtain the information from their hospital records in 69% of the reported hospitalizations. The information obtained from their hospital records proved the reported hospitalization to be right through the agreement of data on admission date and disease name led to hospitalization for almost all verified hospitalizations. Third, since we enrolled women from a single prefecture, our study subjects are expected to have shared a similar exposure to the influenza virus.

However, when interpreting the present results, the following limitations should be kept in mind. First, the self-control method could not control the effect of time-dependent factors, although

Table 2
Hospitalization due to respiratory illnesses during influenza season according to pregnancy status.

Influenza season	Pregnancy status	Observation period (woman-months)	No. of hospitalizations	Rate per 10,000 woman-months
2013/14	Pregnant	19,785	8	4.04
	Nonpregnant	18,712	2	1.07
2012/13	Pregnant	4398	0	0
	Nonpregnant	34,109	4	1.17
2011/12	Pregnant	3874	1	2.58
	Nonpregnant	47,464	5	1.05
2010/11	Pregnant	7418	0	0
	Nonpregnant	57,186	6	1.05
2010/11∼2013/14	Pregnant	35,475	9	2.54
	Nonpregnant	157,471	17	1.08

some behaviors or situations might differ between the pregnancy and non-pregnancy periods. For example, pregnant women typically avoid going to crowded places where many people mingle. These health-conscious behaviors during pregnancy, if any, could be expected to result in an underestimation of the association between pregnancy and the risk of hospitalization due to respiratory illnesses. Second, since the present study subjects were pregnant women under clinical follow-up before the 2013/14 season, their pregnancy period occurred during the 2013/14 season. In other words, if they were pregnant for the first time in the 2013/14 season, their data during the previous seasons (i.e., the 2010/11 to 2012/13 seasons) only contributed to those during the non-pregnancy period in the 2010/11 to 2012/13 seasons. Thus, fewer pregnancies were observed in the 2010/11 to 2012/13 seasons, which resulted in fewer hospitalized cases and unstable hospitalization rates during pregnancy in the 2010/11 to 2012/13 seasons. On the other hand, most of the pregnancy period were concentrated in the 2013/14 influenza season, and thus the hospitalization rate during pregnancy was likely affected by the influenza activity in the 2013/14 season. In that situation, if the 2013/14 season was a larger epidemic season than the other seasons examined in this study, we would not be able to interpret whether the higher hospitalization rate observed during pregnancy was explained by the pregnancy status itself or by the larger influenza epidemic in the 2013/14 season. Fortunately, however, the magnitude of influenza epidemic in the 2013/14 season was similar to that in the 2012/13 season, and was smaller than that in the 2011/12 season. In addition, the hospitalization rate during the pregnancy period in the 2013/14 season was higher than that during the non-pregnancy period in any of the past three seasons, including the 2011/12 season, which was the largest epidemic in the past 10 seasons. Thus, it is not conceivable that the magnitude of influenza epidemic was enough to explain the observed risk of hospitalization during pregnancy. Third, although our results suggested that pregnancy was a high risk condition for hospitalization due to respiratory illnesses, the magnitude of this risk may be biased upward if clinicians had a lower threshold for admitting pregnant women as a precaution. However, this upward bias could also have occurred even in the other study designs unless care providers have identical thresholds for admitting pregnant women. Fourth, the outcome of the present study, hospitalization due to respiratory illnesses during an influenza epidemic, might be less specific to influenza compared with laboratory confirmation, and thus some outcome misclassification might be concerned. However, we considered that this misclassification, if any, should not differ between those in the pregnancy and non-pregnancy periods. Such misclassification, if any, could be expected to result in an underestimation of the association between pregnancy and the risk of hospitalization because of the diluting effect, and was therefore considered not to materially affect the validity of the present results. Finally, since the study subjects were pregnant women under clinical follow-up at hospitals in Osaka Prefecture, there may be some concern about the generalizability of the study results. Therefore, additional studies in other areas or influenza seasons would be desirable to confirm the validity of the present results.

Despite these limitation, the results of our study using the self-control method support previous findings that pregnancy is a high risk condition for hospitalization due to respiratory illnesses during the influenza season. Although the self-control method is used less frequently than other epidemiological methods such as cohort or case-control studies, our results suggest that the self-control method is appropriate for evaluating seasonal influenza disease burden among pregnant women.

Conflict of interest

None.

Acknowledgments

This study was supported by Health and Labour Sciences Research Grants from the Ministry of Health, Labor and Welfare of Japan in 2011–2016.

Appendix A

Other members in the Osaka Pregnant Women Influenza Study Group are as follows (shown in alphabetical order of the affiliation): Shiro Imai (Department of Gynecology and Obstetrics, Aizenbashi Hospital), Eiko Akagaki (Akagaki Ladies Clinic), Mariko Akai (Akai Maternity Clinic), Yoshitsune Azuma (Azuma Ladies Clinic), Shinichi Hamada (Department of Obstetrics and Gynecology, Bell Land General Hospital), Satoru Motoyama (Department of Obstetrics and Gynecology, Chibune General Hospital), Hiroko Chimori (Chimori Medical Clinic), Shoko Nakagawa (Department of Obstetrics and Gynecology, Fuchu Hospital), Takehiko Fukuda (Fukuda Lady's Clinic), Masahisa Hagiwara (Hagiwara Clinic), Hideto Okuda (Hamada Women's Hospital), Takuro Hamanaka (Hamanaka Obstetrics and Gynecology), Seiichi Yamamasu (Obstetrics and Gynecology, Hannan Chuo Hospital), Kenji Hirota (Obstetrics and Gynecology, Hanwasumiyoshi General Hospital), Masataka Oku (Obstetrics and Gynecology, Higashi Osaka City General Hospital), Keizo Hiramatsu (Hiramatsu Obstetrics and Gynecology Clinic), Masanori Hisamatsu (Hisamatsu Maternity Clinic), Yasushi Iijima (Iijima Women's Hospital), Mikio Takehara (Department of Obstetrics and Gynecology, Ikeda City Hospital), Somei Ikeda (Ikeda OB/GYN Clinic), Takeshi Inoue (Inoue Lady's Clinic), Eriko Yamashita (Ishida Hospital), Aisaku Fukuda (The Centre for Reproductive Medicine and Infertility, IVF Osaka Clinic), Itsuko Iwata (Iwata Clinic), Junko Nishio (Department of Obstetrics and Gynecology, Izumiotsu Municipal Hospital), Tateki Tsutsui (Department of Obstetrics and Gynecology, Japan Community Healthcare Organization Osaka Hospital), Kenji Yamaji (Kajimoto Clinic), Takao Kamiya (Kamiya Ladies Clinic), Atsushi Kasamatsu (Department of Obstetrics and Gynecology, Kansai Medical University Hirakata Hospital), Tatsuya Nakajima (Department of Obstetrics and Gynecology, Kansai Medical University Takii Hospital), Kanji Kasahara (Kasahara Clinic), Kenjitsu Kasamatsu (Kasamatsu Obstetrics and Gynecology/Pediatrics), Kawabata Ryoichi (Kawabata Lady's Clinic), Kawabata Kazume (Kawabata Woman's Clinic), Kozo Kadowaki (Department of Obstetrics and Gynecology, Kawachi General Hospital), Hiroshi Nomura (Kawashima Ladies Clinic), Tomoyuki Kikuchi (Kikuchi Ladies Clinic), Ayako Suzuki (Department of Obstetrics and Gynecology, Kinki University), Tadayoshi Nagano (Department of Obstetrics and Gynecology, Kitano Hospital), Yoshitsugu Komeda (Komeda Ladies Clinic), Ryousuke Kondo (Kondo Ladies Clinic), Shinjin Konishi (Konishi Ladies Clinic), Hideo Takemura (Kosaka Womens Hospital), Masako Kasumi (Masako Ladies Clinic), Kazuo Masuhiro (Masuhiro Maternity Clinic), Ryoji Ito (Department of Obstetrics and Gynecology, Matsushita Memorial Hospital), Yoshiki Sakamoto (Department of Obstetrics and Gynecology, Mimihara General Hospital), Kouzo Hirai (Minami-Morimachi Ladies Clinic), Yoshimitsu Yamamoto (Department of Obstetrics and Gynecology, Minoh City Hospital), Yoshitaka Kariya (Minoh Ladies Clinic), Osamu Misaki (Misaki Clinic), Akira Miyake (Miyake Clinic), Yasuko Osako (Mom Women's Clinic Osako), Masao Mori (Mori Obstetrics and Gynecology Clinic), Keizo Naka (Naka Ladies Clinic), Yasumasa Tokura (Nakai Clinic), Jun

Yoshimatsu (Department of Perinatology and Gynecology, National Cerebral and Cardiovascular Center), Keiji Tatsumi (Department of Obstetrics and Gynecology, National Hospital Organization Osaka National Hospital), Takayoshi Kanda (Department of Obstetrics and Gynecology, National Hospital Organization Osaka Minami Medical Center), Masahiro Nishikawa (Nishikawa Ladies Clinic), Sekio Nishimoto (Nishimoto Ladies Clinic), Yoshihiro Nishioka (Nishioka Clinic), Takao Funato (Department of Obstetrics and Gynecology, Nissay Hospital), Kouichi Nozaki (Nozaki Ladies Clinic), Gengo Ohira (Ohira Ladies Clinic), Yoshiyuki Okamura (Okamura Ladies Clinic), Yuzo Oga (Oga Clinic), Osamu Nakamoto (Department of Obstetrics and Gynecology, Osaka City General Hospital), Shinichi Nakata (Department of Obstetrics and Gynecology, Osaka City Juso Hospital), Tetsuo Nakamura (Department of Obstetrics and Gynecology, Osaka City Sumiyoshi Hospital), Masahiko Takemura (Department of Obstetrics and Gynecology, Osaka General Medical Center), Toshiyuki Sadou (Department of Obstetrics and Gynecology, Osaka Gyoumeikan Hospital), Nobuaki Mitsuda (Department of Obstetrics, Osaka Medical Center and Research Institute for Maternal and Child Health), Daisuke Fujita (Department of Obstetrics and Gynecology, Osaka Medical College), Koji Hisamoto (Department of Obstetrics and Gynecology, Osaka Police Hospital), Shinobu Akada (Department of Obstetrics and Gynecology, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases), Takafumi Nonogaki, Chinami Horiuchi (Department of Obstetrics and Gynecology, Osaka Red Cross Hospital), Yasuhiko Shiki (Department of Obstetrics and Gynecology, Osaka Rousai Hospital), Tadashi Kimura (Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine), Koutaro Kitamura (Obstetrics and Gynecology, PL Hospital), Kazuhide Ogita (Department of Obstetrics and Gynecology, Rinku General Medical Center), Shigeki Matsuo (Saint Barnabas Hospital), Yoshihito Ikeda (Department of Obstetrics and Gynecology, Saiseikai Ibaragi Hospital), Akihiro Moriyama (Department of Obstetrics and Gynecology, Saiseikai Nakatsu Hospital), Yukiyoshi Ishikawa (Department of Obstetrics and Gynecology, Saiseikai NOE Hospital), Hiroshi Muso (Department of Obstetrics and Gynecology, Saiseikai Senri Hospital), Fuminori Kitada (Department of Obstetrics and Gynecology, Saiseikai Suita Hospital), Toshiya Yamamoto (Department of Obstetrics and Gynecology, Sakai City Hospital), Megumi Takemura (Department of Obstetrics and Gynecology, Sakibana Hospital), Takeshi Sawada (Sawada Ladies Clinic), Kentaro Shimura (Shimura Women's Clinic), Koh Shinyashiki (Shinyashiki Obstetrics and Gynecology), Mitsuhiko Masuda (Department of Obstetrics and Gynecology, Shiseikai Corporate Juridical Person), Tsuneo Shoda (Shoda Medical Clinic), Takamichi Nishizaki (Department of Obstetrics and Gynecology, Suita Municipal Hospital), Yoshinori Suzuki (Suzuki Clinic), Isao Suzuki (Suzuki Obstetrics and Gynecology), Hiroshi Nanjyo (Department of Obstetrics and Gynecology, Taisho Hospital), Keiko Takabatake (Takabatake Women's Clinic), Kikuya Takase (Takase Ladies Clinic), Satoshi Nakago (Department of Obstetrics and Gynecology, Takatsuki General Hospital), Jun Takeyama (Takeyama Lady's Clinic), Takeshi Taniguchi (Taniguchi Hospital), Keiichi Tasaka (Tasaka Clinic), Toshiaki Tatsumi (Tatsumi Ladies Clinic), Atsushi Tokuhira (Department of Obstetrics and Gynecology, Toyonaka Municipal Hospital), Shogo Tsubokura (Tsubokura Women's Clinic), Kayoko Ueda (Ueda Ladies Clinic), Yukiko Uenae (Uenae Ladies Clinic), Takahiko Unno (Unno Maternity Clinic), Hiroshi Yabuki (Yabuki Maternity Clinic), Tokihiro Yanamoto (Yanamoto Maternity Clinic), Yoshihiko Yamada (Department of Obstetrics and Gynecology, Yao Municipal Hospital), Nobuyuki Maruo (Department of Obstetrics and Gynecology, Yodogawa Christian Hospital), Yoshitsugu Takada (Department of Obstetrics and Gynecology, Yoshikawa Hospital).

References

[1] WHO. Vaccines against influenza WHO position paper – November 2012. Weekly Epidemiol Rec 2012;87:461-76.
[2] Ministry of Health, Labour and Welfare. The number of hospitalized patients diagnosed with influenza A(H1N1)pdm09 in Japan. Available at: http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/rireki/100331-02.html [in Japanese, accessed 13 February 2015].
[3] Ministry of Health, Labour and Welfare. The number of live births in Japan. Available at: http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai11/kekka02.html [in Japanese, accessed 13 February 2015].
[4] Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148:1094–102.
[5] Rothman KJ. Epidemiology: an introduction. New York: Oxford University Press; 2002.
[6] Glanz JM, McClure DL, Xu S, Hambidge SJ, Lee M, Kolczak MS, et al. Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. J Clin Epidemiol 2006;59:808–18.
[7] Baker MA, Lieu TA, Li L, Hua W, Qiang Y, Kawai AT, et al. A vaccine study design selection framework for the postlicensure rapid immunization safety monitoring program. Am J Epidemiol 2015;181:608–18.
[8] Dodds L, McNeil SA, Fell DB, Allen VM, Coombs A, Scott J, et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. CMAJ 2007;176:463–8.
[9] Ministry of Health, Labour and Welfare. The weekly number of influenza cases reported by sentinels in Japan. Available at: http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou01/houdou.html [in Japanese, accessed 13 February 2015].
[10] Osaka Prefectural Institute of Public Health. The weekly number of influenza cases reported by sentinels in Osaka Prefecture; 2013. Available at: http://www.iph.pref.osaka.jp/infection/nenpo/H25/kansen32_3.pdf [in Japanese, accessed 13 February 2015].
[11] Osaka Prefectural Institute of Public Health. The weekly number of influenza cases reported by sentinels in Osaka prefecture; 2012. Available at: http://www.iph.pref.osaka.jp/infection/nenpo/H24/kansen31_3.pdf [in Japanese, accessed 13 February 2015].
[12] Osaka Prefectural Institute of Public Health. The weekly number of influenza cases reported by sentinels in Osaka prefecture; 2011. Available at: http://www.iph.pref.osaka.jp/infection/nenpo/H23/kansen30_3.pdf [in Japanese, accessed 13 February 2015]
[13] IARC. Mantel-Haenszel rate ratio. In: Dos Santos Silva I, editor. Cancer epidemiology: principles and methods. France: IARC Press; 1999. p. 311-3.
[14] IARC. Confidence interval for Mantel-Haenszel rate ratio. In: Dos Santos Silva I, editor. Cancer epidemiology: principles and methods. France: IARC Press; 1999. p. 330.
[15] Yu H, Feng Z, Uyeki TM, Liao Q, Zhou L, Feng L, et al. Risk factors for severe illness with 2009 pandemic influenza A(H1N1) virus infection in China. Clin Infect Dis 2011;52:457–65.
[16] The ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System. Critical illness due to 2009A/H1N1 influenza in pregnant and postpartum women: population based cohort study. BMJ 2010; 340: c1279.
[17] Kelly H, Mercer GN, Cheng AC. Quantifying the risk of pandemic influenza in pregnancy and indigenous people in Australia in 2009. Euro Surveill 2009;14:19441.
[18] Schanzer DL, Langley JM, Tam TWS. Influenza-attributed hospitalization rates among pregnant women in Canada 1994–2000. J Obstet Gynaecol Can 2007;29:622–9.
[19] Ward KA, Spokes PJ, McAnulty JM. Case-control study of risk factors for hospitalization caused by pandemic (H1N1) 2009. Emerg Infect Dis 2011;17:1409–16.
[20] Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. AJOG 2012;207:s3–8.
[21] Goodnight WH, Soper DE. Pneumonia in pregnancy. Crit Care Med 2005;33: S390–7.
[22] Laibl VR, Sheffield JS. Influenza and pneumonia in pregnancy. Clin Perinatol 2005;32:727–38.

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 8, 1923–1930
https://doi.org/10.1080/21645515.2018.1455476

Taylor & Francis
Taylor & Francis Group

Immunogenicity of simultaneous versus sequential administration of a 23-valent pneumococcal polysaccharide vaccine and a quadrivalent influenza vaccine in older individuals: A randomized, open-label, non-inferiority trial

Kei Nakashima[a], Masahiro Aoshima[a], Satoko Ohfuji[b], Satoshi Yamawaki[a], Masahiro Nemoto[a], Shinya Hasegawa[c], Satoshi Noma[a], Masafumi Misawa[a], Naoto Hosokawa[d], Makito Yaegashi[c], and Yoshihito Otsuka[e]

[a]Department of Pulmonology, Kameda Medical Center, Chiba, Japan; [b]Department of Public Health, Osaka City University Graduate School of Medicine, Osaka, Japan; [c]Department of General Internal Medicine, Kameda Medical Center, Chiba, Japan; [d]Department of Infectious Disease, Kameda Medical Center, Chiba, Japan; [e]Department of Laboratory Medicine, Kameda Medical Center, Chiba, Japan

ABSTRACT

It is unclear whether simultaneous administration of a 23-valent pneumococcal polysaccharide vaccine (PPSV23) and a quadrivalent influenza vaccine (QIV) produces immunogenicity in older individuals. This study tested the hypothesis that the pneumococcal antibody response elicited by simultaneous administration of PPSV23 and QIV in older individuals is not inferior to that elicited by sequential administration of PPSV23 and QIV. We performed a single-center, randomized, open-label, non-inferiority trial comprising 162 adults aged ≥65 years randomly assigned to either the simultaneous (simultaneous injections of PPSV23 and QIV) or sequential (control; PPSV23 injected 2 weeks after QIV vaccination) groups. Pneumococcal immunoglobulin G (IgG) titers of serotypes 23F, 3, 4, 6B, 14, and 19A were assessed. The primary endpoint was the serotype 23F response rate (a ≥2-fold increase in IgG concentrations 4–6 weeks after PPSV23 vaccination). With the non-inferiority margin set at 20% fewer patients, the response rate of serotype 23F in the simultaneous group (77.8%) was not inferior to that of the sequential group (77.6%; difference, 0.1%; 90% confidence interval, −10.8% to 11.1%). None of the pneumococcal IgG serotype titers were significantly different between the groups 4–6 weeks after vaccination. Simultaneous administration did not show a significant decrease in seroprotection odds ratios for H1N1, H3N2, or B/Phuket influenza strains other than B/Texas. Additionally, simultaneous administration did not increase adverse reactions. Hence, simultaneous administration of PPSV23 and QIV shows an acceptable immunogenicity that is comparable to sequential administration without an increase in adverse reactions. (This study was registered with ClinicalTrials.gov [NCT02592486]).

ARTICLE HISTORY
Received 22 December 2017
Accepted 9 March 2018

KEYWORDS
23-valent pneumococcal polysaccharide vaccine; Quadrivalent influenza vaccine; Immunogenicity; Simultaneous administration; Elderly population

Introduction

Pneumococcal and influenza infections can cause significant morbidity and mortality, particularly in older individuals.[1,2] Mortality rates due to invasive pneumococcal disease (IPD) are highest in adults older than 65 years. Therefore, immunization with a 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended to prevent IPD; the vaccine's protective efficacy rate is 74%.[3] In most developed countries, however, PPSV23 vaccination rates remain low (31.4–69.8%), whereas influenza vaccination rates are relatively high (50.0–82.0%) in individuals older than 65 years.[4–8] Thus, a global strategy for improving PPSV23 vaccination compliance rates is required.

Simultaneous administration of PPSV23 and influenza vaccines, defined as administering both vaccines on the same day, is a promising strategy for increasing PPSV23 coverage rates to levels similar to those of influenza vaccinations.[9] Furthermore, simultaneous administration facilitates immunization with both vaccines in older individuals who have difficulty accessing hospitals. Vaccination with both the PPSV23 and influenza vaccine, even if not on the same day, is more protective and cost-effective than the administration of either alone.[10,11] However, previous studies that assessed the immunogenicity of simultaneous administration of the PPSV23 and quadrivalent influenza vaccine (QIV) in adults aged ≥65 years are limited.[12,13]

The objective of this study was to compare simultaneous vs. sequential administration of PPSV23 and QIV to test our hypothesis that simultaneous administration was not inferior to sequential administration as determined by the response rate (defined as a ≥2-fold increase of immunoglobulin G [IgG] concentrations in serotype 23F) 4–6 weeks after vaccination. We selected 6 pneumococcus serotypes

CONTACT Kei Nakashima kei.7.nakashima@gmail.com Department of Pulmonary Medicine, Kameda Medical Center, 929 Higashi-cho, Kamogawa, Chiba, 296–8602, Japan.

Supplemental data for this article can be accessed on the publisher's website.

that are highly associated with IPD, namely 23F, 3, 4, 6B, 14, and 19A, for immunogenicity analysis.[14–16]

Results

Patient characteristics

As shown in the CONSORT flowchart (Figure 1), 162 patients were randomized to receive simultaneous (n = 81) or sequential administration (n = 81). After excluding 1 patient for ineligibility, the 81 patients in the former group received simultaneous vaccine administration while the 80 in the latter group received only QIV; the PPSV23 vaccine was administered 2 weeks later. The groups were well balanced upon randomization (Table 1).

Primary endpoint

Figure 2 and Table 2 present the differences in the response rates to 23F between the 2 groups 4–6 weeks after PPSV23 vaccination. The response rate in the simultaneous group (63 of 81 patients [77.8%]) was not inferior to that of the sequential group (59 of 76 patients [77.6%]). The difference was 0.1% (90% confidence interval [CI], −10.8% to 11.1%), which was well above the −20% non-inferiority margin. The non-inferiority of simultaneous administration was maintained in both best-case and worst-case analyses (Supplementary Figure 1). The characteristics of sequential group patients who were analyzed after achieving their primary endpoint as well as those who dropped out are shown in Supplementary Table 1.

Secondary endpoints

Table 3 shows the antibody titers to pneumococcal capsular polysaccharides in all serotypes. Before vaccination, the geometric mean concentrations (GMCs) with 23F, 4, 6B, and 14 were significantly higher in the simultaneous group. The GMCs 4–6 weeks after PPSV23 vaccination were not significantly different in any of the serotypes. At 6 months after PPSV23 vaccination, GMCs exhibited a significant difference for serotype 14 only. Multivariate analysis revealed that only serotypes 4 and 14 had significant reductions in seroresponse odds ratios (ORs) 4–6 weeks after vaccination in the simultaneous administration group (Table 2). According to post-hoc analysis, consistent results were observed on multivariate analysis using pre-vaccination pneumococcal IgG titers as a confounder in addition to age and sex (Supplementary Table 2).

Table 4 shows the comparisons between seroprotection rates 4–6 weeks post-vaccination with the QIV. The seroprotection rates against B/Texas and B/Phuket in the 2 groups were low (40.7–62.3%); however, the rates against H1N1 and H3N2 strains were 77.9–84.0%. There were no significant differences between the 2 groups in seroprotection against H1N1, H3N2, and B/Phuket strains of influenza on multivariate analysis, although significant reductions in the ORs for seroprotection against B/Texas were noted in the simultaneous administration group. There were no significant differences in ORs for seroprotection between the 2 groups with respect to

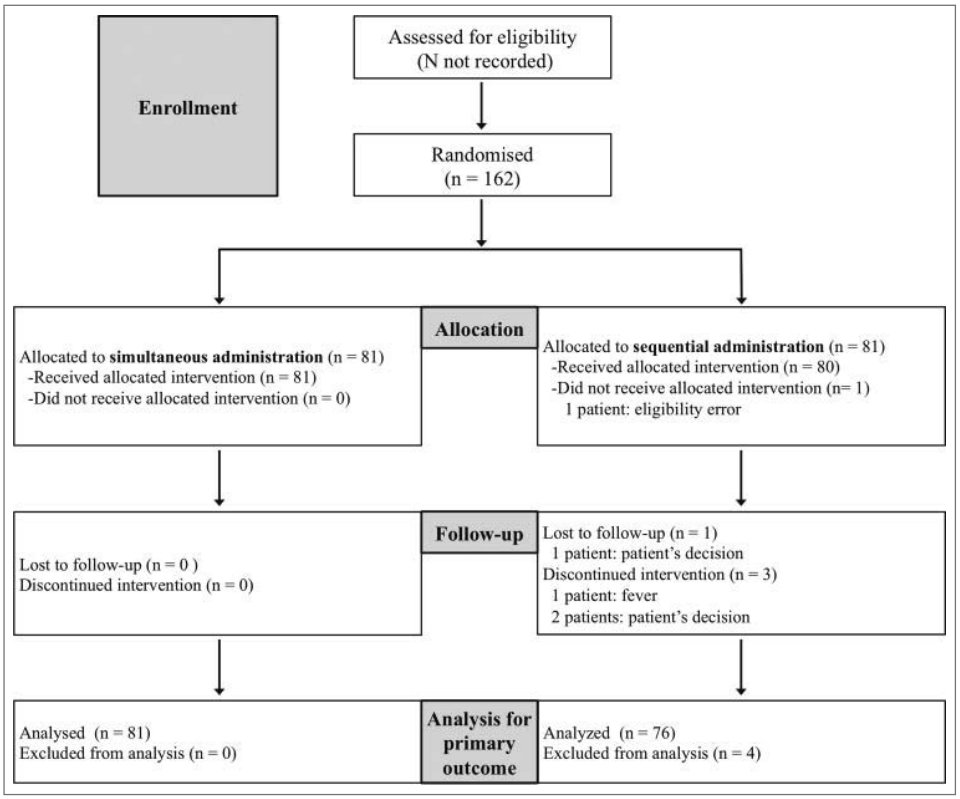


Figure 1. CONSORT flowchart

Table 1. Patients' characteristics at allocation

Variable	Simultaneous group (N = 81)	Sequential group (N = 80)
Age, years (± standard deviation)	71.0 (±5.1)	70.2 (±4.1)
Male	48 (59.3)	49 (61.3)
Influenza vaccination in last year*	20 (25.0)	29 (36.7)
Previous history of pneumonia†	13 (16.0)	14 (17.7)
Previous history of influenza†	10 (12.3)	15 (19.0)
Underlying disease		
Chronic lung disease	54 (66.7)	55 (68.8)
Chronic heart disease	12 (14.8)	10 (12.5)
Hypertension	36 (44.4)	28 (35.0)
Diabetes	19 (23.5)	16 (20.0)
Dyslipidemia	37 (45.7)	28 (35.0)
Chronic renal disease	3 (3.7)	1 (1.2)
Cerebral vascular disorder	4 (4.9)	5 (6.2)
Neuromuscular disease	0 (0.0)	1 (1.2)
Chronic liver disease	1 (1.2)	2 (2.5)

Note. Data are expressed as number (%) of patients, unless otherwise indicated.
*data from 2 subjects are missing.
†data from 1 subject are missing.

any of the influenza antigens 6 months post-vaccination with the QIV on multivariate analysis.

Safety

Table 5 shows the adverse events in the simultaneous and sequential groups. Simultaneous administration did not show any increase in systemic events and local reactions. However, fatigue was more frequent in the sequential group (24.1%) than in the simultaneous group (11.1%; P = 0.038).

Clinical events during the 6-month follow-up period

During the 6-month follow-up period, pneumonia and influenza-like illnesses were observed in 2 (2.5%) and 10 (12.3%) of the patients in the simultaneous group, respectively, and in 1 (1.3%) and 8 (10.7%) of the patients in the sequential group, respectively.

Discussion

We found that the response rate of serotype 23F following simultaneous administration was not inferior to that after sequential administration. There were no significant differences in GMCs 4–6 weeks after PPSV23 vaccination in any of the serotypes. Multivariate analysis revealed no significant differences in serotype 23F, 3, 6B, and 19A seroresponses in the simultaneous administration group, although serotypes 4 and 14 had significantly lower seroresponses. In the H1N1, H3N2, and B/Phuket strains of influenza, there were no significant differences in seroprotection between the 2 groups 4–6 weeks post-QIV administration, although seroprotection against B/Texas was significantly lower in the simultaneous administration group. Furthermore, there was no evidence of increased systemic events and local reactions with simultaneous administration.

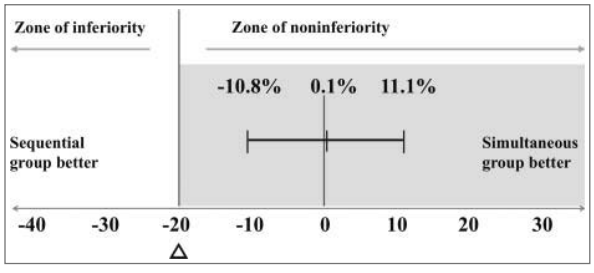


Figure 2. Differences in the response rates of 23F between the 2 groups (the rate in the simultaneous group minus that in the sequential group)

Rational of simultaneous administration of the PPSV23 and QIV

Pneumococcal pneumonia and influenza infections are both vaccine-preventable diseases. As PPSV23 vaccination rates remain low, specific strategies to increase PPSV23 immunization rates are required.[4–7] As influenza vaccinations are administered annually and PPSV23 revaccination is recommended 5 years after first vaccination in older individuals, influenza immunization schedules may provide ideal opportunities for older individuals to receive their primary and secondary PPSV23 administrations. Many countries that annually provide seasonal influenza vaccinations in older individuals also routinely provide PPSV23.[17]

Several studies have reported the additive benefits of influenza and PPSV23 vaccinations.[10,11,17,18] Large-scale cohort studies have also demonstrated the additive preventative effect of vaccination with both the PPSV23 and trivalent influenza vaccine (TIV) compared to either vaccination alone in elderly persons; the benefits included reductions in pneumonia rates, influenza infections, hospitalizations, morbidity, and mortality.[10,18] Prior studies also found that administering both the PPSV23 and influenza vaccine reduced medical costs compared to the influenza vaccine alone.[11,17]

Immunogenicity of the pneumococcal antibody

Several randomized control studies have demonstrated that the immunogenicity of pneumococcal antibody in patients with simultaneous administration of pneumococcal polysaccharide and influenza vaccines is similar to that of separate administration.[12,19,20] In the present study, we evaluated the immunogenicity of 23F, 3, 4, 6B, 14, and 19A, which are the most prevalent serotypes associated with IPD.[14,16] Moreover, these 6 serotypes represent a range of capsular polysaccharides, including serotype 3 that was previously shown to have a relatively weak antibody response.[15] We found no significant differences in the GMCs of any of the 6 serotypes 4–6 weeks after PPSV23 vaccination, and 4 of the 6 serotypes tested showed no significant changes in their seroresponses. Several studies have similarly demonstrated attenuated reductions in seroresponse rates in the serotypes of pneumococcal antibodies, such as serotypes 4 and 14, although most serotypes showed no significant differences.[12,19,21] Thus, the possibility of reduced response rates (≥2-fold IgG) in some serotypes appear to be reproducible; however, the clinical impact may be low, as pneumonia and invasive pneumococcal disease due to serotypes 4 and 14 are low worldwide.[14,22] Additionally, immunogenicity should be assessed using multiple valuables, such as GMCs and seroresponse rates. We propose that the advantages of increasing the immunization rates for both vaccines outweigh the effects of a possible small

Table 2. Odds ratios for seroresponses 4–6 weeks post-vaccination with the 23-valent pneumococcal polysaccharide vaccine.

		Crude analysis		Multivariate analysis*	
Category	n/N (%)	OR (95% CI)	P-value	OR (95% CI)	P-value
23F					
Sequential group	59/76 (77.6)	1 (reference)	0.982	1 (reference)	0.997
Simultaneous group	63/81 (77.8)	1.01 (0.48–2.14)		1.00 (0.47–2.13)	
3					
Sequential group	52/76 (68.4)	1 (reference)	0.923	1 (reference)	0.964
Simultaneous group	56/81 (69.1)	1.03 (0.53–2.03)		1.02 (0.51–2.03)	
4					
Sequential group	66/76 (86.8)	1 (reference)	0.004	1 (reference)	0.003
Simultaneous group	54/81 (66.7)	0.30 (0.14–0.68)		0.30 (0.13–0.67)	
6B					
Sequential group	63/76 (82.9)	1 (reference)	0.133	1 (reference)	0.134
Simultaneous group	59/81 (72.8)	0.55 (0.26–1.20)		0.55 (0.25–1.20)	
14					
Sequential group	67/76 (88.2)	1 (reference)	<0.001	1 (reference)	<0.001
Simultaneous group	49/81 (60.5)	0.21 (0.09–0.47)		0.20 (0.09–0.47)	
19A					
Sequential group	59/76 (77.6)	1 (reference)	0.732	1 (reference)	0.705
Simultaneous group	61/81 (75.3)	0.88 (0.42–1.84)		0.86 (0.40–1.86)	

*Adjusted for age (<70 and ≥70 years) and sex (male and female) as explanatory variables.
OR, odds ratio; CI, confidence interval.

reduction in seroresponse in certain serotypes of the pneumococcal antibody.

Immunogenicity of influenza antibody

We found no significant differences between the 2 groups with respect to seroprotection rates in the A/H1N1, A/H3N2, and B/Phuket strains of influenza 4–6 weeks after vaccination. However, seroprotection against B/Texas was significantly reduced in the simultaneous group. In a double-blind, randomized control study, 126 healthy participants aged 18–26 years who received simultaneous administration of 14-valent pneumococcal polysaccharide vaccine and TIV showed lower geometric mean titers of A/H1N1 and B strains than participants who received separate administrations, although there were no statistically significant differences in seroprotection rates (post-vaccination titer ≥1:40) in the 2 administration groups.[20] Other studies that assessed simultaneous administration of pneumococcal polysaccharide vaccine and TIV found no significant differences in geometric mean titers of the influenza strains between the simultaneous vs. sequential administration groups.[12,19,21] In our study, both groups exhibited lower B/Texas immunogenicity. Considering previous findings and our own results, there exists a possibility of a slight reduction in the immune response against certain strains of influenza with simultaneous administration of PPSV23 and QIV, although the clinical implications of this remain unknown.

Table 3. Antibody titers to pneumococcal capsular polysaccharides.

	Simultaneous group		Sequential group		
Variable	N	GMC	N	GMC	*P*-value*
23F					
Before vaccination (P0)	81	0.40	80	0.20	<0.001
4–6 weeks after vaccination (P1)	81	2.04	76	1.41	0.157
6 months after vaccination (P2)	81	2.12	72	1.70	0.351
3					
Before vaccination (P0)	81	0.07	80	0.07	0.277
4–6 weeks after vaccination (P1)	81	0.24	76	0.21	0.482
6 months after vaccination (P2)	81	0.26	72	0.24	0.632
4					
Before vaccination (P0)	81	0.08	80	0.05	0.004
4–6 weeks after vaccination (P1)	81	0.24	76	0.28	0.520
6 months after vaccination (P2)	81	0.30	72	0.36	0.403
6B					
Before vaccination (P0)	81	0.24	80	0.14	0.007
4–6 weeks after vaccination (P1)	81	0.96	76	0.96	0.993
6 months after vaccination (P2)	80	1.18	72	1.29	0.697
14					
Before vaccination (P0)	81	0.68	80	0.42	0.032
4–6 weeks after vaccination (P1)	81	2.78	76	4.72	0.070
6 months after vaccination (P2)	81	3.57	73	6.21	0.046
19A					
Before vaccination (P0)	81	0.72	80	0.49	0.051
4–6 weeks after vaccination (P1)	81	3.74	76	2.92	0.332
6 months after vaccination (P2)	81	4.61	73	3.38	0.147

Note. Data are presented as the geometric mean concentrations (GMC) of immunoglobulin G to each pneumococcal capsular polysaccharide, in micrograms per milliliter. All changes within each group from P0 to P1 and P2 were statistically significant ($P < 0.001$) based on paired t-tests.
*P-values were calculated using Student's t-tests.

Adverse reactions

Several previous studies that evaluated the safety of simultaneous vaccine administration demonstrated acceptable adverse reactions in older individuals.[12,19–21,23] In a randomized control study assessing young individuals (18–26 years), simultaneous administration of the 14-valent polysaccharide pneumococcal vaccine and TIV did not result in increases in local or systemic reactions except for transient myalgias.[20] In a prospective cohort study assessing 861 elderly individuals, local erythema was reported more frequently by individuals who received simultaneous administration of PPSV23 and TIV; however, no significant differences in other adverse reactions were found between those immunized simultaneously with PPSV23 and TIV (n = 541) and those administered PPSV23 alone (n = 320).[23] In 2 other randomized control studies, simultaneous administration was not associated with an increase in local and

Table 4. Odds ratios for seroprotection 4–6 weeks post-vaccination with the quadrivalent influenza vaccine.

		Crude analysis		Multivariate analysis*	
Category	n/N (%)	OR (95% CI)	P-value	OR (95% CI)	P-value
H1N1					
Sequential group	60/77 (77.9)	1 (reference)	0.336	1 (reference)	0.156
Simultaneous group	68/81 (84.0)	1.48 (0.67–3.30)		1.90 (0.78–4.59)	
H3N2					
Sequential group	68/77 (88.3)	1 (reference)	0.235	1 (reference)	0.259
Simultaneous group	66/81 (81.5)	0.58 (0.24–1.42)		0.56 (0.21–1.52)	
B Texas					
Sequential group	45/77 (58.4)	1 (reference)	0.027	1 (reference)	0.021
Simultaneous group	33/81 (40.7)	0.49 (0.26–0.92)		0.46 (0.24–0.89)	
B Phuket					
Sequential group	48/77 (62.3)	1 (reference)	0.812	1 (reference)	0.842
Simultaneous group	49/81 (60.5)	0.93 (0.49–1.76)		0.93 (0.47–1.86)	

*Adjusted for age at vaccination (<70 and ≥70), sex and pre-vaccination titer (<1:10 and ≥1:10, in H1N1, B texas and B Phuket; and ≤1:10 and >1:10 in H3N2) as explanatory variables.
OR, odds ratio; CI, confidence interval.

systemic adverse reactions.[12,19] Consistent with these findings, simultaneous administration did not show any increase in systemic events and local reactions in our study.

Clinical implications

Vaccination with both the PPSV23 and influenza vaccines is recommended worldwide for adults over 65 years.[17] Our results provide justification for clinicians to simultaneously administer PPSV23 and QIV, and for medical policymakers to recommend the same. The attrition rate in the sequential administration group is likely to be indicative of patients' inconvenience of having to return for a second vaccination in clinical practice. Clinicians should thus attempt to recommend the administration of PPSV23 at the same time as the QIV in adults over 65 years of age who were not previously vaccinated against pneumococci.

Table 5. Adverse events in patients of the simultaneous and sequential groups.

	Simultaneous group %, (n/N)	Sequential group %, (n/N)	P-value†
Systemic events			
Total	24.7 (20/81)	39.2 (31/79)	0.062
Fever	2.5 (2/79)	3.9 (3/76)	0.677
Fatigue	11.1 (9/81)	24.1 (19/79)	0.038
Headache	4.9 (4/81)	6.3 (5/79)	0.744
Joint pain	13.6 (11/81)	13.9 (11/79)	1.000
Pain of axilla	4.9 (4/81)	5.2 (4/77)	1.000
Rash	1.2 (1/81)	2.5 (2/79)	0.618
Local reactions			
Pneumococcal vaccination			
Total	49.4 (40/81)	59.7 (46/77)	0.205
Induration	24.7 (20/81)	19.5 (15/77)	0.450
Itch	19.8 (16/81)	15.6 (12/77)	0.537
Pain	34.6 (28/81)	48.1 (37/77)	0.106
Redness	28.4 (23/81)	26.0 (20/77)	0.858
Swelling	29.6 (24/81)	18.2 (14/77)	0.098
Influenza vaccination			
Total	46.9 (38/81)	36.7 (29/79)	0.204
Induration	23.5 (19/81)	15.2 (12/79)	0.231
Itch	22.2 (18/81)	17.7 (14/79)	0.555
Pain	28.4 (23/81)	19.0 (15/79)	0.195
Redness	23.5 (19/81)	22.8 (18/79)	1.000
Swelling	23.5 (19/81)	19.0 (15/79)	0.564

Note. The population in which safety was assessed comprised study participants who received a minimum of 1 dose of the study vaccine.
†P-values were calculated using Fisher's exact test.

Limitations

First, we did not evaluate the opsonization index, which may be a more appropriate indicator for evaluating immune capability compared to quantitative IgG measurement. However, we employed a 2-fold increase in IgG concentrations as a measure of vaccine response based on previous studies.[24,25] Second, our patients were predominantly enrolled at the Department of Pulmonology; therefore, chronic lung disease was the most frequent underlying disease, and a relatively low proportion of healthy subjects were enrolled. Therefore, our study should be interpreted with caution.

Conclusions

Simultaneous administration of PPSV23 and QIV showed an acceptable immune response that was comparable to that of sequential administration without an increase in adverse reactions. We propose that simultaneous administration of the 2 vaccines may be a promising strategy to increase PPSV23 coverage rates. Further studies assessing the opsonization index or clinical endpoints (such as all-cause pneumonia and all-cause mortality) following simultaneous administration should be performed to clarify the efficacy of simultaneous administration of PPSV23 and QIV.

Material and methods

Study design

This study was a randomized, open-label, non-inferiority trial conducted at Kameda Medical Center (Chiba, Japan) between October 2015 and August 2016. The protocol complied with the Helsinki Declaration and was approved by the Research Ethics Committee of Kameda Medical Center (#15-041-160127). Written informed consent was obtained from all participants. Additionally, CONSORT guidelines were followed during the development of the research plan and reporting of

the results. This study is registered with ClinicalTrials.gov number: NCT02592486.

The primary endpoint was the percentage of patients with positive antibody responses (≥2-fold increase in IgG concentrations 4–6 weeks after PPSV23 vaccination) in serotype 23F of the pneumococcal antibody. This endpoint was compared between 2 groups of patients randomly allocated to receive either simultaneous administration (simultaneous injections of PPSV23 and QIV in 1 day) or sequential administration (injection of PPSV23 2 weeks after QIV vaccination). The 2-week gap was employed because of: 1) patients' ease-of-access to the hospital; and 2) in Japan, sequential vaccination of inactivated vaccine may be performed >7 days after the first vaccination. Serotype 23F was selected because it is a major causative serotype of pneumococcal pneumonia, a representative penicillin-resistant pneumococcus, and has a sufficiently high response rate.[24–26] Secondary endpoints included positive antibody responses in serotypes 3, 4, 6B, 14, and 19A as well as the GMCs of specific antibodies to 6 serotypes (23F, 3, 4, 6B, 14, and 19A) before vaccination, 4–6 weeks post-vaccination, and 6 months (24–27 weeks) post-vaccination with PPSV23. Another endpoint included the percentage of seroprotected patients (post-vaccination titer ≥1:40) 4–6 weeks and 6 months post-vaccination with QIV.

Data for patient characteristics including age, sex, previous influenza vaccination status in the last year, and lifetime history of pneumonia or influenza were obtained from questionnaires completed by the participants. Data for underlying diseases were obtained from existing medical charts at Kameda Medical Center. Patients were followed for 6 months post-vaccination. Pneumonia, influenza-like illness, hospitalization, and other medical events were recorded throughout the 6-month follow-up period. Supportive care, including cold medication and prophylactic antibiotic treatment, was administered.

Eligibility of study subjects

Study participants included individuals aged ≥65 years with no history of a pneumococcal vaccination (PPSV23 or pneumococcal conjugate vaccine) or QIV during the 2015/2016 season. Participants were excluded if they exhibited the following: sensitivity to either pneumococcal or influenza vaccines; vaccination within 14 (inactivated) or 28 (live) days; conditions that impaired their response to pneumococcal vaccination; a diagnosis of cancer; an acute illness necessitating treatment with antibiotics or steroids within 30 days; using oral corticosteroids or immunosuppressive agents; prior history of splenectomy; an acute febrile illness or evidence of a severe acute illness at the timing of vaccination; a limited chance of surviving for 12 months, and other specific conditions as judged by the attending physicians.

Randomization

Randomization was performed at the Data Coordinating Center, Osaka University (Osaka, Japan). Participants were randomly assigned to 1 of 2 study groups: the simultaneous administration group (simultaneous injections of PPSV23 and QIV in 1 day) or the sequential administration group (injection of PPSV23 2 weeks after QIV vaccination). Randomization was stratified according to patient age (<70 and ≥70 years) and sex.

Vaccination

Commercially available PPSV23 (Pneumovax NP®, MSDKK, Tokyo, Japan), containing 25 μg of each of the 23 capsular polysaccharide types was used. Each patient received a single subcutaneous dose of the vaccine (0.5 mL) in their right upper arm. Using a FLUBIK HA syringe (Handai Biken Ltd, Osaka, Japan), the QIV (0.5 mL) containing inactivated A/California/7/2009 (H1N1) pdm09, A/Swiss/9715293/2013 (H3N2), B/Texas/2/2013, and B/Phuket/3073/2013 was administered as a single subcutaneous injection in the left upper arm. In Japan, subcutaneous administration of pneumococcal and influenza vaccinations is routine.

Serum sample collection and antibody measurements

Serum samples were collected at 3 time points: before vaccination; 4–6 weeks after vaccination; and 6 months after vaccination. We evaluated antibody titers at 6 months to assess the antibody titer decay of both the influenza and pneumococcal vaccines. All serum specimens were stored at −20°C until analysis. Serotype-specific IgG antibody concentrations for the 6 pneumococcus serotypes (23F, 3, 4, 6B, 14, and 19A) were measured at PPD® Laboratories (Richmond, VA, USA) using the Merck Sharp & Dohme Corp. multiplex, electrochemiluminescence-based detection assay that was bridged to the World Health Organization reference ELISA.[27] Furthermore, serum antibody levels to influenza hemagglutinin were measured at the Research Foundation for Microbial Diseases of Osaka University using the standard microtiter hemagglutination inhibition method with the same antigens found in the vaccine.[28] Immunogenicity was assessed in patients who received the allocated intervention (i.e., received at least 1 dose of the study vaccine), and had a blood sample taken within the planned time period.

Safety

The safety profiles of the 2 groups were compared. Local reactions at the injection site as well as systemic reactions were monitored for 28 days in the group that received the simultaneous administration, and for 14 days after each injection in the sequential group, using case cards completed by the participants. The population in which safety was assessed consisted of study participants who received a minimum of 1 dose of the study vaccine.

Statistical methods

The primary endpoint was the inferiority/non-inferiority of the immune response following simultaneous administration to that following sequential administration, as measured by the percentage of patients with ≥2-fold increases in IgG concentrations in serotype 23F 4–6 weeks after administration. The non-inferiority margin was set at 20% fewer

patients based on a previous study, given the probable benefits associated with simultaneous administration.[29] The lowest published response rate (≥2-fold rise) for serotype 23F was 55% in adults.[24,25] The primary endpoint was tested using a 90% CI for differences in response rates. If the lower 90% confidence limit was within the non-inferiority region, non-inferiority was established. With $\alpha = 0.05$, 154 patients (77 per group) were required to obtain 80% power ($\beta = 0.20$) for establishing non-inferiority.

Pneumococcal IgG concentrations were converted using natural log transformations and presented as a GMC. The percentage of patients with positive antibody responses (≥2-fold rise) was also calculated for all 6 serotypes of the pneumococcal antibody. Paired t-tests were used to assess the increase in serotype-specific IgG from pre-, to post-vaccination within study groups. Student's *t*-tests were used for between-group comparisons of pre- and post-vaccination IgG titers. We performed univariate and multivariate analyses using logistic regression to determine the relationship between age, sex, and pneumococcal antibody response.

Seroprotection rates (post-vaccination titer ≥1:40) 4–6 weeks and 6 months post-vaccination with QIV were calculated to assess the immunogenicity of influenza vaccination. Logistic regression was used to evaluate the independent effects that potential confounders may have on antibody induction. Seroprotection was used as the dependent variable in the constructed models, and the following potential confounders were used: age at vaccination (<70 and ≥70), sex, and pre-vaccination titer (<1:10 and ≥1:10, in H1N1, B/Texas and B/Phuket; ≤1:10 and >1:10, in H3N2) were considered explanatory variables. The ORs and 95% CIs were also calculated, and all tests performed were 2-sided. The proportions of subjects reporting systemic events or local reactions within 28 days were compared using Fisher exact test. For all tests, $P<0.05$ was considered significant. All analyses were performed using R version 3.2.2 (The R Project for Statistical Computing, Vienna, Austria).

Conflicts of interest

K.N. received a speaker's fee from MSD K.K. M.A. received a speaker's fee from MSD K.K. All the remaining authors report no potential conflicts. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp./MSD K.K.

Acknowledgments

We would like to thank Nobuyuki Tamura, Midori Tada, Mieko Takahashi, and Noriko Maruyama from the Department of Nursing at Kameda Medical Center for their cooperation. We would also like to thank the entire staff of the Departments of Pulmonary Medicine, General Internal Medicine, Infectious Diseases, and Laboratory Medicine at Kameda Medical Center for their involvement in this study. We acknowledge the statistical analysis support provided by Hiroki Matsui (Clinical Research Support Division, Kameda Institute for Health Science, Kameda College of Health Sciences, Japan).

Funding

This research was supported in part by a research grant from the Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp./MSD K.K.

References

1. Blasi F, Mantero M, Santus P, Tarsia P. Understanding the burden of pneumococcal disease in adults. Clin Microbiol Infect. 2012;18(Suppl 5):7–14. doi:10.1111/j.1469-0691.2012.03937.x.
2. Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza — United States, 1976–2007. MMWR Morb Mortal Wkly Rep. 2010;59:1057–62. PMID:20798667.
3. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013:CD000422.
4. Kohlhammer Y, Schnoor M, Schwartz M, Raspe H, Schafer T. Determinants of influenza and pneumococcal vaccination in elderly people: a systematic review. Public Health. 2007;121:742–51. doi:10.1016/j.puhe.2007.02.011. PMID:17572457
5. Public Health England. Pneumococcal Polysaccharide Vaccine (PPV) coverage report, England, April 2014 to March 2015. Health Protection Report. 2015. Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/448406/hpr2615_ppv.pdf. (Accessed Dec 21, 2017).
6. National Center for Health Statistics. 2016. Early release of selected estimates based on data From the January–June 2016 National Health Interview Survey. https://www.cdc.gov/nchs/data/nhis/earlyrelease/earlyrelease201611.pdf (accessed Dec 21, 2017).
7. Poethko-Muller C, Schmitz R. Vaccination coverage in German adults: results of the German Health Interview and Examination Survey for Adults (DEGS1). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2013;56:845–57. PMID:23703506
8. Organisation for Economic Co-operation and Development. 2017. Influenza vaccination rates (indicator) https://data.oecd.org/healthcare/influenza-vaccination-rates.htm. (accessed Dec 21, 2017).
9. National Center for Immunization and Respiratory Diseases. General recommendations on immunization — recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60:1–64.
10. Christenson B, Hedlund J, Lundbergh P, Ortqvist A. Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. Eur Respir J. 2004;23:363–8. doi:10.1183/09031936.04.00063504. PMID:15065822
11. Kawakami K, Ohkusa Y, Kuroki R, Tanaka T, Koyama K, Harada Y, Iwanaga K, Yamaryo T, Oishi K. Effectiveness of pneumococcal polysaccharide vaccine against pneumonia and cost analysis for the elderly who receive seasonal influenza vaccine in Japan. Vaccine. 2010;28:7063–9. doi:10.1016/j.vaccine.2010.08.010. PMID:20723631
12. Grilli G, Fuiano L, Biasio LR, Pregliasco F, Plebani A, Leibovitz M, Ugazio AG, Vacca F, Profeta ML. Simultaneous influenza and pneumococcal vaccination in elderly individuals. Eur J Epidemiol. 1997;13:287–91. doi:10.1023/A:1007398606807. PMID:9258527
13. Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. Hum Vaccin Immunother. 2012;8:81–88. doi:10.4161/hv.8.1.17623. PMID:22252006
14. Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. Lancet Infect Dis. 2011;11:760–8. doi:10.1016/S1473-3099(11)70090-1. PMID:21621466
15. Musher DM, Manof SB, Liss C, McFetridge RD, Marchese RD, Bushnell B, Alvarez F, Painter C, Blum MD, Silber JL. Safety and antibody response, including antibody persistence for 5 years, after primary vaccination or revaccination with pneumococcal polysaccharide vaccine in middle-aged and older adults. J Infect Dis. 2010;201:516–24. doi:10.1086/649839. PMID:20092407
16. Chiba N, Morozumi M, Sunaoshi K, Takahashi S, Takano M, Komori T, Sunakawa K, Ubukata K, IPD Surveillance Study Group. Serotype and antibiotic resistance of isolates from patients with invasive pneumococcal disease in Japan. Epidemiol Infect. 2010;138:61–68. doi:10.1017/S0950268809990239. PMID:19538821
17. Gilchrist SA, Nanni A, Levine O. Benefits and effectiveness of administering pneumococcal polysaccharide vaccine with seasonal

influenza vaccine: an approach for policymakers. Am J Public Health. 2012;102:596–605. doi:10.2105/AJPH.2011.300512. PMID:22397339
18. Hung IF, Leung AY, Chu DW, Leung D, Cheung T, Chan CK, Lam CL, Liu SH, Chu CM, Ho PL, et al. Prevention of acute myocardial infarction and stroke among elderly persons by dual pneumococcal and influenza vaccination: a prospective cohort study. Clin Infect Dis. 2010;51:1007–16. doi:10.1086/656587. PMID:20887208
19. Fletcher TJ, Tunnicliffe WS, Hammond K, Roberts K, Ayres JG. Simultaneous immunisation with influenza vaccine and pneumococcal polysaccharide vaccine in patients with chronic respiratory disease. BMJ. 1997;314:1663–5. doi:10.1136/bmj.314.7095.1663. PMID:9193290
20. DeStefano F, Goodman RA, Noble GR, McClary GD, Smith SJ, Broome CV. Simultaneous administration of influenza and pneumococcal vaccines. JAMA. 1982;247:2551–4. doi:10.1001/jama.1982.03320430055032.
21. Carlson AJ, Davidson WL, McLean AA, Vella PP, Weibel RE, Woodhour AF, Hilleman MR. Pneumococcal vaccine: dose, revaccination, and coadministration with influenza vaccine. Proc Soc Exp Biol Med. 1979;161:558–63. doi:10.3181/00379727-161-40596. PMID:39297
22. Richter SS, Heilmann KP, Dohrn CL, Riahi F, Diekema DJ, Doern GV. Pneumococcal serotypes before and after introduction of conjugate vaccines, United States, 1999–2011(1.). Emerg Infect Dis. 2013;19:1074–83. doi:10.3201/eid1907.121830. PMID:23763847
23. Socan M, Frelih T, Janet E, Petras T, Peternelj B. Reactions after pneumococcal vaccine alone or in combination with influenza vaccine. Vaccine. 2004;22:3087–91. doi:10.1016/j.vaccine.2004.02.003. PMID:15297059
24. Dransfield MT, Nahm MH, Han MK, Harnden S, Criner GJ, Martinez FJ, Scanlon PD, Woodruff PG, Washko GR, Connett JE, et al. Superior immune response to protein-conjugate versus free pneumococcal polysaccharide vaccine in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180:499–505. doi:10.1164/rccm.200903-0488OC. PMID:19556517
25. Mori S, Ueki Y, Akeda Y, Hirakata N, Oribe M, Shiohira Y, Hidaka T, Oishi K. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. Ann Rheum Dis. 2013;72:1362–6. doi:10.1136/annrheumdis-2012-202658. PMID:23345600
26. Oishi K, Yoshimine H, Watanabe H, Watanabe K, Tanimura S, Kawakami K, Iwagaki A, Nagai H, Goto H, Kudoh S, et al. Drug-resistant genes and serotypes of pneumococcal strains of community-acquired pneumonia among adults in Japan. Respirology. 2006;11:429–36. doi:10.1111/j.1440-1843.2006.00867.x. PMID:16771912
27. Marchese RD, Puchalski D, Miller P, Antonello J, Hammond O, Green T, Rubinstein LJ, Caulfield MJ, Sikkema D. Optimization and validation of a multiplex, electrochemiluminescence-based detection assay for the quantitation of immunoglobulin G serotype-specific antipneumococcal antibodies in human serum. Clin Vaccine Immunol. 2009;16:387–96. doi:10.1128/CVI.00415-08. PMID:19158284
28. Hirst GK. The quantitative determination of influenza virus and antibodies by means of red cell agglutination. J Exp Med. 1942;75:49–64. doi:10.1084/jem.75.1.49. PMID:19871167
29. Cordonnier C, Labopin M, Chesnel V, Ribaud P, De La Camara R, Martino R, Ullmann AJ, Parkkali T, Locasciulli A, Yakouben K. et al. Randomized study of early versus late immunization with pneumococcal conjugate vaccine after allogeneic stem cell transplantation. Clin Infect Dis. 2009;48:1392–401. doi:10.1086/598324. PMID:19368505

Vaccine 35 (2017) 3264–3271

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness of varicella vaccine against herpes zoster and post-herpetic neuralgia for elderly in Japan

Shu-ling Hoshi *, Masahide Kondo, Ichiro Okubo

Department of Health Care Policy and Health Economics, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennoudai, Tsukuba, Ibaraki 3058577, Japan

ARTICLE INFO

Article history:
Received 12 October 2016
Received in revised form 18 April 2017
Accepted 19 April 2017
Available online 4 May 2017

Keywords:
Cost-effectiveness
Economic evaluation
Herpes zoster
Varicella vaccine
Vaccination
Quality-adjusted life year

ABSTRACT

Background: The extended use of varicella vaccine in adults aged 50 and older against herpes zoster (HZ) was recently approved in Japan, which has raised the need to evaluate its value for money.
Methods: We conducted a cost-effectiveness analysis with Markov modelling to evaluate the efficiency of varicella vaccine immunisation programme for the elderly in Japan. Four strategies with different ages to receive a shot of vaccine were set, namely: (1) 65–84, (2) 70–84, (3) 75–84 and (4) 80–84 years old (y.o.). Incremental cost-effectiveness ratios (ICERs) compared with no programme from societal perspective were calculated. The health statuses following the target cohort are as follows: without any HZ-related disease, acute HZ followed by recovery, post-herpetic neuralgia (PHN) followed by recovery, post HZ/PHN, and general death. The transition probabilities, utility weights to estimate quality-adjusted life year (QALY) and disease treatment costs were either calculated or cited from literature. Costs of per course of vaccination were assumed at ¥10,000 (US$91). The model with one-year cycle runs until the surviving individual reached 100 y.o.
Results: ICERs ranged from ¥2,812,000/US$25,680 to ¥3,644,000/US$33,279 per QALY gained, with 65–84 y.o. strategy having the lowest ICER and 80–84 y.o. strategy the highest. None of the alternatives was strongly dominated by the other, while 80–84 y.o. and 70–84 y.o. strategy were extendedly dominated by 65–84 y.o. strategy. Probabilistic sensitivity analyses showed that the probabilities that ICER is under ¥5,000,000/US$45,662 per QALY gained was at 100% for 65–84 y.o., 70–84 y.o., 75–84 y.o. strategy, respectively, and at 98.4% for 80–84 y.o. strategy.
Conclusion: We found that vaccinating individuals aged 65–84, 70–84, 75–84, and 80–84 with varicella vaccine to prevent HZ-associated disease in Japan can be cost-effective from societal perspective, with 65–84 y.o. strategy as the optimal alternative. Results are supported by one-way sensitivity analyses and probabilistic sensitivity analyses.

1. Introduction

Herpes zoster (HZ) results from reactivation of the varicella-zoster virus (VZV) in sensory ganglia after a long latency period following primary infection from varicella [1,2]. Epidemiological data of reports from high-income settings noted that age-adjusted HZ incidence in the total population ranging from 3.4 to 5.0 per 1000 person-years, while for those aged over 65 are from 8.0 to 11.0 per 1000 person-years [3]. The most common serious complication of HZ is post-herpetic neuralgia (PHN), i.e., persistent pain beyond the acute phase of vesicular rash [3]. Antiviral therapy can shorten the length and severity of acute HZ, but therapy must be started as soon as the rash appears [3]. In Japan, there are two large-scale epidemiological studies, which reported age-specific HZ incidence rates, namely: Miyazaki study and Shozu Herpes Zoster (SHEZ) study [4,5]. The former reported an HZ incidence rate of 7.48 per 1000 person-year for adult aged 50 and over, while the latter at 5.3–8.2. Although healthcare in Japan is easily accessible, percentage of HZ patients visiting within the ideal period for antiviral chemotherapy, day 0–2, is still low at 37% [6].

A single dose, high-potency, live-attenuated Oka VZV vaccine against HZ (Zostavax®) has been licensed for use among immunocompetent adults ≥50 years old [3], and has been used in over 60 countries for individuals ≥50 years old. The vaccine is formulated with a minimal potency of 194,000 plaque-forming units (PFU) and administered as a single 0.65 ml subcutaneous injection [7]. Cost-effectiveness studies from high-income countries found HZ vaccination to be less than US$50,000 per quality-adjusted life year (QALY) in 12 out of 15 studies, when the vaccine is given to those

* Corresponding author.
E-mail address: hoshi@hcs.tsukuba.ac.jp (S.-l. Hoshi).

http://dx.doi.org/10.1016/j.vaccine.2017.04.046
0264-410X/

60–79 years old, and in 5 out of 5 studies when given to ≥65 years old [8].

Zostavax® is not available in Japan, while a Japan-approved Oka varicella vaccine with similar annual mean titer at 42,000–67,000 PFU per dose exists [9] (Table S1). In March 2016, the Ministry of Health, Labour and Welfare (MHLW) approved the extended use of varicella vaccine in adults aged 50 and older against HZ. On June 22, 2016, the Health Science Council in charge of Immunisation and Vaccine added varicella vaccine against HZ as one of the topics for discussion in one of their recent conferences [10], which has raised the need to evaluate its value for money. This study aimed to appraise the value for money of giving varicella vaccine to the Japanese elderly, likewise, also explored the appropriate age for vaccine uptake due to varying incidence of HZ, PHN, and vaccine efficacy.

2. Method

We conducted a cost-effectiveness analysis with Markov modelling to evaluate the efficiency of varicella vaccine immunisation programmes among Japanese elderly from a societal perspective. Incremental cost-effectiveness ratios (ICERs) were calculated to determine resource use efficiency. The software used in this study is TreeAgePro 2016 [11].

In defining immunisation programmes and constructing the model, we conducted a literature survey to find out the best available evidence (Table S2).

2.1. Programme and model

The target population of the immunisation programmes to be evaluated were those aged 65–84 in 2016 [12]. We set four different strategies with different ages to receive a vaccine shot, namely: (1) 65–84 years old (y.o.), (2) 70–84 y.o., (3) 75–84 y.o., and (4) 80–84 y.o. We set the upper age at 84 and the lower age at 65 due to the uncertainty of long-term vaccine efficacy of patients under 65 as well as beyond 85 years old. Since the coverage rate of seasonal influenza vaccine in 2014 was 50.6% [13], we expect that varicella vaccine coverage for HZ among elderly to be lower, hence, we assumed the vaccine uptake rates to be at 40% for all four strategies.

A static Markov model of courses followed by the cohort under consideration was constructed based on epidemiological data, vaccine effectiveness and models from previous studies [14–34]. Five mutually-exclusive health states were modelled: health (without any HZ-related diseases), acute HZ followed by recovery, PHN followed by recovery, post HZ/PHN, and general death (Fig. 1). Our model did not include VZV-related complications (ophthalmic, neurological, or ocular) due to insufficient data in Japan. A Markov cycle for each stage was set at one year, the model continued until the surviving individual/s reached 100 y.o. Adverse effects associated with vaccination were not considered in our model based on systematic reviews [35]. Death directly from HZ/PHN was omitted because the occurrence is rare in Japan.

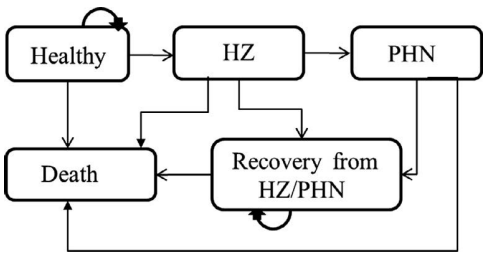


Fig. 1. Markov model.

2.2. Outcomes estimation

Outcomes in terms of QALY were estimated by assigning transition probabilities and utility weights from literature with incidence rates taken from the relevant Japanese studies; Miyazaki study and SHEZ [4,5]. Miyazaki study, a retrospective study conducted from 1997 to 2006 in Miyazaki Prefecture, reported the HZ incidence at 6.36, 8.08, 7.8, and 6.39 per 1000 person-year for persons aged 60–69, 70–79, 80–89, and 90 and over, respectively. While, SHEZ, a prospective cohort study, which recruited participants aged ≥50 from 19,058 residents between 12, 2008 and 11, 2009, reported higher HZ incidence than Miyazaki study, at 6.5 11.3, 10.8 per 1000 persons for men, 12.4, 14.1 13.6 per 1000 persons for women. In our model, HZ incidence was conservatively adopted from Miyazaki study, while proportion of PHN cases among HZ cases, namely 19.4%, 12.5%, 34.8% for men and 10.8%, 24.7%, 32.0% for women for person age 60–69, 70–79 and ≥80, respectively, were from SHEZ, because data related to PHN is not available in the Miyazaki study. Rates of general death are from vital statistics [36].

2.3. Vaccine effectiveness

The approval of extended use of varicella vaccine in adults ≥50 years old against HZ in Japan was through an application based on public knowledge. This type of application is submitted on the pretense that overseas usage of drug and medical literature published both in Japan and other countries are sufficient to prove that the drug's safety and efficiency is public knowledge within the medical and pharmacological community, and does not require additional clinical studies be conducted, either in whole or in part. Therefore, we used the vaccine effectiveness (VE) of varicella vaccine in reducing HP/PHN incidence rates from overseas' studies on Zostavax®.

Even though the Shingles Prevention Study, Short-Term Persistence Sub-study and Long-Term Persistence Sub-study (LTPS), have continuously reported VE by year after vaccination [37–39], these studies were not able to demonstrate how VE changed with chronological age (age at start of each year since vaccination) and duration after vaccination. We believe that the duration of protection and chronological age are important factors in evaluating HZ vaccination strategy cost-effectiveness, hence, we adopted the VE of model 3 from Li et al.'s study [40]. We further conservatively assumed that the vaccine will decrease HZ incidence and PHN proportion per HZ case, with no direct effects on PHN decrease. Age-specific VE data are shown in Table 1 and Fig. S1.

2.4. Utility weights

Since no study has reported the utility weights or health-related quality-of-life of HZ/PHN in Japan, we estimated these data based on two studies. Drolet et al. reported mean ED-5D score of HZ in different follow-up points after onset of rash as: 0.52 (0 day), 0.68 (30 days ~ 180 days) for patients 61–70 years old; 0.63 (0 days), 0.61 (30 days), 0.63 (90 days), 0.65 (180 days) for patients over 70 years old [41]. They also reported that "the score remained stable after 90 days (with a change of 0.2 points observed per week)". We therefore estimated the utility weights at 0.73 for 210 days and at 0.81 for 270 days and after. These figures were then weighted by the proportion of local patients with pain by month reported by Imafuku et al., which were 73.3%, 12.4%, 5.1%, 2.5%, 1.3%, 0.9% for month 0 to month 6, respectively [42]. These calculations were used to estimate average HZ QALY at 0.9548 for individuals age 60–69 and 0.9544 for those ≥70 years old, while, PHN utility weights, 0.79 (60–69 years old) and 0.76 (≥70 years old), were the averages of month 0 to month 12.

Table 1
Variables.

Base case					One-way sensitivity analyses[a]				PAS[b]	Reference
					Lower		Upper			
Target Population of alternative strategies (×1000)										[12]
Age 65–69 strategy	28,090									
Age 70–74 strategy	18,990									
Age 75–79 strategy	11,099									
Age 80–84 strategy	4854									
Male and female population in different age strata (×1000)										
Age	Male	Female								
65–59	4391	4715								
70–74	3673	4218								
75–79	2758	3487								
80–84	1938	2916								
Age-specific incidence rates of HZ (per 1000 persons)									β	[4]
Age	Male	Female			Male	Female	Male	Female		
60–69	6.36	7.78			5.09	6.22	6.50	12.40	Male:(4217; 62, 456)[c] Female (5, 854; 72, 473)	
70–79	8.08	8.25			6.46	6.60	11.30	14.10	Male:(3, 749; 44, 887) Female (5, 378; 62, 426)	
80+	7.80	7.13			6.24	5.70	10.80	13.60	Male:(1, 244; 15, 200) Female (2, 269; 32, 010)	
Percentage of PHN cases among HZ cases									β	[5]
Age	Male	Female			Male	Female	Male	Female		
60–69	19.4%	10.8%			15.5%	8.6%	23.3%	8.6%	Male: (7; 29); Female (8; 66)	
70–79	12.5%	24.7%			10.0%	19.8%	15.0%	19.8%	Male: (6; 42); Female (20; 61)	
80+	34.8%	32.0%			27.8%	25.6%	41.8%	25.6%	Male: (8; 15);Female (16; 34)	
General death (per 100,000 persons)										[36]
Age	Male	Female								
65	1,345.2	554.0								
70	2,104.0	890.2								
75	3,591.8	1,655.3								
80	6,481.9	3,272.5								
85	11,388.1	6,546.8								
90	18,861.4	12,874.9								
95	30,679.0	22,524.6								
100	42,375.0	39,256.9								
Vaccine effectiveness (%)[d]										[37–40]
	Age 65	Age 70	Age 75	Age 80					Uniform	
Year 1	66.0	58.9	52.3	45.7		(95 CI 60, 70)[e]			(95 CI 60, 70)[e]	
Year 2	64.2	57.2	50.8	44.4		[e]			[e]	
Year 3	61.9	55.2	49.0	42.8		[e]			[e]	
Year 4	59.6	53.1	47.2	41.3		[e]			[e]	
Year 5	57.3	51.1	45.4	39.7		[e]			[e]	
Year 6	55.0	49.0	43.6	38.1		[e]			[e]	
Year 7	51.9	46.3	41.1	35.9		[e]			[e]	
Year 8	48.8	43.5	38.6	33.8		[e]			[e]	
Year 9	45.7	40.7	36.2	31.6		[e]			[e]	
Year 10	42.5	37.9	33.7	29.5		[e]			[e]	
Year 11	39.4	35.1	31.2	27.3		[e]			[e]	
Utility weights										[41–42]
Age	HZ	PHN			HZ	PHN	HZ	PHN		
65–69	0.9548	0.7900			0.9518	0.7610	0.9698	0.8800		
70+	0.9544	0.7600			0.9514	0.7320	0.9693	0.8461		
Cost per vaccine shot					¥10,000					Assumed
Treatment costs[f]									γ	
HZ			¥15,000	¥7500	¥22,500				(1, 1/15,000)	[43]
PHN			¥200,000	¥100,000	¥300,00				(1, 1/200,000)	[43]

[a] Upper limits for incidence rates were from SHEZ, while lower limits were assumed to be 80% of the base-case data, with costs/utility weights assumed to be +50%/+20% for upper limits and −50%/−20% for lower limits.
[b] For PSA, β distribution is used for HZ incidence rates and PHN proportion among HZ; γ distributions were assumed for costs. For utility weights/VE, though β/lognormal distribution is more favourable, however, since there is no information about the probability density function, we used a uniform distribution instead.
[c] First and second values in parentheses correspond to α and β in β distribution, or α and λ in γ distribution.
[d] Also shown in Fig. S1.
[e] The 95% CI was first given to vaccine at age 65 (year 1) based on study of Li et al. [47], which was considered as the reference. CI for remaining age groups or remaining years after vaccination were determined by multiplying relative likelihood ratios among these ages and the reference age by the aforementioned reference.
[f] Treatment costs including consultation fee, prescription fee, Pharmaceutical management fee, dispensing fee (total of these 4 items were was estimated around ¥1720 (US$15.7) per visit), and drug fee (about ¥3200 per week). We assumed that a PHN patient sees a doctor once every two weeks.

2.5. Costing

To estimate the opportunity cost of resource use from societal perspective, we aggregated the direct medical costs borne by the government, vaccinees, patients and third party payers. Non-direct medical costs related to the immunisation programme, such as new staff, new cold chain were not included, because the vaccination programme was built within the public health services

routine; amount of direct payments to healthcare providers by these entities were estimated as costs, whereby cost items were identified along the decision tree and Markov model. We used the literature along with some assumptions to estimate the necessary data. Productivity cost and direct non-medical cost related to morbidity and immunisation were not incorporated, following the recommendation of the MHLW Vaccine Committee.

One vaccine shot is assumed to be ¥10,000 (US$91; US $1 = ¥109.5, average of 2016 January to August), which is the sum of vaccine price, doctor fee and technical fee per shot. Average treatment cost of per HZ case (¥15,000/US$14) and per PHN case (¥200,000/US$1826) were from Ikeda et al. [43]. We incorporated the costs reported before 2016 with no adjustment because the variation of consumer price index of services related to medical care was less than 0.1% during these 10 years. On the other hand, sensitivity analyses were conducted on cost-related data.

2.6. Discounting

Outcomes and costs were discounted at a rate of 3% [44].

2.7. Sensitivity analyses

To appraise the ICERs' stability with the assumptions made in our economic model, and to explore the impact of each variable relative to each other, we performed one-way sensitivity analyses, four sets of 1000 Monte Carlo simulations, i.e., probabilistic sensitivity analyses (PSA), and a threshold analysis on vaccination costs.

Table 2
Results of base-case analyses.

Strategies	Vaccination Cost (¥/person)	Treatment Costs ¥/person)	Total Costs (¥/person)	Effectiveness (QALY/person)	ICER (¥/QALY)[a]	
					Compared to no programme	Compared to next lowest cost alternative[b]
No programme	0	5581	5581	12.96049	–	–
Age 80–84	691	5477	6168	12.96065	3,643,599	3,643,599
Age 75–84	1580	5324	6904	12.96090	3,227,530	2,958,506
Age 70–84	2704	5109	7813	12.96127	2,883,491	2,495,974
Age 65–84	4000	4879	8879	12.96166	2,811,688	2,672,401

[a] ICERs, incremental cost-effectiveness ratios; QALY, quality-adjusted life years.
[b] When compared to next lowest cost alternative, we have observed that ICER of moving from 80–84 y.o. strategy to 75–84 y.o. strategy (¥2,959,000/US$27,023 per QALY) was higher than moving from 75–84 y.o. to 70–84 y.o. strategy (¥2,496,000/US$22,795 per QALY), which means that moving from 75–84 y.o. to 70–84 y.o. strategy offers greater health improvements at lower ICER. Thus, 75–84 y.o. strategy was ruled out as an alternative that will never be chosen because it was extendedly dominated by 80–84 y.o. strategy. After the second and third rounds of comparison using the next lowest cost procedure, 80–84 y.o. and 70–84 y.o. strategies were observed to be extendedly dominated by 65–84 y.o. strategy, which resulted to 65–84 y.o. strategy being the most cost-effective strategy.

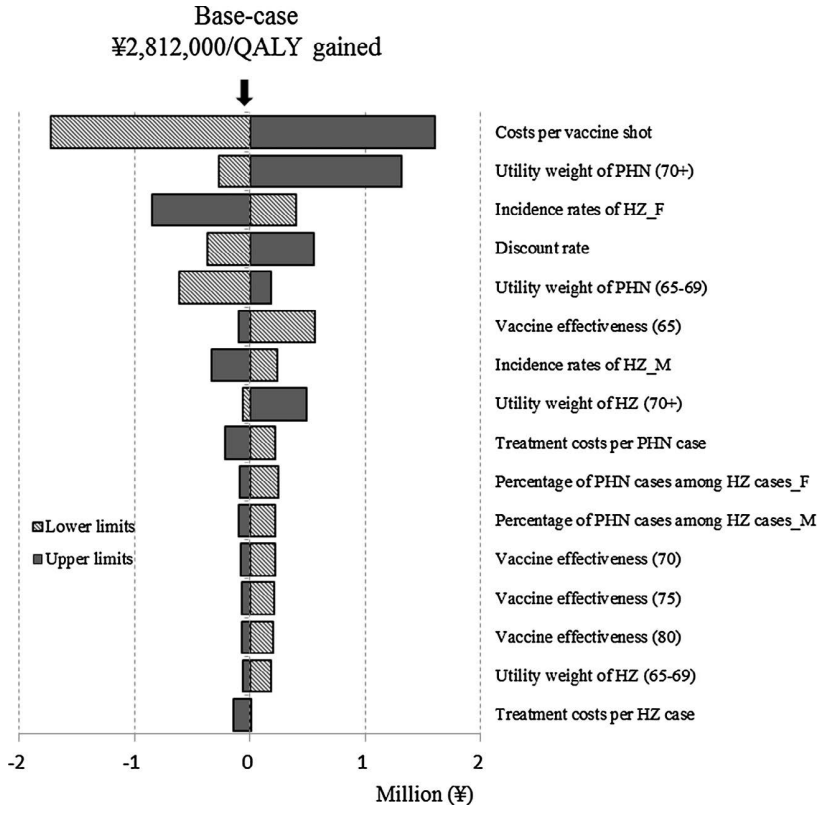


Fig. 2. Results of one-way sensitivity analyses (only 65–84 strategy vs. no immunisation programme was shown because others were in same pattern). One-way sensitivity analyses were performed by varying one input at a time while holding others constant at their base-case estimates.

The probability density functions and the ranges for sensitivity analyses are shown in Table 1.

3. Model validation

We validated our model by summing the annual cases of HA and PHN in the vaccinated and non-vaccinated groups, and then calculated the vaccine efficacy for time periods corresponding to the vaccine effectiveness used.

4. Cost-effectiveness threshold

Although MHLW has not yet set a willingness-to-pay threshold for judging the cost-effectiveness of public health programmes in the country [45], local studies have initially begun citing the willingness-to-pay threshold (at ¥5,000,000 (US$45,662) per QALY gained) from Shiroiwa et al. [46] to facilitate the analysis. There are also other existing thresholds being used by other studies, namely, the "favourable" level set by the Committee to Study Priority for Vaccine Development in the United States at US$ 10,000–100,000 per QALY [47], and WHO's suggested "cost-effective" criterion at 1 to 3 times of GDP [48].

5. Results

5.1. Results of base-case analyses

Table 2 reports the expected costs per person and expected QALYs per person associated with no immunisation programme and four alternatives. We have observed that compared to the lowest cost alternative, i.e., no immunisation programme, all four strategies reduced disease treatment costs, however, these reduced costs did not offset vaccination costs, which means it gained more QALYs but cost more. Incremental costs per person ranged from ¥587/US$5 (80–84 y.o. strategy) to ¥3298/US$30 (65–84 y.o. strategy), while incremental effect ranged from 0.000161 QALYs (80–84 y.o. strategy) to 0.001173 QALYs (65–84 y.o. strategy) per person. Both incremental costs and incremental effectiveness decreased with increasing age to uptake of vaccine. ICERs of all four strategies ranged from ¥2,812,000/US$25,680 to ¥3,644,000/US$33,279 per QALY gained, with 65–84 y.o. strategy having the lowest ICER, followed by 70–84 y.o., 75–84 y.o. and 80–84 y.o. strategies. None of the alternatives was strongly dominated by the other. If 65–84 y.o. strategy was to be adopted, at the 40% vaccine uptake rate, the total vaccine cost will be around ¥112.4 billion, while it will save ¥19.7 billion treatment costs and 32,957 QALYs, compared to current no immunisation programme.

5.2. Results of sensitivity analyses

One-way sensitivity analyses (Fig. 2) showed that, 65–84 y.o. strategy was always identified as the most cost-effective strategy among the four strategies. 80–84, 75–85 and 70–85 y.o. strategies were always extendedly dominated by other strategies, except for two variables, which are the HZ utility weight upper limit (=1) and VE lower limit on reducing HZ. The variables which changed the ICER more than ¥1,000,000/US$9132 per QALY gained, but did not make the ICER larger than ¥5,000,000/US$45,662 per QALY gained were: (1) cost per shot, and (2) PHN utility weight upper limit for ≥70 years old patient. Threshold analysis on cost per shot showed that the cost-saving cut-off point for immunisation programmes is at ¥1900/US$17. Table 3 and Fig. 3 shows the results of PSA of four alternative strategies compared to no programme.

Table 3
Results of probabilistic sensitivity analyses: incremental cost, incremental effectiveness, and ICER.

	Age 65–84 vs. no programme			Age 70–84 vs. no programme			Age 75–84 vs. no programme			Age 80–84 vs. no programme		
	Incr cost[a] (¥/person)	Incr eff[b] (QALY/person)	ICER (¥/QALY)	Incr cost (¥/person)	Incr eff (QALY/person)	ICER (¥/QALY)	Incr cost (¥/person)	Incr eff (QALY/person)	ICER (¥/QALY)	Incr cost (¥/person)	Incr eff (QALY/person)	ICER (¥/QALY)
Mean	1465	0.002017	769,229	959	0.00129	797,014	582	0.000682	929,623	238	0.00024	1,141,461
SD	2146	0.000440	1,162,922	1508	0.000303	1,300,682	874	0.000173	1,458,147	420	0.000079	2,149,605
Min	−9318	0.000918	−6,596,896	−6960	0.000550	−7,919,961	−4153	0.000277	−9,054,196	−2915	0.000067	−15,352,438
2.5%	−4171	0.001198	−2,075,02	−3024	0.000740	−2,577,404	−1826	0.000364	−2,962,891	−957	0.000104	−4,163,032
Median	2048	0.001995	1,003,758	1400	0.001279	1,062,361	848	0.000677	1,202,124	375	0.000242	1,445,776
97.5%	3746	0.002876	2,398,460	2533	0.001894	2,597,915	1479	0.001008	3,050,488	649	0.000396	4,510,405
Max	3936	0.003222	3,554,482	2660	0.002123	4,013,632	1555	0.001196	4,581,682	679	0.000474	8,737,822

[a] Incr cost: incremental cost.
[b] Incr eff: incremental effectiveness.

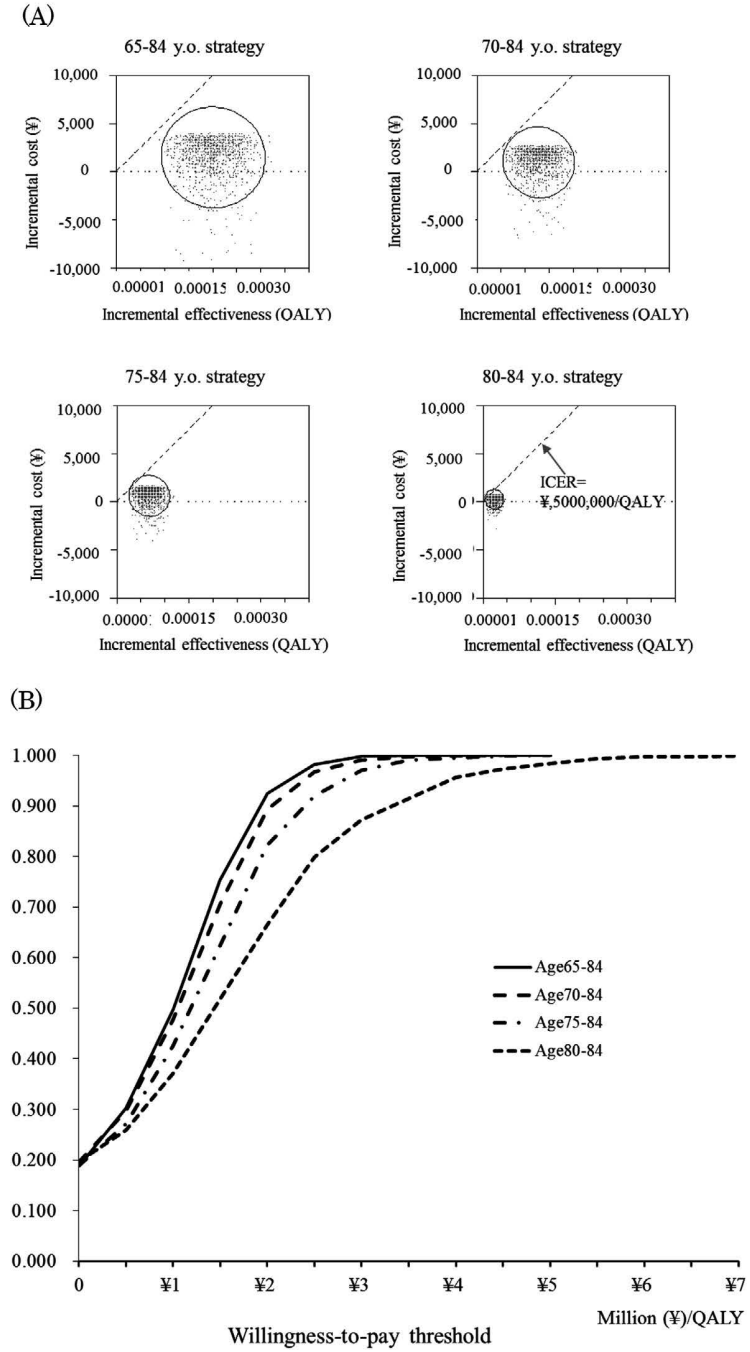


Fig. 3. Results of probabilistic sensitivity analyses (vs. no immunisation programme). PSA simultaneously varied all the inputs according to pre-specified distributions in 1000 iterations. (A) Scatterplots of incremental cost and incremental effectiveness per person on cost-effectiveness plane. Each dot represents the incremental costs and incremental effects per person obtained from one simulation following the random draw of model parameters from their respective distributions. (B) Acceptability curves. The probabilities that ICER is under ¥5,000,000 (US$45,662) per QALY gained was at 100% for 65–84 y.o. strategy, 70–84 y.o. strategy, 75–84 y.o. strategy, respectively, and at 98.4% for aged 80–84 y.o. strategy. The probability that the simulation resulted in cost less and gained more QALY was around 20% for all the four strategies.

6. Discussion

This is the first study which evaluated the value for money of giving varicella vaccine to the elderly in preventing HZ-associated diseases, and has also explored the appropriate age to uptake the vaccine in Japan. We set four strategies with different ages to receive the vaccine, which were 65–84, 70–84, 75–84 and 80–84 y.o. Results showed that all strategies were likely to provide public health benefits in Japan and ICERs were estimated to be lower than the cost-effective threshold, at ¥5,000,000/US$4 5,662 per QALY gained. We have also determined that the 65–84 strategy is the most cost-effective among the four. Sensitivity analyses confirmed the robustness of our findings, wherein vaccinated strategies always had an ICER less than ¥5,000,000/US$45,662 per QALY within the plausible range of model inputs. PSA showed that the probabilities that ICER is under ¥5,000,000/US$45,662 per QALY gained were at 100% for 65–84 y.o., 70–84 y.o., 75–84 y.o. strategy, respectively, and at 98.4% for 80–84 y.o. strategy.

We were able to identify 21 previously-published studies from developed countries: five from United States, three from United Kingdom, two from Canada, Belgium, Netherlands, France, Germany, respectively, and one from Switzerland, Spain, and Italy, respectively [14–34]. Although there were 5 studies which included the VZV-related complications in the models, the remaining 16 out of the 21 reviewed studies used a simplified model, in which we have opted to follow. When comparing our age-specific HZ incidence rates to those of the 21 studies, we found that the variables in our model are below the average (Fig. S2). While, percentages of PHN cases among HZ cases compared with those of the previous studies, are almost at the same level of the average of the previous studies, except for those aged greater than 80 (Fig. S3). All the previous studies except one study from Germany [22] assumed that VEs were not age-specific, lifelong or would remain stable for 10 years before decreasing annually by certain percentages. These assumptions seem unrealistic after the LTPS was published. Even with lower values of incidence of HN, percentage of PHN, and lower VEs, our study revealed that immunisation elderly aged 65 and over is cost-effective, which is consistent with those of previous studies. This may be due to the low vaccination cost in Japan. The vaccination cost for one shot (including vaccine price, doctor fee and technical fee) in our study is conservatively assumed at ¥10,000 (US$91), which is the highest cost from the internet survey. Previous studies set vaccine cost per shot at US$123-US$250, which is 140–270% of the cost in our study. The low vaccination cost may be due to the low price of live-attenuated Oka varicella vaccine, which was developed in Japan in 1947 and has been in supply from 1976.

We believe that the study's strengths are primarily due to the (1) usage of a Japanese data source with HZ incidence rates coming from a large-scale epidemiological study, the Miyazaki study, and (2) incorporation of VE waning assumption with age and time since vaccination. However, our study faced certain limitations, such as: (1) Markov model used in the study is simple compared to previous studies. For example, we did not model the reduction in HZ pain in patients who have HZ despite vaccination, nor did we incorporate ophthalmic zoster cases. Exclusion of these aspects of HZ infection could underestimate health benefits, while accounting these as part of prevention could lead to cost-savings for HZ vaccination, (2) due to the absence of Japanese disease-specific utilities, data were estimated by using a combination of overseas' data and Japanese data, with moderate impact on results using the combined data, (3) average duration of PHN which can persist for 12 months, may represent an overestimation for younger patients and underestimation for older patients, (4) we defined PHN as a persistent pain for 90 days after zoster onset, however, this is still subject to validation since there are different definitions of PHN, and can pose a difficulty when comparing our study with previous ones, and (5) since Japan started to give childhood varicella vaccination programme from October 2014, it has been hypothesised that varicella vaccine introduction might increase HZ incidence in the population because of VZV reduction circulating in the community, which can result to a decrease in the opportunity for boosting immunity against VZV [2]. In recent studies, they have reported that there is no conclusive evidence in whether varicella vaccination programmes have been associated with an HZ incidence increase [49]. Thus, we cannot incorporate the influence of childhood varicella vaccination programme into our model. Nevertheless, we believe that the incorporation of robust, locally-published epidemiologic data and costs, may have reduced this uncertainty to a certain level. We acknowledge that the study is limited to the Japanese setting. Nevertheless, we believe that the results of this study are fundamental components for policy-relevant strategies.

7. Conclusion

From our analyses, we found out that vaccinating individuals aged 65–84, 70–84, 75–84, 80–84 with local varicella vaccine to prevent HZ-associated disease in Japan can be cost-effective from societal perspective, with 65–84 strategy as the optimal alternative. The results are supported by one-way sensitivity analyses and by PSA. Aside from the cost per vaccination, we have observed that PHN utility weight for $\geq$70 years old has considerably influenced the result. A further budget impact analysis is needed for a well-informed policymaking.

Author's contributions

Shu-Ling Hoshi participated in the concept and design of the study, performed the literature searches, acquired the data, participated in the analysis and interpretation of the data, and wrote the manuscript. Masahide Kondo and Ichiro Okubo participated in the concept and design of the study, and in the interpretation of the data.

Conflict of interest

None.

Sponsors role

None.

Acknowledgements

This study was supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan. The authors declare no conflict of interest associated with this manuscript. We would also like to acknowledge the help of Dr. Xerxes Seposo regarding the language check of this manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.04.046.

References

[1] Whitley RJ. Varicella zoster virus. In: Mandell GC, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia, PA: Churchill Livingstone; 2015. p. 1731–7.
[2] Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Med 1965;58(1):9–20.
[3] Varicella and Herpes Zoster vaccines. WHO position paper position paper, June 2014. Wkly Epidemiol Rec 2014 20;89(25):265–87.
[4] Toyama N, Shiraki K. Society of the Miyazaki Prefecture Dermatologists. Epidemiology of herpes zoster and its relationship to varicella in Japan: A 10-year survey of 48,388 herpes zoster cases in Miyazaki prefecture. J Med Virol 2009;81(12):2053–8.
[5] Takao Y, Miyazaki Y, Okeda M, Onishi F, Yano S, Gomi Y, et al. Incidences of herpes zoster and postherpetic neuralgia in Japanese adults aged 50 years and older from a community-based prospective cohort study: the SHEZ study. J Epidemiol 2015;25(10):617–25.
[6] Miyachi M, Imafuku S. Relationship between prior knowledge about herpes zoster and the period from onset of the eruption to consultation in patients with herpes zoster. J Dermatol 2016;43(10):1184–7.
[7] Merck & Co., Inc. ZOSTAVAX® (Zoster Vaccine Live) [HIGHLIGHTS OF PRESCRIBING INFORMATION]. Available from: <http://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi2.pdf>.
[8] Kawai K, Preaud E, Baron-Papillon F, Largeron N, Acosta CJ. Cost-effectiveness of vaccination against herpes zoster and postherpetic neuralgia: a critical review. Vaccine 2014;32(15):1645–53.

[9] Kamiya H, Asano Y, Ozaki T, Baba K, Kumagai T, Nagai T, et al. Varicella vaccine potency and stability during transport and delivery. Kansenshogaku Zasshi 2011;85:161–5 [Japanese].
[10] Record of proceedings of the committee of Immunisation and Vaccine, Health Science Council, Ministry of Health, Welfare and Labour of Japan; 2016. June 22. Available from: <http://www.mhlw.go.jp/stf/shingi2/0000130809.html> [Japanese].
[11] TreeAge Pro 2015, R1.0. TreeAge Software, Williamstown, MA; software available at <https://www.treeage.com>.
[12] Ministry of Internal Affairs and Communications. Population estimates of Japan. Statistics Bureau, Tokyo; 2002.
[13] Ministry of Health, Labour and Welfare. [Teiki no yobou seshu jishisyshu (Uptake rates of routine vaccinations), 1995–2015]. Ministry of Health, Labour and Welfare, Tokyo. Available from: <http://www.mhlw.go.jp/topics/bcg/other/5.html> [Japanese].
[14] Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine 2001;19(23–24):3076–90.
[15] Pellissier JM, Brisson M, Levin MJ. Evaluation of the cost-effectiveness in the United States of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. Vaccine 2007;25(49):8326–37.
[16] Moore L, Remy V, Martin M, Beillat M, McGuire A. A health economic model for evaluating a vaccine for the prevention of herpes zoster and post-herpetic neuralgia in the UK. Cost Eff Resour Alloc 2010;8:7.
[17] van Lier A, van Hoek AJ, Opstelten W, Boot HJ, de Melker HE. Assessing the potential effects and cost-effectiveness of programmatic herpes zoster vaccination of elderly in the Netherlands. BMC Health Serv Res 2010;10:237.
[18] Annemans L, Bresse X, Gobbo C, Papageorgiou M. Health economic evaluation of a vaccine for the prevention of herpes zoster (shingles) and post-herpetic neuralgia in adults in Belgium. J Med Econ 2010;13(3):537–51.
[19] Szucs TD, Kressig RW, Papageorgiou M, Kempf W, Michel JP, Fendl A, et al. Economic evaluation of a vaccine for the prevention of herpes zoster and post-herpetic neuralgia in older adults in Switzerland. Hum Vaccin 2011;7(7):749–56.
[20] Bilcke J, Marais C, Ogunjimi B, Willem L, Hens N, Beutels P. Cost-effectiveness of vaccination against herpes zoster in adults aged over 60 years in Belgium. Vaccine 2012 Jan 11;30(3):675–84.
[21] Ultsch B, Weidemann F, Reinhold T, Siedler A, Krause G, Wichmann O. Health economic evaluation of vaccination strategies for the prevention of herpes zoster and postherpetic neuralgia in Germany. BMC Health Serv Res 2013;13:359.
[22] Préaud E, Uhart M, Böhm K, Aidelsburger P, Anger D, Bianic F, et al. Cost-effectiveness analysis of a vaccination program for the prevention of herpes zoster and post-herpetic neuralgia in adults aged 50 and over in Germany. Hum Vaccin Immunother 2015;11(4):884–96.
[23] Le P, Rothberg MB. Cost-effectiveness of herpes zoster vaccine for persons aged 50 years. Ann Intern Med 2015;163(7):489–97.
[24] Coretti S, Codella P, Romano F, Ruggeri M, Cicchetti A. Cost-effectiveness analysis of herpes zoster vaccination in Italian elderly persons. Int J Technol Assess Health Care 2016;32(4):233–40.
[25] Lopez-Belmonte JL, Cisterna R, Gil de Miguel A, Guilmet C, Bianic F, Uhart M. The use of Zostavax in Spain: the economic case for vaccination of individuals aged 50 years and older. J Med Econ 2016;19(6):576–86.
[26] Belchior E, Lévy-Bruhl D, Le Strat Y, Herida M. Cost-effectiveness of a herpes zoster vaccination program among the French elderly people. Hum Vaccin Immunother 2016;12(9):2378–82.
[27] Le P, Rothberg MB. Determining the optimal vaccination schedule for herpes zoster: a cost-effectiveness analysis. J Gen Intern Med. 2017;32(2):159–67.
[28] Brisson M, Pellissier JM, Camden S, Quach C, De Wals P. The potential cost-effectiveness of vaccination against herpes zoster and post-herpetic neuralgia. Hum Vaccin 2008;4(3):238–45.
[29] Hornberger J, Robertus K. Cost-effectiveness of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. Ann Intern Med 2006;145(5):317–25.
[30] Rothberg MB, Virapongse A, Smith KJ. Cost-effectiveness of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. Clin Infect Dis 2007;44(10):1280–8.
[31] Bresse X, Annemans L, Préaud E, Bloch K, Duru G, Gauthier A. Vaccination against herpes zoster and postherpetic neuralgia in France: a cost-effectiveness analysis. Expert Rev Pharmacoecon Outcomes Res 2013;13(3):393–406.
[32] Najafzadeh M, Marra CA, Galanis E, Patrick DM. Cost effectiveness of herpes zoster vaccine in Canada. Pharmacoeconomics 2009;27(12):991–1004.
[33] van Hoek AJ, Gay N, Melegaro A, Opstelten W, Edmunds WJ. Estimating the cost-effectiveness of vaccination against herpes zoster in England and Wales. Vaccine 2009;27(9):1454–67.
[34] de Boer PT, Pouwels KB, Cox JM, Hak E, Wilschut JC, Postma MJ. Cost-effectiveness of vaccination of the elderly against herpes zoster in The Netherlands. Vaccine 2013;31(9):1276–83.
[35] Gagliardi AM, Andriolo BN, Torloni MR, Soares BG. Vaccines for preventing herpes zoster in older adults. Cochrane Database Syst Rev 2016;3(3):CD008858. http://dx.doi.org/10.1002/14651858.CD008858.pub3.
[36] Ministry of Health, Labour and Welfare. Vital statistics of Japan 2015. Health and Welfare Statistics Association, Tokyo. Available from: <http://www.e-stat.go.jp/SG1/estat/List.do?lid=000001158448> [Japanese].
[37] Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. Shingles Prevention Study group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352(22):2271–84.
[38] Schmader KE, Oxman MN, Levin MJ, Johnson G, Zhang JH, Betts R, et al. Shingles Prevention Study Group. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. Clin Infect Dis 2012;55(10):1320–8.
[39] Morrison VA, Johnson GR, Schmader KE, Levin MJ, Zhang JH, Looney DJ, et al. Shingles Prevention Study Group. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis 2015;60(6):900–9.
[40] Li X, Zhang JH, Betts RF, Morrison VA, Xu R, Itzler RF, et al. Modeling the durability of ZOSTAVAX® vaccine efficacy in people ≥60 years of age. Vaccine 2015;33(12):1499–505.
[41] Drolet M, Brisson M, Schmader KE, Levin MJ, Johnson R, Oxman MN, et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. CMAJ 2010;182(16):1731–6.
[42] Imafuku S, Nakayama J, Higa K, Furue M, Takahara M, Katayama I, et al. One-year follow-up of zoster-associated pain in 764 immunocompetent patients with acute herpes zoster treated with famciclovir (FAMILIAR study). Eur Acad Dermatol Venereol 2014;28(12):1716–22.
[43] Ikeda S, Ogawa S, Hosokawa T, Murakawa K, Hotta N, Konno S, et al. Cost-effectiveness analysis of pregabalin for treatment of peripheral neuropathic pain. Jpn J Pharmacoepidemiol 2011;16(1):1–9 [Japanese].
[44] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 4th ed. Oxford: Oxford University Press; 2015.
[45] Record of proceedings of the committee of cost-effectiveness, Central Social Insurance Medical Council, Ministry of Health, Welfare and Labour of Japan. 2017. March 15. Available from: <http://www.mhlw.go.jp/stf/shingi/shingi-chuo.html?tid=128159> [Japanese].
[46] Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Econ 2010;19(4):422–37.
[47] Institute of Medicine (US) Committee to Study Priorities for Vaccine Development; Stratton KR, Durch JS, Lawrence RS, editors. Vaccines for the 21st century: a tool for decisionmaking. Washington (DC): National Academies Press (US); 2000.
[48] World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. Geneva, Switzerland: WHO Document Production Services; 2008.
[49] Ogunjimi B, Van Damme P, Beutels P. Herpes zoster risk reduction through exposure to chickenpox patients: a systematic multidisciplinary review. PLoS ONE 2013;8(6):e66485.

Ohfuji et al. BMC Infectious Diseases (2019) 19:95
https://doi.org/10.1186/s12879-019-3719-7

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Safety of live attenuated varicella-zoster vaccine in patients with underlying illnesses compared with healthy adults: a prospective cohort study

Satoko Ohfuji[1,2*], Kazuya Ito[1,2], Megumi Inoue[3], Motoki Ishibashi[3], Hiroko Kumashiro[3], Yoshio Hirota[4], Eiji Kayano[5] and Naoshi Ota[5]

Abstract

Background: In Japan, freeze-dried live attenuated varicella-zoster vaccine is available for adults aged ≥50 years to prevent herpes zoster. However, limited evidence has been accumulated regarding vaccine safety for patients with underlying illnesses, who have been considered as the high-risk group for herpes zoster.

Methods: A prospective cohort study of 1200 healthy adults and 300 patients with underlying illnesses such as malignancy, diabetes mellitus, autoimmune diseases, and renal diseases was conducted. All subjects were vaccinated and then their adverse events (AEs) were followed for 28 days after vaccination. Key safety measures included any AEs, severe AEs (SAEs), and vaccine-related AEs such as injection-site AEs and systemic AEs. The frequencies and 95% confidence intervals of AEs were calculated.

Results: During the follow-up period, 2 SAEs (bone fracture and acute cholecystitis) among healthy adults and 1 SAE (disseminated mycobacteriosis) among patients with underlying illnesses were reported, although none of them was diagnosed as vaccine-related. Vaccine-related AEs were reported in 42% of healthy adults and patients with underlying illnesses, and the proportions were similar between the groups. The most frequent AEs were injection-site AEs in both groups (i.e., 41 and 39%), and systemic AEs were observed in 4% of both groups. Only among healthy adults, those with a history of herpes zoster were more likely to report injection-site AEs than those without a history of herpes zoster (53% vs 39%).

Conclusions: The present study confirmed the safety of freeze-dried, live attenuated varicella-zoster vaccine even in patients with underlying illnesses. A history of herpes zoster might be related to development of injection-site AEs in healthy adults.

Trial registration: The study was prospectively registered on Japic-Clinical Trials Information as JapicCTI-163415 on October 31, 2016.

Keywords: Adverse events, Autoimmune diseases, Diabetes mellitus, Herpes zoster, Malignancy, Reactogenicity, Renal diseases, Safety, Varicella-zoster vaccine

* Correspondence: satop@med.osaka-cu.ac.jp
[1]Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan
[2]Research Center for Infectious Disease Sciences, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan
Full list of author information is available at the end of the article

Background

Herpes zoster (HZ), or shingles, is one of the important diseases that could decrease quality of life of older adults. It is caused by reactivation of varicella-zoster virus (VZV) in individuals with latent infections, and is characterized by unilateral radicular pain and a vesicular rash generally limited to a single dermatome, corresponding to the sensory ganglion in which the latent VZV reactivated [1]. It can expand to involve several dermatomes, especially in immunocompromised subjects. The frequency and severity of HZ increase with age, which correlates closely with a progressive decline in cell-mediated immunity to VZV [2]. The most common complication is post-herpetic neuralgia (PHN), which is a very problematic condition because it is often difficult to control the intolerable pain and results in decreased quality of life for the affected individuals.

The incidence of HZ has been increasing with the current ageing population in Japan. According to a Japanese study using medical records between 1997 and 2006, the annual incidence of HZ was 1.96–2.85/1000 person-years among individuals below the age of 50 years, but it increased to 5.23–7.84/1000 person-years among those aged 50 years or more [3]. The more recent studies in Japan indicated that the incidence of HZ among older individuals has been increasing to 10.2/1000 person-years [4] or 10.9/1000 person-years [5].

Patients with diabetes mellitus, autoimmune diseases, renal failure, and malignancies have a higher risk of HZ than those with other diseases [6, 7]. In addition, the proportion developing PHN among HZ patients ranged from 9% [4] to 19% [5], and its risk was increased in males, age ≥ 65 years, and immunosuppressive therapy [4]. Thus, it is important to protect these high-risk populations from the threat of HZ and PHN.

Since immunity to VZV plays a role in the pathogenesis of HZ [1], ZOSTAVAX® (Merck & Co., Inc) as a live attenuated virus vaccine for Oka strain (19,400 PFU or more, based on the package insert) has been approved in more than 60 countries or counties for prophylactic use in older individuals. The clinical efficacy was reported to be 51.3% for reducing the incidence of HZ and 66.5% for reducing the incidence of PHN [8]. In Japan, freeze-dried live attenuated varicella vaccine for Oka strain (1000 PFU or more, based on the package insert), which was originally used to prevent varicella in children since 1986, was additionally approved for use to reduce the risk of HZ in individuals aged ≥50 years in 2016. Since this varicella-zoster vaccine generally contains live attenuated Oka virus of 23,000–95,000 PFU [9], the identical vaccine is used to prevent not only varicella in children but also HZ in adults in Japan. However, the clinical trial prior to approval targeted healthy adults aged ≥50 years, and the safety profiles for patients with underlying illnesses have been limited.

Thus, the present study focused on adults aged ≥50 years with particular underlying illnesses (i.e., malignancy, diabetes mellitus, autoimmune diseases, and chronic renal disease), which were reported to be high-risk conditions for HZ, and compared the reactogenicity of freeze-dried live attenuated varicella-zoster vaccine with that in healthy adults aged ≥50 years.

Methods

Setting and study subjects

A prospective cohort study was conducted to compare the safety of live attenuated varicella-zoster vaccine between patients with underlying illnesses and healthy adults. Study subjects included patients with malignancy, diabetes mellitus, autoimmune diseases, or chronic renal disease attending the collaborating hospitals, SOUSEIKAI, in Japan. This study was run between November 3, 2016 and November 24, 2017. All patients were Japanese adults aged ≥50 years; were regarded as having a health condition compatible with participation by their physicians; and in the case of childbearing-aged women, those who had taken appropriate birth control for the preceding 1 month and those who consented to continue birth control for 2 months after vaccination. Exclusion criteria included receipt of transfusion or a γ-globulin preparation within the preceding 3 months, or a large amount of γ-globulin preparation (≥200 mg/kg) within the preceding 6 months; a history of anaphylaxis due to vaccine components; participation in other clinical trials within the preceding 4 months; lactating women or pregnant women, including those with suspected pregnancy at enrollment or those desiring pregnancy during the study period; or other condition making participation inappropriate.

Patients with malignancy included those with (a history of) malignant solid tumor such as colon cancer, lung cancer, gastric cancer, liver cancer, breast cancer, prostate cancer (males), cervical cancer (females), or with malignant lymphoma or acute lymphocytic leukemia, who were in the remission stage at the time of enrollment. Among them, the following patients were excluded: those who received immunosuppressive chemotherapy or radiation therapy within the preceding 6 months (or were planned to receive it within 28 days after vaccination); for patients with acute lymphocytic leukemia, those who had reached the remission stage within the preceding 3 months, those whose number of lymphocyte was less than 500/mm^3, those with a negative result on the delayed skin hypersensitivity test, those who received chemotherapy for remission maintenance using medications other than 6-mercaptopurine within the preceding 1 week (or were planned for it within 28 days after vaccination); and for patients with malignant solid tumor, those whose tumor development could not be controlled by surgery or chemotherapy, those whose tumor development was under control but who received immunosuppressive

chemotherapy or radiation therapy within the preceding 6 months (or were planned for it within 28 days after vaccination).

The inclusion criteria for diabetes mellitus patients were: patients diagnosed with diabetes mellitus; those without diabetic neuropathy, diabetic retinopathy, or diabetic nephropathy; those whose diabetes was not caused by the side effects of immunosuppressants (corticosteroid, tacrolimus, etc.); and those who did not receive cortical hormones, immunosuppressants, or antiplatelet therapy including aspirin.

Regarding autoimmune diseases, patients with rheumatoid arthritis, systemic lupus erythematosus, collagen diseases, ulcerative colitis, etc. were candidates for enrollment. Among them, patients who received cortical hormones, immunosuppressants, biologic agents, or JAK inhibitors within the preceding 6 months (or were planned to receive them within 28 days after the vaccination) were excluded.

Patients with chronic renal diseases were regarded as those with findings compatible with renal disease on urinalysis, imaging, laboratory, or pathological examination. For example, patients whose albuminuria (≥30 mg/gCr) or proteinuria (≥0.15 g/gCr) had continued for ≥3 months, or those with eGFR levels of 46–59 mL/min/1.73 m^2 were included. Patients receiving cortical hormones or immunosuppressants were excluded.

For comparison, healthy adults aged ≥50 years were also enrolled. Those with mild underlying illnesses such as hypertension and dyslipidemia, if well-controlled, were allowed to participate.

Sample size calculation

A total of 1500 subjects (300 patients and 1200 healthy adults) were needed for enrollment based on the following calculation. Based on the results of a domestic clinical trial involving 259 healthy adults aged ≥50 years, the proportion of any adverse events (AEs) after vaccination was 51%, and the most uncommon events were fatigue and rash (2% for each) [9]. Assuming that patients with underlying illnesses had a 3-fold higher risk for the most uncommon AEs than healthy adults, 1283 subjects (257 patients and 1026 healthy adults) were required to obtain 80% power ($\beta = 0.20$) for detecting significant differences with an α level of 0.05. When considering loss to follow-up (10%), a total of 1500 subjects were needed.

Information collection

At the time of enrollment, the physicians were asked to complete a standardized case reporting form to collect the following information: demographic characteristics such as date of birth, age at vaccination, sex; a history of HZ and, if present, date of diagnosis; a history of varicella-zoster vaccination and, if present, date of vaccination; a history of any diseases; underlying illnesses (i.e., malignancy, diabetes mellitus, autoimmune diseases, renal disease) and name of medications; laboratory data (i.e., white blood cell counts and fractions within the preceding 6 months) if available; and HbA1c level and duration from diagnosis for patients with diabetes mellitus; and eGFR level, creatinine level, and dialysis treatment for patients with chronic renal diseases.

Vaccination

All subjects received one subcutaneous injection of 0.5 mL of Live attenuated varicella virus vaccine BIKEN (Lot Nos. VZ184, 189, 200) manufactured by The Research Foundation for Microbial Diseases of Osaka University. To avoid confusion, this varicella virus vaccine is called varicella-zoster vaccine in this paper. Each vaccine was supplied as a single-dose vial containing live attenuated Oka varicella-zoster virus (29,000–58,000 PFU). No adjuvant was included in the vaccine.

Safety assessment

All subjects were carefully observed for signs of any reactions for 30 min after vaccination at the hospitals. In addition, they maintained a daily log of body temperature, symptoms related to the injection-site (erythema, swelling, induration, pain, itching, warmth, and others), systemic symptoms (rash and others), any medications, and hospitalization during the 28 days after vaccination. Thereafter, they reported any symptoms until the next visit to the study clinic. If subjects experienced erythema, swelling, or induration at the injection site, they also reported the length of the major axis. Major axis length < 2 cm was regarded as mild, and an axis length > 5 cm was regarded as severe. For the other local symptoms (i.e., pain, itching, warmth, and others) and systemic symptoms, they selected the severity (i.e., mild, moderate, or severe). In general, mild symptoms were regarded as unnecessary to treat and did not interfere with daily activities, moderate symptoms needed treatment or interfered with daily activities, and severe symptoms needed hospitalization and interfered with daily activities. As for fever, a temperature < 38.0 °C was defined as mild fever, and a temperature ≥ 39.0 °C was defined as severe fever.

According to their daily logs, the physicians transferred the information to the case reporting forms and offered their opinions whether the symptoms were related to the vaccination. After this review, a MedDRA code was assigned to each AE.

Statistical analysis

Key safety measures included proportions of subjects with any AEs, severe AEs (SAEs), and vaccine-related AEs such as injection-site AEs and systemic AEs. In the analysis, the frequencies and 95% confidence intervals (CIs) of AEs were calculated. Stratified analyses were performed to examine the effect of the following variables on the safety assessment:

study population (patients and healthy adults); age at vaccination (50–59, 60–69, and ≥ 70 years); and sex. The χ^2 test or Fisher's exact test was used to compare the frequency of AEs and their severity among the above-mentioned stratified groups. Student's *t*-test was also used as appropriate. Furthermore, to assess the risk of AEs among patients compared to healthy adults, logistic regression analyses were also performed with adjustment for age categories and sex, and the odds ratios (ORs) and 95% CIs were obtained. All tests were 2-sided. All analyses were performed using SAS, version 9.4 (SAS Institute).

Results

Study population

During the study period, 1201 healthy adults and 300 patients with underlying illnesses (49 malignancies, 180 diabetes mellitus, 10 autoimmune diseases, 61 renal diseases) were enrolled (Fig. 1). However, 1 healthy adult refused to participate after providing informed consent and was thus not vaccinated. Eventually, 1200 healthy adults and 300 patients with underlying illnesses were included in the safety analysis.

Table 1 shows the characteristics of the study subjects. Approximately half of the healthy adults were males, while male patients constituted more than half of the patients with other than autoimmune diseases. The mean age of healthy adults was 62.0 years, whereas older aged subjects were enrolled as patients with underlying illnesses, especially malignancy, diabetes mellitus, and chronic renal diseases. Patients with malignancy had a higher rate of HZ history and VZV vaccination history than healthy adults. Details of the sites of malignancy were: 11 breast cancer, 9 colon cancer, 8 prostate cancer, 7 gastric cancer, 3 uterine cancer, 3 lung cancer, 3 bladder cancer, 3 thyroid gland cancer, 1 gallbladder cancer, and 1 renal cancer. Regarding clinical information about diabetes mellitus, the HbA1c range was 5.0–11.0, and 41% of patients were considered to have well-controlled disease (i.e., HbA1c < 7.0%) at a mean of 8.0 years since diagnosis. Details of autoimmune diseases were: 6 Basedow's disease, 3 autoimmune thyroiditis, 1 Sjögren's syndrome with Basedow's disease, and 1 Vogt-Koyanagi-Harada disease. Among patients with chronic renal diseases, ranges of creatinine levels and eGFR levels were 0.71–1.20 mg/dL and 46–59 mL/min/1.73 m^2, respectively, suggesting that their disease activities were mild. None of the patients had undergone dialysis.

Safety assessment according to the study population

Table 2 shows the incidences of AEs within 28 days after vaccination. A total of 1623 events were reported from 603 healthy adults (50%), whereas 395 events were reported from 146 patients with underlying illnesses (49%). SAEs were reported from 2 healthy adults (fractures, acute cholecystitis) and 1 patient (disseminated mycobacteriosis), although both cases were considered to have no causal relationship with the vaccine. A total of 1362 events from 509 healthy adults and 328 events from 125 patients with underlying illnesses were diagnosed as vaccine-related AEs. The incidences of vaccine-related AEs were similar between healthy adults and patients with underlying illnesses (42% vs. 42%). Inject ion-site AEs were reported from 491 healthy adults (41%) and 118 patients (39%), and these were not significantly different between the groups. The incidences of systemic AEs were also similar between healthy adults (4%) and patients (4%). However, when each symptom was analyzed separately, the incidence of fever was slightly higher among patients with underlying illnesses (2%), more specifically malignancy patients and diabetes patients, compared with healthy adults (0.4%). When the risk of fever was examined among patients with underlying illnesses compared with healthy adults, a 4.1 times higher OR (95% CI: 1.2–14.1) was obtained. The age- and sex-adjusted OR reached the null value but remained 3.2 times higher (95% CI: 0.9–11.3) with marginal significance ($P = 0.08$).

Regarding the severity of AEs, no significant difference was observed in injection-site AEs between the groups. On the other hand, a higher incidence of mild to moderate fever was reported in patients with underlying illnesses (especially malignancy patients, diabetes patients) compared to healthy adults. In addition, mild headache and mild fatigue were found in one patient with autoimmune disease, and the incidences were higher than in healthy adults.

Most of the vaccine-related AEs occurred within 0–3 days (mean: 2 days, median: 2 days) after vaccination in both groups. Injection-site AEs were improved within 6 days, and systemic AEs were improved within a few days (data not shown).

Safety assessment according to the history of herpes zoster

Table 3 shows the incidence of vaccine-related AEs according to the history of HZ. Among healthy adults, those with an HZ history were more likely to report injection-site AEs than those without an HZ history (53% vs 39%, $P = 0.017$). In particular, only erythema was significantly more common in those with an HZ history than in those without (43% vs. 32%, $P = 0.026$). The severity of erythema was mild to moderate, and it occurred most frequently the day after vaccination, with an average duration of 5 days (data not shown). When the risk of erythema was examined in healthy adults with an HZ history compared to those without, a 1.7 times higher OR (95%CI: 1.2–2.4) was observed even after adjustment for age and sex. Further, among patients with underlying illnesses, no significant differences were observed in the incidences of AEs between patients with and without a history of HZ (Table 3).

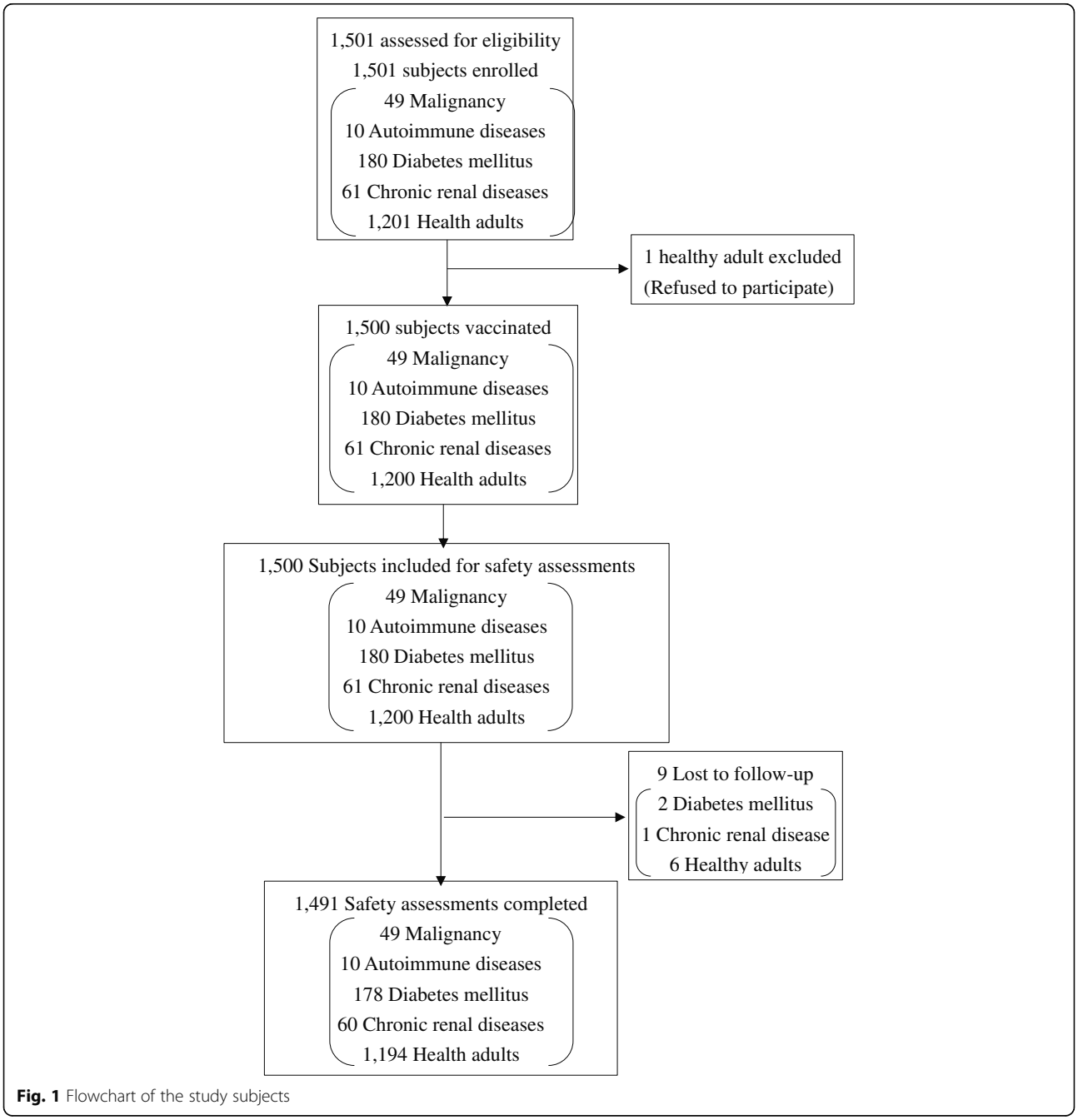


Fig. 1 Flowchart of the study subjects

Safety assessment in patients by disease severity

Additionally, the effect of disease condition on vaccine safety in patients with underlying illnesses was examined. In diabetes patients, no significant association was observed between the HbA1c level and the incidence of AEs (data not shown). However, those with a shorter time since diabetes diagnosis had a higher incidence of injection-site pain compared with those with a longer duration (within 4 years vs. 4–9 years vs. 10 years or more, 20% vs. 23% vs. 5%; $P = 0.01$). As for patients with renal diseases, those with a lower creatinine level had significantly higher rates of injection-site erythema (< 0.9 mg/dL vs. 0.9–1.08 mg/dL vs. > 1.08 mg/dL, 70% vs. 28% vs. 22%; $P < 0.01$), itching (40% vs. 11% vs. 4%; $P < 0.01$), pain (30% vs. 6% vs. 4%; $P = 0.01$), and induration (40% vs. 0% vs. 13%; $P = 0.03$), and those with a higher eGFR level had significantly higher rates of injection-site erythema (< 51 vs. 51–56 vs. more than 56 mL/min/1.73 m^2, 29% vs. 32% vs. 55%; $P = 0.04$) and itching (12% vs. 5% vs. 36%; $P = 0.03$). No other significant differences were observed in AEs and background characteristics.

Table 1 Baseline characteristics of the study subjects

Characteristics		Healthy adults (*N* = 1200)	Patients with underlying illnesses (*N* = 300)	Patients with malignancy (*N* = 49)	Patients with diabetes mellitus (*N* = 180)	Patients with autoimmune diseases (*N* = 10)	Patients with chronic renal diseases (*N* = 61)
Sex	Male	607 (51%)	188 (63%)*	26 (53%)	120 (67%)*	2 (20%)**	40 (66%)*
Age (y)	Mean ± SD	62.0 ± 8.0	66.0 ± 8.0	71.0 ± 9.0*	65.0 ± 8.0*	61.0 ± 7.0	69.0 ± 8.0*
	50–59	530 (44%)	63 (21%)*	3 (6%)*	46 (26%)*	4 (40%)	10 (16%)*
	60–69	425 (35%)	129 (43%)	21 (43%)	80 (44%)	4 (40%)	24 (39%)
	70+	245 (20%)	108 (36%)	25 (51%)	54 (30%)	2 (20%)	27 (44%)
History of HZ	Present	155 (13%)	49 (16%)	11 (22%)**	28 (16%)	1 (10%)	9 (15%)
Previous vaccination	Present	3 (0.3%)	3 (1%)**	2 (4%)*	1 (1%)	0 (0%)	0 (0%)
White blood cells (/μL)	Mean ± SD	–	6289 ± 1685	5386 ± 1223	6505 ± 1811	6100 ± 520	5980 ± 1430
HbA1c (%)	Mean ± SD	–	–	–	7.0 ± 1.0	–	–
Duration of diabetes mellitus (y)	Mean ± SD	–	–	–	8.0 ± 7.0	–	–
Creatinine (mg/dL)	Mean ± SD	–	–	–	–	–	0.99 ± 0.15
eGFR (mL/min/1.73 m^2)	Mean ± SD	–	–	–	–	–	53 ± 4
Dialysis	Present	–	–	–	–	–	0 (0%)

Data are expressed as n (%) unless otherwise indicated
HZ Herpes zoster, *SD* Standard deviation
*$P < 0.05$, **$P < 0.1$ (compared with the proportion of subjects among healthy adults)

Discussion

In the present study, no vaccine-related SAEs were observed in both patients with underlying illnesses and healthy adults. The incidence of AEs in healthy adults was almost the same as reported in domestic clinical trials for healthy adults > 50 years old (any AE: 50% vs. 56%; injection-site AEs: 41% vs. 50%) [10], suggesting that the present results are reliable. The present study also indicated that the incidences of most AEs were similar between healthy adults and patients with underlying illnesses, although the incidence of fever was significantly higher in patients than in healthy adults. In particular, fever was not observed in patients with autoimmune diseases and patients with chronic kidney disease, but only in patients with malignancy or diabetes. It is therefore considered that they are more likely to develop fever due to the background diseases rather than the vaccination itself. The period of emergence of fever in patients with underlying illnesses ranged from 0 to 5 days after vaccination, the extent of fever was mild to moderate, and all improved in 1–3 days, suggesting that it was a transient response. However, just as a precaution, patients with malignancy and diabetes patients should be aware of the possibility of fever for several days after vaccination.

Most of the previous studies that evaluated the safety of HZ vaccine were based on randomized, controlled trials. According to these studies, injection-site AEs were more commonly reported in the HZ-vaccinated group than in the placebo group, while the incidence of systemic AEs was similar between the HZ-vaccinated group and the placebo group, not only in elderly people with underlying illnesses, considered at high risk for HZ (AIDS, diabetes, steroid administration, autoimmune disease, renal disorder) [11–13], but also in healthy adults [14, 15]. These results suggested that the reported systemic AEs are less likely to be related to HZ vaccination. Furthermore, based on AE reports after ZOSTAVAX® had been used around the world for 10 years, injection-site AEs were the most frequently reported [16]. Therefore, this seemed to indicate that we need not be overly concerned about systemic AEs.

The present study also showed that healthy adults with an HZ history had a higher incidence of erythema after vaccination than those without. As far as we know, only one previous study examined vaccine safety by comparing 420 subjects with an HZ history and 13,254 subjects without an HZ history and showed that the incidence of SAEs during the 28 days after vaccination was similar between these groups (0.95% vs. 0.66%) [17]. However, the study targeted only the incidence of SAEs rather than all AEs or vaccine-related AEs, and, thus, the incidence of injection-site AEs including erythema was not reported. Since cellular immunity against VZV was activated by the HZ history [1], it is possible that the local reaction after vaccination was more likely to develop among those with a history of HZ. As additional information, however, erythema was self-controlled and recovered within an average of 5 days, and no severe erythema was observed in the present study.

Table 2 Adverse events within 28 days after vaccination in healthy adults and patients with underlying illnesses

Adverse events	Healthy adults (*N* = 1200)		Patients with underlying illnesses (*N* = 300)		Patients with malignancy (*N* = 49)		Patients with diabetes mellitus (*N* = 180)		Patients with autoimmune diseases (*N* = 10)		Patients with chronic renal diseases (*N* = 61)	
	No. of events	No. of subjects (%) (95% CI)	No. of events	No. of subjects (%) (95% CI)	No. of events	No. of subjects (%) (95% CI)	No. of events	No. of subjects (%) (95% CI)	No. of events	No. of subjects (%) (95% CI)	No. of events	No. of subjects (%) (95% CI)
Any AEs	1623	603 (50%) (47–53%)	395	146 (49%) (43–54%)	54	25 (51%) (36–66%)	234	85 (47%) (40–55%)	16	5 (50%) (19–81%)	91	31 (51%) (38–64%)
SAEs	2	2 (0.2%) (0–1%)	1	1 (0.3%) (0–2%)	0	0 (0%)	1	1 (0.6%) (0–3.0%)	0	0 (0%)	0	0 (0%)
Vaccine-related AEs	1362	509 (42%) (40–45%)	328	125 (42%) (36–47%)	44	20 (41%) (27–56%)	197	73 (41%) (33–48%)	14	5 (50%) (19–81%)	73	27 (44%) (32–58%)
Injection-site AEs	1306	491 (41%) (38–44%)	314	118 (39%) (34–45%)	41	18 (37%) (23–52%)	191	71 (39%) (32–47%)	12	4 (40%) (12–74%)	70	25 (41%) (29–54%)
Erythema	405	405 (34%) (31–37%)	94	94 (31%) (26–37%)	14	14 (29%) (17–43%)	52	52 (29%) (22–36%)	4	4 (40%) (12–74%)	24	24 (39%) (27–53%)
Itching	244	243 (20%) (18–23%)	60	59 (20%) (15–25%)	8	8 (16%) (7–30%)	39	38 (21%) (15–28%)	2	2 (20%) (3–56%)	11	11 (18%) (9–30%)
Swelling	179	179 (15%) (13–17%)	47	47 (16%) (12–20%)	9	9 (18%) (9–32%)	27	27 (15%) (10–21%)	1	1 (10%) (0.3–45%)	10	10 (16%) (8–28%)
Pain	183	182 (15%) (13–17%)	41	41 (14%) (10–18%)	3	3 (6%) (1–17%)**	28	28 (16%) (11–22%)	2	2 (20%) (3–56%)	8	8 (13%) (6–24%)
Warmth	170	170 (14%) (12–16%)	36	36 (12%) (9–16%)	5	5 (10%) (3–22%)	23	23 (13%) (8–19%)	2	2 (20%) (3–56%)	6	6 (10%) (4–20%)
Induration	124	124 (10%) (9–12%)	36	36 (12%) (9–16%)	2	2 (4%) (0.5–14%)	22	22 (12%) (8–18%)	1	1 (10%) (0.3–45%)	11	11 (18%) (9–30%)**
Eruption	1	1 (0.1%) (0–0.5%)	0	0 (0%)	0	0 (0%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Systemic AEs	56	46 (4%) (3–5%)	14	11 (4%) (2–6%)	3	2 (4%) (0.5–14%)	6	5 (3%) (0.9–6%)	2	1 (10%) (0.3–45%)	3	3 (5%) (1–14%)
Fever	6	5 (0.4%) (0.1–1.0%)	5	5 (2%) (0.5–4.0%)*	2	2 (4%) (0.5–14%)*	3	3 (2%) (0.3–5%)**	0	0 (0%)	0	0 (0%)
Headache	8	8 (0.7%) (0.3–1.0%)	2	2 (0.7%) (0.1–2.0%)	0	0 (0%)	0	0 (0%)	1	1 (10%) (0.3–45%)**	1	1 (2%) (0.04–9%)
Fatigue	5	5 (0.4%) (0.1–1.0%)	3	3 (1%) (0.2–3.0%)	1	1 (2%) (0.1–11%)	1	1 (0.6%) (0–3.0%)	1	1 (10%) (0.3–45%)*	0	0 (0%)
Rash	18	17 (1%) (0.8–2.0%)	1	1 (0.3%) (0.008–2.0%)	0	0 (0%)	1	1 (0.6%) (0–3.0%)	0	0 (0%)	0	0 (0%)
Others	19	17 (1%) (0.8–3%)	3	3 (1%) (0.2–3%)	0	0 (0%)	1	1 (0.6%) (0.01–3.0%)	0	0 (0%)	2	2 (3%) (0.4–11%)

AE Adverse event, *CI* Confidence interval, *SAE* Severe adverse event

*$P < 0.05$, **$P < 0.1$ (compared with the proportion of subjects among healthy adults)

Table 3 Incidence of selected vaccine-related adverse events by a history of herpes zoster

Adverse events	Healthy adults		Patients with underlying illnesses		Patients with malignancy		Patients with diabetes mellitus		Patients with autoimmune diseases		Patients with chronic renal diseases	
	No. of events	No. of subjects (%) (95% CI)	No. of events	No. of subjects (%) (95% CI)	No. of events	No. of subjects (%) (95% CI)	No. of events	No. of subjects (%) (95% CI)	No. of events	No. of subjects (%) (95% CI)	No. of events	No. of subjects (%) (95% CI)
Subjects with HZ history	*N* = 155		*N* = 49		*N* = 11		*N* = 28		*N* = 1		*N* = 9	
Vaccine-related AEs	198	87 (56%) (48–64%)*	54	23 (47%) (33–62%)	8	4 (36%) (11–69%)	30	13 (46%) (28–66%)	6	1 (100%)	10	5 (56%) (21–86%)
Injection-site AEs	189	82 (53%) (45–61%)*	54	23 (47%) (33–62%)	8	4 (36%) (11–69%)	30	13 (46%) (28–66%)	6	1 (100%)	10	5 (56%) (21–86%)
Systemic AEs	9	8 (5%) (2–10%)	0	0 (0%)	0	0 (0%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Subjects without HZ history	*N* = 1045		*N* = 251		*N* = 38		*N* = 152		N = 9		*N* = 52	
Vaccine-related AEs	1164	422 (40%) (37–43%)	274	102 (41%) (35–47%)	36	16 (42%) (26–59%)	167	60 (39%) (32–48%)	8	4 (44%) (14–79%)	63	22 (42%) (29–57%)
Injection-site AEs	1117	409 (39%) (36–42%)	260	95 (38%) (32–44%)	33	14 (37%) (22–54%)	161	58 (38%) (30–46%)	6	3 (33%) (7–70%)	60	20 (38%) (25–53%)
Systemic AEs	47	38 (4%) (3–5%)	14	11 (4%) (2–8%)	3	2 (5%) (0.6–18%)	6	5 (3%) (1–8%)	2	1 (11%) (0.3–48%)	3	3 (6%) (1–16%)

AE Adverse event, *HZ* Herpes zoster
*$P < 0.05$, **$P < 0.1$ (compared with the proportion of reported subjects without HZ history within the category of subjects)

Patients with diabetes are considered to have a high risk for HZ, since cellular immunity against VZV is lower than that of healthy adults [7, 18]. In the present study, the incidences of injection-site AEs and systemic AEs in diabetic patients were 39 and 3%, respectively, similar to healthy adults, irrespective of their HbA1c levels, although their disease condition, on the whole, tended to be mild. Further, patients with a shorter time since diabetes diagnosis had a higher incidence of injection-site pain. However, other AEs were similarly reported by patients, irrespective of time since diagnosis. Thus, a higher incidence of pain in patients with a shorter time since diagnosis may be obtained by chance. Therefore, we considered that the benefit of receiving a live attenuated varicella-zoster vaccine to prevent HZ and PHN exceeds the safety concerns, at least among such milder diabetes patients.

Patients with chronic renal diseases are also regarded as a high-risk group for HZ and would need vaccination. However, some injection-site AEs were reported more often from patients with lower creatinine levels or higher eGFR levels, with relatively mild disease. There is no possible explanation for why injection-site AEs were more frequently reported from milder renal disease patients. Further investigations of chronic renal disease patients may clarify the potential difference in AE occurrence after vaccination by disease severity.

As far as we know, few studies have compared the safety of a live attenuated HZ vaccine in patients with underlying illnesses with that in healthy adults, and only small-scale studies are available [19, 20]. In a study comparing safety in 10 diabetic patients and 10 healthy adults, no systemic AEs were observed in both groups [19]. In a study of 41 patients with rheumatism and 28 patients with osteoarthritis, 17 (25%) AEs occurred within 7 days after vaccination, of which 8 were injection-site AEs [20]. When investigating rare AEs after vaccination, it is difficult to detect AEs in such small-scale studies. From this point of view, the present study was a large-scale study comparing 1200 healthy adults and 300 patients with underlying illnesses, and the safety comparison is highly reliable. Although patients with diabetes and patients with chronic renal diseases in the present study had relatively mild disease, the evidence for the safety of these patients receiving a live attenuated HZ vaccine is valuable.

However, the present study has the following limitations. First, the number of patients with autoimmune diseases was too small and heterogeneous, which may not have been sufficient to examine disease-specific vaccine safety. In particular, statistical power may have been insufficient for systemic AEs, which usually occur with a low frequency, when comparing the incidence of disease-specific AEs. In addition, the cancer group was also heterogeneous, with small patient numbers per cancer type. As for vaccine safety in patients with autoimmune diseases, a previous study that included a larger number of patients with several kinds of autoimmune diseases did not identify any safety signal in the use of immunosuppressive therapies within 42 days after vaccination [21]. Second, the generalizability of the present study needs to be considered. Since the present

vaccine contains a similar amount of live attenuated Oka virus as ZOSTAVAX®, the present results could be applicable to ZOSTAVAX® users. In the present study, however, diabetes patients accounted for 60% of patients with underlying illnesses, which means that the present patients may not be representative of the general population of patients with underlying illnesses. In addition, it is important to note that the present findings would be limited for malignancy patients in longer remission and without therapy for more than 6 months, non-severe diabetes (i.e., no organ damage) patients, autoimmune disease patients without immunosuppressive therapy, and patients with only mild renal disease. Third, since sex and age distributions differed between healthy adults and patients with underlying illnesses, the incidence of AEs may have been influenced by these background factors. In the present study, sex- and age-adjusted analyses were also performed, but the possibility of residual confounding cannot be excluded. Fourth, there was no primary outcome, since it was considered that comparing every AE outcome between healthy adults and patients with underlying illnesses was an important goal. However, it resulted in many comparisons in the analyses, which might run the risk of some spurious findings. In the present results, there was no possible explanation for why injection-site AEs were more common in those with milder renal diseases, which may be spurious.

To recommend vaccination for patients with underlying illnesses, evidence for vaccine efficacy is also needed. A retrospective cohort study of 463,541 patients aged 60 years or older with immune-mediated diseases reported that HZ vaccine was associated with a 39% (95%CI: 29–48%) decreased risk for HZ [21]. In a large-scale US study, the efficacy of HZ vaccine was 52% (95%CI: 44–61%) among subjects aged ≥65 years, and 63% (95%CI: 42–94%) among immunosuppressed patients [22]. In another study of 180,000 patients with chronic renal disease, vaccine efficacy was reported to be 51% (95%CI: 35–64%) among all patients and 54% (95%CI: 32–91%) among patients with diabetes mellitus [23]. Therefore, we believe that it is highly valuable to recommend vaccination for such patients with underlying illnesses, although it should be noted that live-attenuated varicella-zoster vaccine is contraindicated for some immunosuppressed patients (e.g. receiving cortical hormones, immunosuppressants including rituximab, chemotherapy, radiation, etc.).

Conclusions

The present study confirmed the safety of freeze-dried live attenuated varicella-zoster vaccine even among patients with underlying illnesses who are at high risk for HZ. These results would be useful when providing vaccines to such patients.

Abbreviations

AE: Adverse event; CI: Confidence interval; HZ: Herpes zoster; OR: Odds ratio; PHN: Post-herpetic neuralgia; SAE: Severe adverse event; SD: Standard deviation; VZV: Varicella-zoster virus

Acknowledgments

The authors wish to thank the doctors and staff at the participating hospitals for their kind cooperation.

Funding

This study was funded by The Research Foundation for Microbial Diseases of Osaka University. The study sponsor was involved in the design of the study and overall management of the study, and in the decision to submit the paper for publication.

Availability of data and materials

The dataset used and/or analyzed during the current study are available from the Research Foundation for Microbial Diseases of Osaka University on reasonable request.

Authors' contributions

All authors provided comments on the drafts and have read and approved the final manuscript. SO and KI contributed to study design, statistical analysis, data interpretation, and manuscript writing. MI1, MI2, HK, and YH contributed to study design, data collection, and data management. EK and NO contributed to conception of study design and overall management.

Ethics approval and consent to participate

The study protocols were approved by the Clinical Study Review Board of SOUSEIKAI (No. 1668CP) and BIKEN Ethical and COI Review Board (No.16–03), and was performed in accordance with the Declaration of Helsinki. All participants received an explanation of the study from their physician and provided written, informed consent prior to participation.

Consent for publication

Not applicable.

Competing interests

EK and NO are members of the Research Foundation for Microbial Diseases of Osaka University (funding company). Other authors declare that they have no conflict of interest.

Publisher's Note

Author details

[1]Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan. [2]Research Center for Infectious Disease Sciences, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan. [3]PS Clinic, Medical Co. LTA, 6-18, Ten-ya-machi, Hakata-ku, Fukuoka-city, Fukuoka 812-0025, Japan. [4]Clinical Epidemiology Research Center, Medical Co. LTA, 3-6-1 Kashii-Teriha Higashi-ku, Fukuoka 813-0017, Japan. [5]Kanonji Institute, Research Foundation for Microbial Diseases of Osaka University, 4-1-70, Seto-Cho, Kanonji, Kagawa 768-0065, Japan.

Received: 13 November 2018 Accepted: 11 January 2019
Published online: 28 January 2019

References

1. Oxman MN. Zoster vaccine: current status and future prospects. Clin Infect Dis. 2010;51:197–213. https://doi.org/10.1086/653605.
2. Levin MJ, Smith JG, Kaufhold RM, Barber D, Hayward AR, Chan CY, et al. Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. J Infect Dis. 2003;188:1336–44.
3. Toyama N, Shiraki K. Society of the Miyazaki Prefecture Dermatologists. Epidemiology of herpes zoster and its relationship to varicella in Japan: a

10-year survey of 48,388 herpes zoster cases in Miyazaki prefecture. J Med Virol. 2009;81:2053–8. https://doi.org/10.1002/jmv.21599.
4. Sato K, Adachi K, Nakamura H, Asano K, Watanabe A, Adachi R, et al. Burden of herpes zoster and postherpetic neuralgia in Japanese adults 60 years of age or older: results from an observational, prospective, physician practice-based cohort study. J Dermatol. 2017;44:414–22. https://doi.org/10.1111/1346-8138.13639.
5. Takao Y, Miyazaki Y, Okeda M, Onishi F, Yano S, Gomi Y, et al. Incidences of herpes zoster and postherpetic neuralgia in Japanese adults aged 50 years and older from a community-based prospective cohort study: the SHEZ study. J Epidemiol. 2015;25:617–25. https://doi.org/10.2188/jea.JE20140210.
6. Hata A, Kuniyoshi M, Ohkusa Y. Risk of herpes zoster in patients with underlying diseases: a retrospective hospital-based cohort study. Infection. 2011;39:537–44. https://doi.org/10.1007/s15010-011-0162-0.
7. Papagianni M, Metallidis S, Tziomalos K. Herpes zoster and diabetes mellitus: a review. Diabetes Ther. 2018;9:545–50. https://doi.org/10.1007/s13300-018-0394-4.
8. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. Shingles prevention study group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352:2271–84.
9. Kamiya H, Asano Y, Ozaki T, Baba K, Kumagai T, Nagai T, et al. Varicella vaccine potency and stability during transport and delivery. Kansenshogaku Zasshi. 2011;85:161–5 (In Japanese).
10. Okada S, Kataoka C, Akechi M. An examination of the immunogenicity and safety of BK1303 (freeze-dried live attenuated varicella vaccine) in healthy adults aged 50 years or older: a phase III, single-center, open-label, uncontrolled trial. J Clin Ther Med. 2014;30:963–74 (In Japanese).
11. Benson CA, Andersen JW, Macatangay BJC, Mailliard RB, Rinaldo CR Jr, Read S, et al. Safety and immunogenicity of zoster vaccine live in HIV-infected adults with CD4+ cell counts above 200 cells/ml virologically supperessed on antiretroviral therapy. Clin Infect Dis. 2018 (In Press. https://doi.org/10.1093/cid/ciy242.
12. Hata A, Inoue F, Hamamoto Y, Yamasaki M, Fujikawa J, Kawahara H, et al. Efficacy and safety of live varicella zoster vaccine in diabetes: a randomized, double-blind, placebo-controlled trial. Diabet Med. 2016;33:1094–101. https://doi.org/10.1111/dme.13038.
13. Russell AF, Parrino J, Fisher CL Jr, Spieler W, Stek JE, Coll KE, et al. Safety, tolerability, and immunogenicity of zoster vaccine in subjects on chronic/maintenance corticosteroids. Vaccine. 2015;33:3129–34. https://doi.org/10.1016/j.vaccine.2015.04.090.
14. Schmader KE, Levin MJ, Gnann JW Jr, McNeil SA, Vesikari T, Betts RF, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clin Infect Dis. 2012;54:922–8. https://doi.org/10.1093/cid/cir970.
15. Simberkoff MS, Arbeit RD, Johnson GR, Oxman MN, Boardman KD, Williams HM, et al. Shingles prevention study group. Safety of herpes zoster vaccine in the shingles prevention study: a randomized trial. Ann Intern Med. 2010;152:545–54. https://doi.org/10.7326/0003-4819-152-9-201005040-00004.
16. Willis ED, Woodward M, Brown E, Popmihajlov Z, Saddier P, Annunziato PW, et al. Herpes zoster vaccine live: a 10 year review of post-marketing safety experience. Vaccine. 2017;35:7231–9. https://doi.org/10.1016/j.vaccine.2017.11.013.
17. Morrison VA, Oxman MN, Levin MJ, Schmader KE, Guatelli JC, Betts RF, et al. Shingles prevention study group. Safety of zoster vaccine in elderly adults following documented herpes zoster. J Infect Dis. 2013;208:559–63. https://doi.org/10.1093/infdis/jit182.
18. Okamoto S, Hata A, Sadaoka K, Yamanishi K, Mori Y. Comparison of varicella-zoster virus-specific immunity of patients with diabetes mellitus and healthy individuals. J Infect Dis. 2009;200:1606–10. https://doi.org/10.1086/644646.
19. Hata A, Inoue F, Yamasaki M, Fujikawa J, Kawasaki Y, Hamamoto Y, et al. Safety, humoral and cell-mediated immune responses to herpes zoster vaccine in subjects with diabetes mellitus. J Inf Secur. 2013;67:215–9. https://doi.org/10.1016/j.jinf.2013.04.010.
20. Koh JH, Lee J, Kim SH, Kwok SK, Ju JH, Park SH. Safety, and humoral and cell-mediated immune responses to herpes zoster vaccine in patients with rheumatoid arthritis. J Rheumatol. 2018;45:465–9. https://doi.org/10.3899/jrheum.170936.
21. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA. 2012;308:43–9.
22. Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. PLoS Med. 2013;10:e1001420. https://doi.org/10.1371/journal.pmed.1001420.
23. Langan SM, Thomas SL, Smeeth L, Margolis DJ, Nitsch D. Zoster vaccination is associated with a reduction of zoster in elderly patients with chronic kidney disease. Nephrol Dial Transplant. 2016;31:2095–8.

Ohfuji et al. BMC Infectious Diseases (2019) 19:400
https://doi.org/10.1186/s12879-019-4007-2

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Nationwide epidemiologic study of norovirus-related hospitalization among Japanese older adults

Satoko Ohfuji[1,2], Kyoko Kondo[3], Kazuya Ito[1,2], Tetsuo Kase[1,2], Akiko Maeda[1], Wakaba Fukushima[1,2], Taisei Masuda[4] and Munehide Kano[4*]

Abstract

Background: Older adults are vulnerable to hospitalization or death from norovirus infection, but the actual disease burden remains unknown. Therefore, we conducted a nationwide survey to estimate the number of inpatients with norovirus gastroenteritis and associated deaths among Japanese older adults.

Methods: We performed a nationwide two-step query targeting 4184 hospital departments selected from 17,575 departments using stratified random sampling according to the number of beds. We asked each department to complete a mail-back questionnaire on the annual numbers of inpatients with infectious gastroenteritis and associated deaths between administrative years 2012 and 2014, and the implementation status of norovirus infection testing. In a second query, we investigated the annual number of inpatients with norovirus gastroenteritis and associated deaths in departments that had reported infectious gastroenteritis inpatients in the first query. Clinical information was collected for inpatients with norovirus gastroenteritis in administrative year 2014.

Results: Norovirus testing for patients hospitalized for acute gastroenteritis was routinely conducted in 16% of the responding departments. Although half the departments responded that some acute gastroenteritis inpatients received such testing but others did not. In this situation, numbers of inpatients with norovirus gastroenteritis in Japan were estimated as 31,800 (95% CI: 25,700-37,900) in administrative year 2012, 21,600 (95% CI: 17,700–25,500) in administrative year 2013, and 15,700 (95% CI: 12,900–18,500) in administrative year 2014. The estimated number of associated deaths was approximately 600 in each administrative year. Factors associated with death included higher age, living in long-term care facilities, underlying illnesses such as chronic respiratory diseases, and complications such as aspiration pneumonia.

Conclusions: The actual number of norovirus inpatient would be higher than the estimated here due to the low rate of routinely implemented norovirus testing. Considering Japan's rapidly aging society and the disease burden of norovirus infection among Japanese older adults, it is important to protect this high-risk population from norovirus infection.

Keywords: Older adults, Epidemiology, Hospitalization, Mortality, Norovirus gastroenteritis

Background

Noroviruses typically circulate from late fall through winter and causes gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain. The symptoms are generally mild and resolve within a few days. In older adults, however, norovirus infection can be serious and in some cases can lead to death from pulmonary aspiration of vomit. A 2016 review found hospitalization for norovirus and associated medical expenses and mortality rates are high in older adults [1]. As Japan is rapidly becoming a "super-aging" society, measures to maintain the health of older people are crucial [2]. However, there are currently no therapeutic medications for norovirus gastroenteritis, and symptomatic therapy is the main treatment. For these reasons, vaccines to prevent norovirus infection are under development [3].

In order to introduce vaccines, accurate information about the disease burden of norovirus gastroenteritis is

* Correspondence: munehide.kano@takeda.com
[4]Global Vaccine Business Unit, Takeda Pharmaceutical Company Limited, 1-1 Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103-8668, Japan
Full list of author information is available at the end of the article

needed. In Japan, the incidence of infectious gastroenteritis can be estimated from disease surveillance data obtained as part of the National Epidemiological Surveillance of Infectious Diseases [3]. However, the surveillance of infectious gastroenteritis is based on sentinel surveillance reports from pediatric hospital departments, and so it is not possible to estimate the potential number of older adults affected by norovirus. Furthermore, infectious gastroenteritis includes not only norovirus gastroenteritis, but also infections by other viruses such as rotavirus, adenovirus, and sapovirus, as well as bacterial infections [4, 5]. Consequently, the number of patients infected with each pathogen is unknown. Moreover, many cases of infectious gastroenteritis resolve within a few days so it is unusual for a diagnostic examination to be conducted in typical outpatient settings.

Therefore we conducted a nationwide epidemiologic study in Japan to assess the number of Japanese older adults hospitalized for infectious gastroenteritis and norovirus gastroenteritis and to clarify the clinical and epidemiologic features of these patients.

Methods

The study was conducted in accordance with existing procedures proposed by the Research Committee on Epidemiology of Intractable Diseases in Japan [6]. The general method has been described previously [7–9]. The study consisted of two queries: the first intended to estimate the number of inpatients with infectious gastroenteritis among older adults, and the second to estimate the number of inpatients with norovirus gastroenteritis and to clarify their clinical and epidemiologic features.

First query

A number of hospital departments were selected using stratified random sampling from a total of 17,575 departments of internal medicine, digestive diseases, gastroenterology, respiratory diseases, and cardiovascular diseases nationwide. These are the departments in which older people with aggravated infectious gastroenteritis predominantly receive treatment in Japan. The sampling was stratified by the number of hospital beds; sampling proportions were as follows: general hospitals with 99 beds or fewer, 5%; 100–199 beds, 10%; 200–299 beds, 20%; 300–399 beds, 40%; 400–499 beds, 80%; 500 beds or more, 100%; and university hospitals, 100%. A final total of 4184 departments were selected (Additional file 1: Table S1).

In January 2016, we asked these departments to complete a mail-back questionnaire, which was designed to ascertain the presence or absence of hospitalized patients with infectious gastroenteritis among adults aged ≥60 years between administrative years 2012 and 2014 (i.e., between April 1, 2012, and March 31, 2015). The information of the hospitalized patients included both community-acquired infection and nosocomial infection. We obtained data by administrative year, as hospital reporting is typically done in this manner in Japan. If present, the number of inpatients and deaths in each administrative year were additionally solicited. We also collected information on whether norovirus tests were routinely conducted at the department (routinely conducted, often conducted, or not conducted). A reminder was mailed to non-respondents in April 2016.

Second query

In September 2016, we sent a second query to departments that had responded "yes" to the presence of patients hospitalized for infectious gastroenteritis in the first query. The second query was to collect data on the numbers of inpatients and deaths of those diagnosed with norovirus gastroenteritis among adults aged ≥60 years between administrative years 2012 and 2014. Determination of norovirus gastroenteritis depended on the physician's diagnosis of each hospital. Clinical diagnosis without viral examination such as possible epidemiological link was allowed for counting number of norovirus gastroenteritis. To take into account the nosocomial infected cases, cases of norovirus gastroenteritis diagnosed not only at admission but also during the hospital stay were included. For patients hospitalized in administrative year 2014, the following clinical information was also collected: birth month and birth year, sex, residence at the onset of gastroenteritis (i.e., home, long-term care facility, or hospital), underlying diseases (hypertension, heart disease, diabetes, stroke, malignant tumor, renal disease, chronic respiratory disease, liver disease, hematological disorders, or collagen diseases), date of admission, date of discharge, possible cause of infection based on the physician's medical examination including interview to the patients (contaminated food, contact with infected person(s), disease epidemic in the area), results of tests for norovirus, clinical symptoms (presence, frequency, and duration of diarrhea and vomiting; presence of fever), date of symptom onset and duration, complicated diseases (such as aspiration pneumonia), laboratory data at the time of admission, treatment (e.g., intravenous drip, antibiotics, and intensive care unit therapy), clinical outcome (recovered, moved to another hospital, self-discharged, or deceased), and cause of death if deceased. We assumed that the clinical information of norovirus gastroenteritis did not change significantly between administrative years 2012 and 2014, and due to research budget constraints we did not obtain the clinical information for patients hospitalized in administrative years 2012 and 2013, but choose to investigate the latest information available, i.e. in administrative year 2014. We confirmed our assumption that the epidemic trend of norovirus infection in the three administrative years was stable in Japan using national surveillance data

[10]. We mailed a reminder to non-respondents in November 2016. Additionally, we asked the departments that had responded to confirm or revise those parts of the previously returned questionnaire that had missing or conflicting information. If there were missing data even after confirmation or revision, the data were considered incomplete.

Statistical analysis

Accounting for sampling and response proportions in the first query, we estimated the total numbers of inpatients and deaths due to infectious gastroenteritis among adults aged ≥60 years between administrative years 2012 and 2014 according to the following formula: estimated total number of inpatients = reported number of inpatients / (sampling proportion × response proportion). Additionally, 95% confidence intervals (CIs) were calculated with an assumption of multinomial hypergeometric distribution [6–9].

We also estimated the total numbers of inpatients and deaths due to norovirus gastroenteritis among adults aged ≥60 years between administrative years 2012 and 2014 using data from the second query. In this calculation, we used the following formula: estimated total number of inpatients with norovirus gastroenteritis = estimated total number of inpatients with infectious gastroenteritis × proportion of reported number of inpatients with norovirus gastroenteritis among the reported number of inpatients with infectious gastroenteritis. This latter proportion was based on information from departments that responded to the second query. Total estimated numbers and 95% CIs were rounded to three significant digits, except for the hundreds, which were rounded to two significant digits.

Hospitalization and mortality rates in each administrative year were calculated using the number of Japanese people aged ≥60 years at October 1 in each administrative year (i.e., 41,038,000 in administrative year 2012, 41,561,000 in administrative year 2013, and 41,980,000 in administrative year 2014) [11–13].

The clinical characteristics of inpatients with norovirus gastroenteritis were also examined. Age at admission was calculated using information on birth month and birth year and date of admission. If the admission date had not been recorded, it was regarded as October 1 for the calculation. Disease severity was assessed using modified Vesikari scores [14]. In order to assess the disease severity using laboratory data such data were categorized into two or three levels according to standard values for the Japanese population [15]. To examine factors associated with death, a logistic regression model was used to obtain odds ratios (ORs) and 95% CIs. Since age and sex are the important predictors for death, these variables were included as co-factors in a logistic regression model.

All tests were two-sided. All analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

Results

In the first query, 1325 out of 4184 departments responded (response proportion: 31.7%). Among these, 561 departments reported the presence of inpatients with infectious gastroenteritis; numbers of reported inpatients were 9857 in administrative year 2012, 8361 in administrative year 2013, and 8410 in administrative year 2014 (Additional file 1: Table S1). The response rates from gastroenterology departments in large hospitals were low (e.g. 20% in five University hospitals, 0% in four ≥500 beds hospitals). Since there were only nine gastroenterology departments, the low response rate did not have a major impact on the present results (Additional file 1: Table S1). Based on the results of the first query, the numbers of inpatients with infectious gastroenteritis among Japanese adults aged ≥60 years were estimated to be 118,000 (95% CI: 95,700–141,000) in administrative year 2012, 95,100 (95% CI: 77,700–112,000) in administrative year 2013, and 96,900 (95% CI: 79,500–114,000) in administrative year 2014. Infectious gastroenteritis was estimated to have caused 2060 (95% CI: 1370–2750), 1940 (95% CI: 1230–2640), and 1970 (95% CI: 1280–2650) deaths among Japanese adults aged ≥60 years in administrative years 2012, 2013, and 2014, respectively (Table 1).

In the second query, 271 out of 561 departments responded (response proportion: 48.0%), and 126 departments reported the presence of inpatients with norovirus gastroenteritis. Among these departments, the proportions of reported number of inpatients with norovirus gastroenteritis among the reported number of inpatients with infectious gastroenteritis were 26.9% in administrative year 2012, 22.7% in administrative year 2013, and 16.2% in administrative year 2014. Thus, the estimated numbers of inpatients with norovirus gastroenteritis among Japanese adults aged ≥60 years were calculated as 31,800 (95% CI: 25,700–37,900) in administrative year 2012, 21,600 (95% CI: 17,700–25,500) in administrative year 2013, and 15,700 (95% CI: 12,900–18,500) in administrative year 2014 (Table 2). The hospitalization rates (per 10,000 persons) were 7.75, 5.20, and 3.74, respectively. Among the reported number of deaths from infectious gastroenteritis 31.3% in administrative year 2012, 30.0% in administrative year 2013, and 29.6% in administrative year 2014 were due to norovirus, and norovirus gastroenteritis was estimated to have caused a total of 650 (95% CI: 430–860), 580 (95% CI: 370–790), and 580 (95% CI: 380–790) deaths in administrative

Table 1 Estimated number of hospitalized patients and deaths due to infectious gastroenteritis among adults aged ≥60 years in Japan

Stratum (No. of hospital beds)	Administrative year 2012		Administrative year 2013		Administrative year 2014	
	Hospitalized patients	Deaths	Hospitalized patients	Deaths	Hospitalized patients	Deaths
University hospital	1366	16	1251	30	1119	14
≥500	9502	469	8152	461	7684	415
400–499	9152	181	7797	180	8310	182
300–399	20,879	470	17,919	448	19,072	583
200–299	18,365	133	15,640	119	15,200	191
100–199	39,120	661	28,289	697	27,879	512
< 99	20,056	130	16,012	0	17,632	74
Total estimated number	118,000	2060	95,100	1940	96,900	1970
(95% confidence interval)	(95,700–141,000)	(1370–2750)	(77,700–112,000)	(1230–2640)	(79,500–114,000)	(1280–2650)

years 2012, 2013, and 2014, respectively (Table 2). The respective mortality rates (per 100,000 persons) were 1.58, 1.40, and 1.38.

Figure 1 shows the implementation status of norovirus infection testing in Japanese hospitals. Approximately 15.8% of departments replied that norovirus testing (mainly rapid antigen testing) was "routinely conducted" for patients hospitalized for acute gastroenteritis; 49.7% of departments responded that such testing was "often conducted", which means that some acute gastroenteritis inpatients received norovirus testing but other acute gastroenteritis inpatients did not; 22.9% of departments did not conduct norovirus tests for patients hospitalized for gastroenteritis. In particular, university hospitals or general hospitals with larger numbers of beds tended to respond "not conducted."

Table 3 summarizes the clinical characteristics of inpatients with norovirus gastroenteritis in administrative year 2014. Male patients accounted for 42% of inpatients. Approximately 55% of patients were aged ≥80 years. Most patients (90%) had underlying illnesses. Regarding the possible cause of infection, only 9% were suspected to be caused by contaminated food, and 21% were presumably caused by contact with an infected person considered to be possible epidemiological link. However, the cause was not known for about half of the patients. Only 61% of inpatients received norovirus testing. Among those, half had positive results. Most patients had diarrhea and half had symptoms of vomiting or fever. Approximately 6% of cases were complicated by aspiration pneumonia. The median duration of hospital admission was 11 days; although 93% of patients recovered, 4% died. The main cause of death was pneumonia ($n = 7$). Other causes were as follows: heart failure ($n = 4$), malignant tumor (n = 4), and ileus, digestive tract hemorrhage, respiratory failure, multi-organ failure, and perforation of the digestive tract ($n = 1$ each).

Higher mortality in 470 clinical diagnosed cases was observed among males, older patients, those living in long-term care facilities, those with particular underlying illnesses such as chronic respiratory diseases, and those with complications such as aspiration pneumonia (Table 4). Female patients had a significantly decreased adjusted OR (aOR) for death compared with male patients (aOR = 0.41, 95% CI: 0.16–1.00). Moreover, those living in long-term care facilities (aOR = 3.39, 95% CI: 1.15–9.55), those with chronic respiratory diseases (aOR = 3.90, 95% CI: 1.01–12.5), and those with aspiration

Table 2 Estimated number of hospitalized patients and deaths due to norovirus gastroenteritis among adults aged ≥60 years in Japan

Stratum (No. of hospital beds)	Administrative year 2012		Administrative year 2013		Administrative year 2014	
	Hospitalized patients	Deaths	Hospitalized patients	Deaths	Hospitalized patients	Deaths
University hospital	367	5	284	9	181	4
≥500	2552	147	1853	138	1246	123
400–499	2458	57	1772	54	1347	54
300–399	5608	147	4072	135	3092	172
200–299	4932	42	3554	36	2464	56
100–199	10,507	207	6429	209	4519	151
< 99	5387	41	3639	0	2858	22
Total estimated number	31,800	650	21,600	580	15,700	580
(95% confidence interval)	(25,700–37,900)	(430–860)	(17,700–25,500)	(370–790)	(12,900–18,500)	(380–790)

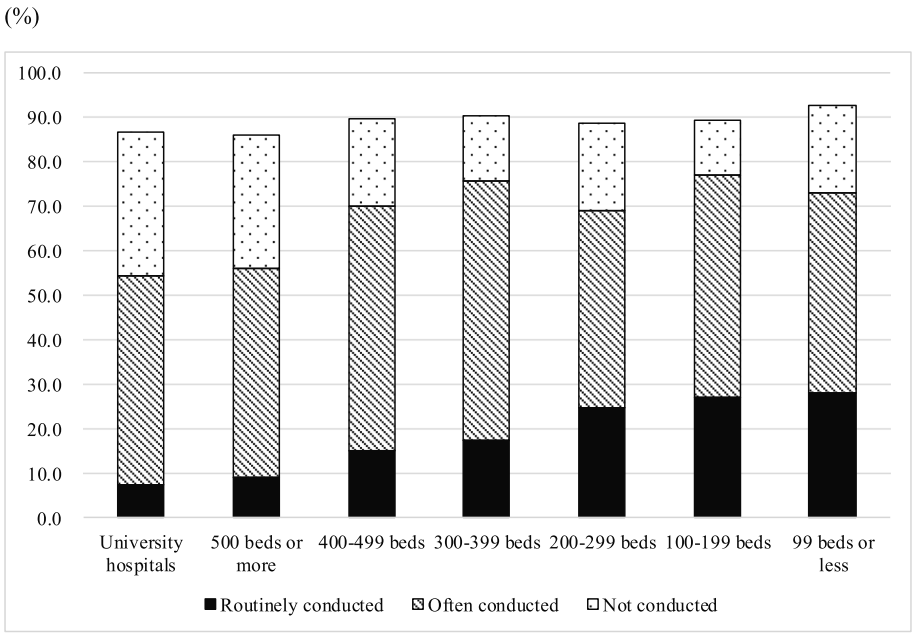


Fig. 1 Implementation status of norovirus infection testing at university hospitals and general hospitals according to number of hospital beds. According to answers of "unknown data", each total has not reached 100%

pneumonia (aOR = 8.97, 95% CI: 3.06–24.7) had significantly increased aORs for death.

Discussion

The results of our study suggest that approximately 100,000 persons aged ≥60 years are hospitalized for infectious gastroenteritis annually in Japan, of which approximately one-quarter are hospitalized for norovirus gastroenteritis. The number of inpatients with norovirus gastroenteritis was approximately 15,000 in administrative year 2014 (when the disease occurred at a low rate) and approximately 30,000 in administrative year 2012 (when it became epidemic, with approximately 600 annual deaths). The annual hospitalization rate (per 10,000 population) for norovirus gastroenteritis was 3.74–7.75 and the annual mortality rate (per 100,000 population) was 1.38–1.58 among persons aged ≥60 years. However, since the proportion of departments which routinely conducted norovirus testing for acute gastroenteritis inpatients was lower than expected, the actual number of norovirus inpatients would be higher than the estimated number here.

The present study showed a large number of inpatients in administrative year 2012 and relatively few inpatients in administrative year 2014, and this trend was consistent with the National Surveillance Data of infectious gastroenteritis patients reported by sentinels [4]. Additionally, the proportion of norovirus inpatients among infectious gastroenteritis inpatients in the present study (16–27%) was similar to that reported in a meta-analysis of 175 research papers (17–20%) [16]. However, the proportion was somewhat lower than the proportions reported by other studies in Japan (34–39%) [17–19]. As norovirus gastroenteritis is an infectious disease, its epidemic status varies between geographical regions. It is possible therefore that the differences in the proportion of norovirus patients between the present study and other studies in Japan merely indicate differences in epidemic status among geographical regions.

In Japan, norovirus testing is not routinely conducted by all hospitals so it is possible that the results of our study were influenced by the status of implementation of testing at the hospitals that were surveyed. In fact, institutions not testing for norovirus accounted for one-quarter of the hospitals that were studied. In the present study, it is possible that such institutions reported having no inpatients with norovirus gastroenteritis. Therefore, the present data may underestimate the annual number of inpatients with norovirus gastroenteritis and also the proportion of nosocomial infection. In addition, university hospitals or general hospitals with larger numbers of beds tended to report that they had not conducted norovirus testing. We assumed that these hospitals were more likely to contain patients with infectious gastroenteritis and assigned a higher sampling proportion to these hospitals in the study protocol. However, the unexpectedly lower implementation status of norovirus testing might have affected the study results. One study that estimated the burden of norovirus gastroenteritis in Japan using a modelling approach accounting for the absence of routine diagnostic testing showed higher incidence rates in

Table 3 Characteristics of patients hospitalized for norovirus gastroenteritis ($N = 470$)

Characteristics		n (%) or median (range)[a]	Characteristics		n (%) or median (range)[a]
Sex	Male	194 (42)	Laboratory data at the time of admission		
Age (years)	60–69	66 (14)	White blood cell (/μL)	Decreased	17 (4)
	70–79	145 (31)		Normal	231 (51)
	≥80	259 (55)		Increased	202 (45)
Residence at symptom onset			Hemoglobin (g/dL)	Decreased	190 (42)
	Home	287 (62)		Normal	249 (55)
	Long-term care facility	62 (13)		Increased	17 (4)
	Hospital	115 (25)	Platelet count ($\times 10^4$/μL)	Decreased	47 (10)
Underlying illnesses		424 (90)		Normal	386 (84)
	Hypertension	213 (45)		Increased	28 (6)
	Heart disease	121 (26)	C-reactive protein (mg/dL)	Increased	349 (77)
	Diabetes	106 (23)	Blood sugar (mg/dL)	Decreased	18 (5)
	Stroke	121 (26)		Normal	102 (26)
	Malignant tumor	66 (14)		Increased	268 (69)
	Renal disease	38 (8)	Albumin (g/dL)	Decreased	230 (59)
	Chronic respiratory disease	32 (7)	Aspartate aminotransferase (IU/L)	Increased	205 (45)
	Liver disease	24 (5)	Creatinine (mg/dL)	Increased	200 (44)
	Hematological disorders	13 (3)	Sodium (mEq/L)	Decreased	81 (18)
	Collagen diseases	7 (1)		Normal	375 (82)
Possible causes of infection				Increased	4 (1)
	Contaminated food	43 (9)	Potassium (mEq/L)	Decreased	106 (23)
	Contact with infected person(s)	95 (21)		Normal	329 (72)
	Disease epidemic in the area	99 (21)		Increased	24 (5)
Tested for norovirus		287 (61)	Chloride (mEq/L)	Decreased	54 (12)
Test result	Positive	153 (53)		Normal	376 (83)
Clinical symptoms at the time of admission				Increased	23 (5)
Diarrhea	Present	377 (80)	Treatment		
	Duration (days)	4 (1–36)[a]	Intravenous drip		386 (82)
	Frequency per day	3.5 (1–33)[a]	Antibiotics		201 (43)
Vomiting	Present	232 (49)	Oxygen supplementation		73 (16)
	Duration (days)	2 (1–14)[a]	Intensive care unit therapy		10 (2)
	Frequency per day	1.5 (1–25)[a]	Use of respirator		7 (1)
Fever	Present	262 (56)	Duration of hospital admission (days)		11 (1–2359)[a]
	Maximum fever (°C)	37.85 (37.0–40.3)[a]	Clinical outcome	Recovered	438 (93)
Complications	Aspiration pneumonia	28 (6)		Moved to hospital	10 (2)
	Others	35 (8)		Deceased	21 (4)
Modified Vesikari scale		8 (0–16)[a]		Self-discharged	1 (0.2)

[a]median (range)

Table 4 Association between selected background characteristics and death from norovirus gastroenteritis[a]

Characteristics		Mortality	Univariate analysis	Age/sex-adjusted analysis
		n/N (%)	OR (95% CI)	aOR (95% CI)
Sex	Male	12/194 (6)	1.00	1.00
	Female	9/273 (3)	0.52 (0.21–1.25)	0.41 (0.16–1.00)
Age (years)	60–69	2/66 (3)	1.00	1.00
	70–79	3/145 (2)	0.68 (0.11–5.22)	0.69 (0.11–5.35)
	≥80	16/259 (6)	2.11 (0.58–13.5)	2.63 (0.71–17.1)
			(Trend $P = 0.11$)	(Trend $P = 0.05$)
Residence at symptom onset	Home	11/287 (4)	1.00	1.00
	Long-term care facility	7/62 (11)	3.19 (1.13–8.48)	3.39 (1.15–9.55)
	Hospital	3/115 (3)	0.67 (0.15–2.20)	0.67 (0.15–2.22)
Underlying illnesses	Absent	1/45 (2)	1.00	1.00
	Present	20/424 (5)	2.18 (0.44–39.5)	2.16 (0.43–39.4)
Chronic respiratory disease	Absent	17/438 (4)	1.00	1.00
	Present	4/32 (13)	3.54 (0.97–10.4)	3.90 (1.01–12.5)
Collagen diseases	Absent	20/463 (4)	1.00	1.00
	Present	1/7 (14)	3.69 (0.19–23.1)	4.11 (0.21–28.1)
Hematological disorders	Absent	19/457 (4)	1.00	1.00
	Present	2/13 (15)	4.19 (0.62–17.1)	4.40 (0.64–18.9)
Complications				
Aspiration pneumonia	Absent	14/439 (3)	1.00	1.00
	Present	7/28 (25)	10.1 (3.53–27.2)	8.97 (3.06–24.7)
Others	Absent	15/427 (4)	1.00	1.00
	Present	6/35 (17)	5.68 (1.91–15.2)	5.42 (1.79–14.8)

Abbreviations: *OR* odds ratio, *aOR* adjusted odds ratio, *CI* confidence interval
[a]Logistic regression model

the elderly than our study [20]. However, the database used in that study had relatively few older adults and therefore may not have been representative of the Japanese population. Compared with the previous study, our findings seem to suggest a lower norovirus disease burden in older adults according to laboratory-confirmed cases. This represents a possible limitation of our study in that many hospitals did not conduct norovirus testing. Another limitation was a lower response proportion to the first query (31.7%), which may have introduced bias. According to a nationwide epidemiologic investigation manual issued by the Japanese Ministry of Health, Labour and Welfare [5], a response proportion of approximately 60% can produce a reliable estimation of number of patients; however, we did not obtain this response proportion. If non-response were associated with nosocomial norovirus infection due to the hesitancy to disclose negative clinical practice in hospitals, the present results might be biased. In general, however, medical institutes that are highly conscious of measures against infectious diseases, such as having their own manual for infectious diseases, are likely to have responded in our study, and their responses seemed to be highly reliable. On the other hand, in the non-response departments, norovirus gastroenteritis may not be sufficiently understood. In the present study protocol, assuming that non-response departments had a similar proportion of inpatients with norovirus gastroenteritis as those departments which responded, we estimated the number of inpatients or deaths with norovirus gastroenteritis in Japan. However, we cannot deny the possibility that precision of the present results may be low, although we believe that the present results may be validated.

The annual hospitalization and mortality rates for norovirus gastroenteritis in the present study are similar to those in other countries. A systematic review of 39 studies in adults aged > 65 years worldwide reported the hospitalization rate for norovirus gastroenteritis as 1–19 per 10,000 persons and the mortality rate as 0.4–3.2 per 100,000 persons [21]. Our results fall within these ranges. The systematic review also reported the annual rate of outpatient visits for norovirus gastroenteritis as 18–54 per 10,000 persons and the annual incidence rate as 29–125 per 10,000 persons. In this study, we did not obtain information on outpatient visits and incidence;

thus, we cannot compare these rates. If the results of the systematic review are applied to Japan, the number of outpatient visits for norovirus gastroenteritis among the population aged ≥60 years (42.75 million, October 2016) would be estimated at 76,950–230,850, and the annual number of incident cases would be estimated at 123,975–534,375, suggesting that norovirus gastroenteritis has a substantial influence on the health of Japanese older adults.

We found that the possible cause of norovirus gastroenteritis was consumption of contaminated food in 9% of inpatients and person-to-person transmission in 21%. Compared with an outbreak investigation conducted in Spain, the present study found a higher proportion of cases of unknown cause; in the Spanish outbreak investigation, 42% of cases were probably caused by consumption of contaminated food and 52% were likely caused by person-to-person transmission [22]. The present results highlight the difficulties in determining the cause of norovirus gastroenteritis infection occurring in the community.

Regarding clinical symptoms, diarrhea was reported in 80% of cases, vomiting in 49%, and fever in 56%. These proportions are lower than those reported in pediatric studies. In young children in an Israeli study diarrhea was reported in 81%, vomiting in 86%, and fever in 64% of patients [23]. Disease severity was lower in the present study than in a study of young children conducted in Taiwan, which reported a median Vesikari value of 12.5 [24]. However, intravenous drip was more often administered to inpatients in the present study compared with children in the Israeli study (82% vs. 68%) [23]. The median duration of hospital admission was longer in the present study compared with children in the Taiwanese study (11 days vs. 3 days) [24]. Differences in treatment may simply reflect differences in medical care between study regions. Nonetheless, the present results also suggest that, compared with children, older adults tend to experience more dehydration and require more time to recover. Such information may be important when the disease burden of norovirus gastroenteritis is considered from a medical economics perspective.

In our study, 4% of hospitalized patients died. Factors associated with death include greater age, living in long-term care facilities, underlying illnesses (particularly chronic respiratory diseases), and complications such as aspiration pneumonia. In a study of 1877 cases in an outbreak of norovirus gastroenteritis in England and Wales between 1992 and 2000, all deaths from norovirus gastroenteritis occurred in patients who were hospitalized or institutionalized [25]. A systematic review of reports from 1988 to 2011 found more deaths among older adults, those living in long-term care facilities, and those in an immunosuppressed state, and the most common cause of death was aspiration pneumonia (32%) [26]. Older adults with underlying illnesses (particularly chronic respiratory diseases) are considered to be highly susceptible to infectious diseases, which may lead to a high risk of death when norovirus gastroenteritis develops as a complication. Taken together, the factors associated with death in the present study are consistent with these previous reports. Therefore, we hope that these results will provide useful information for the future introduction of vaccine measures.

Conclusions

In conclusion, although the actual number of norovirus inpatients is probably higher than the estimates here due to the low rate of routinely implemented norovirus testing, the annual number of patients hospitalized for norovirus gastroenteritis was estimated to range from 15,700 (administrative year 2014) to 31,800 (administrative year 2012), and the annual number of deaths was estimated to be between 580 (administrative years 2013, 2014) and 650 (administrative year 2012). The annual hospitalization rate was 3.74 (administrative year 2014) to 7.75 (administrative year 2012) per 10,000 persons, and the annual mortality rate was 1.38 (administrative year 2014) to 1.58 (administrative year 2012) per 100,000 persons. The factors associated with death among inpatients with norovirus gastroenteritis included higher age, living in long-term care facilities, underlying illnesses (particularly chronic respiratory diseases), and complications such as aspiration pneumonia. Considering Japan's rapidly aging society and the disease burden of norovirus infection among Japanese older adults, it is important to protect this high-risk population from norovirus infection.

Additional file

Additional file 1: Table S1. The numbers of reported inpatients and reported deaths due to infectious gastroenteritis among Japanese older adults: results of the first query. (DOCX 24 kb)

Abbreviations

aOR: Adjusted odds ratio; CI: Confidence interval; OR: Odds ratio

Acknowledgments

We thank all the medical doctors for participating in this study despite their busy schedules in medical practice, education, and research. We also thank Yoshio Hirota (College of Healthcare Management), Takashi Nakano (Kawasaki Medical School), Tomoyuki Tanaka (Hidaka General Hospital), Naomi Sakon (Osaka Institute of Public Health), Motoki Ishibashi, Eunhee Chung, Andrew Melli (SOUSEIKAI, Global Clinical Research Center), Koji Suzuki, Tsutomu Aoki, Miwako Ozawa, Toshie Amano, Kazufusa Ito, and Hiroto Takahashi (Mediscience Planning Inc.) for their valuable help. Diane Williams, PhD, from Edanz Medical Writing edited a draft of this manuscript.

Funding

This work was supported by funding from Takeda Pharmaceutical Company Limited. The study sponsor was involved in the design and overall management of the study, and in the decision to submit the paper for publication.

Availability of data and materials
The dataset analyzed during the current study are available upon request to corresponding author.

Authors' contributions
SO contributed to study design, overall management, statistical analysis, data interpretation, and drafting of the work or revising it critically for important intellectual content. KI and KK contributed to study design, and data management and statistical analysis. TK, AM, and WF contributed to study design and data interpretation. SO, TM, and MK developed the study concept. TM and MK engaged project managements. All authors provided comments on the drafts and have read and approved the final manuscript.

Ethics approval and consent to participate
The study protocol was approved by the ethics committees of Osaka City University Graduate School of Medicine (No. 3140) and Takeda Pharmaceutical Company Limited (EPI-011). Informed consent of each patient was waived by the ethics committees (No. 3140 and EPI-011), because this study used anonymized data which was retrospectively collected from medical records at the responded medical institutes.

Consent for publication
Not applicable.

Competing interests
SO received a research grant from Takeda Pharmaceutical Company Limited. TM and MK are employees of Takeda Pharmaceutical Company Limited. Other authors declare no conflicts of interest.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
[1]Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan. [2]Research Center for Infectious Disease Sciences, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan. [3]Administration Division, Osaka City University Hospital, 1-5-7 Asahi-machi, Abeno-ku, Osaka 545-8586, Japan. [4]Global Vaccine Business Unit, Takeda Pharmaceutical Company Limited, 1-1 Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103-8668, Japan.

Received: 29 August 2018 Accepted: 22 April 2019
Published online: 09 May 2019

References

1. Lopman BA, Steele D, Kirkwood CD, Parashar UD. The vast and varied global burden of norovirus: prospects for prevention and control. PLoS Med. 2016; 13:e1001999.
2. Muramatsu N, Akiyama H. Japan: super-aging society preparing for the future. Gerontologist. 2011;51:425–32.
3. Glass RI, Parashar UD, Estes MK. Norovirus gastroenteritis. N Engl J Med. 2009;361:1776–85.
4. Ministry of Health, Labour and Welfare/National Institute of Infectious Diseases. Infectious Diseases Weekly Report, Japan [in Japanese]. IDWR. 2016;18:11 https://www0.niid.go.jp/niid/idsc/idwr/IDWR2016/idwr2016-01.pdf (accessed April 26, 2017).
5. Nakamura N, Kobayashi S, Minagawa H, Matsushita T, Sugiura W, Iwatani Y. Molecular epidemiology of enteric viruses in patients with acute gastroenteritis in Aichi prefecture, Japan, 2008/09-2013/14. J Med Virol. 2016;88:1180–6.
6. Kawamura T, editor. The manual of nationwide epidemiologic investigation to ascertain the number of patients with intractable diseases and their related clinical epidemiologic features, 2nd Edition [in Japanese]. Tokyo: The Ministry of Health, Labour and Welfare, Japan; 2006.
7. Hashimoto S, Fukutomi K, Nagai M, et al. A note on methods for estimating the number of patients in the nationwide epidemiological survey on intractable diseases [in Japanese. Nippon Koshu Eisei Zasshi. 1990;37:768–74.
8. Hashimoto S, Fukutomi K, Nagai M, et al. A method of interval estimation for number of patients in the nationwide epidemiological survey on intractable diseases [in Japanese. Nippon Koshu Eisei Zasshi. 1991;38:880–3.
9. Nakamura Y, Matsumoto T, Tamakoshi A, et al. Prevalence of idiopathic hypoparathyroidism and pseudohypoparathyroidism in Japan. J Epidemiol. 2000;10:29–33.
10. Ministry of Health, Labour and Welfare/National Institute of Infectious Diseases. Current information of detection of norovirus and other gastroenteritis viruses [in Japanese]. https://www.niid.go.jp/niid/ja/iasr-noro.html [accessed February 19, 2019]
11. Population Estimates, Statistics Bureau of the Ministry of Internal Affairs and Communications, Japan. http://www.e-stat.go.jp/SG1/estat/List.do?lid=000001109855 (accessed April 20, 2017).
12. Population Estimates, Statistics Bureau of the Ministry of Internal Affairs and Communications, Japan. http://www.e-stat.go.jp/SG1/estat/List.do?lid=000001118081 (accessed April 20, 2017).
13. Population Estimates, Statistics Bureau of the Ministry of Internal Affairs and Communications, Japan. http://www.e-stat.go.jp/SG1/estat/List.do?lid=000001132435 (accessed April 20, 2017).
14. Atmar RL, Bernstein DI, Harro CD, et al. Norovirus vaccine against experimental human Norwalk virus illness. N Engl J Med. 2011;365:2178–87.
15. Website of SRL General Testing Information. http://test-guide.srl.info/ (accessed February 1, 2017).
16. Ahmed SM, Hall A, Robinson AE, et al. Global prevalence of norovirus in cases of gastroenteritis: a systematic review and meta-analysis. Lancet Infect Dis. 2014;14:725–30.
17. Thongprachum A, Chan-it W, Khamrin P, et al. Molecular epidemiology of norovirus associated with gastroenteritis and emergence of norovirus G2.4 variant 2012 in Japanese pediatric patients. Infect Genet Evol. 2014;23:65–73.
18. Thongprachum A, Takahashi S, Kalesaran AFC, et al. Four-year study of viruses that cause diarrhea in Japanese pediatric outpatients. J Med Virol. 2015;87:1141–8.
19. Kawada J, Arai N, Nishimura N, et al. Clinical characteristics of norovirus gastroenteritis among hospitalized children in Japan. Microbiol Immunol. 2012;56:756–9.
20. Chang CH, Sakaguchi M, Weil J, Verstraeten T. The incidence of medically-attended norovirus gastro-enteritis in Japan: modelling using a medical care insurance claims database. PLoS One. 2018;13:e0195164.
21. Lindsay L, Wolter J, De Coster I, Van Damme P, Verstraeten T. A decade of norovirus disease risk among older adults in upper-middle and high income countries: a systematic review. BMC Infect Dis. 2015;15:425.
22. Torner N, Martinez A, Broner S, et al. Epidemiology of acute gastroenteritis outbreaks caused by human calicivirus (norovirus and sapovirus) in Catalonia: a two year prospective study, 2010-2011. PLoS One. 2016;11: e0152503.
23. Muhsen K, Kassem E, Rubinstein U, et al. Incidence and characteristics of sporadic norovirus gastroenteritis associated with hospitalization of children less than 5 years old age in Israel. Pediatr Infect Dis J. 2013;32:688–90.
24. Ku MS, Sheu JN, Lin CP, Chao YH, Chen SM. Clinical characteristics and outcome in norovirus gastroenteritis. Indian J Pediatr. 2014;81:1321–6.
25. Lopman BA, Adak GK, Reacher MH, Brown DWG. Two epidemiologic patterns of norovirus outbreaks: surveillance in England and Wales, 1992-2000. Emerg Infect Dis. 2003;9:71–7.
26. Trivedi TK, Desai R, Hall AJ, Patel M, Parashar UD, Lopman BA. Clinical characteristics of norovirus-associated deaths: a systematic review. Am J Infect Cont. 2013;41:654–7.

Case Report

A case report on parainfluenza virus type 4a infection in a 1-year-old boy with biphasic fever

Keiko Oda[1,2], Hidekazu Nishimura[2], Ohshi Watanabe[2], Toru Kubo[2,3,4], Shizuo Shindo[5]

[1]Department of Health Management, College of Healthcare Management, Miyama, Japan; [2]Virus Research Center, Clinical Research Division, Sendai Medical Center, National Hospital Organization, Sendai, Japan; [3]Nagasaki Genbaku Isahaya Hospital, Isahaya, Nagasaki, Japan; [4]Department of Virology, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Nagasaki, Japan; [5]Shindo Children's Clinic, Fukuoka, Japan

Correspondence to: Hidekazu Nishimura, MD, PhD. Virus Research Center, Clinical Research Division, Sendai Medical Center, National Hospital Organization, 2-8-8, Miyagino, Miyagino, Sendai, Miyagi 983-8520, Japan. Email: hide-nishimura@mte.biglobe.ne.jp.

Abstract: A 1-year-old boy was infected with parainfluenza virus type 4a (PIV4a) during an influenza epidemic in January 2016. His body temperature was 38.2 ℃ on day 1 of the illness followed by an intermittent phase of 36.5 ℃ on days 2 and 3, and it rose again on day 3 and peaked at 39.6 ℃ on day 4, of which the fever pattern was reminiscent of an influenza case with biphasic fever. However, results of rapid influenza virus (IFV) antigen tests performed at the first clinical visit and during the second fever phase on day 4 were both negative. The PIV4a was isolated from all the nasal aspirate specimens on days 1, 4, and 7. Other common respiratory viruses were negative in all the specimens in the viral isolation trials using the multiplex cell culture system and RT-PCR tests. The fever disappeared within 5 days after the onset without any antibiotic treatment, which strongly suggested the PIV4a as the causative agent of the patient's illness. On the basis of the incubation period required for the appearance of the cytopathic effect (CPE) in the infected cells, from specimen inoculation to the cells, the viral load in the nasal cavity was speculated to be greatest on day 4. His cough started on day 1 and persisted until day 9, and the viral isolation indicated that the shedding of the active virus continued with the coughing even after the termination of fever.

Keywords: Parainfluenza virus type 4a (PIV4a); pediatric infection; biphasic fever; persistent cough; virus isolation

Submitted Aug 21, 2017. Accepted for publication May 22, 2018.
doi: 10.21037/jtd.2018.05.159
View this article at: http://dx.doi.org/10.21037/jtd.2018.05.159

Introduction

Pediatricians sometimes encounter cases that showed a symptom of fever with two distinct peaks (biphasic fever) in the clinical course of patients with influenza (1-3). However, it is not well understood how an infection with influenza virus (IFV) alone causes it. Occurrence of such a fever pattern in infection with PIVs 1, 2, 3 and respiratory syncytial virus (RSV) was recorded in the 1980s on the hospitalized pediatric patients (4) but, thereafter, has not been well-studied. In outpatient clinics, it is important to determine further drug prescription, whether the biphasic fever occurs by pure viral infection without involvement of the effect of medication or by other pathogens. We wanted to clarify whether any respiratory virus other than the one that caused the first fever peak are involved in the second peak or not, but we do not have a general conclusion for now. We had been conducting virological investigations since 2012 on pediatric patients who had influenza-like illness and visited clinics. We present here a case of a boy who showed biphasic fever in the course of upper respiratory disease with long-lasting cough. The possibility of single infection with parainfluenza virus type 4a (PIV4a) was strongly suggested with virological evidence through viral isolation and PCR analyses.

Case presentation

A 1-year-old boy experiencing fever of 38.2 ℃, slight cough, and uneasiness visited his home doctor on January 26, 2016.

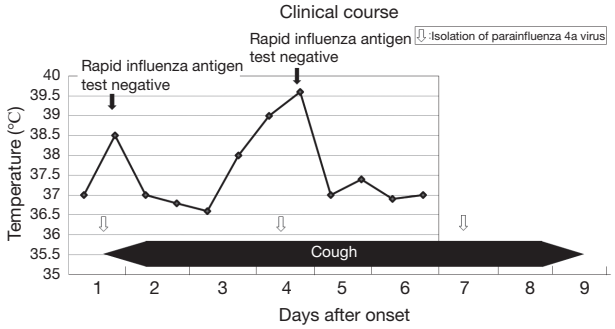


Figure 1 Clinical course of the case. The recurrent fever was observed. Parainfluenza virus type 4a was isolated on days 1, 4, and 7.

The result of the rapid IFV-antigen test (Immuno Ace Flu®, Tauns, Izunokuni, Japan) performed on his nasal aspirate was negative. Neither anti-influenza drug nor antibiotics was prescribed, and careful follow-up was advised. His body temperature returned to normal at 36.5 ℃ on the next day, but the fever rose again on day 3, and the temperature peaked at 39.6 ℃ on day 4.

During the recurrent fever, his nasal specimen was collected, and the specimen was tested for rapid IFV-antigen. However, the result was negative again. The fever started to decline after the peak, and one and a half days after the onset of the recurred fever, his body temperature became close to normal at 37 °C.

Aside from having fever, the patient had persistent cough from days 1 to 9, which started with the fever and gradually augmented. The cough continued even during the intermittent phase of the fever between days 2 and 3, and until 3 days after resolution of the fever and gradually disappeared (*Figure 1*).

Microbiological analyses

The nasal aspirate specimens obtained on days 1, 4, and 7 were inoculated into six kinds of cells (HFL-III, HEp-2, Vero, MDCK, LLC-MK2, and MNT-1). These cell culture systems are optimized for isolation of various kinds of viruses, including IFV types A, B, C, PIV types 1, 2, 3, 4, RSV, human metapneumovirus, mumps virus, enteroviruses, rhinovirus, adenovirus, and herpes virus (5). Cell fusion appeared in LLC-MK2 cells inoculated with all the specimens obtained at days 1, 4, 7 under microscopic investigation on days 7, 2, and 5 after inoculation, respectively. Occurrence of the multinuclear giant cell formation by cell fusion is the cytopathic effect (CPE) characteristic for PIV4 multiplication (6-8). Final identification of PIV4a isolation was confirmed by the detection of the viral NP gene using conventional RT-PCR (6) from the culture medium of the LLC-MK2 cells that showed CPE. Meanwhile, none of the other viruses except for PIV4 were isolated in the cell systems. In addition, none of major respiratory viruses including RSV, PIV1-3, hMPV, IFV-A, B, AdV, RV and bocavirus was detected in the RNA extracted from the clinical specimens—using real-time PCR system of Cycler PCR® respiratory viruses detection kit Ver.3 (Takara Bio., Kusatsu, Japan) (9). Involvement of coronaviruses was excluded also by another real-time PCR system that was described previously (10,11). Those systems could detect the above-mentioned viruses at the detection limit of 10 gene copies/μL of clinical specimen. Therefore, PIV4a was strongly suggested as the causative agent of the patient's illness.

Discussion

A case of infection caused by PIV4a that showed two distinct peaks in fever was described in this report. A possibility of bacterial involvement in the fever could be excluded, judging from the clinical course that the fever declined rapidly after its second peak without antibiotic treatment. The infection was determined by virus isolation and involvement of other major respiratory viruses with PIV4 in the illness (12) was almost excluded by the negative results in isolation in our virus isolation system and in viral gene-detection with multiplex real-time PCR, though the exclusion was not definitely conclusive since there were limitations in their competency in viral detection. Many reports of PIV4 infections have been reported so far from an epidemiological or clinical view point. They enumerated the symptoms of the infection including the frequency and/or duration of the fever, but they did not provide the information on the pattern of the fever nor the duration of the cough (8,12). Thus, this case report is significant as it describes details of a PIV4 infection.

Epidemiological and clinical studies on PIV4 infection have been mainly based on the detection of the viral gene in the clinical specimen using PCR (12-15), with some exceptions (8,16-18). We were able to isolate PIV4a from the specimens obtained on days 1, 4, and 7 that caused CPE in the LLC-MK2 cell on the 7th, 2nd, and 5th day after inoculation, respectively. If the duration from the inoculation to appearance of CPE inversely correlate to the load of active virus in the inoculated specimen as is frequently experienced in viral infection experiments, the duration difference might mean that active viral load in the

nasal cavity was the highest on day 4 among those collected on three separate times. Those results were supported by quantitative analyses on the amounts of the virus in the specimens using a real-time PCR system (11), as well (data not shown). The isolation on day 7 would be consistent with the finding that the virus shedding in patients with PIV infections other than type 4 tends to linger long (13) and continue until even after the disappearance of the symptoms. This kind of viral shedding pattern is different from that of IFV infections, in which the shedding of active virus peaks at the initial phase of the illness and rapidly decreases thereafter (19). Understanding those pattern differences might be important for infection control of each viral infection. Analyses with PCR may provide information on virus accumulation in the specimens both of active and inactive viruses, but that of the active virus was possible in our study because the virus isolation was successful.

The biphasic fever itself was not rarely observed among pediatric influenza cases. It was reported that the cases with biphasic fever accounted for approximately 7% of all pediatric influenza cases in Kitakyushu City in 1986, without anti-influenza drug treatment (20). However, there was also a report that the frequency of biphasic fever declined after introduction of the neuraminidase inhibitor drug (21). In any case, the possibility that the biphasic fever during the winter season is caused by an infection with IFV is relatively high. Therefore, it might be reasonable that physicians tend to empirically prescribe neuraminidase inhibitor drugs at the second peak of the biphasic fever even if the result of the rapid IFV-antigen test is negative when influenza is circumstantially suspected (22). Our case would call for a caution that influenza-like cases caused by a respiratory virus other than IFV can also cause biphasic fever.

Viral isolation or gene analysis is not always available in many medical institutions. It would be of great importance for clinical information on various kinds of infections to be collected and consolidated, and easy and accurate methodologies with reasonable costs to identify causative agents to be developed. Fundamentally, the mechanisms of the occurrence of biphasic fever have not been clarified in many respiratory viral diseases including influenza, and even its frequency among the cases has been unclear. Basic data on the biphasic fever should be accumulated.

Acknowledgements

The authors greatly appreciate Drs. Kenji Takasaki, Yuji Yamashita, and Takahito Yokoyama for their helpful discussion, and Dr. Isolde Dapat and Enago (www.enago.jp) for English language review by a native speaker. This work was financially supported by the Clinical Research Division of Sendai Medical Center and the Research Program on Promoting Development of Innovative Drugs against Emerging and Reemerging Infectious Diseases from Japan Agency for Medical Research and Development, AMED.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: A written informed consent from his parent and an approval of the ethic committee of Sendai Medical Center were obtained for the presentation.

References

1. Adams JM, Thigpen MO, Rickerd ER. An epidemic of influenza A in infants and children: A clinical and laboratory investigation. JAMA 1944;125:437-77.
2. Sakuma T. Infant influenza. Acta Paediatr Jpn 1997;39:669-75.
3. Koseki N, Kaiho M, Kikuta H, et al. Comparison of the clinical effectiveness of zanamivir and laninamivir octanoate for children with influenza A(H3N2) and B in the 2011-2012 season. Influenza Other Respir Viruses 2014;8:151-8.
4. Putto A, Ruuskanen O, Meurman O. Fever in respiratory virus infections. Am J Dis Child. 1986;140:1159-63.
5. Numazaki Y, Oshima T, Ohmi A, et al. A microplate method for isolation of viruses from infants and children with acute respiratory infections. Microbiol Immunol 1987;31:1085-95.
6. Abiko C, Mizuta K, Aoki Y, et al. An outbreak of parainfluenza virus type 4 infections among children with acute respiratory infections during the 2011-2012 winter season in Yamagata, Japan. Jpn J Infect Dis 2013;66:76-8.
7. Sato K, Watanabe O, Ohmiya S, et al. Efficient isolation of human parainfluenza viruses 1 and 3 using MNT-1, a human malignant melanoma cell line system that exhibits apparent cytopathic effect. Microbiol Immunol 2016;60:801-5.
8. Billaud G, Morfin F, Vabret A, et al. Human parainfluenza virus type 4 infections: a report of 20 cases from 1998 to 2002. J Clin Virol 2005;34:48-51.
9. Hamano-Hasegawa K, Morozumi M, Nakayama E, et al.

Comprehensive detection of causative pathogens using a real-time OCR to diagnose pediatric community-acquired pneumonia. J Infect Chemother 2008;14:424-32.
10. Gaunt ER, Hardie A, Claas EC, et al. Epidemiology and clinical presentations of the four Coronaviruses 229 E, HKU 1, NL63, and OC43 detected over 3 years using a novel multiples real time PCR method. J Clin Microbiol 2010;48:2940-7.
11. Nishimura H, Sato K, Kadji FM, et al. Case study-based time-course analysis of symptoms of respiratory syncytial virus infections followed by acute sinusitis in otherwise-healthy adults. J Thorac Dis 2018. [Epub ahead of print].
12. Ren L, Gonzalez R, Xie Z, et al. Human parainfluenza virus type 4 infection in Chinese children with lower respiratory tract infections: a comparison study. J Clin Virol 2011;51:209-12.
13. Frost HM, Robinson CC, Dominguez SR. Epidemiology and clinical presentation of parainfluenza type 4 in children: a 3-year comparative study to parainfluenza types 1-3. J Infect Dis 2014;209:695-702.
14. Lau SK, Li KS, Chau KY, et al. Clinical and molecular epidemiology of human parainfluenza virus 4 infections in Hong Kong: subtype 4B as common as subtype 4A. J Clin Microbiol 2009;47:1549-52.
15. Fathima S, Simmonds K, Invik J, et al. Use of laboratory and administrative data to understand the potential impact of human parainfluenza virus 4 on cases of bronchiolitis, croup, and pneumonia in Alberta, Canada. BMC Infect Dis 2016;16:402.
16. Tyrrell DA, Bynoe ML. Studies on Parainfluenza type 2 and 4 viruses obtained from patients with common colds. BMJ 1969;1:471-4.
17. Lau SK, To W, Tse PW. Human parainfluenza virus-4 outbreak and the role of diagnostic tests. J Clin Microbiol 2005;43:4515-21.
18. Vachon ML, Dionne N, Leblanc E, et al. Human parainfluenza type 4 infections, Canada. Emerg Infect Dis 2006;12:1755-8.
19. Suess T, Remschmidt C, Schink SB, et al. Comparison of shedding characteristics of seasonal influenza virus (sub) types and influenza A (H1N1) pdm09; Germany, 2007-2011. PloS One 2012;7:e51653.
20. Sakuma T. Influenza infection in a pediatric clinic. J Kitakyushu City Medical Association. 1986;30-8. (in Japanese).
21. Suzuki E, Ichihara K. The course of fever following influenza virus infection in children treated with oseltamivir. J Med Virol 2008;80:1065-71.
22. Wang K, Shun-Shin M, Gill P, et al. A. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev 2012;18;1.

Cite this article as: Oda K, Nishimura H, Watanabe O, Kubo T, Shindo S. A case report on parainfluenza virus type 4a infection in a 1-year-old boy with biphasic fever. J Thorac Dis 2018;10(Suppl 19):S2305-S2308. doi: 10.21037/jtd.2018.05.159

