表1　米国予防接種諮問委員会（US-ACIP）勧告によるインフルエンザ予防接種の対象（1997）

Ⅰ．特別接種の対象
1）合併症を起こし易いハイリスク・グループ
- 65歳以上の者
- 老人施設入所者，慢性疾患長期療養施設に入所する全年齢層の者
- 呼吸器系・循環器系の慢性疾患（気管支喘息を含む）を有する成人および小児
- 慢性代謝性疾患（糖尿病を含む），腎機能異常，異常血色素症（hemoglobinopathy），または免疫低下状態（投薬に起因する者やHIV感染による者を含む）により，過去1年間に定期の通院，あるいは入院を要した成人および小児
- 長期のアスピリン投与を受けているため，インフルエンザに感染したらライ症候群を起こすリスクが高い，6か月～18歳の者
- 妊娠第2三半期以降（14週0日から分娩まで）にインフルエンザシーズンを迎える妊婦

2）ハイリスク者にインフルエンザを伝播する者
- 医療施設の医師，看護婦，およびその他の医療従事者
- 老人施設や慢性疾患療養施設の従業員
- ハイリスク者の在宅看（介）護に従事する，看護婦やボランティアなど
- ハイリスク者の同居家族（子供を含む）

Ⅱ．その他の対象
1）HIV感染者
2）授乳中の婦人
3）海外への旅行者
熱帯（一年中）および南半球（4～9月）への旅行者（とくにハイリスク者）
4）一般人
接種希望者，地域にとって必須な活動に従事する者，学生，共同生活をしている者（寮など），など

文献2）より，廣田訳および作表

ループに含めたこと
② ハイリスク妊婦の対象を，第2三半期以降の妊婦から全妊婦に拡大したこと
③ 何らかの神経・筋症状を呈する基礎疾患を有しており，誤嚥性肺炎を起こす恐れのある者をハイリスク・グループに含めたこと
④ インフルエンザに罹患すると診療所，救急外来，病院を受診するリスクが高い者というカテゴリーを新たに設定したこと，またその中に月齢24～59か月の小児と50～64歳の者を含めたこと
⑤ ハイリスク者にインフルエンザを伝播する者として，月齢0～59か月の小児と接触する者を含めたこと
⑥ ハイリスク者にインフルエンザを伝播する者を大きく3群（保健医療従事者，ハイリスク者との接触者，月齢0～59か月の小児と接触する者）に分類したこと

月齢6～23か月の乳幼児は，2002年に「奨励接種（encourage）」の対象として取り上げられ，2004年以降は「勧告接種（recommendation）」の対象に格上げされた。奨励接種に取り上げられることとなった理由は，月齢23か月までの乳幼児はインフルエンザ罹患時に重篤化しやすく，入院頻度が極めて高いからである（死亡頻度は高齢者のように高くない）（表3）[3~8]。その後，2003年秋に乳幼児における重症例や死亡例の発生が相次いだため，2003年11月に急遽2004/05シーズンから月齢6～23か月児への接種を勧告接種に格上げすることが決定された。同時に月齢6～23か月児をハイリスク者とみなし，彼らの接触者をも勧告接種の対象とした。ただし，この年齢層におけるワクチン有効性は必ずしも十分に確立していない。したがって，これら乳幼児にインフルエンザを伝播する者（接触者）への接種を強調し，特にインフルエンザワクチンの適応外である月齢0～5か月児との接触者に関してその重要性を強調している。

さらに，月齢24～59か月の幼児は，インフルエンザに罹患すると診療所，救急外来，病院を受診するリスクが高い者として，2006年より勧告接種

表2　米国予防接種諮問委員会（US-ACIP）勧告によるインフルエンザ予防接種の対象（2006）

* 不活化インフルエンザワクチンは月齢6か月以上の者に適用する

Ⅰ．特別接種の対象

1）合併症を起こし易いハイリスク・グループ

- 月齢6～23か月の乳幼児
- 長期のアスピリン投与を受けているため，インフルエンザに感染したらライ症候群を起こすリスクが高い，6か月～18歳の者
- 妊娠中にインフルエンザシーズンを迎える妊婦
- 呼吸器系・循環器系の慢性疾患（気管支喘息を含む）を有する成人および小児（高血圧はハイリスク状態とみなさない）
- 慢性代謝性疾患（糖尿病を含む），腎機能異常，異常血色素症（hemoglobinopathy），または免疫低下状態（投薬に起因する者やHIV感染による者を含む）により，過去1年間に定期の通院，あるいは入院を要した成人および小児
- 何らかの神経・筋症状を呈する基礎疾患（認知障害，脊髄損傷，痙攣性疾患，その他の神経・筋障害）を有しており，そのため呼吸障害をきたしたり，気道分泌物を喀出できなくなる恐れがある，あるいは誤嚥性肺炎を起こす恐れがある，成人および小児
- 老人施設入所者，慢性疾患長期療養施設に入所する全年齢層の者
- 65歳以上の者

2）インフルエンザに罹患すると診療所，救急外来，病院を受診するリスクが高い者

- 月齢24～59か月の小児
- 50～64歳の者（ハイリスク状態を有する者が多い：34%）

3）ハイリスク者にインフルエンザを伝播する者

- 保健医療従事者
  病院や診療所などの医師，看護師，およびその他の保健医療従事者。救急医療従事者（救命救急士，救護員，その他の補助者を含む）。
- ハイリスク者との接触者
  ハイリスク者の生活支援施設などの従業員，ハイリスク者の在宅看（介）護に従事する者，ハイリスク者の同居家族（小児を含む）
- 月齢0～59か月の小児と接触する者
  同居家族，それらの小児を家庭外で世話する者。特に月齢0～5か月の乳児と接触する者（6か月未満児はインフルエンザワクチンの適用外であるため）

Ⅱ．その他の対象

- HIV感染者
- 海外への旅行者（特にハイリスク者）
  熱帯（一年中）および南半球（4～9月）への旅行者，世界中から参加者が集まる大規模団体旅行参加者（一年中）
- 一般人
  接種希望者（ワクチン供給状況にもよる），必須の公共サービス従事者，学生およびその他の集合的環境（寮など）にいる者

文献1）より，廣田訳および作表

の対象となった。同時にこれら幼児の接触者も勧告接種の対象となった。表3に示すように，インフルエンザ関連の入院率が最も高いグループは月齢0～11か月の乳幼児であり，これは65歳以上の入院率に匹敵する。5歳未満児における10万人当たりの入院率は，おおむね500（ハイリスク児）から100（ハイリスク児以外）の範囲であり，24か月未満児における入院率の2倍に満たない。また，健康維持機構（HMO）のデータによる研究では，2～4歳の入院率は，月齢0～23か月の乳幼児と比べてはるかに低く，5～17歳の入院率とほぼ同等である[5]。しかしながら，月齢24～59か月の幼児はインフルエンザ関連で診療所や救急外来を受診するリスクが高い。また，死亡に関しては，

表3　インフルエンザ関連の推定入院率（年齢別・リスクグループ別）*—米国

調査年	対象集団	年齢グループ	入院数（10万対） ハイリスク者	非ハイリスク者
1973–1993†§¶	テネシー	0–11か月	1,900	496–1,038 **
	メディケイド	1– 2歳	800	186
		3– 4歳	320	86
		5–14歳	92	41
1992–1997††§§	健康維持機構（HMO）2社	0–23か月		144–187
		2– 4歳		0– 25
		5–17歳		8– 12
1968–1969	健康維持機構（HMO）	15–44歳	56–110	23– 25
1970–1971		45–64歳	392–635	13– 23
1972–1973¶¶***		65歳以上	399–518	—
1969–1995***†††	病院退院データ（全国調査）	65歳未満	—	20– 42 §§§¶¶¶
		65歳以上	—	125–228 ¶¶¶
1979–2001****††††	病院退院データ（全国調査）	全年齢	—	88 §§§§

* 上記の入院率は接種率が低いシーズンあるいは集団で得られた推定値である。接種率が高くなるほど，入院率は低下すると考えられる。ワクチン株と流行株の抗原性が良好に合致したシーズンには，インフルエンザ関連の入院は高齢者で30%–70%低下，若年者ではさらに大きな低下を示すと考えられる。
† 出典：文献3）
§ 結果指標：急性心肺疾患。
¶ 出典：文献4）
** 推定値の下限は月齢6–11か月の乳児，推定値の上限は月齢0–5か月の乳児
†† 出典：文献5）
§§ 結果指標：急性肺疾患。ハイリスク児の入院率は記載なし。
¶¶ 出典：文献6）
*** 結果指標：肺炎またはインフルエンザのいずれかが退院時記録の第1病状に記録されているか（Simonsen），あるいは退院時診断名の中に含まれている場合（Barker）に限定。
††† 出典：文献7）
§§§ インフルエンザ関連合併症のハイリスク者と非ハイリスク者を合わせて算出。
¶¶¶ 推定値の下限はA（H1N1）またはB型主流行シーズンの平均，推定値の上限はA（H3N2）主流行シーズンの平均。
**** 結果指標：主に呼吸器および循環器疾患による入院。
†††† 出典：文献8）
§§§§ 入院率はハイリスク状態の有無にかかわらず全年齢について算出。

文献1）より，藤枝訳および作表

2003/04シーズンに米国40州から報告された小児の検査確定インフルエンザ関連死亡153例のうち，96例（63%）は5歳未満であった，という研究もある[9]。

妊婦は，2004年以降の勧告から，妊娠中にインフルエンザシーズンを迎える妊婦は総てハイリスク・グループとして勧告接種の対象となった。これは世界的大流行（pandemic）の際に妊婦で観察された超過死亡の報告や，妊娠によるインフルエンザ関連合併症のリスク増大に関する報告が根拠となっている。なお，2006年勧告には，約2000人の妊婦へのワクチン接種で胎児に有害事象の発現を認めなかったこと，分娩前6か月以内にワクチン接種を受けた妊婦252人でも同様の結果であったことが記載されている。

50～64歳の者は，2000年以降，勧告接種の対象に含まれている。この年齢層ではハイリスク者の割合が大きいにも拘らずワクチン接種率が低いため，接種率の向上を目的として当該年齢層の全員を対象に含めることとなった。また，50～64歳でハイリスクに該当しない者でも，ワクチン接種によりインフルエンザ発病率の低下，欠勤の減少，

医療機関受診の減少，抗生物質を含む薬剤使用の減少，などの利益を得ることとなる。

1997年勧告では，特別接種の対象は，合併症を起こし易いハイリスク・グループ，ハイリスク者にインフルエンザを伝播する者，の2群に大別されていた。一方，2006年勧告では，インフルエンザに罹患すると診療所，救急外来，病院を受診するリスクが高い者，というカテゴリーが新たに加えられ，3群に整理されることとなった。また，ハイリスク者にインフルエンザを伝播する者は，保健医療従事者，ハイリスク者との接触者，月齢0～59か月の小児と接触する者，の3群に整理された。

2000年に50歳以上の者総てが勧告接種の対象となり，月齢6～23か月の乳幼児は奨励接種の対象（2002年）を経て2004年に勧告接種の対象となった。また，同2004年に妊婦の接種対象が全妊婦へと拡大された。さらに，乳幼児の接種対象は2006年に月齢6～59か月児へと拡大された。今後，例年のインフルエンザ予防接種をuniversal vaccination（すべての人々に一律にワクチンを接種すること）に向けて拡大する可能性についても，2006年勧告に記載されている。

Ⅳ 考　　察

US-ACIPは不活化インフルエンザワクチンの有効性を表4のように要約している[10]。65歳未満の健常者では，予防接種は発病リスクを0.1～0.3に減少させる（有効率70～90%）。60歳以上の一般高齢者を対象とした無作為化試験では，インフルエンザ呼吸器疾患の発病リスクを0.42（有効率58%）に低下させた。高齢というハイリスク状態にあり，かつウイルスへの曝露が生じやすい施設入所の高齢者では，発病リスクの減少は0.6～0.7に留まるが（有効率30～40%），肺炎やインフルエンザによって入院するリスクを0.4～0.5に（有効率50～60%），死亡リスクを0.2に低下させる（有効率80%）。

表4　インフルエンザ予防接種の効果

対　象	結果指標	相対危険	有効率(%)
65歳未満健常成人	発病	0.1～0.3	70～90
一般高齢者	肺炎・インフルエンザ入院	0.3～0.7	30～70
施設入所高齢者	発病	0.6～0.7	30～40
〃	肺炎・インフルエンザ入院	0.4～0.5	50～60
〃	死亡	0.2	80

文献10）より廣田作表

「学童」における有効性は「65歳未満の健常者」に合致すると考えてよい。ただし，小学児童の場合，学年によってウイルス曝露歴が大きく異なるので，感受性も大きく異なることに注意が必要である。下級生の発病リスクを1としたとき，上級生の発病リスクは0.2程度に低下する[11]。したがって，小学上級生を調査対象とした場合ワクチン有効性を検出しにくくなるし，臨床的にも有効性を実感しにくくなる。「乳幼児」に対するワクチン有効性は，要約されるには至っていない。

インフルエンザ予防接種の目的は，ハイリスク者における重篤な合併症や死亡を予防することにある。従来，US-ACIPはこの目的に沿って接種をより効果的に推進するため，ハイリスク者本人にワクチンを接種することによる効果を主，接触者に接種することによる伝播防止効果を副，といった位置づけのもとに勧告接種の対象を決定してきた。これに加え，2006年に，準ハイリスク者のような位置づけで，インフルエンザ罹患により外来を受診するリスクが高い者というグループを提唱し，彼らにワクチンを接種することの重要性をも強調した。

この10年間にとくに大きく変化したのは，月齢6～59か月の乳幼児に対する勧告である。乳幼児を勧告接種へ格上げすることに関しては，ワクチン有効性研究の結果からの判断というより見切り発車的に決定した様子がうかがえる。実際に当該年齢の小児を対象とした研究は少なく，有効性に関して必ずしも安定した結果は得られていない。引用されるデータには，もともと幅広い年齢層を対象とした研究の中のsubgroup analysisもあり，結果の信頼性が十分でない。しかし，わが国の小児科医の一部では，US-ACIPは乳幼児でのワクチン有効性を確認した上で，勧告接種の対象としたように説明されている。これが誤りであることは当該勧告の起草委員の発言からも明らかである。

当該勧告の起草委員は乳幼児を奨励接種の対象とした理由を以下のように説明している。「2002年に勧告ではなく奨励するという形で6～23か月の乳幼児に対するワクチン接種が勧められた。奨励という形には，これから2，3年のうちに勧告という形に発展させたいという意図が含まれていた。なぜこのような方向に進んだのかというと，乳幼児の入院率に関する調査で，5歳以上の健常な小児に比べ，6～23か月の乳幼児ではインフルエンザ流行期における入院のリスクが12倍も高いという結果がでたからである。にもかかわらず，勧告という形にしなかったのは，現実的に勧告を行った場合の実行可能性がはっきりしなかったからである。つまり，比較的短期間にワクチン接種を求めて外来受診する患者に小児科医が対応できるかどうか，経済的にワクチン接種費用を保険償還できるかどうか，を検討する必要があった。

当該年齢におけるワクチンの効果についてはデータが限られている。また，成人に比べると少ないのではないかと考えられている。しかし，ゼロではないある程度の効果があるならば，それで十分だというのがACIPの考え方である。これを土台にして奨励という形で勧告したということになる。」
(「http://www.med.osaka-cu.ac.jp/kouei/flulec/fukuda/fukuda01.pdf」；「http://www.med.osaka-cu.ac.jp/kouei/2003flufukuda/2003%20word%20fukuda.pdf」；「http://www.med.osaka-cu.ac.jp/kouei/2005.10.13.flu%20fukuda/4.2005.10.13.word%20fukuda.pdf」を参照)。

2006年の勧告では，例年のインフルエンザ予防接種を今後universal vaccination（すべての人々に一律にワクチンを接種すること）に向けて拡大することも含めて検討されている。2005年勧告では，2～49歳の年齢層のみが勧告の対象外であるため，この年齢層を含めればuniversal vaccinationが達成されることになる。しかし，実行に当たってはワクチンの製造能力・実施可能性・費用負担などさまざまな問題が指摘されている。したがって，当面は罹患リスクが高く，実行可能な4歳児までを勧告対象とすることになった[12]。

なお，ACIPは専ら医学的見地から接種対象を勧告するものであり，この勧告が直ちに当該対象に対する予算措置を含んだ接種制度の確立を意味するものではない。

V 結　　語

US-ACIP勧告は，ワクチン有効性研究から得られた「インフルエンザ発病の予防」，「インフルエンザ関連合併症や死亡の予防」，「欠勤の減少を含めたその他の利益」に関する結果に加えて，費用効果，接種率，インフルエンザによる重症例・死亡の報告数など，幅広い分野のデータを検討して毎年更新される。本勧告は，多くの国々でインフルエンザ対策を検討する際の重要な参考情報として取り扱われている。当該情報を公衆衛生分野の関係者に伝えるため，最新勧告の概要，ならびにこの10年間における勧告接種の変遷について報告した。

(受付 2006.11.29
採用 2007. 5.21)

文　　献

1) Centers for Disease Control and Prevention. Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006; 55 (RR-10): 1-48.
2) Centers for Disease Control and Prevention. Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997; 46 (RR-9): 1-25.
3) Neuzil KM, Mellen BG, Wright PF, et al. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000; 342: 225-231.
4) Neuzil KM, Wright PF, Mitchel EF Jr, et al. The burden of influenza illness in children with asthma and other chronic medical conditions. J Pediatr 2000; 137: 856-864.
5) Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med 2000; 342: 232-239.
6) Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. Am J Epidemiol 1980; 112: 798-811.
7) Simonsen L, Fukuda K, Schonberger LB, et al. The impact of influenza epidemics on hospitalizations. J Infect Dis 2000; 181: 831-837.
8) Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004; 292: 1333-1340.

9) Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003–2004. N Engl J Med 2005; 353(24): 2559–2567.
10) Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendation of the Advisory Committee on Immunization Practices (ACIP). MMWR 2005; 54(RR-8): 1–41. (日本語版：㈶日本公衆衛生協会，ISBN4-8192-0192-1 C3047)
11) Hirota Y, Takeshita S, Ide S, et al. Various factors associated with the manifestation of influenza-like illness. Int J Epidemiol 1992; 21: 574–578.
12) Schwartz B, Hinman A, Abramson J, et al. Universal influenza vaccination in the United States: Are we ready? Report of a meeting. J Infect Dis 2006; 194: s147–154.

Target groups for influenza vaccination

Satoko OHFUJI*, Megumi FUJIEDA*, Wakaba FUKUSHIMA*, Akiko MAEDA* and Yoshio HIROTA*

Key words : Influenza vaccine, Young children, US-ACIP (The US Advisory Committee on Immunization Practices)

Purpose To assess target groups for influenza vaccination.

Methods The target groups for influenza vaccination specified in the recommendations of the US Advisory Committee on Immunization Practices (ACIP) were summarized and compared between 1997 and 2006.

Results Principal changes after the 1997's recommendation are as follows: 1) all children aged 6–59 months became included into the high risk group for active vaccination; 2) recommendation for vaccination timing of pregnant women was extended from those at the second trimester or after to all women who are pregnant during the influenza season; 3) persons with neuro- or muscular-disorders and therefore prone to development of respiratory systems or aspiration pneumonia became included into the high risk group; 4) a category with increased risk to visit a clinic, hospital or emergency department due to influenza-related symptoms was newly established, covering children aged 24–59 months and persons aged 50–64 years; 5) healthy household contacts and caregivers of children aged 0–59 months were included into the group who can transmit influenza to persons in the high risk group; 6) people likely to transmit influenza to persons in the high risk group were classified into 3 categories (health-care providers, household contacts and caregivers, and those in close contact with children aged 0–59 months).

Conclusion The ACIP has gradually expanded the target populations for routine influenza vaccination. The most notable change during past 10 years seems to be the recommendation for inclusion of all children aged 6–59 months and people in close contact with babies for active vaccination.

* Department of Public Health, Osaka City University Graduate School of Medicine

International Medical Journal

Volume 12, Number 2 June, 2005

Efficacy of Influenza Vaccine in Reducing Hospital Admissions among Elderly Nursing Home Residents in Winter: The Hokkaido Influenza Study

Kota Kobayashi, Masakazu Washio, Fumio Sakauchi, Sae Miyachi, Tsuneharu Jinnohara, Hideki Kakiuchi, Toshiyuki Higashide, Yasunori Sato, Makoto Kawaharada, Tetsuo Kase, Mitsuko Okada, and Mitsuru Mori

EDITORIALS

Efficacy of Influenza Vaccine in Reducing Hospital Admissions among Elderly Nursing Home Residents in Winter: The Hokkaido Influenza Study

Kota Kobayashi[1], Masakazu Washio[1], Fumio Sakauchi[1], Sae Miyachi[2], Tsuneharu Jinnohara[3], Hideki Kakiuchi[4], Toshiyuki Higashide[5], Yasunori Sato[6], Makoto Kawaharada[6], Tetsuo Kase[7], Mitsuko Okada[8], and Mitsuru Mori[1]

ABSTRACT

Background: **Although there are many reports supporting the effectiveness of influenza vaccination for the elderly in western countries, we have few reports supporting this for the elderly in Japan.**

Objective: **The aim of the present study was to evaluate the influenza vaccine effectiveness among the institutionalized elderly.**

Methods: **A prospective cohort study was conducted to evaluate the effectiveness of influenza vaccine in reducing influenza-like illness, pneumonia, and hospital admission among elderly nursing home residents during the 2002-2003 influenza season (from November 2002 to March 2003). Four hundred and twenty four elderly nursing homes residents in 2 nursing homes and 2 skilled nursing homes in the city of Sapporo, Hokkaido Prefecture, Japan, agreed to take part in this study. Outcomes were influenza-like illness, pneumonia, and hospital admission.**

Results: **Influenza vaccination reduced pneumonia (hazard ratio: 0.26, 95% confidence interval: 0.07,0.98) and hospital admission (hazard ratio: 0.03, 95% confidence interval: 0.00, 0.23) during the influenza season. Even after adjusting for other factors such as age, sex, institution, hypoalbuminemia, activities of daily living, dementia and other underlying medical conditions, the residents with influenza vaccination had a decreased risk of hospital admission (hazard ratio: 0.02, 95% confidence interval: 0.00, 0.34).**

Conclusion: **Influenza vaccination is effective in reducing hospital admission for elderly nursing home residents during the influenza season.**

KEY WORDS

influenza, vaccination, aged, nursing home, hospitalization

INTRODUCTION

Influenza virus is the most common cause of lower respiratory tract infections[1,2]. Influenza typically resolves after a limited number of days in most persons[1,2]. However, it can worsen underlying medical conditions such as lung diseases and heart diseases through leading to secondary bacterial pneumonia or primary influenza viral pneumonia[1,2]. The secondary complications induced by influenza infec-

Received on December 2, 2004 and accepted on February 10, 2005

1) Department of Public Health, School of Medicine, Sapporo Medical University South 1 West 17, Sapporo 060-8556, Japan
2) Jikeikai Elderly Nursing Home
3) Tojyuen Elderly Skilled Nursing Home
4) Jikeikai Elderly Skilled Nursing Home
5) Jikeikai Fureainosato Elderly Nursing Home
6) Jikeikai Hospital
7) Osaka Prefectural Institute of Public Health
8) Department of Public Health, Faculty of Medicine, Osaka City University
Correspondence to: Kota Kobayashi
(e-mail: koutak@sapmed.ac.jp)

Table 1. Characteristics of the participants (n=424)

Age (years)	83.5±7.5
Gender Male/Female	90/334
Influenza vaccination	373 (88.0%)
Hypoalbuminemia*1	69 (16.3 %)
Barthel Index	11.7±8.1
Activities of daily living	
Able to perform daily activities without any help	106 (25.0%)
Need some help to perform their daily activities	164 (38.7%)
Bedridden	154 (36.3%)
Dementia	131 (30.9%)
Underlying disease	
Chronic lung disease	49 (11.6%)
Cerebrovascular disease	115 (27.1%)
Heart disease	177 (41.8%)
Cancer	23 (5.4%)

Hypoalbuminemia*1 :serum albumin <3.5 g/dl

tion increase 'excess' hospitalizations and death[2].

The attack rates of influenza are highest among school-age children and lowest among the elderly, whereas the rates of serious secondary complications are highest among the elderly, the very young and those with underlying chronic medical conditions[2]. Therefore, influenza vaccines are strongly recommended in developed countries for groups at high risk of serious secondary complications[3]. In Japan, however, influenza vaccine distribution markedly decreased from 1987 to 1994[4,5] because influenza was considered a minor illness[4,5] and the efficacy of the currently used inactivated influenza vaccine was regarded as very low or nonexistent[5,6]. Finally, influenza vaccination for school-age children became was dropped from the immunization practice law in 1994[5,7] although Hirota et al. demosntrated the effectiveness of influenza vaccination for school children[8,9]. No official recommendation as to what groups should be targeted for vaccination was left to us[5]. It was not until 2001 that influenza vaccination came to be officially recommended for the elderly in Japan[7].

Although there are many reports supporting the effectiveness of influenza vaccination for the elderly in western countries[10-15], it was not until the end of the 20th century that we had a few reports supporting its effectiveness for the elderly[16-18] in Japan. However, these studies[16-18] were conducted in the middle part of Japan which extends from subfrigid regions in the northeast to subtropical regions in the southwest. Since epidemics of influenza usually occur in winter months[20], prevention of influenza infection seems to be one of the most important issues for the elderly in Hokkaido, the northernmost prefecture in Japan. Thus, the present cohort study was conducted to evaluate the effectiveness of influenza vaccination for the instititionalized elderly in Hokkaido, Japan.

METHODS

Subjects and methods

This prospective cohort study was carried out in the city of Sapporo, Hokkaido prefecture, Japan, which is the northernmost prefecture in Japan. Four hundred twenty-four institutionalized elderly residents of 2 elderly care nursing homes and 2 elderly care skilled nursing homes agreed to take part in this study. Both elderly care nursing homes and elderly care skilled nursing homes are for the elderly who require constant care, the elderly care skilled nursing homes being for those with more severe conditions. They were 90 males and 334 females with an average (± SD) age of 83.5 ± 7.5 years old (Table1). Among them, 373 (88.0%) of the participants received influenza vaccination while 51 residents (12.0%) did not. Hypoalbuminemia (serum albumin <3.5 g/dl) was observed among 16.3% of residents. Their activities of daily living were as follows: the average (± SD) Barthel index[21] was 11.7 ± 8.1; 106 residents (25.0%) performed their daily activities without any help, 164 residents (38.7%) needed some help to perform their daily activities, and 154 residents (36.3%) were bedridden. One hundred thirty-one residents (30.9%) were demented.

Table 1 shows underlying diseases. Fourty-nine residents (11.6%) were diagnosed as having chronic lung disease, 115 residents (27.1%) cerebrovascular disease, 177 residents (41.8%) heart disease, and 23 residents (5.4%) cancer.

Influenza vaccines that were used over the 2002-2003 influenza season in Japan contained 30 micrograms/ml of hemagglutinin of each of the following influenza srains: A/New Caledonia /20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Sandong7/97. Influenza vaccines are recommended for all institutionalized elderly persons by the government, but the decision is left to the elderly and their surrogates. A total of 373 (88.0%) of 424 residents agreed to be immunized, and influenza vaccines (0.5ml for each person) were administred early in November. In Sapporo, the influenza A (H3N2) strain was first isolated on December 9, 2002 and the influenza B strain was first isolated on January 11, 2003.

Participants were followed from November 2002 to March 2003. Outcomes were influenza-like illness (ILI), pneumonia and hospitalization. Fever with upper respiratory symptoms was considered to be ILI. During the follow-up period, 13 residents developed ILI with fever of 39.0℃ or higher, 16 residents developed pneumonia and 5 resi-

Table 2. Effect of influenza vaccination on influenza-like illness, pneumonia and hospitalization

Outcome	Vaccinated (n=373)	Non-vaccinated (n=51)	Hazard ratio* (95% confidence interval)	Hazard ratio*2 (95% confidence interval)
Influenza-like illness with fever of 39.0℃	12 (3.2%)	1 (2.0%)	0.82 (0.10, 6.75)	1.06 (0.10, 11.12)
Pneumonia	13 (3.5%)	3 (5.9%)	0.26 (0.07, 0.98)	0.28 (0.06, 1.19)
Hospitalization	2 (0.5%)	3 (5.9%)	0.03 (0.00, 0.23)	0.02 (0.00, 0.34)

*: adjusted for age, sex, instituion

*2: adjusted for age, sex, instituion, hypoalbuminemia, activities of daily living, dementia and underlying diseases

dents were admitted to hospitals. All information was obtained from medical records and nurses working in the nursing homes and skilled nursing homes.

All statistical analyses were conducted using the Statistical Analysis System (SAS) package. The hazard ratios (HRs) of outcomes (i.e., ILI, pneumonia and hospitalization) and 95% confidence intervals (95% CIs) were estimated with Cox's proportional hazards model. Age was treated as a continuous variable, and indicator variables were used for sex, institution and other confounding factors. P values of less than 0.05 were considered to be significant.

RESULTS

As shown in Table 2, influenza vaccination reduced pneumonia (hazard ratio: 0.26; 95% confidence interval: 0.07, 0.98) and hospital admission (hazard ratio: 0.03; 95% confidence interval: 0.00, 0.23) during the influenza season. Even after adjusting for other factors such as age, sex, institution, hypoalbuminemia, activities of daily living, dementia and other underlying medical conditions, the residents with influenza vaccination had a decreased risk of hospital admission (hazard ratio: 0.02; 95% confidence interval: 0.00, 0.34).

DISCUSSION

Improvement of public health and advances in medicine after World War II have given Japan the highest life expectancies in the world (78.3 years for men and 83.8 years for women in 2002)[22]. The dramatic increase in the number of older people in this country is well documented. This increase in the elderly population means an increase in the number of elderly persons who need care in daily life. Long-term care facilities such as elderly care nursing homes and elderly care skilled nursing homes are provided for the elderly who require constant care.

The elderly population is the one of the highest risk groups for community-acquired pneumonia[23] as well as the one of the highest risk groups for some respiratory virus infections (e.g., influenza virus)[20]. The majority of adult patients who die from community-acquired pneumonia have chronic diseases (e.g., chronic obstructive pulmonary disease, ischemic heart disease, malignancy or neurological disease), which are more often present in the elderly[23]. Furthermore, pneumonia complicates influenza predominantly in the elderly[20]. Most respiratory pathogens are more common in the winter[23]. It is very important to protect the residents against viral infections in the winter. In the present study, influenza vaccination reduced pneumonia and hospital admission during the influenza season. The results of present study supported the effectiveness of influenza vaccination for the elderly as reported in previous studies in Japan[16-18] as well as in western countries[10-15].

In the present study, influenza vaccination reduced the risk of pneumonia but failed to remain significant after controlling for other factors. Since influenza vaccine can not prevent respiratory infections caused by organisms other than influenza virus, dilution (i.e., nondifferential missclassification[24]) with pneumonia caused by other pathogens such as respiratory syntial virus[20,23] may lead to underestimation of the effect of influenza vaccination. Furthermore, dilution with aspiration pneumonia may also cause underestimation of the preventive effect against pneumonia because silent aspiration, which is caused by the depression of the cough reflex due to the degenerative changes of aging[25], plays an important role in the development of pneumonia in the elderly[26]. Since pneumonia is a risk factor for hospitalization among the frail elderly in the winter[27] and infections such as pneumonia are a major cause of death among the institutinalized elderly with dementia[28], infection control for the frail elderly seems to be an important issue. Furthermore, the elderly with pneumonia need treatment with antibiotics, which increases the risk for Methicillin-resistant Staphylococcus aureus (MRSA) infection among those living in elderly care nursing homes[29,30]. In addition, previous hospitalization also increases the risk of MRSA infection among the residents of elderly care nursing homes[30].

There are certain limitations in the current study. First, most of the participants (87.6%) received influenza vaccination. However, it is not justifiable to conduct an interventional study to evaluate the effect of influenza vaccination because many studies[10-18] have revealed the effectiveness of influenza vaccination for the elderly (i.e, preventing ILI, pneumonia, hospitalization and death). Second, the number of participants was small. Finally, we did not confirm influenza virus infection with virus isolation or serology. Since most respiratory pathogens are more common in winter[23], we might have underestimated the effect of influenza vaccination by dilution with upper respiratory viral infections, which may explain the finding that influenza vaccination failed to prevent ILI in our study. Further studies are needed to evaluate the effect of influenza vaccination for ILI in the elderly in Japan.

In summary, the present study clearly showed that influenza vaccination reduced pneumonia and hospitaliza-

tion among the institutionalized elderly. Even after controlling for other factors, influenza vaccination reduced hospitalization among the elderly in long-term care facilities in the winter. Our results are consistent with the vaccine-recommendation of the Centers for Disease Control and Prevention in the United States[31]. Since elderly persons easily develop pneumonia after a common cold or influenza[20,23], it is important to look after the frail elderly to prevent them from catching cold or influenza. Since influenza vaccination is safe even for the hospitalized elderly[32], health care professionals should recommend influenza vaccination for nursing home residents and their family members.

ACKNOWLEDGEMENT

This work was partly supported by a Grant for Research on Emerging and Re-emerging Infectious Diseases (H14-Shinko-8) from the Japanese Ministry of Health, Labour and Welfare.

Appreciation is expressed to Prof. Yoshio Hirota, Department of Public Health, Faculty of Medicine, Osaka City University, Head of Research Project on the evaluation of influenza vaccination policy, for his comment on this paper.

REFERENCES

1) Belshe RB, Maassab HF, Mendelman PM. Influenza Vaccine-Live. In SA. Plotkin, WA. Orenstein, PA. Offit (Eds.), Vaccines. 4th ed. Philadelphia: Elsevier Inc, 2004: 371-388.
2) Fukuda K, Levandowski RA, Bridges CB, Cox NJ. Inactivated Influenza Vaccines. In SA. Plotkin, WA. Orenstein, PA. Offit. (Eds.), Vaccines. 4 th ed. Philadelphia: Elsevier Inc, 2004: 339-370.
3) Centers for Diseases Control and Prevention. Prevention and control of influenza: recommendations of the advisory committee on immunization practice (ACIP). MMWR 2003; 52(RR-8): 1-34.
4) Hirota Y, Fedson DS, Kaji M. Japan lagging in influenza jabs. Nature 1996; 380(6569): 18.
5) Hirota Y. International trends in influenza control: preparing for the next pandemic and vaccination. Nihon Koshu Eisei Zasshi (Jpn J Public Health) 1996; 43(11): 946-953 (in Japanese).
6) Hirota Y, Kaji M. Scepticism about influenza vaccine efficacy in Japan. Lancet 1994; 344(8919): 408-409.
7) Nakatani H, Sano T. Prevention of influenza: revision of immunization practice law and present status of vaccination in Japan. Rinsho To Kenkyu (Jpn J Clin Exp Med) 2002; 79(12): 2123-2129. (in Japanese)
8) Hirota Y, Takeshita S, Ide S, Kataoka K, Ohkubo A, Fukuyoshi S, et al. Various factors associated with the manifestation of influenza-like illness. Int J Epidemiol 1992; 21: 574-582.
9) Hirota Y, Takeshita S, Kataoka K, Hirohata T, Kaji M. Individual and environmental characteristics related to influenza-like illness among children: a school-based case control study. Jpn J Hygiene 1992; 47: 587-599.
10) Foster DA, Taisma A, Furumoto-Dawson A, Ohmit SE, Margulies JR, Arden NH, et al. Influenza vaccine effectiveness in preventing hospitalization for pneumonia in the elderly. Am J Epidemiol 1992; 136: 269-307.
11) Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knotterus JA. The efficacy of influenza vaccination in elderly indivisuals: a randomized double-blind placebo-controlled trial. JAMA 1994; 272: 1661-1665.
12) Ohmit SE, Monto AS. Influenza vaccine effectiveness in preventing hospitalization among the elderly during influenza type A and type B seasons. Int J Epidemiol 1995; 24: 1240-1248.
13) Nichol KL, Margolis KL, Wouremna J, von Sternberg T. Effectiveness of influenza vaccine in the elderly. Gerontology 1996; 42: 274-279.
14) Monto AS, Horunbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. Am J Epidemiol 2002; 154: 155-160.
15) 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: 665-670.
16) Oshitani H, Satio R, Seki N, Tanabe N, Yamazaki O, Hayashi S, et al. Influenza vaccination levels and influenza-like illness in long-term-care facillities for elderly people in Niigata, Japan, during an influenza A (H3N2) epidemic. Infect Control Hospital Epidemiol 2000; 21: 728-730.
17) Deguchi Y, Takasugi Y, Tatara K. Efficacy of influenza vaccine in the elderly in welfare nursing homes: reduction in risks of mortality and morbidity during an influenza A (H3N2) epidemic. J Med Microbiol 2000; 49: 553-556.
18) Deguchi Y, Takasugi Y, Nishimura K. Vaccine effectiveness for influenza in the elderly in welfare nursing homes during an influenza A (H3N2) epidemic. Epidemiol Infect 2000; 125: 393-397.
19) Saito R, Suzuki H, Oshitani H, Sasaki T, Seki N, Tanabe T. The effectiveness of influenza A (H3N2) virus infections in nursing homes in Niigata, Japan, during the 1998-1999 and 1999-2000 seasons. Infect Control Hospital Epidemiol 2002; 23: 82-86.
20) La Rosa AM, Whimbey E. Respiratory viruses. In J. Cohen, WG. Powderly, (Eds.), Infectious diseases, 2nd ed. Edinburgh: Mosby, 2004: 2067-2082.
21) Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Maryland State Med J 1965; 14: 61-65.
22) Statistics and Information Department, Minister's Secretariat, Japanese Ministry of Health, Labour and Welfare. Life expectancy. J Health Welfare Stat 2003; 50(9): 65-70. (in Japanese)
23) Baldwin DR, Macfarlane JT. Community-acquired pneumonia. In J. Cohen, WG. Powderly, (Eds.), Infectious Diseases, 2nd ed. Edinburgh: Mosby, 2004: 369-380.
24) Rothman JK. Epidemiology, An Introduction. New York: Oxford University Press, 2002.
25) Pontoppidan H, Beecher HK. Progressive loss of protective reflexes in the airway with the advance of age. JAMA 1960; 174: 2209-2213.
26) Kikuchi R, Watanabe N, Konno T, Mishima N, Sekikawa K, Sasaki H. High incidence of silent aspiration in elderly patients with community-acquired pneumonia. Am J Respir Crit Care Med 1994; 150: 251-253.
27) Washio M, Nakayama, Izumi H, Oura A, Kobayashi K, Arai Y, et al. Factors related to hospitalization among the frail elderly with home-visiting nursing service in the winter months. Int Med J (in press).
28) Washio M, Nohtomi A, Ikeda M, Koga H, Hamada T, Okayama M, et al. Dementia and other risk factors for mortality in the institutionalized Japanese elderly. J Epidemiol 1995; 5: 117-123.
29) Kajioka T, Washio M, Yoshimitsu T, Hamada T, Shogakiuchi Y, Nohtomi A, et al. Methicillin-resistant Staphylococcus aureus (MRSA) infection in the elderly. J Epidemiol 1993; 3: 117-120.
30) Washio M, Nishisaka S, Kishikawa K, Irie K, Shinkawa A, Tashiro T, et al. Incidence of Methicillin-resistant Staphylococcus aureus (MRSA) isolation in a skilled nursing home: a third report on the risk factors for the occurrence of MRSA infection in the elderly. J Epidemiol 1996; 6: 69-73.
31) CDC: Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2004; 53(RR-06): 1-40.
32) Berry BB, Ehlert DA, Battiola RJ, Sedmak G. Influenza vaccination is safe and immunogenic when administered to hospitalized patients. Vaccine 2001; 19: 3493-3498.

総説

施設入所高齢者に対するインフルエンザワクチンの有効性の評価

小林幸太，鷲尾昌一，森　　満
札幌医科大学医学部公衆衛生学講座（主任　森　満　教授）

The Effectiveness of Influenza Vaccine for the Institutionalized Elderly: A Review of Literatures

Kota KOBAYASHI, Masakazu WASHIO, Mitsuru MORI
Department of Public Health, Sapporo Medical University School of Medicine (Chief: Prof.M.MORI)

札幌医学雑誌　第74巻 3-4号　別刷
平成17年8月
Reprinted from The Sapporo Medical Journal Vol. 74, No. 3-4, August, 2005

看護・介護職員のインフルエンザ罹患が施設内流行に及ぼす影響

—北海道インフルエンザ研究—

大浦 麻絵　鷲尾 昌一　小笹 晃太郎
田中 隆　長谷川 伸作　森 満

月刊 臨牀と研究 別冊

平成18年1月発行

第83巻 第1号

Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 6511–6521
Vaccine
www.elsevier.com/locate/vaccine

Cost–effectiveness analysis of influenza vaccination for people aged 65 and over in Japan

Shu-Ling Hoshi *, Masahide Kondo, Yasushi Honda, Ichiro Okubo

University of Tsukuba, Graduate School of Comprehensive Human Sciences, Doctoral Program in Human-Care Sciences, Department of Health Care Policy and Management, Japan

Received 5 April 2006; received in revised form 15 March 2007; accepted 26 May 2007
Available online 21 June 2007

Abstract

In 2001, Japan launched a national influenza immunisation program for the elderly which provides a subsidy. In order to evaluate the efficiency of the strategy taken in this current program which provides 71% subsidy for all and explore alternative strategies, authors carried out a cost–effectiveness analysis. Authors compared strategies with different levels of subsidy and the use of risk-base targeting by constructing a decision tree model based on the literature. Incremental cost–effectiveness ratios of alternative strategies were estimated deterministically and probabilistically from societal perspective. Probabilistically estimated mean incremental cost–effectiveness ratio of current strategy is US$ 15,535 per YOLS, which can be concluded that current program is cost–effective. Authors also conclude that switching from current strategy to strategy which provides 100% subsidy for all, or strategy which provides 100% subsidy for high-risk elderlies only, can be cost–effective as well.

Keywords: Influenza; Vaccination; Cost–effectiveness analysis

1. Introduction

Epidemics of influenza break out annually throughout the world, although their extent and severity vary widely [1]. Recurring epidemics are known to have consequences such as morbidity that disrupts work in schools, companies, and elsewhere [2,3]. Although influenza affects the entire population, the elderly or individuals with pre-existing disease are at high-risk of becoming seriously ill enough to be hospitalised or die after contraction [1–6]. Due to the aging population, numbers of the elderly continue to increase in developed countries, and consequently, these countries confront serious morbidity and mortality problems of influenza.

In order to control the consequences of influenza epidemics, efforts have been focused primarily on the administration of vaccinee to the elderly. Today, in addition to issuing recommendations for immunisation, subsidies to vaccinees are provided in many countries to encourage the elderly [6]. There are variations in the level of subsidy, as well as setting the target population of immunisation programs, to which financial incentives are given. An "age-base" immunisation program targets persons who are over a certain age such as 60, 65, or 75 years old; a "risk-base" program targets persons who have pre-existing disease [6]. Japan, whose population of the elderly (aged 65 years and over) constitutes 18.0% of the total population [7], launched a government-funded age-base national influenza immunisation program in December 2001 [8]. Under this program, every person aged 65 years and over is entitled to a subsidy for influenza vaccination; one-dose of vaccination administered to one voluntary vaccinee in the target population is partially paid by public expenditure.

Although the extent of influenza vaccination in reducing hospitalisation and death reported by numerous observational studies has been questioned recently [9–11], the effectiveness of influenza vaccinee in preventing contraction among persons aged 65 years and over is well established [12].

* Corresponding author. Tel.: +81 298 53 3255; fax: +81 298 53 3255.
E-mail address: s0335772@ipe.tsukuba.ac.jp (S.-L. Hoshi).

0264-410X/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2007.05.067

Therefore, it may be desirable to have more vaccinees every year. However, in face of limited resources for health care, it is important to consider how to organise an efficient immunisation program. Studies from several countries or areas such as the United States [13–15], Canada [16], New Zealand [17], Netherlands [18], Hong Kong [19], England & Wales, France, Germany [20], and Taiwan [21] have reported that vaccination programs to those aged 65 years and over are efficient. A study from Japan [22] also concluded that vaccinating the elderly is cost–effective, but no comparison was made on age-based strategies with risk-based alternatives. Therefore, in this study, we performed an economic evaluation in detail to investigate the following two questions: (1) is the current subsidy strategy efficient? (2) is there any alternative strategy which could be efficient? The results of this study can provide implications not just for policy makers of Japan to consider future directions of the program, but also for other countries to start or to re-organise their immunisation programs.

2. Method

We conducted a cost–effectiveness analysis in order to compare alternative strategies for organising a vaccination program from societal perspective.

2.1. Alternative strategies

Under Japan's current national influenza immunisation program, setting the level of subsidy is devolved to municipalities, so that there is a wide variation among them.

We defined five alternative strategies as follows for comparison (Table 1). Strategy N stands for no program which represents the situation before the start of national immunisation program. Strategy A1 represents the status quo, that is, an age-base partial-subsidy immunisation program. We estimated an average subsidy rate of 71% for Strategy A1 based on the subsidy to receive vaccinee US$ 27, and the average cost of immunisation program US$ 38, which were calculated according to the replies from 282 respondents among 300 random samples out of about 22 million elderly population during year 2002–2004. Strategy A2 is defined as an age-base full subsidy immunisation program in order to evaluate the potential of increasing subsidies. Strategy B1 and Strategy B2 are defined in order to evaluate the potential of risk-base immunisation programs. Strategy B1 provides 100% subsidy for high-risk vaccinees and no subsidy for normal-risk vaccinees, while Strategy B2 provides 100% subsidy for high-risk vaccinees and 71% subsidy for normal-risk vaccinees. We defined elderlies of 65 years and over who had pre-existing disease such as cardiovascular diseases, diabetes, asthma, or renal diseases as high-risk [6,23], and elderlies of 65 years and over without those pre-existing diseases as normal-risk.

Table 1
Strategies

Strategy	Subsidy rate	
	Normal-risk individual (%)	High-risk[a] individual (%)
N[b]	0	0
A1[c]	71	71
A2	100	100
B1	0	100
B2	71	100

[a] High-risk individual: person with pre-existing disease such as cardiovascular disease, diabetes, asthma or renal disease.
[b] Strategy N stands for no subsidy strategy representing the situation before the start of national immunisation program.
[c] Strategy A1 represents the status quo.

2.2. Decision tree model

We constructed a decision tree model to describe courses that individuals follow in an influenza epidemic season as shown in Fig. 1. It has a decision node with five alternative strategies and five chance nodes in regards to the following circumstances: (1) age, (2) individual's risk status, (3) vaccination, (4) influenza contraction, and (5) clinical courses after the contraction of influenza. We used the literature to estimate probabilities at each chance node.

Probability at the first chance node, i.e., the probability for an individual aged 65–74 among all the elderly age 65 and over was estimated to be 0.586, based on the population estimate [24]. We divided the population in each strategy into two subgroups: persons aged 65–74 as "younger-elderly", and persons aged 75 or over as "older-elderly", because both health status and vaccinee effectiveness vary with aging [12,25].

Probability at the second chance node, i.e., the probability that an individual would have any defined pre-existing disease was estimated to be 0.326 for younger-elderly and 0.448 for older-elderly, based on the patient survey [26] and population estimate [24].

Probabilities at the third chance node, i.e., probabilities of receiving vaccinee were estimated by the risk status and the level of subsidy based on: (1) a vaccinee uptake rate under the current immunisation program from 2001 to 2004; (2) an assumption that there would be no difference in uptake rate by age, while high-risk individuals would be 0.019 points higher than those of normal-risk individuals [27]; (3) the price elasticity of demand for vaccinee [28]. We assumed the continuous uprising of vaccinee uptake rate observed in the last three seasons is due to the diffusion of the program, and adopted the latest rate, 47% of 2004/2005 season [29], as the rate among both normal-risk and high-risk individuals. The probabilities of receiving vaccinee under 71% subsidy were calculated as 0.463 for normal-risk and 0.482 for high-risk; and probabilities under no subsidy were calculated as 0.076 for normal-risk and 0.095 for high-risk; those under 100% subsidy were 0.542 for normal-risk and 0.561 for high-risk.

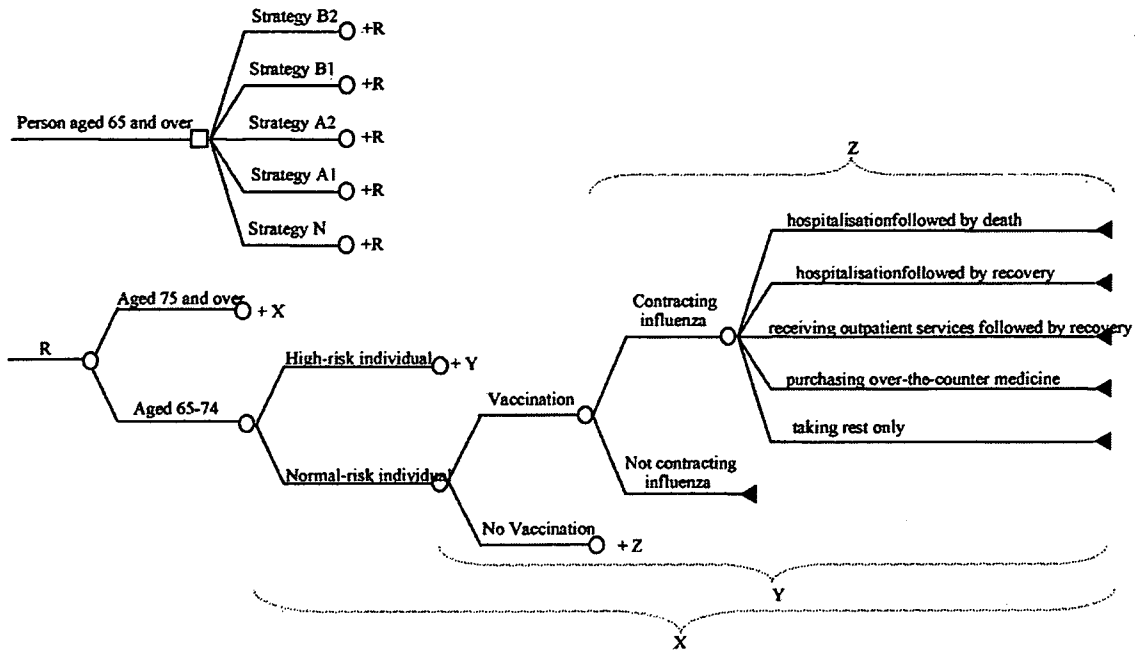

Fig. 1. Decision tree model. (□, decision node) The choices of strategy sough to be evaluated; (○, chance node) the probability of two or more possible events; (▲, terminal node) the end point to be evaluated.

Probabilities at the fourth chance node, i.e., probabilities of an individual to contract influenza including both clinically diagnosed disease and sub-clinical disease for non-vaccinated individual, P_{cont}, were estimated based on: (1) the attack rate of clinically diagnosed influenza among the non-vaccinated, 0.009 [30–32]; (2) the probability of a symptomatic individual to visit a physician, 0.65, is calculated for this study using the raw data of relevant surveys by the author who reported the price elasticity of demand for vaccinee [27]; and (3) an assumption that there would be no difference in probabilities of contracting influenza between high-risk and normal-risk individuals [23]. P_{cont} for a non-vaccinated individual was calculated as 0.014, by dividing the attack rate by the probability of symptomatic individuals to visit a physician. Those for vaccinated were calculated as: P_{cont} for non-vaccinated × (1-vaccinee effectiveness). The effect of vaccination reducing the probability of contracting influenza is 0.58 for younger-elderly [12], and half of that is assumed for older-elderly considering the immune senescence [25].

The fifth chance node has five branches. Probabilities of a patient to follow each branch: (1) P_{death} (hospitalisation followed by death); (2) P_{hosp} (hospitalisation followed by recovery); (3) P_{out} (receiving outpatient services followed by recovery); (4) P_{OTC} (taking self-medication, i.e., purchasing over-the-counter drugs followed by recovery); and (5) P_{rest} (spontaneous cure, i.e., taking rest only), were estimated as follows.

P_{death} for non-vaccinated patients were estimated by risk status based on: (1) an average all-causes excess mortality rate from 1990 to 1999 from Takahashi and Tango [33] and (2) an assumption that the mortality rate of high-risk patients would be 3.08 times that of normal-risk patients [13].

We used all-causes excess mortality rate to describe the overall impact of influenza on mortality, because influenza has been reported to cause additional deaths, not only registered as influenza in vital statistics, but also in arterial thrombosis, pneumonia and others [2,3]. Based on the age specific all-causes excess deaths from Takahashi and Tango [33] and age-specific population from 1990 to 1999 [34], average excess mortality rate, 39.1 per 100,000 persons was calculated. This was assumed as the mortality rate among non-vaccinated normal-risk and high-risk individuals, because vaccinee uptake rates from 1990 to 1999 were limited [35]. Average excess mortality rate 21.9 for normal-risk and 67.7 for high-risk were then estimated. Using these mortality rates and probability to contract influenza, P_{death} for non-vaccinated patients were calculated as 0.016 and 0.049 for normal-risk and high-risk, respectively.

Using the same method as above, we also derived lower and upper values of P_{death} for probabilistic estimation and sensitivity analysis based on pneumonia excess deaths and all-causes excess deaths (from the same study, but calculated differently).

P_{hosp}, P_{out}, P_{OTC}, and P_{rest} for non-vaccinated patient were calculated by risk status based on: (1) an assumption that among patients who sought a physician for care after contracting influenza, 7.7% of them would fall into the branch of "hospitalisation followed by recovery", while the rest would fall into the branch of "receiving outpatient services followed by recovery" [36]; (2) the probability of symptomatic individual to visit a physician is 0.65 as mentioned before; (3)

an assumption that among patients who did not seek care from physicians after contracting influenza, 57.1% of them would "purchase OTCs", while the others would fall into the branch of "taking rest only" [37]; and (4) P_{hosp} and P_{out} for non-vaccinated high-risk patients were 1.37 times [5] and 1.15 times [38] those of normal-risk patients, respectively. Equations to calculate these probabilities for non-vaccinated normal-risk are as follows:

$$P_{hosp} = 0.077 \times 0.65 - P_{death},$$

$$P_{out} = (1 - P_{hosp} - P_{death}) \times 0.65,$$

$$P_{OTC} = (1 - P_{death} - P_{hosp} - P_{out}) \times 0.571,$$

$$P_{rest} = 1 - P_{death} - P_{hosp} - P_{out} - P_{OTC}$$

Thus, P_{hosp}, P_{out}, and P_{OTC} for non-vaccinated were calculated as: 0.028, 0.527, and 0.245 for normal-risk; 0.036, 0.697, and 0.124 for high-risk, respectively.

P_{death}, P_{hosp}, P_{out}, and P_{OTC} for vaccinated were calculated by multiplying each respective probability for non-vaccinated with (1 − relevant vaccinee effectiveness). The vaccinee effectiveness was assumed as: reducing P_{death} 0.3, regardless of either age or risk status; reducing P_{hosp} 0.38 for normal-risk and 0.30 for high-risk, regardless of age [39,40]; reducing P_{out} and P_{OTC} 0.4 respectively for younger-elderly [23], 0.2 respectively for older-elderly, regardless of risk status [23,25].

We then performed sensitivity analyses on all of the discussed probabilities and vaccinee effectiveness.

We did not include the side effects of vaccination in our model, because severe adverse reactions such as shock or anaphylaxis occur rarely, and only mild adverse reactions have been reported [41].

2.3. Outcome

We adopted years of life saved (YOLS) as health outcome instead of quality adjusted life years (QALY), because the duration of influenza is short. Each year of future life gained was calculated, because vaccination increases the chances of an individual to live up to one's life expectancy. The estimated average life expectancies were 17.3 years for younger-elderly and 10.0 years for older-elderly, based on the life table [42]. High-risk individuals are thought to have shorter life expectancy than normal-risk individuals. However, to our knowledge, there is no study that reports such figures, therefore we assumed the same life expectancies for both individuals in base case analysis, and performed sensitivity analysis on it by giving ±10–30% difference between normal-risk and high-risk individuals.

2.4. Cost

In order to estimate the opportunity cost of resource use from societal perspective, we aggregated direct medical costs borne by the government, vaccinees, patients and third party payers. Non-direct medical costs related to the immunisation program are not included, because the vaccination program is built within the public health services routine. Productivity cost and direct non-medical cost related to morbidity and immunisation are also not incorporated, because influenza is an acute infectious disease, and these affect little to the total cost [13]. In order to avoid double counting, productivity cost related to mortality is not determined [43]. We used the literature along with some assumptions to estimate necessary cost data. All cost data are shown in Table 2.

Cost of the immunisation program became to be US$ 38 per dose according to our investigation mentioned above. Costs of treating influenza were estimated according to the five clinical courses on the model. Firstly, costs of a patient who received outpatient services followed by recovery were estimated as US$ 144 and US$ 260 for non-vaccinated normal-risk and high-risk patient, respectively; US$ 135 and US$ 244 for vaccinated normal-risk and high-risk patient, respectively. These figures consider: (1) an average cost for influenza treatment of US$ 117 for the first visit and US$ 33 for the second visit, estimated by summing up the fees for physicians, diagnosis, prescription and medicine (including neuraminidase inhibitors) [44]; (2) that the cost for high-risk patients is 1.8 times that of normal-risk patients [45,46] and (3) that 82% of non-vaccinated and 57% of vaccinated patients consult a physician twice [45,47].

'Costs of non-vaccinated patient who recovered after hospitalisation' were US$ 3468 for younger-elderly, and US$ 4488 for older-elderly patient. They were calculated as hospitalisation cost per day multiplied by hospital stays. The hospitalisation cost per day was adopted as US$ 204 for all patients [46]. However, the hospital stay was 17 days for younger-elderly patients and 22 days for older-elderly patients, regardless of risk status [46]. Based on an assumption that the hospital stays of vaccinated patients would be 0.7 times that of non-vaccinated patients [47], then, 'costs of vaccinated patient who recovered after hospitalisation' would be US$ 2428 for younger-elderly patients and US$ 3142 for older-elderly patients.

'Costs of a patient who died after hospitalisation' was US$ 9180 per person regardless of either age or risk status. This was estimated using a formula, US$ 204 × 1.5 × 30 days, based on: (1) an assumption that daily hospitalisation cost for a patient who died was 1.5–4 times that of a patient who recovered [48] and (2) the average hospitalisation stay before death was 30 days [5].

Cost for OTC purchases was assumed to be US$ 18. No costs were incurred by a patient who only rested after contracting influenza.

Sensitivity analyses on the costs to deal with uncertainty will be discussed later. All costs were adjusted to the values of 2002 year by the medical consumer price index [49] (exchange rate: US $1 = ¥110).

Table 2
Data used on the model

	Aged 65–74		Aged 75+		Reference
	Normal-risk	High-risk	Normal-risk	High-risk	
Probabilities					
Probability among all the elderly	0.586		0.414		[24]
To be a high-risk individual	0.326		0.488		[24,26]
To receive a vaccinee					[27–29]
Without subsidy	0.076	0.095	0.076	0.095	
71% subsidy	0.463	0.482	0.463	0.482	
100% subsidy	0.542	0.561	0.542	0.561	
P_{cont} [a,b]	0.014	0.014	0.014	0.014	[23,27,30–32]
P_{death} [b,c]	0.016	0.049	0.016	0.049	[13,33–35]
P_{hosp} [b,d]	0.028	0.036	0.028	0.036	[5,36]
P_{out} [b,e]	0.527	0.697	0.527	0.697	[37,38]
P_{OTC} [b,f]	0.245	0.124	0.245	0.124	[37]
P_{rest} [g]	$1 - P_{death} - P_{hosp} - P_{out}$				
Vaccinee effectiveness					
Preventing infection	0.58	0.58	0.29	0.29	[12,25]
Reducing death	0.30	0.30	0.30	0.30	[39,40]
Reducing hospitalisation	0.38	0.30	0.38	0.30	[39,40]
Reducing out-patient visits	0.40	0.40	0.20	0.20	[23,25]
Reducing OTC purchase	0.40	0.40	0.20	0.20	[23,25]
Cost (per person)[h] (US$)					
Immunisation program	38	38	38	38	Estimated
Out-patient (non-vaccinated)	144	260	144	260	[44–47]
Out-patient (vaccinated)	135	244	135	244	[44–47]
Hospitalisation (non-vaccinated)	3468	3468	4488	4488	[46,47]
Hospitalisation (vaccinated)	2428	2428	3142	3142	[45,46]
Died after hospitalisation	9180	9180	9180	9180	[5,45,48]
OTCs	18	18	18	18	Assumed
Average life expectancy (years)					[42]
Without discounting	17.3	17.3	10.0	10.0	
3% discounted	13.7	13.7	8.8	8.8	
5% discounted	12.0	12.0	8.1	8.1	

[a] Probability of an individual to contract influenza.
[b] Probability for vaccinated individual = probability for non-vaccinated individual × (1 − vaccinee effectiveness).
[c] Probabilities of following "hospitalisation followed by death" after contracting influenza.
[d] Probabilities of following "hospitalisation followed by recovery" after contracting influenza.
[e] Probabilities of following "receiving outpatient services followed by recovery" after contracting influenza.
[f] Probabilities of following "purchasing over-the-counter drugs followed by recovery" after contracting influenza.
[g] Probabilities of following "spontaneous cure, i.e., taking rest only", after contracting influenza.
[h] All values were adjusted to 2002 in Japanese Yen and converted to US dollars, $1 = ¥110 (2002).

2.5. End point

We used incremental cost–effectiveness ratios (ICERs) to determine the efficiency of alternative strategies. ICER was calculated as follow:

$$\text{ICER} = \frac{\text{total cost}_{\text{strategy comparator}} - \text{total cost}_{\text{strategy reference}}}{\text{YOLS}_{\text{strategy comparator}} - \text{YOLS}_{\text{strategy reference}}},$$

$$\text{total cost} = \text{cost of immunisation program} + \text{cost of treating influenza}$$

We computed cost, outcomes (YOLS) and ICERs both deterministically and probabilistically. In probabilistic estimation, we conducted 1000 times Monte Carlo simulation. Lower and upper values of the variables used in the simulation were derived from published literature, or were assigned as point estimate ±30% if no datum was available (Table 4). Variables were randomly sampled from uniform distribution assigned to probabilities and triangle distribution to costs items, except for vaccinee uptake rates, life expectancy, and cost of immunisation program.

3. Discounting

Health benefits accrued after the first year was discounted at an annual rate of 3% in base case, and 0%, 5% in sensitivity

Table 3
Incremental costs per person, incremental effects per person, and ICERs

	Deterministic estimation			Probabilistic estimation (5th and 95th percentile)		
	Incremental cost (US$)	Incremental YOLS	ICER (US$ per YOLS)	Incremental cost (US$)	Incremental YOLS	Mean ICER (US$ per YOLS)
Compared with no program (Strategy N)						
SA1	12.9	0.00111	11,622	13.0 (12.3–13.6)	0.00098 (0.00046–0.00166)	15,535 (7,414–29,409)
SA2	15.6	0.00138	11,729	15.7 (14.8–16.4)	0.00119 (0.00056–0.00200)	15,535 (7,414–29,409)
SB1	5.5	0.00084	6,548	5.6 (5.0–6.0)	0.00075 (0.00035–0.00126)	8,838 (4,036–16,998)
SB2	13.9	0.00125	11,120	14.0 (13.1–14.7)	0.00111 (0.00052–0.00187)	14,771 (7,023–27,993)
Compared with current strategy (Strategy A1)						
SA2	2.7	0.00020	12,273	2.6 (2.5–2.8)	0.00020 (0.00009–0.00034)	15,535 (7,414–29,409)
SB1	−7.4	−0.00027	27,407	−7.4 (−7.6 to −7.2)	−0.00024 (−0.00040 to −0.00011)	36,606 (18,217–67,670)
SB2	1.0	0.00014	7,143	0.9 (0.9–1.0)	0.00013 (0.00006–0.00021)	8,838 (4,036–16,998)

analysis [43]. No discounting was required on cost because all costs accrue within the first year [43].

4. Results

Table 3 shows ICERs or mean ICERs per YOLS, relevant incremental cost and relevant incremental YOLS per person of each alternative strategy, compared to do nothing strategy (Strategy N), as well as to current strategy (Strategy A1) by deterministic estimation and probabilistic estimation (5th and 95th percentiles). Compared to Strategy N, Strategy A1 costed more and gained more YOLS; estimated ICERs were US$ 11,622 per YOLS by deterministic estimation, or US$ 15,535 (US$ 7414, US$ 29,409) per YOLS by probabilistic estimation. Incremental costs were US$ 12.9 by deterministic estimation, or US$ 13.0 (US$ 12.3, US$ 13.6) by probabilistic estimation; incremental YOLS were 0.00111 year by deterministic estimation, or 0.00098 (0.00046, 0.00166) year by probabilistic estimation. Compared to Strategy A1, Strategy A2 and B2 costed more and gained more YOLS, while Strategy B1 costed less and gained less YOLS. Estimated ICERs for Strategy A2, B1 and B2, were US$ 12,273, US$ 27,407, US$ 7143 per YOLS by deterministic estimation; US$ 15,535 (US$ 7414, US$ 29,409), US$ 36,606 (US$ 18,217, 67,670), US$ 8838 (US$ 4036, 16,998) per YOLS by probabilistic estimation, respectively. Incremental costs were US$ 2.7, US$ −7.4, US$ 1.0 by deterministic estimation; US$ 2.6 (US$ 2.5, US$ 2.8), US$ −7.4 (US$ −7.6, US$ −7.2), US$ 0.9 (US$ 0.9, US$ 1.0) by probabilistic estimation, respectively. Incremental YOLS were 0.00022, −0.00027, 0.00014 year by deterministic estimation, 0.00020 (0.00009, 0.00034), −0.00024 (−0.00040, −0.00011), 0.00013 (0.00006, 0.00021) year by probabilistic estimation, respectively.

5. Cost–effectiveness acceptability curves

Cost–effectiveness acceptability curves are shown in Fig. 2. The curve of Strategy A1 compared to Strategy N ascends from 0% and reaches 100% at US$ 44,000 per YOLS on the left panel. The curve of Strategy A2 and Strategy B2 compared to Strategy A1 ascends from 0%, reaches 100% at US$ 26,000 and US$ 43,000 per YOLS, respectively. The curve of Strategy B1 compared to Strategy A1 descends from 100% to 0% as shown on the right panel.

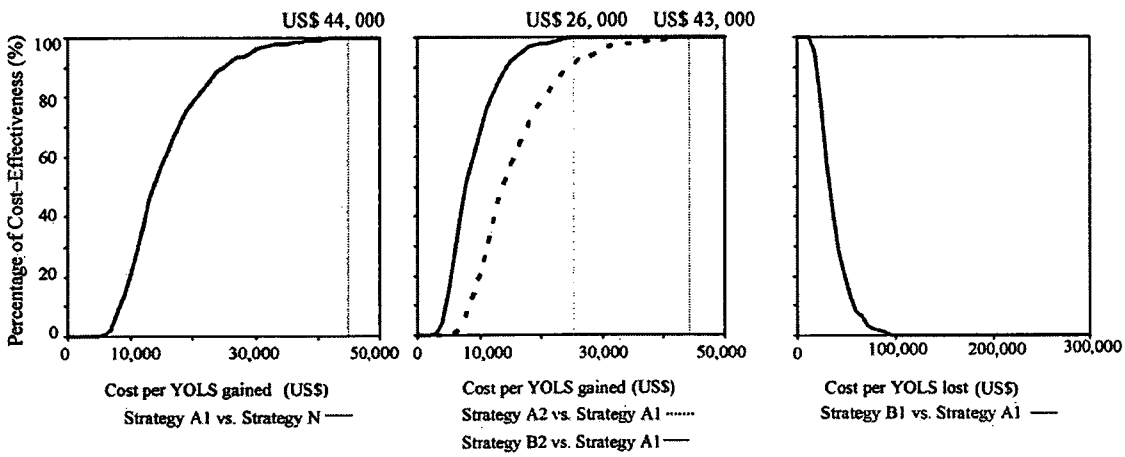

Fig. 2. Cost–effectiveness acceptability curves.

6. Sensitivity analyses

One-way sensitivity analyses were conducted on: the probability to contract influenza, the respective probabilities of five clinical courses after the contraction of influenza, each of the cost items, discounting rate, and life expectancy. Lower and upper values of each variable and the results are shown in Table 4. Probabilities as well as vaccinee effectiveness which have potential to change mortality directly or indirectly have more influence than other variables on ICERs. They are the probability of hospitalisation followed by death, probability to contract influenza, vaccinee effectiveness in reducing

Table 4
Results of sensitivity analyses

	Incremental cost–effectiveness ratio (US$ per YOLS)					
	vs. Strategy N				vs. Strategy A1	
Alternative strategies	A1	A2	B1	B2	A2	B2
ICERs in base-case analysis	11,622	11,727	6,548	11,120	12,273	7,143
(1) One-way (ranges (L: lower limit; U: upper limit))						
Probability to contract influenza (un-vaccinated individual)						
L: −30%	16,763	16,646	9,538	15,820	16,100	8,964
U: +30%	8,560	8,541	4,691	8,102	8,447	4,605
P_{death} (probability of hospitalisation followed by death)						
L: NR = 0.011; HR = 0.034[a]	16,914	16,900	9,666	16,091	16,831	9,670
U: NR = 0.021; HR = 0.064	8,806	8,775	4,870	8,331	8,627	4,737
P_{hosp} (probability of hospitalisation followed by recovery)						
L: −30%	10,531	10,539	5,819	9,986	10,580	5,800
U: 30%	10,329	10,336	5,711	9,795	10,372	5,687
Vaccinee effectiveness (preventing contracting)						
L: 30%	15,996	15,987	9,122	15,161	15,941	8,855
U: 70%	10,398	10,406	5,809	9,932	10,444	6,107
VE_{death}[b]						
L: 0%	15,861	15,853	9,176	15,032	15,812	8,773
U: 60%	9,208	9,217	5,068	8,724	9,264	5.011
Cost of immunisation program						
L: −30%	7,689	7,727	4,180	7,304	7,918	4,250
U: +30%	15,604	15,680	8,918	14,872	16,068	9,071
Costs of a patient who recovered after hospitalisation						
L: −30%	11,712	11,805	6,548	11,200	12,273	7,143
U: +30%	11,532	11,654	6,548	11,040	12,273	7,143
Costs of a patient who died after hospitalisation						
L: −30%	11,885	11,944	6,789	11,327	12,241	6,907
U: +30%	11,423	11,480	6,319	10,864	11,768	6,429
Costs of a patient who received outpatient services followed by recovery						
L: −30%	11,774	11,832	6,662	11,214	12,123	6,771
U: +30%	11,534	11,592	6,445	10,977	11,882	6,557
Cost purchases for OTCs						
L: −30%	11,658	11,715	6,555	11,098	12,005	6,664
U: +30%	11,650	11,708	6,552	11,092	12,000	6,664
Discounting rate						
L: 0%	9,485	9,512	5,340	9,085	9,643	5,882
U: 5%	13,163	13,109	7,333	12,523	12,857	7,692
Different life expectancy for NR and HR individual (discounting rate: 3%)						
NR: +10%; HR: −10%	11,944	12,000	7,274	11,488	12,273	7,692
NR: +20%; HR: −20%	12,170	12,283	8,184	11,880	12,857	9,091
NR: +30%; HR: −30%	12,647	12,683	9,353	12,411	12,857	10,000
NR: +40%; HR: −40%	13,579	13,684	10,912	13,365	14,211	11,111
NR: +50%; HR: −50%	13,299	13,333	13,094	13,365	14,286	13,500
(2) Two-way						
$VE_{death} = 0$ and VE_{hosp}[b] = 0	15,904	15,920	9,194	15,106	15,882	9,091

[a] NR: normal-risk; HR: high-risk.
[b] VE_{death}: vaccinee effectiveness in preventing contracting; VE_{hosp}: vaccinee effectiveness in preventing hospitalisation.