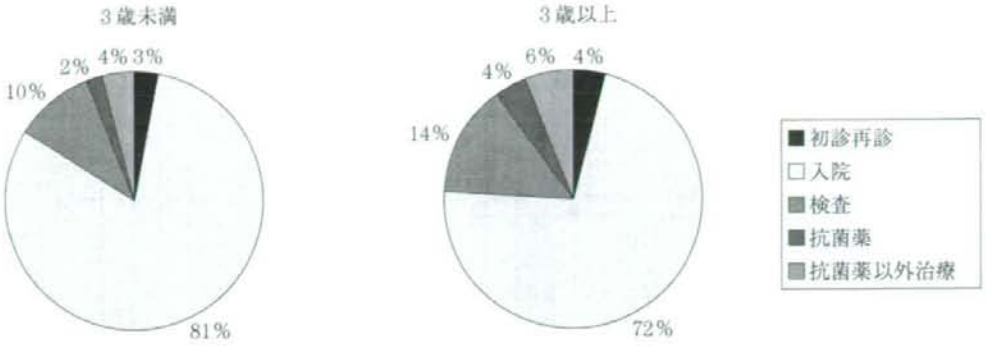
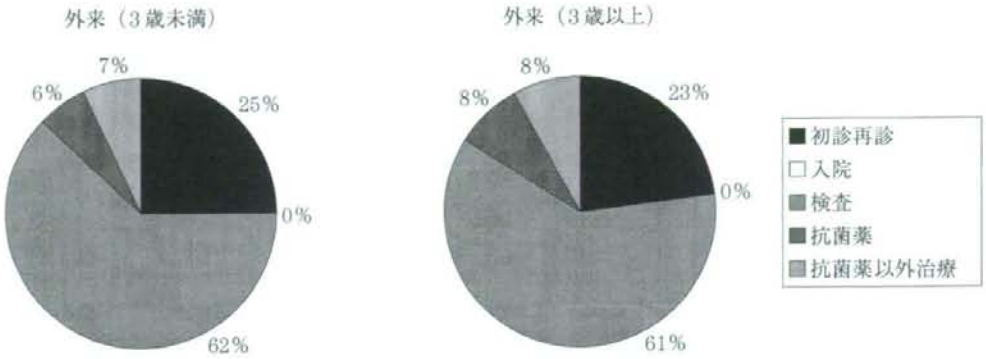
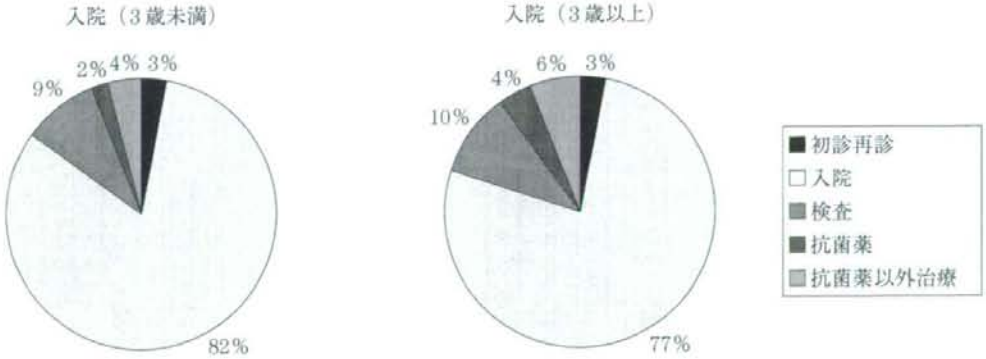


a）患者一人当たり





b）外来・入院別

図2　項目毎の医療費の割合

より，医療費を推計した。このような方法による医療費の推計は，以前から海外ではよく行われており，わが国の感染症領域においてもすでにいくつかの先行的な試みがなされている[6,7]。この方法により，本分析では，肺炎球菌による肺炎の患者1人あたりの医療費を3歳未満・3歳以上でそれぞれ221,133円，164,916円（平均193,025円）と推計した。本分析結果の妥当性の検証として，公的な資料との比較を行った。平成17年患者調査[8]によれば，0歳，1歳～4歳の肺炎入院患者

表5　小児肺炎球菌性肺炎患者1人あたり期待費用および全国規模費用推計

	値
患者1人あたり期待費用	
急性期医療費（円）	193,025
親の生産損失（円）	104,455
1人あたり費用計（円）	297,480
全国規模推計	
5歳未満人口（万人）	550.4
10万人あたり罹患率220人の場合	
5歳未満年間患者数（人）	12,107
年間費用（億円）	36.0
10万人あたり罹患率300人の場合	
5歳未満年間患者数（人）	16,512
年間費用（億円）	49.1

の在院日数はそれぞれ7.5日，6.1日となっている。本分析の治療フローによる入院期間の推計値は6.8日（3歳未満），4.9日（3歳以上）となっており，患者調査の数字と非常に近い値となっている。一方，平成17年社会医療行為別調査報告[9]では，入院外の肺炎の診療日数は1.7日となっている。この数字は全年齢を対象とした場合であり，なおかつすべての肺炎を対象としているが，本分析結果の2.7回よりも小さい値となっている。小児の肺炎球菌性肺炎ではより慎重に治療が行われることを考慮すれば，本推計結果はおおむね妥当なものと考えられる。そこで本分析結果を基に，全国規模の肺炎球菌肺炎の疾病負担の推計を試みた。肺炎がもたらす経済負担は，急性期医療費だけではない。患者の通院・入院のために親が費やす時間もそのひとつである。今回の調査では，外来・入院でそれぞれ4.6時間，13.1時間の親の介護時間が発生していた。この結果を基に，仕事をしている親が介護のために休業しなければならない時間を，外来4時間（半休），入院8時間（欠勤）とすれば，わが国における就労者の平均時給1,807円[10]から，介護のために損なわれる親の労働損失は，治療フローから計算した外来回数（3歳未満2.7回，3歳以上2.8回），入院日数（3歳未満6.8日，3歳以上4.9日）から，3歳未満，3歳以上でそれぞれ117,829円，91,082円と推計される。これに急性期医療費を加えた金額が，肺炎球菌肺炎患者1人あたり経済負担と推計され，3歳未満，3歳以上でそれぞれ338,962円，255,998円（平均297,480円）となる。全国規模の推計を行うためには，5歳未満の年間肺炎球菌肺炎の患者数が必要となる。小児に限らず，肺炎の全国規模の発生数に関するプロスペクティブな研究報告はわが国では未だなされていないが，河野ら[11]は公的な資料を用いた推計により，年間109.8万人の肺炎患者が発生していると報告している。平成17年の患者調査[8]から，肺炎患者の7.4%が5歳未満の小児とすれば，5歳未満の年間肺炎患者数は81,252人と推計される。一方，網羅的に細菌・ウイルス・マイコプラズマ等を含め小児肺炎の原因微生物検索を行った中村[12]の報告によれば，急性肺炎入院例のうち肺炎球菌が関与するものは14.9%となっている。以上の数字を用いると，5歳未満の年間肺炎球菌肺炎の患者数は12,107人と推計され，10万人あたり罹患率に換算すれば220人となる。患者1人あたりの疾病負担額に，3歳未満・3歳以上の平均を用いて全国規模の疾病負担を推計すると，36.0億円と推計される。仮に罹患率をやや多めに見積もって300人とした場合は49.1億円となる（**表5**）。肺炎球菌による小児肺炎の臨床上の重要性は言うまでもないが，出生数が年々減少する中，特にその重要性は増していると考えられる。本研究から，肺炎球菌による小児肺炎は，多大なる医療経済的な損失をもたらしていることが明らかになったが，耐性菌も増加しており，今後抗菌薬に頼るような医療を続けることは賢明ではない。したがって，感染症の基本である予防できるものは予防するという原則を守り，ワクチンを導入すべきことは当然であると考えられる。

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Burden of illness of pneumonia caused by *Streptococcus pneumoniae* in children

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インフルエンザ菌b型感染症の過去10年間における入院例の検討

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原　著

インフルエンザ菌b型感染症の過去10年間における入院例の検討

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要　旨

1996年から2005年までの10年間に，当院小児科病棟に入院した症例について検討した．化膿性髄膜炎27例のうち，17例（63.0%）はインフルエンザ菌b型（*Haemophilus influenzae* type b, Hib）が起因菌であった．Hib髄膜炎患者の中に死亡例はなかったが，17例中3例（17.6%）で後遺症を残した．Hib髄膜炎患者の年齢分布は，1歳未満児6例（35.3%），1歳以上2歳未満児4例（23.5%）で，これまでの報告と同様に乳児や低年齢児が多数を占めた．急性喉頭蓋炎は3例あり，全例Hibが起因菌であった．化膿性関節炎・骨髄炎の症例は10例あり，うち2例の起因菌はHibであった．病院を受診する背景人口から計算した5歳未満人口10万人当りのHib疾患年間罹患率は，髄膜炎8.9，喉頭蓋炎2.4，化膿性関節炎・骨髄炎1.6となり，決して稀な疾患ではないという結果であった．抗菌薬感受性の検討では，βラクタマーゼ非産生アンピシリン耐性菌（β-lactamase negative ampicillin resistant strain, BLNAR）が6割以上を占めた．重症感染症罹患後でさえ，2歳未満児の血清抗Hib抗体価上昇は良好ではなかった．以上より，小児期Hib感染症対策として，わが国でも乳児期早期からの結合型Hibワクチン接種を早急に普及させることが必要である．

キーワード：インフルエンザ菌b型，化膿性髄膜炎，急性喉頭蓋炎，骨関節感染症，Hibワクチン

目　的

インフルエンザ菌b型（*Haemophilus influenzae* type b, Hib）は，化膿性髄膜炎，急性喉頭蓋炎，化膿性関節炎・骨髄炎など小児における重症感染症の起因菌としてよく知られている[1~3]．諸外国では，乳児に対する結合型Hibワクチンの定期予防接種導入により同菌による疾患は激減し，すでに1990年代にHib感染症はワクチンによる予防が可能な疾患と位置づけられた．しかしわが国では，2007年1月にようやく結合型Hibワクチンが認可2008年12月から使用が可能となったところである．

過去に実施された全国サーベイランス調査の結果によると，わが国におけるHibによる化膿性髄膜炎の発生頻度は5歳未満人口10万人当り年間7.5であり，国内で1年間に500人以上の患者が発生していると推計される[6]．抗菌薬や支持療法の進歩により死亡例は少なくなったが，約2割の症例に後遺症を残し，そのほとんどは精神運動発達障害など重篤なものである．急性期入院治療や後遺症による経済的損失も大きい[7]．

さらに，化膿性髄膜炎のみならず急性喉頭蓋炎や関節炎・骨髄炎においても，Hibは特に小児では代表的な起因菌である．今回，小児におけるHib重症感染症の当院における実態を明確にするために，入院治療を行った化膿性髄膜炎，急性喉頭蓋炎，化膿性関節炎・骨髄炎の症例について検討した．

対象と方法

1996年1月から2005年12月までの10年間に，国立病院機構三重病院小児科病棟に入院した児を対象として，患者年齢，性別，臨床経過，検査所見，治療について検討した．調査期間中にHib重症感染症で入院した児の中に，免疫不全症や先天奇形など基礎疾患を有する者は居なかった．一部の症例では，分離されたHibの抗菌薬感受性，血清抗Hib抗体価についても検討した．統計学的解析方法は，マン―ホイットニーのU検定を用いた．

髄液検体に対する細菌迅速診断キットは，スライデックスメニンギート-5®（日本ビオメリュー株式会社，東京）を使用した．Hibに対する血清抗体価は，BINDAZYME Human Anti Haemophilus Influenzae Enzyme Immunoassay Kit®（The binding Site Ltd., Bir-

（平成19年9月14日受付）（平成20年6月14日受理）
別刷請求先：（〒514-0125）津市大里窪田町357
独立行政法人国立病院機構三重病院小児科
中野　貴司

mingham, UK) を用いて抗 PRP (polyribosyl-ribitol phosphate) 抗体価を測定した.「化膿性髄膜炎」,「急性喉頭蓋炎」,「化膿性関節炎・骨髄炎」の診断基準, 分離された Hib の抗菌薬感受性検討の方法については以下に示した.

(1) 診断基準

A. 化膿性髄膜炎:

臨床症状より髄膜炎が疑われ, 腰椎穿刺により採取した髄液において 1,000/3μl 以上の髄液細胞数増多があり, 下記①~③のいずれかに合致する症例.

①髄液あるいは血液培養で細菌が分離された症例.

②髄液・血液培養の結果が陰性であっても, 髄液の迅速診断検査により 1 種類の細菌が陽性と判定された症例.

③髄液・血液の細菌培養, 髄液の迅速診断検査の結果が陰性であっても, 臨床症状, 末梢血白血球数, 血清 CRP 値, 髄液グラム染色塗末標本鏡検所見から, 細菌感染症の可能性が高いと考えられた症例 (起因菌不明の化膿性髄膜炎).

B. 急性喉頭蓋炎:

急激に発症する特徴的な呼吸困難症状があり, 気管挿管時の直視所見あるいは喉頭ファイバースコープによる観察所見で喉頭蓋の発赤と腫脹が確認され, 末梢血白血球数・血清 CRP 値の推移から細菌感染症を裏付ける所見があった症例.

C. 化膿性関節炎・骨髄炎:

罹患局所の炎症所見に加えて, レントゲン検査・CT 検査・MRI 検査など画像所見の異常を伴い, 下記①, ②のいずれかに合致する症例.

①血液あるいは関節穿刺液の培養で細菌が分離された症例.

②血液あるいは関節穿刺液の培養結果が陰性であっても, 臨床症状, 末梢血白血球数, 血清 CRP 値, 関節穿刺液グラム染色塗末標本鏡検所見から, 細菌感染症の可能性が高いと考えられた症例 (起因菌不明の化膿性関節炎・骨髄炎).

D. Hib 感染症:

下記 i)~iii) のいずれかを満たすものを, Hib が原因による感染症と診断した.

i) 血液・髄液・関節液からインフルエンザ菌が分離され, その莢膜型が b 型であった場合.

ii) 髄液検体に対する細菌迅速診断の結果が, Hib のみ陽性であった場合.

iii) 抗菌薬開始前の血液培養が採取されていない喉頭蓋炎症例については, ペア血清による Hib 抗体価の推移が有意な変動を示したと考えられた場合.

なお, 抗菌薬の前投薬があった化膿性股関節炎の症例で, 血液・関節穿刺液とも培養陰性であったが, 関節穿刺液を検体とした迅速診断の結果が Hib 陽性であった 1 例は Hib による化膿性関節炎に含めた.

(2) 抗菌薬感受性

抗菌薬感受性については, 各薬剤の最小発育阻止濃度 (Minimum Inhibitory Concentration, MIC) を, 日本化学療法学会標準法に基づいた微量液体希釈法により測定した. β ラクタマーゼ産生能は Nitrocefin 法を用いた. PCR 法による耐性遺伝子に関する検査は, TEM 型 β ラクタマーゼ産生遺伝子の有無と細胞壁合成酵素 (Penicillin binding protein, *pbp*) 遺伝子の変異 (*pbp 3-1*, *pbp 3-2*) について検討した.

結 果

今回調査対象期間とした 10 年間に, 当院小児科病棟に入院した患者総数は 15,906 例であった. 化膿性髄膜炎症例が 27 例あり, Hib が起因菌であったものは 17 例 (化膿性髄膜炎症例の 63.0%) であった. 急性喉頭蓋炎は 3 例で, 全例 Hib が起因菌であった. 化膿性関節炎・骨髄炎は 10 例あり, うち 2 例の原因は Hib であった (表 1).

(1) 化膿性髄膜炎

Hib 髄膜炎 17 例の内訳は, 男児 8 例女児 9 例で, 発症時年齢は生後 3 か月から 5 歳 1 か月 (平均 22.8 か月) に分布し, 1 歳未満児が 6 例 (35.3%), 1 歳以上 2 歳未満児が 4 例 (23.5%) で, 2 歳未満の小児が全体の約 6 割を占めた (図 1).

化膿性髄膜炎と確定診断されたのは, 発症から 1.47±1.43 日目であった (発症日を病日 0 とした). 髄膜炎と診断されるまでに認められた症状を図 2 に示した. 全例で発熱があり, 次いで多かった症状は嘔吐 (10 例, 58.8%) であった. けいれん, 意識障害, 髄膜刺激徴候, 大泉門膨隆など中枢神経系異常を疑わせる特異的な所見を認めた症例は, いずれも半数にも満たなかった. 診断以前に近医で内服抗菌薬の処方を受けていたことが明らかであった者は 17 例中 6 例 (35.3%) であった. Hib 髄膜炎と確定診断後, 十分量の抗菌薬を経静脈的に投与した. また全症例に対して, デキサメタゾンを一日量体重 kg 当たり 0.6mg, 分 4 で経静脈的抗菌薬治療開始から 4 日間併用した.

予後に関して, 死亡例はなかったが, 3 例 (17.6%) で後遺症を認めた. 後遺症の内訳とその患者の髄膜炎発症年齢は, てんかん (3 か月), 高度難聴 (1 歳 1 か月), 発達障害・てんかん・水頭症・四肢麻痺 (1 歳 6 か月) であった. 後遺症を認めた 3 例は, 認めなかった 14 例に比して, 髄膜炎発症が低年齢で, 発症してから抗菌薬の全身投与を開始されるまでの日数が長く (後遺症例 : 2.4±2.4 日, 中央値 2 日//非後遺症例 : 1.33±1.23 日, 中央値 1 日), 治療開始時の髄液糖濃度が低い

表1　疾患別患者数と起因菌

	Hib	肺炎球菌	B群連鎖球菌	黄色ブドウ球菌	起因菌不明	小計
化膿性髄膜炎	17	2	3	1	4	27
急性喉頭蓋炎	3*	0	0	0	0	3
化膿性関節炎・骨髄炎	2**	1	0	2	5	10

（国立病院機構三重病院小児科：1996年～2005年入院患者総数15,906名）
*急性喉頭蓋炎3例のうち2例は，血清抗体価の推移によりHibが原因と診断した．
**化膿性関節炎・骨髄炎2例のうち1例は，関節液を検体とした迅速診断検査によりHibが原因と診断した．

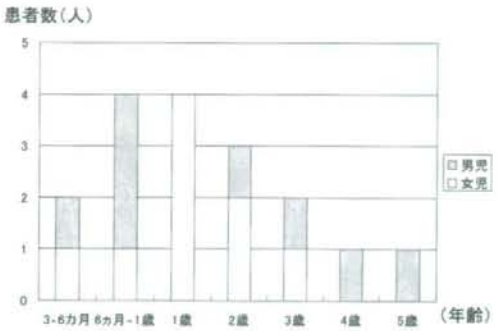

図1　Hib髄膜炎患者の年齢と性別（n = 17）

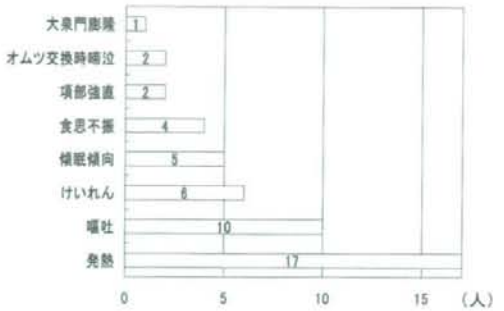

図2　髄膜炎と診断されるまでに認めた症状（n = 17）

（後遺症例：12.0±20.5mg/dl，中央値3.0mg/dl//非後遺症例：41.7±34.2mg/dl，中央値38.0mg/dl）という結果であったが，統計学的有意差は認めなかった．Hib髄膜炎患者の入院期間は17日～51日（平均27.7日，中央値23日）であった．

(2) 急性喉頭蓋炎

3例とも男児で，全例Hibが起因菌であった．患者の平均月齢は29.7か月で，Hib髄膜炎より発症年齢が高かった．全例が発症当日に呼吸困難を主訴に入院していたが，初診医により急性喉頭蓋炎と診断されていた症例は無かった．その症状進行の速さと診療現場における救命処置優先のため，抗菌薬開始前に適切な血液培養検体が採取されたのは1例のみであったが，本例からHibが分離された．残る2例は，Hib抗体価の推移（後述）によりHibによる急性喉頭蓋炎と診断した．全例に対して十分量の抗菌薬投与を行い，2例では気管挿管と人工呼吸管理を行った．気管挿管を行った期間は2例とも2日間で，3例の平均入院日数は9.7日であった．全例後遺症無く回復した．

(3) 化膿性関節炎・骨髄炎

化膿性関節炎・骨髄炎の症例は10例中2例（20.0%）でHibが起因菌であり，1歳男児と1歳7か月女児であった．静注抗菌薬による入院治療が開始されたのは，それぞれ病日4と病日1（関節炎・骨髄炎発症日を病日0と定義）であり，入院期間は42日間と30日間であった．2例の観察期間はそれぞれ発症後4年6か月と1年9か月であるが，共に現状で運動機能障害は認めていない．しかし，前者（1歳男児，化膿性股関節炎）では画像検査において大腿骨頭の成長障害が認められている．

(4) 抗菌薬感受性

化膿性髄膜炎8例，化膿性骨髄炎1例の計9例から分離されたHibに対して，抗菌薬感受性を検討した（表2）．MICはABPC，CTX，MEPMの3薬剤を測定した．CTXのMICが最も良好な値であり，次いでMEPM，ABPCの順であった．βラクタマーゼ産生菌は1株のみで，Nitrocefin法とPCR法によるTEM型βラクタマーゼ産生遺伝子解析の結果は一致していた．PCR法による*pbp*遺伝子変異検討の結果は，*pbp 3-1*，*pbp 3-2*の双方に変異を認めた株（g-BLNAR）が2株，*pbp 3-1*のみに変異を認めた株（g-Low-BLNAR）が4株であった．

(5) 抗PRP抗体価

血清抗PRP抗体価は，Hib髄膜炎12例（免疫グロブリン製剤使用例9例，免疫グロブリン製剤非使用例3例），急性喉頭蓋炎3例（3例とも免疫グロブリン製剤非使用例），骨関節感染症2例（2例とも免疫グロブリン製剤非使用例）について検討した．その結果を，測定病日とともに表3に示した．発症当日（0病日）かその翌日（1病日）に血清抗PRP抗体価を測定することができた10例において，抗PRP抗体価が感染防御閾値といわれる0.15μg/ml以上[6]，より強固な長期の感染防御閾値とされる1.0μg/ml以上[6]であった例は，それ

表2　分離されたHibの抗菌薬感受性

	年齢	疾患	ABPC (MIC μg/ml)	CTX (MIC μg/ml)	MEPM (MIC μg/ml)	β-L 産生能 (Nitrocefin 法)	TEM 型 β-L 産生遺伝子の有無	変異を認めた *pbp* 遺伝子 (遺伝子による耐性識別判定)
1	3か月	髄膜炎	2	0.06	0.125	-	無	*pbp3-1* (g-Low-BLNAR)
2	5か月	髄膜炎	0.125	≦0.015	0.06	-	無	無 (感受性菌)
3	9か月	髄膜炎	0.125	≦0.015	0.03	-	無	無 (感受性菌)
4	1歳1か月	髄膜炎	1	0.06	0.125	-	無	*pbp3-1* (g-Low-BLNAR)
5	1歳5か月	髄膜炎	2	検索せず	検索せず	-	無	*pbp3-1*, *pbp3-2* (g-BLNAR)
6	2歳3か月	髄膜炎	0.25	≦0.015	0.03	-	無	無 (感受性菌)
7	2歳10か月	髄膜炎	>32	0.06	2	産生	有り	*pbp3-1* (g-Low-BLNAR)
8	3歳1か月	髄膜炎	16	2	0.5	-	無	*pbp3-1*, *pbp3-2* (g-BLNAR)
9	1歳7か月	骨髄炎	1	検索せず	検索せず	-	無	*pbp3-1* (g-Low-BLNAR)

MIC:Minimum Inhibitory Concentration (最小発育阻止濃度), ABPC:アンピシリン, CTX:セフォタキシム, MEPM:メロペネム, β-L:βラクタマーゼ, *pbp*:penicillin binding protein, BLNAR:β-lactamase negative ABPC resistant (βラクタマーゼ非産生アンピシリン耐性)

ぞれ7例, 0例であった. 免疫グロブリン製剤の投与を受けた例では, 投与後は受動免疫により抗体価の上昇が認められた. 抗体価上昇の程度は様々であったが, 1か月後以降には下降した. 免疫グロブリン製剤投与を行わなかった例では, Hib感染症罹患後の抗体価の推移は, 2歳以上の児では回復期に上昇を認めたが, 2歳未満児では回復期の抗PRP抗体価は上昇していなかった (表3).

これら症例の中で, Hib髄膜炎症例では全例に対して「結果 (1) 化膿性髄膜炎」の項で記載したようにデキサメタゾンが投与された. 喉頭蓋炎症例では, 急性期あるいは気管内チューブ抜管時にデキサメタゾンあるいはヒドロコルチゾンが投与された. 関節炎の2例 (A-No.1, A-No.4) では, 副腎皮質ステロイドホルモン剤は使用しなかった.

後遺症を残したHib髄膜炎3例のうち抗PRP抗体価が測定できたのは, 高度難聴を来たした1例のみ (A-No.2) で, 急性期(第1病日)血清のみの測定であった.

考　察

1996年から2005年までの10年間に, 三重病院で入院治療を行ったHib髄膜炎症例は17例. うち5歳未満の症例は16例であった. 人口30万弱の津市において, 当院は唯一の小児二次医療担当機関であり, 24時間体制で隣接市町村の患者も含めて診療を行っている. 今回の16例のうち11例は津市に住む患者であり, 他の5例は近隣地域からの入院であった. 津市の5歳未満人口 (約12,300人) から5歳未満10万人当りのHib髄膜炎年間罹患率を計算すると8.9となり, 過去の全国調査[6]とほぼ一致する. 同様に計算した他のHib疾患罹患率は, 急性喉頭蓋炎2.4, 化膿性関節炎・骨髄炎1.6であった. この結果から, 小児におけるHib重症感染症は決して稀な疾患ではないと考えられた.

またHib髄膜炎と診断されるまでに認められた症状は発熱が最多で, 次いで嘔吐であった. けいれん, 意識障害, 髄膜刺激徴候, 大泉門膨隆など中枢神経系の異常を疑わせる所見はいずれも半数にも満たず, 患者の約6割が2歳未満と低年齢であることと合わせて, 早期の診断は困難と考えられた. 化膿性髄膜炎以外のHib疾患, すなわち急性喉頭蓋炎や骨関節感染症も低年齢児に目立ち (患者平均月齢:急性喉頭蓋炎29.7か月, 骨関節感染症15.5か月), やはり早期の症状把握が困難な年齢層である. 黄色ブドウ球菌など他の細菌による化膿性関節炎・骨髄炎は年齢の高い学童にも発生し, 骨関節感染症患者10例の平均年齢は4歳6か月であったのと比較して, Hibによる骨関節感染症患者は低年齢であった. このことから, Hib疾患を予防すれば, 症状の訴えが乏しく診断困難な低年齢児の骨関節感染症を予防できることが期待された.

有意差は認めなかったが, 後遺症例は後遺症を認めなかった例に比して, 発症後十分な抗菌薬経静脈治療を開始されるまでの日数が長い傾向にあった. また, 確定診断以前に近医で内服抗菌薬の処方を受けていた者の割合は3割以上と多く, 内服抗菌薬では化膿性髄膜炎の病状進展阻止は困難と考えられた. そして, 分離された菌にはBLNARを主とした耐性菌が目立った (全分離菌の66.7%). このことから, Hib疾患対策ではワクチンによる予防が何より大切と考える.

重篤なHib疾患の発症を予防するためには, 最低でも0.15μg/mlの抗PRP抗体価, より強固な免疫効果のためには1.0μg/mlが必要とされている[8]. 今回全身性Hib感染症を発症した児の急性期における抗体価はい

表3　重症 Hib 感染症患者における血清抗 PRP 抗体価の経時的推移

A. 免疫グロブリン製剤非投与症例

No.	発症時年齢	性別	診断名	PRP 抗体価①（測定病日）	PRP 抗体価②（測定病日）	PRP 抗体価③（測定病日）
1	1歳	男	右股関節炎	0.93（4）	0.68（37）	0.39（94）
2	1歳1か月	女	髄膜炎	0.20（1）		
3	1歳4か月	男	喉頭蓋炎	0.15（0）	0.25（1）	0.11（15）
4	1歳7か月	女	右肘関節炎	0.09（7）	0.11（14）	0.10（21）
5	2歳4か月	男	喉頭蓋炎	0.54（1）	12.01（7）	7.57（208）
6	3歳1か月	女	髄膜炎	0.33（0）	17.75（31）	
7	3歳4か月	男	髄膜炎	0.20（3）	2.53（17）	
8	3歳9か月	男	喉頭蓋炎	0.83（1）	17.77（4）	

B. 免疫グロブリン製剤投与症例

No.	発症時年齢	性別	診断名	PRP 抗体価①（測定病日）	PRP 抗体価②（測定病日）	PRP 抗体価③（測定病日）	体重あたりの免疫グロブリン投与量（mg/kg）
1	5か月	男	髄膜炎	0.08（0）			313
2	7か月	男	髄膜炎	0.55（2）	2.90（4）	0.50（11）	294
3	9か月	男	髄膜炎	0.01（0）	20.89（1）	6.29（13）	313
4	9か月	女	髄膜炎	0.08（0）	13.22（23）	1.64（242）	563
5	1歳1か月	女	髄膜炎	0.14（3）	0.29（64）		798
6	1歳5か月	女	髄膜炎	0.09（3）	0.97（4）	0.09（35）	476
7	2歳3か月	男	髄膜炎	0.35（1）			442
8	2歳4か月	女	髄膜炎	0.62（1）	23.49（3）	10.25（19）	308
9	2歳10か月	女	髄膜炎	0.16（4）			682

（PRP 抗体価の単位は μg/ml）
（PRP 抗体価を測定した病日については，発症日を「病日0」とした）

ずれも 1.0μg/ml 以下であった（表3）．また，重症 Hib 感染症から回復した後でも，免疫グロブリン製剤投与後を除けば2歳未満児では抗 PRP 抗体価は 1.0μg/ml 以上には上昇しなかった．それに対して，Hib ワクチンを乳児期早期から開始し規定回数接種すれば，抗 PRP 抗体価 1.0μg/ml 以上の強固な免疫が獲得されることが，わが国の臨床試験でも確認されている[9]．

これまでに，Hib 髄膜炎において後遺症を残すなど予後不良症例では抗 PRP 抗体価の上昇が不良であったという報告がある[10]．今回の私たちの検討では，予後が悪かった症例における抗 PRP 抗体価の解析までは十分にはできなかったが，低年齢児で後遺症の頻度が高かったこと，2歳未満児で抗 PRP 抗体価の上昇が不良であったことを考えると，今後多数例に対するさらなる調査が望ましい．

今回検討した症例では，化膿性髄膜炎と喉頭蓋炎に対しては全例にデキサメタゾンなど副腎皮質ステロイドホルモン剤が使用されており，ステロイド剤の抗 PRP 抗体価上昇に対する影響の解析，ステロイド剤非使用例との比較はできなかった．一方，ステロイド剤を使用しなかった化膿性関節炎2症例においても抗 PRP 抗体価の上昇は不良であった．これら2例の年齢は1歳と1歳7か月であり，2歳未満の低年齢児では重症 Hib 感染症罹患後も抗 PRP 抗体価は上昇しないことを裏付けていると考えた．

今回の結果や Hib 疾患の入院や後遺症による負担・経済損失[3]を考えると，今後のわが国における制御戦略は予防に重点を置くべきである．ようやく認可された Hib ワクチンが，日本の隅々まで乳児期早期から高い接種率で普及するよう努めなければならない．

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Analysis on Admitted Children with Invasive *Haemophilus influenzae* Type b Diseases for the Past Ten Years

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The admitted pediatric patients with invasive *Haemophilus influenzae* type b (Hib) diseases for ten years (from 1996 to 2005) were analyzed. Seventeen (63.0%) among 27 bacterial meningitis cases were caused by Hib. Although there was no death, it left sequelae to 3 children (17.6%). Similarly to previous reports, high incidence of Hib meningitis was reported in younger children and infants；6 cases (35.3%) were children under 1 year of age, and 4 (23.5%) were aged 1 to 2 years. All 3 epiglottitis cases were caused by Hib. There were 10 patients with suppurative arthritis and osteomyelitis, and among them, two were infected by Hib. From the demographic background of those visiting hospital, the annual incidence of invasive Hib disease per 100,000 children aged less than 5 years were calculated as follows；meningitis 8.9, epiglottitis 2.4, and arthritis or osteomyelitis 1.6. This result suggested that the invasive Hib infection is never a rare disease. In antimicrobial susceptibility tests, the beta-lactamase non-producing ampicillin resistant strain (BLNAR) accounted for 60 percent or more. Acquisition of serum anti-Hib antibody value was not good enough even after the serious illness. Our results revealed that expanded use of Hib vaccine in early infancy should be immediately encouraged to control childhood Hib invasive infections in Japan.

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History of influenza vaccination programs in Japan

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ABSTRACT

In 1976, influenza mass vaccination among schoolchildren was started under the Preventive Vaccination Law, which was intended to control epidemics in the community. However, in the late 1980s, questions about this policy and vaccine efficacy arose, and a campaign against vaccination began. In 1994, influenza was excluded from the target diseases list in the Preventive Vaccination Law, without considering the immunization policy with respect to the common indications in high-risk groups. In 2001, the Law was again amended, specifying target groups, such as the elderly aged 65 or over, for influenza vaccination. In the 2005–2006 season, vaccine coverage among the elderly reached 52%. This shows that the need for vaccination has gradually become understood. However, the anti-vaccination campaign, which claims that the influenza vaccine has no efficacy, is still active. Vaccine efficacy studies that were not properly conducted are also being reported. In 2002, the Ministry of Health, Labor, and Welfare organized a research group on vaccine efficacy consisting of epidemiologists. The present symposium, as part of the 9th Annual Meeting of the Japanese Society for Vaccinology in 2005, was planned to further introduce epidemiological concepts useful in studying influenza vaccine efficacy.

1. Introduction

Japan is the only country in the world to have adopted mass vaccination of schoolchildren for influenza control, which resulted in an anti-vaccination campaign that still continues and claims that influenza vaccine has no efficacy. This has resulted in two peculiar circumstances in Japan. First, many people are concerned about influenza vaccine efficacy, whether or not they have the specialized knowledge required to understand the issue. Second, self-proclaimed specialists, who often lack specialized knowledge, nevertheless consider themselves specialists. As a result, people interested in influenza vaccine efficacy hear contradictory comments from real specialists, would-be specialists, and lay people, with lay people having the loudest voice.

The present symposium was planned to summarize the essential knowledge needed to understand the issues involved in influenza vaccine efficacy. Here, as a prologue to the symposium, we will briefly review the history of influenza vaccination programs in Japan, so that international readers can appreciate how lack of knowledge has contributed to difficulties in program implementation.

2. The beginning of influenza mass vaccination

In Japan, the Preventive Vaccination Law was promulgated in 1948, although influenza was not listed at that time. After the great impact of the 1957 Asian flu pandemic, a special program to promote influenza vaccination among schoolchildren was started in 1962, though it was not mandated by the Law. After the 1968 Hong Kong flu pandemic, the government was determined to establish further effective countermeasures against influenza. However, the rationale behind influenza control, which is to prevent severe complications and death among high-risk individuals, was not reflected in the vaccination strategy, and schoolchildren continued to be the sole target of active influenza vaccination. This somewhat one-sided policy gradually became entrenched, and studies that supported the approach were emphasized [1]. In 1976, the Preventive Vaccination Law was amended to include influenza among the target diseases, and mass vaccination of schoolchildren was started. This policy was intended to control influenza epidemics in the entire community by suppressing transmission in schools, while in Western countries, on the other hand, influenza vaccine was being given mainly to high-risk individuals, such as the elderly, at that time [2]. This was the beginning of chaos in influenza vaccination policy and in the influenza vaccine efficacy

Abbreviations: CI, confidence interval; MHW, Ministry of Health and Welfare; MHLW, Ministry of Health, Labor, and Welfare.

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debate that took place during the following 20 or more years in Japan.

3. Effect of mass vaccination on influenza impact

The unconventional policy of mass vaccination of schoolchildren attracted attention about whether it could actually mitigate the impact of influenza. However, no positive result of the policy was clearly shown [3]. A recent study reported that mass vaccination of schoolchildren reduced influenza mortality among the elderly; excess deaths among the elderly were lower during mass vaccination and then increased after discontinuation of the program [4]. However, this finding was criticized from several perspectives, including the increase in the elderly population, the rapid increase in the number of nursing homes and other living centers for seniors, and the definition of the influenza season [5]. Another study inferred that the discontinuation of mass vaccination among schoolchildren was responsible for an increase in influenza-associated deaths among young children [6]. On the other hand, a study focusing on the elderly in the United States failed to correlate increased vaccine coverage with a decline in mortality in any age groups [7]. In any case, these studies, whether the results were positive or negative, cannot provide solid evidence for influenza vaccine efficacy both at the population level and at an individual level, because they are "ecological studies." The subtlety involved in interpreting such studies has been discussed elsewhere [8].

4. Scepticism about influenza vaccine efficacy

From 1976 to 1987, more than 10 million schoolchildren annually received influenza vaccine, with the peak of 16.5 million vaccinees in each of 1983 and 1984. However, seasonal epidemics continued to occur, the elimination of which had been the objective of the mass vaccination policy. Furthermore, in Japan, individuals use the term "Kaze" (meaning cold) almost interchangeably with flu, and would say "I contracted Kaze, even though I received an influenza vaccine" [9]. School physicians, who were mostly private community practitioners who were in charge of school mass vaccination, were often asked about influenza vaccine efficacy by parents and teachers. This was an unexpected question for these frontline clinicians, since they had seldom been queried about the other vaccines. Many of them decided to study influenza vaccine efficacy by comparing the frequencies of Kaze, severe Kaze, or absenteeism due to Kaze between vaccinees and non-vaccinees in the school setting. Many such studies failed to detect vaccine efficacy due to misclassification of disease; however, they played an important role in stigmatizing influenza vaccine. Thus, in the late 1980s, two issues arose: whether influenza mass vaccination effectively prevents community epidemics; and whether influenza vaccine effectively prevents influenza attacks in individuals. With the blending of these two questions by the campaign against influenza vaccination, which involved the mass media, teachers' union, consumers' union, and other groups, influenza vaccine coverage among schoolchildren declined steeply from about 80% at its peak to 18% in 1992.

5. Discontinuation of mass vaccination programs

In contrast to the many reports that alleged that influenza vaccine had little or no efficacy, three quality Japanese studies were also published. The first one, a randomized, controlled study, was done among high school students during the 1968–1969 season. This study demonstrated that vaccine efficacy against serologically confirmed infection was 80% ($P < 0.001$) for A(H3) and 43% ($P < 0.01$) for B [10]. The second study, a case–control study among elementary schoolchildren, was done during the 1988–1989 season when A(H1) viruses were predominant. After adjusting for several confounders, the odds ratio of vaccination against influenza-like illness with fever ≥39 °C was calculated to be 0.33 (95% confidence interval (CI): 0.14–0.78) [11]; of interest, this finding was wrongly cited in a recent systematic review article [12]. The third study, an observational follow-up study among asthmatic children aged 2–14 years in the clinic setting, showed that vaccine efficacy against infection was 67.5% ($P < 0.01$) for A(H3), 43.7% ($P < 0.01$) for B, and 42.1% ($P < 0.01$) for both A(H3) and B combined [13]. However, these scientific reports were not considered when the vaccination program was being evaluated, since the vaccination policy and vaccine efficacy were being studied and discussed mainly by pediatric practitioners, who had an interest in school health, and by microbiologists, who were interested in the vaccine. In June 1994, the Preventive Vaccination Law was amended to exclude influenza from the list of target diseases without considering an immunization policy that would be based on the common indications for high-risk groups. Thus, influenza mass vaccination among schoolchildren that had lasted for nearly 20 years under the Law was discontinued. This is in striking contrast to what happened in the United States, where, in 1993, the federal government's Medicare program started reimbursement for the cost of influenza vaccine and its administration.

6. The pendulum swings back

At a time when interest in influenza disease and the influenza vaccine was extraordinarily low, several authors reviewed the misunderstandings about the vaccine and vaccination strategy [9,14]. Then, in 1997, the first Committee for Influenza Pandemic Preparedness was established by the Ministry of Health and Welfare (MHW) and clearly specified the rationale of influenza control and influenza vaccine efficacy, given the results of the three above-mentioned studies [10,11,13]. The committee also reviewed the frequency of influenza vaccine side effects, which had been officially recognized and compensated for during the mass vaccination era (1977–1994): 116 events among 329,339,615 vaccinations, that is "0.35×10^{-6} (95% CI: 0.29×10^{-6} to 0.42×10^{-6}) per vaccination", which can also be stated as "0.07×10^{-6} per week after vaccination", assuming that the maximum duration between vaccination and the onset of side effects is 35 days. Once again, the mass media began to show their interest in influenza, and newspapers headlined influenza deaths in nursing homes. Thus, it appeared as if the pendulum were swinging back, though the negative view of influenza vaccine persisted. At that time, there was an article published in a magazine alleging that the group of people with favorable views towards influenza vaccine had been the result of collaboration among vaccine manufactures, scientifically biased researchers, and the MHW [15]. It also presented survey data on influenza attack rates (vaccinees 71.0%, non-vaccinees 75.4%) and absenteeism due to influenza (vaccinees 73.3%, non-vaccinees 72.8%) and concluded that it would be hard to accept that influenza vaccine is effective. Fortunately, unlike the period from the late 1980s to the early 1990s, few people agreed with this view, but unfortunately, there were still only a few individuals who could instantly understand the drawbacks of such data reported in the magazine. It is quite clear that the survey data reported suffered substantially from misclassification of disease due to loose criteria, such as "Kaze", particularly when compared to the reported attack rates (45–60%) among schoolchildren during the 1957 Asian flu pandemic.

7. A new vaccination strategy and the present status

During the 1996–1997 influenza season, the MHW issued a notice to all prefecture governments that welfare institutes were to make the necessary arrangements to ensure that all residents could receive influenza vaccine. In 1999, the MHW and the Japan Medical Association collaborated on a campaign whose slogan was, "Don't confuse influenza with Kaze. Don't underrate influenza." Finally, in 2001, the Preventive Vaccination Law was amended to again include influenza, specifying two target groups: the elderly aged 65 or older and those aged 60–64 years with heart, kidney, lung, and other chronic disorders. Under this Law, more than 99% of eligible persons are elderly, since the 60–64-year-old age group is normally classified as the disabled people who are officially registered for special welfare services. Under the Law, municipalities have to take responsibility for offering vaccinations to the target groups. The cost of providing the influenza vaccine, including not only the cost of the vaccine and the cost of its administration, but also a health consultation fee to determine whether it is indicated, is roughly 5000 Japanese Yen (¥); the municipality provides a subsidy (¥4000), and the individual contributes a self-payment (¥1000). The cost and the division of the cost are not equal among the municipalities, but they depend on the agreement between the municipal government and the community medical association. The relatively high cost of vaccination reflects the need to deal with the negative perception of influenza vaccine safety, since the anti-vaccination campaign always exaggerates the side effects of the vaccine.

Since 2001, vaccine coverage among the target population has been consistently increasing: 28% in 2001–2002, 35% in 2002–2003, 45% in 2003–2004, 47% in 2004–2005, and 52% in the 2005–2006 season. These figures reflect the coverage among the elderly aged 65 or over, since they account for almost all of the target population. Thus, the significant health impact of influenza and the important role that vaccination plays have gradually become understood by the general public. Geriatric hospital physicians have played an important role in disseminating information about influenza vaccine efficacy. They closely observe each patient throughout the influenza season, since influenza-related complications, such as pneumonia, are critical issues in their hospitals. They can, therefore, themselves observe the reduction in severe complications and death among vaccinated patients compared to non-vaccinated patients. This situation is quite different from that of the school physicians who were previously engaged in mass vaccination; they only had contact with the children who visited their clinics during influenza season. Many or almost all such children suffering from flu symptoms had received influenza vaccine due to the high vaccine coverage rates that had been achieved with the mass vaccination programs.

8. Recent developments surrounding influenza vaccine

In Japan, while anti-vaccination campaigns are still active, they have weakened and have some peculiar features. The opposition is based upon the view that influenza vaccine has a little or no efficacy but a high risk of side effects, and that influenza is not a serious disease for which preventive intervention is required. It is really regrettable that there are physicians who inexplicably share the views of the anti-vaccination activists and object to influenza vaccination. This situation is in sharp contrast with that in Western countries where the major reasons for refusing vaccination are typically religious beliefs or personal principles.

Many physicians and pediatricians still feel frustrated by the degree of efficacy of the present influenza vaccine. They usually make apologies when administering influenza vaccine, explaining that "Every vaccine recipient cannot necessarily avoid contracting influenza." To resolve this dilemma, they perform their own studies of vaccine efficacy. They believe that the failure to detect vaccine efficacy during the mass vaccination era was solely due to the use of a clinically defined outcome. Now, they are confident that laboratory-confirmed influenza can be identified in their clinics using a newly developed commercial rapid diagnostic kit. Thus, they tend to first register vaccinated and non-vaccinated subjects before the influenza season, and then simply calculate the proportion of clinic visitors with positive rapid antigen tests among the initially enrolled subjects by vaccination status; they do not include any information on non-clinic visitors. It appears difficult for frontline clinicians to recognize that observing individual study subjects with equal intensity is of paramount importance in these types of studies. As in the 1980s, although fewer in number, several studies have been conducted by clinicians who lack even a rudimentary appreciation of epidemiologic principles, including selection bias, confounding, and misclassification. Of even greater concern is that there are few Japanese researchers who can critically review such flawed studies, which results in the presentation at scientific meeting or publication in journals of fundamentally flawed studies [16].

Thus, in 2002–2004, the Ministry of Health, Labor, and Welfare (MHLW; the former MHW was reorganized in 2001) created a research group consisting of epidemiologists, for the "Appraisal of influenza vaccine efficacy and vaccination policy in conformity with evidence-based medicine", and granted them a total of ¥99,750,000. This was the first research group created by the MHLW that focused on the epidemiological aspects of influenza vaccine. The formation of this group attracted the attention of epidemiologists to influenza vaccine. Most of the epidemiologists had never considered that vaccine research was a field in which they could be involved. It is also undeniable that pediatricians and microbiologists had considered influenza vaccine to be their own exclusive research area and felt reluctant to work with epidemiologists. Several epidemiologists in the research group took a great interest in the field and have successfully conducted studies of vaccine efficacy [17–20].

Following the success of the first research group, in 2005–2007, the MHLW set up a successor group for "Analytical epidemiologic study on the effectiveness of influenza and other vaccines and vaccination policy" and has already granted ¥94,900,000 for the first 2 years. In this second research group, the epidemiologists who gained experience doing influenza research in the first group are expected to expand their investigations in close cooperation with pediatricians, physicians, and microbiologists, as well as to transfer their epidemiological knowledge and skills to their co-researchers. Thus, as a result of the common perception of the vaccine efficacy study, the present symposium on influenza vaccine from the epidemiological viewpoint was held at the 9th Annual Meeting of the Japanese Society for Vaccinology in Osaka on October 15–16, 2005. The following articles dealing with the topics covered at the symposium were collected to serve as the basis to convey the essential knowledge of epidemiology, to review the prior studies for use as a reference, and to present community-based studies recently carried out by epidemiologists with the cooperation of clinicians and virologists.

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Essential tools for assessing influenza vaccine efficacy in improperly conducted studies: A Japanese perspective

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ABSTRACT

The fundamental issue in assessing influenza vaccine efficacy is to observe all study subjects with equal intensity throughout the surveillance period. The case definition can be adopted within the scope of the budget and the logistics of the study; however, there is no doubt that culture-proven influenza is currently the best outcome index. More pronounced vaccine efficacy can be detected if stricter case definition criteria are applied and/or if observations are confined to the peak epidemic period. Patients identified through passive case-finding in clinics do not properly represent all influenza cases that occur in the study subjects. Almost all non-randomized studies which have so far been conducted by Japanese clinicians do not take confounders into consideration. Even though laboratory-confirmed influenza is identified, vaccine efficacy should primarily be estimated based on the presence of any influenzal illness, since efficacy calculated by virus type or subtype often results in loss of statistical power. The results from post hoc subgroup analysis may not offer a solid base for assessing vaccine efficacy and should be cautiously interpreted.

1. Introduction

During the height of the influenza anti-vaccination campaign in the 1980s, many pediatricians working in school health conducted studies of vaccine efficacy based on their extensive clinical experience. The studies they designed were done in the school setting, and information on vaccination status and outcomes, such as cold symptoms or absenteeism, were obtained. However, most of the studies failed to detect vaccine efficacy due to the diluting effect of outcome misclassification. With the availability of rapid influenza diagnostic test kits, pediatricians and other physicians who had been discouraged by the difficulties involved in proper case definition were delighted; they immediately began to perform studies of influenza vaccine efficacy using these kits. Vaccinees and nonvaccinees were enrolled before the influenza season. Subjects who visited their clinics during the influenza season were tested with the rapid diagnostic kits, and the proportions of positive test results in the vaccinated and nonvaccinated groups were simply compared. The principal outcome of these studies was "laboratory-confirmed influenza". However, subjects that were lost to follow-up and those that died tended not to be properly handled, and no information was obtained about illness attacks among subjects who did not visit their clinics [1]. Such studies are typical of those that have been recently reported from Japan. Both the researchers and the readers are impressed by "laboratory-confirmed influenza" as the outcome, and overlook the fact that a study must "observe all study subjects with equal intensity throughout the surveillance period." Regrettably, it is not rare that journal reviewers and chairpersons of scientific sessions fail to identify this fatal flaw in such studies.

2. Studies of acellular pertussis vaccine

In Japan, there is a long-standing notion that the inactivated influenza vaccine has little or no efficacy. However, worldwide, the efficacy of acellular pertussis vaccine compared to that of whole-cell vaccine has been the most widely debated, as has been previously discussed in detail [2].

In Europe and Africa between 1985 and 1993, nine major studies on the efficacy of acellular pertussis vaccine were conducted, including a case–control study. They differed in many aspects, including study design, case definition, surveillance methods, and choice of comparison group. In these studies, the duration of surveillance or observation ranged from 7.2 to 25.6 months. The surveillance/follow-up methods included: telephone interviews every 2 weeks, every month, or every 6–8 weeks; clinic visits at 5, 12, and 18 months; or weekly home visits by field workers. How-

Abbreviations: CI, confidence interval; HMO, Health Maintenance Organization; ICD, International Classification of Diseases; ILI, influenza-like illness.

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ever, initial efficacy results were not consistent in judging whether acellular or whole-cell vaccines were superior, since the estimation of vaccine efficacy is strongly influenced by case definition [2].

In 1991, the World Health Organization convened an expert committee to formulate a pertussis case definition that would be used in vaccine efficacy studies. The definition included "at least 21 days of paroxysmal cough plus bacteriological, serological, or epidemiological confirmation." Using this case definition, it became possible to obtain stable estimates of pertussis vaccine efficacy and to compare these estimates among different studies. Thus, compared to whole-cell vaccine, acellular pertussis vaccine was found to have nearly the same efficacy (75–90% vs. 85–95%) and fewer adverse events (about one-third in frequency); acellular pertussis vaccine has replaced the whole-cell vaccine and is widely used [2].

The process of studying acellular pertussis vaccine offers two key lessons. First, all study subjects, both vaccinees and nonvaccinees, must be observed with equal intensity throughout the surveillance period. Second, the case definition that is used to assess vaccine efficacy is not identical to the one used in clinical settings. Thus, after satisfying the first condition, which requires full observation, case definition(s) can be adopted within the scope of the study's budget, logistics, and other relevant parameters.

3. Selected studies demonstrating the principles of study methods

There have been several studies that satisfy the essential criteria for assessing influenza vaccine efficacy. The four studies mentioned below are especially recommended to Japanese researchers, since they were well designed, well performed, well analyzed and well interpreted; they contain all of the requisites that are often overlooked in Japanese studies.

3.1. Belshe et al. (1998)

This was a randomized, multi-center, double-blind, placebo-controlled trial using live attenuated, cold-adapted influenza virus vaccine in children 15–71 months old [3]. Study subjects were assigned to a vaccine group ($n = 1070$) or a placebo group ($n = 532$). They were then observed during the period from vaccination up to the end of influenza outbreaks at the study sites during 1996–1997 season. Parents were contacted by telephone every 2 or 3 weeks until the beginning of an influenza epidemic, and then weekly during the epidemic. The staff at the study sites collected viral-culture specimens from symptomatic subjects. From among a total 3005 specimens, 109 culture-positive cases were identified. Thus, a case was defined as any patient with an illness detected by active surveillance that had a positive culture. Vaccine efficacy was reported to be 93% (95% confidence interval (CI): 88–96%) based upon the attack rates of 1.3% (14/1070) in the vaccine group and 17.9% (95/532) in the placebo group.

This can be regarded as one of the best studies on influenza vaccine efficacy reported to date. Most Japanese readers would first consider that the outcome (culture-confirmed influenza) confers the greatest value to this study. In fact, there is currently no doubt that culture-confirmed influenza is the best outcome measure for studying influenza vaccine efficacy. However, it is also important to note that active case-finding was successfully performed by telephone contact on a weekly basis. The collection of specimens from symptomatic subjects and the performance of virus culture examinations only became meaningful after thorough case finding had been conducted. It is also noteworthy that a total of 3005 specimens were collected from symptomatic subjects due to the active case-finding procedure. This means that each child under 6 years of age presented with influenza-like symptoms approximately twice during the season.

3.2. Govaert et al. (1994)

This was a randomized, multi-center, double-blind, placebo-controlled trial using inactivated influenza vaccine in elderly individuals aged 60 years or older [4]. The subjects were assigned to a vaccine group ($n = 927$) or a placebo group ($n = 911$) and observed for attacks or infections up to 5 months after vaccination during the 1991–1992 season. Four outcomes were compared between the groups: (1) serologically confirmed influenza infection; (2) physician-diagnosed influenza-like illness (ILI), based on the *International Classification of Health Problems in Primary Care (ICHPPC-2-Defined)*, made at the time the subject visited the participant's clinic; (3) ILI based upon the information obtained from postal questionnaires sent 10 and 23 weeks after vaccination that collected self-reported ILI episodes classified using the criteria of the Dutch Sentinel Stations; (4) similarly, self-reported ILI defined by the *ICHPPC-2-Defined* based on the questionnaire information. Paired sera were collected from 97% of all subjects; the response to the questionnaires was 98% and 96% at the first and second mailings, respectively.

For the outcomes (1)–(4) listed above, the relative risks of vaccination were 0.50 (95% CI: 0.35–0.61), 0.53 (0.39–0.73), 0.69 (0.50–0.87), and 0.83 (0.65–1.05), respectively. When observation was confined to the peak epidemic period of 10 weeks, lower relative risks for the outcomes (1)–(4) were obtained: 0.39 (0.22–0.68), 0.40 (0.19–0.87), 0.41 (0.28–0.61), and 0.74 (0.24–1.00), respectively.

This study highlights important aspects of assessing influenza vaccine efficacy. It clearly demonstrates that a more pronounced efficacy can be detected if stricter criteria are applied to measure the outcome and if the observations are confined to the influenza peak epidemic period. This is attributed to the increase in specificity of classifying non-diseased subjects as a negative outcome, which clinicians usually consider achievable only by applying more sophisticated laboratory tests. Moreover, this study implicitly indicates the authors' profound knowledge on a randomized controlled trial. The authors did not perform statistical significance testing to compare the distribution of subjects' baseline characteristics between vaccine and placebo groups; they conducted multivariate analysis to consider potential confounding effects. The authors recognized that the imbalances that do occur in a randomized study are due to chance and therefore one cannot reject the null hypothesis.

The authors also performed subgroup analyses and reported the relative risks of vaccination for two different age groups, e.g., 0.43 (0.28–0.67) for ages 60–69 and 0.77 (0.39–1.51) for ages 70 or older. They stated, "The post hoc analysis suggests that the efficacy may be lower in those aged 70 years and older, and therefore further evaluation of this group would be interesting." At that time, some anti-vaccination activists in Japan cited this data and wrongly asserted that influenza vaccine had no efficacy among those aged 70 or older, since the relative risk decrease was not statistically significant.

3.3. Nichols et al. (1994)

This was a retrospective cohort study among elderly individuals aged 65 or older that used information collected during three seasons (1990–1991, 1991–1992, and 1992–1993) in the administrative database of a large Health Maintenance Organization (HMO) in the United States [5]. The outcome included hospitalizations for pneumonia and influenza, all acute and chronic respiratory condi-

tions, and congestive heart failure. Cases were identified using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM). Information about potential confounders was also obtained from the same database. The observation period lasted from the date of the first influenza virus isolation in the community through March in each season. For example, during the 1991–1992 season, 15,288 vaccinees and 11,081 nonvaccinees were identified in the database, and the outcome frequencies were compared. The adjusted difference in hospitalization was: 5.8×10^{-3} (95% CI: 3.0×10^{-3} to 8.5×10^{-3}) for pneumonia and influenza; 15.3×10^{-3} (8.2×10^{-3} to 22.4×10^{-3}) for all acute and chronic respiratory conditions; 2.3×10^{-3} (0.1×10^{-3} to 4.4×10^{-3}) for congestive heart failure. Vaccination was also effective in preventing death from all causes; the adjusted odds ratios were 0.49 (0.35–0.70) in 1990–1991, 0.46 (0.35–0.61) in 1991–1992, and 0.61 (0.47–0.81) in 1992–1993.

This study is quite instructive for Japanese researchers. First, in applying passive case-finding, the authors chose hospitalization as a study outcome, not the influenza illness attack confirmed in the outpatient clinic. In an HMO, disease severity requiring hospitalization can be judged fairly consistently. Therefore, it seems unlikely that many patients who did not require hospitalization were actually hospitalized, and that many patients who required hospitalization were not hospitalized. This means that the both sensitivity and specificity of the outcome (hospitalization) were properly maintained, and the diluting effect of misclassification was minimized. On the other hand, the use of influenza illness attacks identified in the clinic through passive case-finding causes a biased estimate of vaccine efficacy, since, other than in young children, visiting a clinic due to uncomplicated influenza is strongly affected by factors other than illness severity. With passive case-finding as is used in Japan, it can become extremely difficult to ensure the homogeneity of the outcome and to minimize non-differential/differential misclassification of the outcome, not only for illness attacks but also for hospitalizations. This is because, in principle, the Japanese health insurance system guarantees the patient's freedom to choose the medical institution, whether a clinic or hospital, that they attend and makes a payment according to the amount claimed by the doctor.

Second, in this study, outcome measures were adjusted for potential confounders, such as age, gender, diagnoses indicating high risk, use of medications, and previous use of health care services. Almost none of the influenza vaccine efficacy studies so far conducted by Japanese clinicians have taken into consideration the confounding effects of other factors, despite their non-randomized observational designs.

3.4. Hoberman et al. (2003)

This was a randomized, double-blind, placebo-controlled trial using inactivated influenza virus vaccine in children 6–24 months old during the 1999–2000 and 2000–2001 seasons; the study was originally designed to evaluate vaccine efficacy against acute otitis media (AOM) [6]. Children were assigned to receive either vaccine or placebo in a 2:1 ratio (273:138 in the first season, and 252:123 in the second season) and were followed to the end of March with biweekly visits. Parents were instructed to contact study staff if their children developed any signs or symptoms so that an interim visit could be arranged. Throat culture specimens were collected during visits if the patients showed symptoms or signs of an upper respiratory tract infection accompanied by fever $\geq$38 °C, AOM, or both. There were a total of 1260 episodes of illness, from which 1113 specimens (88%) were obtained. In the first season, the frequency of culture-proven influenza was 5.5% in the vaccine group and 15.9% in the placebo group; in the second season, the corresponding figures were 3.6% and 3.3%, respectively. Accordingly, the efficacy of the vaccine to prevent culture-proven influenza was calculated to be 66% (95% CI: 34% to 82%) in the first season, and −7% (−247% to 67%) in the second season. No efficacy against AOM was detected.

This study shows that even well-designed studies using a proper protocol do not always consistently detect influenza vaccine efficacy. This tendency is particularly marked in studies focused on young children and/or studies done during a season with low-influenza activity. Several factors make it difficult to detect vaccine efficacy among very young children, including, among others: a low-immune response to the vaccine possibly due to the child's unique biological characteristics or less previous exposure to influenza viruses or antigens; susceptibility to co-circulating infectious agents; the illness definition used to measure the outcome event; the method used to obtain clinical information. In addition, antigenic similarity between circulating viruses and vaccine strains differs every year. Therefore, a randomized, controlled study investigating influenza vaccine efficacy cannot have results that are as conclusive as other randomized trials dealing with other preventive or curative interventions. Furthermore, observational studies of the influenza vaccine are even less likely to obtain stable results. Thus, to demonstrate influenza vaccine efficacy, particularly among young children, repeated studies in different populations under varying circumstances using a variety of methods are needed.

4. Discussion and conclusion

Belshe et al. appear to achieve almost perfect case-finding by observing all study subjects with equal intensity throughout the season and by detecting culture-proven influenza. Hoberman et al. also successfully performed surveillance, although active contact by study staff was biweekly as compared to the weekly contact in the study by Belshe et al. It should also be noted that the postal questionnaire sent 10 and 23 weeks after vaccination used in the study by Govaert et al. is an appropriate instrument for observing subjects equally and can thereby secure the validity of the study. However, the use of self-reported influenza-like illnesses (ILI) is likely to underestimate vaccine effectiveness due to the non-differential misclassification of the outcome. Although dilution is unavoidable, self-reported ILI can provide fairly accurate results if efforts are made to enable frequent contact, such as with telephone interviews or postal questionnaires on a weekly basis, and/or if the observation of the occurrence of outcomes is confined to the peak epidemic period [4,7]. In the study by Nichols et al., hospitalization was retrospectively identified using the HMO database; this is also considered to be a valid estimate of vaccine efficacy in the light of the severity of the outcome and the parameters of the HMO health insurance system scheme. Japanese researchers should not simply use passive case-finding to identify the outcome, since the Japanese health insurance system strongly affects patients' behavior in choosing to consult a doctor, and the doctors' approach to practicing medicine. Readers should take a critical view of Japanese studies that compare outcomes identified using passive case-finding.

Even in studies that are based on laboratory confirmation, the primary outcome should be the presence of any illness, regardless of virus type or subtype, as in the studies by Belshe et al., Govaert et al., and Hoberman et al.; type- or subtype-specific illness should be treated as a secondary outcome. This approach can be rationalized as follows. When the attack rate is 10% in vaccinees and 20% in nonvaccinees, statistically significant vaccine efficacy can be detected if 199 subjects are enrolled in each group, under the conditions of $\alpha = 5\%$ and $(1-\beta) = 80\%$. If the attack rate decreases to 5% in vaccinees and 10% in nonvaccinees by comparing virus type- or

subtype-specific diseases, 435 subjects are required in each group using the same conditions. Thus, vaccine efficacy calculated by virus type or subtype is not always as straightforward to interpret as vaccine efficacy calculated against any illness; however, virus type or subtype-specific estimates may provide further biological insight.

The conservative and careful interpretation by Govaert et al. of the relative risk of vaccination for the ages 70 or older subgroup is a good example to researchers, since the results were obtained from a post hoc subgroup analysis. Such data cannot offer a solid basis for determining vaccine efficacy, whether they do or do not favor the vaccine. In Japan, medical professionals who have an interest in influenza often mistakenly argue about vaccine efficacy among young children relying on data from subgroup analyses with limited numbers of subjects, as if such data could provide a solid basis for discussion. The level of knowledge among such medical professionals seems unlikely to be different from that of anti-vaccination activists who wrongly alleged, citing Govaert's article, that influenza vaccine has no efficacy among the elderly (aged 70 years or over).

There have been many Japanese observational studies that have not taken confounders into consideration; the need to do so has not been appreciated by so-called influenza specialists. This is likely due to the fact that few epidemiologists have been involved in vaccine research. All Japanese medical professionals who are interested in and involved in discussing influenza vaccine efficacy should recognize the elegance of the study by Govaert et al., who performed a multivariate analysis of the results of their randomized, controlled trial. Currently in Japan, it is unfortunate that proficient researchers are sometimes censured by so-called influenza specialists as being anti-vaccination activists when they criticize studies that report vaccine efficacy but overlook significant confounding effects.

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Ecological fallacy and scepticism about influenza vaccine efficacy in Japan: The Maebashi Study

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ABSTRACT

In 1979, Maebashi City discontinued influenza mass vaccination immediately after a case of vaccine-related convulsion occurred. A research group of the Maebashi City Medical Association studied the effects of mass vaccination on influenza activity in two cities without mass vaccination programs and three cities with mass vaccination programs (Maebashi Study). Due to possible issues of validity arising from the non-randomized design of the study, the authors of the Maebashi Study reserved discussion on the vaccine efficacy that they calculated from the attack rates among the non-vaccinees and vaccinees. Instead, they compared the overall attack rates in Maebashi and among the twice-vaccinees in the cities with mass vaccination programs. The authors limited their discussion to the fact that influenza activity in Maebashi was not materially different from that in cities with mass vaccination programs. Anti-vaccination activists misconstrued this to mean that the absence of a correlation between attack rate and vaccine coverage implies that influenza vaccine has no efficacy. This is a good example of the "ecological fallacy", which refers to the fact that a relationship between two variables at the population level does not necessarily imply the same relationship at an individual level.

1. Introduction

It has been said that one report played a decisive role in instilling scepticism about influenza vaccine efficacy in Japanese society. The study, known as the "Maebashi Study", was performed by a research group organized by the Maebashi City Medical Association and was conducted primarily between 1981 and 1986.

The Maebashi Study is almost always cited by anti-vaccination activists, as well as by medical professionals, as evidence that influenza vaccination is not effective. During the 1979–1980 season, Maebashi City discontinued its influenza mass vaccination program for school children when a case of severe convulsion occurred in a child after the first dose; the second dose inoculation program was cancelled that season. Subsequently, the Medical Association investigated influenza vaccine efficacy. The results of the study were published in 1987, in a report entitled "Influenza Epidemics in a Non-vaccinated Area" [1]. However, it is important to note that most influenza specialists have never read this report; they simply believe that, based on mass media reports, the Maebashi Study demonstrated that influenza vaccine had little or no efficacy.

In the preface to the report, the authors stated the background and aim of their study as follows:

> "...We have no intention of fully investigating the protective effect of influenza vaccine against infection or attack. However, we are greatly concerned with whether vaccination of pupils and students would provide any protection against an influenza epidemic. Now is the time to review the compulsory mass vaccination program for these age groups."

Thus, it is clear that the aim of the Maebashi Study was to investigate the effect of mass vaccination on influenza activity in the community, as shown by the title of the report "Influenza Epidemics in a Non-vaccinated Area."

2. An outline of the Maebashi Study

2.1. Subjects and methods

Most of the study was done during the 1984–1985 season, which had a type B virus epidemic, and during the 1985–1986 season, when A(H3) viruses were circulating. The attack rate in all school children was investigated in five selected cities in the Gunma Prefecture: Maebashi and Annaka, which had discontinued mass vaccination; Takasaki, Kiryu, and Isesaki, which were still continuing mass vaccination. Information on influenza attacks was

Abbreviation: ILI, influenza-like illness.

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retrospectively collected from more than 99% of the subjects. An influenza-like illness (ILI) was defined as "fever ≧37 °C plus absenteeism ≧2 consecutive days" or "absenteeism ≧3 consecutive days" during an influenza outbreak in the appropriate school. An outbreak was characterized as the period during which the proportion of absenteeism due to influenza symptoms among school children was 2% or more.

The authors again emphasized in the beginning of this section that:

> "...The vaccine effectiveness we discuss hereafter indicates the one relevant to the group of people, not to the individuals."

2.2. Results and discussions

The main results of the Maebashi study are shown in Tables 1 and 2.

First (noted by superscript "b" in the Table), the authors pooled the data for the three cities that were still continuing with mass vaccination and calculated the attack rate as a whole for the 1984–1985 season (Table 1): it was 54.7% (3962/7241) among non-vaccinees and 40.6% (13,255/32,641) among twice-vaccinees, for an estimated effectiveness of twice-vaccination of 25.8% [(54.7–40.6)/54.7]. The corresponding attack rates for the 1985–1986 season (Table 2) were 33.3% (2564/7702) among non-vaccinees and 20.3% (5729/28,207) among twice-vaccinees, for a vaccine effectiveness of 39.0% [(33.3–20.3)/33.3]. At this point, the authors recognized that the non-randomized study design could have introduced a validity problem. They suggested that asthmatic children, who usually account for about 5% of Japanese school children, were likely not vaccinated; of note, the Japanese vaccination guideline includes asthma as well as egg allergy as conditions that require special attention if influenza vaccine is to be given. The authors also believed that children in poor health might not have been vaccinated if they had symptoms at the time that the vaccine was being given. Thus, the non-vaccinated group was thought to include more subjects that were prone to develop influenza symptoms, which would have led to vaccine effectiveness being overestimated. Thus, the authors undertook additional analyses.

Second (noted by superscript "a" in the Table), the authors regarded the overall attack rate in Maebashi city as the reference rate (non-vaccinated area), and compared it with the attack rate among all twice-vaccinees in the three cities that continued their mass vaccination programs (vaccinated area). In the 1984–1985 season (Table 1), the comparison of the attack rates between the non-vaccinated (42.8%) and vaccinated areas (40.6%) showed that vaccination program was associated with an absolute risk reduction of 2.2% points, with a prevented fraction of 5% (calculated in the same way as ordinary vaccine efficacy). In the 1985–1986 season (Table 2), comparison of the two attack rates (27.7% vs. 20.3%) demonstrated an absolute risk reduction of 7.4% points, with a prevented fraction of 2.7%. Thus, the vaccination program appeared to have only a limited effect.

3. Interpretation by the research group

When interpreting the results of their first analysis, the authors emphasized that the groups had an imbalance of characteristics, though they did not use the term "confounding." Had a more complete epidemiological analysis been done, it would have adjusted for the confounding effects, using the information on potential confounders collected initially. Of note, it should be emphasized that, even 20 years after the Maebashi Study, the issue of confounding is not often adequately addressed in vaccine efficacy studies done by Japanese clinicians.

With respect to the study's second analysis, it seems unlikely that attack rates in the non-vaccinated and vaccinated areas were sufficiently comparable, since influenza activity is a phenomenon that is time- and place-specific. In addition, the unit of observation was changed from individuals in the first analysis to groups in the second analysis. Had the authors contrasted the overall attack rate between the non-vaccinated and vaccinated areas, as would be done in an ordinary ecological study, they would have noticed that their analysis was illogical, given that the comparison showed that the vaccination program had a negative effect (Table 1): a 42.8% attack rate in Maebashi and a 43.7% attack rate in the three cities that were grouped together as the vaccinated area during the 1984–1985 season.

The authors avoided discussing vaccine efficacy at the individual level, as they mentioned in the preface to the report and in the beginning of the main chapter. Based upon the slight effect of the vaccination program shown in their second analysis, they concluded:

> "...Influenza activity in Maebashi in non-vaccinated areas did not show any material difference from that in vaccinated areas. We therefore believe that the idea of preventing an influenza epidemic in the community by using school children as a breakwater has been proven a complete failure."

Thus, the authors interpreted their study's results carefully, recognized that it had some limitations, and never deviated from scientifically sound principles in explaining influenza vaccine efficacy.

4. Ecological fallacy drawn from the Maebashi Study

Anti-vaccination activists incorrectly cite the Maebashi Study in their campaign and have put the following statement on their website:

> "...The doctors of the Maebashi City Medical Association ... thoroughly surveyed absenteeism and illness attack rates in the vaccinated and non-vaccinated areas. This outstanding epidemiologic study comparing 45,000 school children in a vaccinated area with 25,000 school children in a non-vaccinated area revealed that influenza vaccine cannot prevent epidemics, not only in the community but also among children, and the efficacy of vaccine was thus negated."

> "...As shown by the data of the 1984–1985 season with type-B virus circulation, ... vaccine coverage was 0.1% in Maebashi as compared to 91.5% in Takasaki, but the actual incidence was nearly the same, 42.8% and 40.1%, respectively. The situation was similar in cities other than Takasaki. These data demonstrate good reasons for concluding that influenza vaccine has no efficacy."

In their statements, the activist group compared the attack rate in relation to the vaccine coverage; the unit of observation was each city, not the individual, although the original data had included information on each individual subject. To assert that influenza vaccine had no efficacy provides a good example of the "ecological fallacy." On the other hand, the authors of the Maebashi Study carefully focused their discussion on the effect of mass vaccination programs.

5. Consideration

The Maebashi Study group conducted a large-scale survey, though there were some limitations. They must be respected for the enormous effort they made to conduct the study and for their pru-