1) アウトカム観測期間

T1: peak outbreak period：各地それぞれのピーク週をはさむ前後の週で、分離株数の 80%を含む期間（平均 7 週間)

T2: Total outbreak period： 13 地域の分離株数の結果を結合させ、ヒストグラムを用いて専門委員会が定義する期間（平均 14 週間）

T3: Total outcome period：11～3 月,outcome が確認できる期間

2) 症例定義

D1: Febrile upper respiration illness (以下は「発熱を伴う URI」とする)：URI 症状(鼻、喉の痛み,咳) が 2 つ以上、2 日間続き、発熱が 1 日以上あるもの。

D2: Any URI： URI 症状(鼻、喉の痛み、咳) が 1 つ以上、2 日間続くもの。

D3: Any symptom：1 日でも熱、鼻、喉の痛み、咳、頭痛、筋肉痛、悪寒、疲労・衰弱などの症状が 1 つ以上のもの。

【結果】

- 表 1 はアウトカム観測期間が、表 2 は症例定義がイベント率, イベント回避絶対日数、ワクチン効果に与える影響を表している。観察期間が長いほど、症例定義の感度が高いほど、イベント率、イベント回避絶対日数が増える。
- 図 1 は症例定義とアウトカム観測期間の二次元から見た結果である。灰色は D1 と T1 の組み合わせ,黒は D3 と T3 の組み合わせの結果を示している。後者(つまり感度が最も高いシナリオの病欠回避日数、生産性低下回避日数、医療機関受診回避日数は前者のそれぞれの 4.4 倍、3.4 倍、2.7 倍であった。
- 図 2 はイベント絶対回避日数の結果とイベント相対回避率の結果が逆になっていることを示している。最も高い感度のシナリオ（偽陽性が最も高いシナリオ）のワクチン効果（1－ relative rate reduction）は最も高い PPV が得られるシナリオ（D1 と T1 の組み合わせ）のそれより低いことを示している。
- 表 3 と表 4 は Nichol ら（2003）のオリジナルシナリオ（感度が最も高い症例定義を用いたシナリオ）と本研究（特異度の高いシナリオ）の費用便益分析の結果を示している。
- 前者の接種損益平衡点は 43.07 ドルで、後者の接種損益平衡点は 6.58 ドルであった。

【結論】

異なるインフルエンザ症例定義と観測期間の設定はワクチンの臨床効果や経済効果に大きく影響を与える。症例定義と観測期間のミスマッチはワクチン効果やワクチンがもたらす便益の過小評価に繋がる。

【考察】

フランスの研究は受診に来た患者に、発熱、呼吸器症状、筋肉痛を症例定義に用いた場合の PPV と感度の高い定義（熱、咳喉の痛み)の PPV を報告した。前者と後者の PPV はそれぞれ 40%と 30%であった。オランダの研究は受診に来た高齢 ILI 患者に、発熱、咳、急な発病（acute onset）を症例定義に用いた場合の PPV は 30%と報告した。別のオランダの研究では、発熱、頭痛、急な発病、咳、接種状況を用いた場合の PPV は 75%に達することを報告した。我々の結果は先行研究の結果に一致した。

場所：米国 13 地域　研究デザイン：無作為二重盲検偽薬－対照臨床試験のデータを用いた費用効果分析。 主な結果：観察期間が長いほど、症例定義の感度が高いほど、イベント率、イベント回避絶対日数が増加。 要約者コメント：異なるインフルエンザ症例定義と観測期間の設定はワクチンの臨床効果や経済効果に大きく影響するため、2 次的データを用いて経済評価を行う場合、原論文の症例定義を見極める必要が有る。

Table 1
Influence of outcome period on event rate and vaccine effective estimates: example of febrile upper respiratory tract illnesses (URIs)[a]

	Rate in unvaccinated	Rate in vaccinated	Number prevented by vaccination (per 1000)	Vaccine effectiveness (%)	*P*-value
Febrile URI for peak outbreak period					
Work loss days	149.4	107.0	42.4	28.4	<0.0001
Days with impaired work productivity	321.2	242.2	79.0	24.6	0.0002
Days with health care provider visits	40.3	23.8	16.5	40.9	<0.0001
Febrile URI for total outbreak period					
Work loss days	268.0	195.1	72.9	27.2	<0.0001
Days with impaired work productivity	300.3	253.6	46.7	15.6	0.0007
Days with health care provider visits	72.0	52.3	19.7	27.3	<0.0001
Febrile URI for total outcome period					
Work loss days	388.1	269.9	118.2	30.5	<0.0001
Days with impaired work productivity	456.9	391.6	65.3	14.3	0.0002
Days with health care provider visits	107.0	77.9	29.1	27.2	<0.0001

[a] Rates represent absolute number of events per 1000 participants. Rates for the peak outbreak period have been adjusted for an average, site-peak outbreak period duration of 7 weeks. Rates for the total outbreak period have been adjusted for the combined, 14-week outbreak period. Rates for the total outcome period represent the numbers of events per total, 5-month outcome period (November–March). Febrile URI was defined as 2 days of URI symptoms (runny nose, sore throat, cough) with two or more symptoms on at least 1 day, and fever on at least 1 day.

Table 2
Influence of clinical case definition on event rate and vaccine effective estimates[a]

Clinical case definition	Rate in unvaccinated	Rate in vaccinated	Number prevented by vaccination (per 1000)	Vaccine effectiveness (%)	*P*-value
Febrile URI					
Work loss days	388.1	269.9	118.2	30.5	<0.0001
Days with impaired work productivity	456.9	391.6	65.3	14.3	0.0002
Days with health care provider visits	107.0	77.9	29.1	27.2	<0.0001
Any URI					
Work loss days	757.5	610.6	146.9	19.4	0.0002
Days with impaired work productivity	997.2	900.8	96.4	8.7	0.006
Days with health care provider visits	258.5	199.0	59.5	23.0	<0.0001
Any symptom					
Work loss days	1030.0	843.6	186.4	18	0.0002
Days with impaired work productivity	1502.5	1231.0	271.5	18	0.0003
Days with health care provider visits	338.9	294.1	44.8	13	0.024

[a] Rates represent absolute numbers of events per 1000 persons for the entire outcome period (November–March). The clinical case definitions are—febrile upper respiratory illness: 2 days of URI symptoms (runny nose, sore throat, cough) with two or more symptoms on at least 1 day, and fever on at least 1 day; any URI: 2 days of at least one URI symptom (runny nose, sore throat, cough); any symptom: any day with at least one symptom (fever, runny nose, sore throat, cough, headache, muscle aches, chills, tiredness/weakness).

Table 3
Most likely values, ranges, and probability distributions used for parameter estimates in the cost–benefit models: comparison of values for the most sensitive scenario and the most specific scenario[a]

Variable	Probability distribution for Monte Carlo simulation models	Most likely values (range for probability distributions)	
		Primary model (analysis based on events due to any symptom for entire outcome period)	Alternate model (analysis based only on events due to febrile URI for peak outcome period)
Likelihood of missing work for vaccination	Triangular	0.5 (min = 0.2, max = 0.8)	Same
Hourly wage (US$)	Triangular	15 (min = 10, max = 30)	Same
Work lost for vaccination (h)	Triangular	0.5 (min = 0.25, max = 0.75)	Same
Days of work lost due to side effects (per 1000)	Triangular	10 (min = 0, max = 20)	Same
Health care provider visits due to side effects (per 1000)	Triangular	5 (min = 0, max = 10)	Same
Cost of health care provider visits (US$)	Triangular	122 (±50%)	Same
Health care provider visits among unvaccinated (per 1000)	Poisson	338.9 (rate parameter = 338.9)	40.3 (rate parameter = 40.3)
Relative rate of health care provider visits due to illness among vaccinated persons	Normal on log scale	0.87 (mean ln 0.87; 95% CI = ln 0.77, ln 0.98)	0.59 (mean ln 0.59; 95% CI = ln 0.50, ln 0.70)
Days of work lost due to illness among unvaccinated persons (per 1000)	Poisson	1030.0 (rate parameter = 1030.0)	149.4 (rate parameter = 149.4)
Relative rate of work lost due to illness among vaccinated vs. unvaccinated persons	Normal on log scale	0.82 (mean ln 0.82; 95% CI = ln 0.74, ln 0.91)	0.72 (mean ln 0.72; 95% CI = ln 0.61, ln 0.84)
Days of impaired work productivity among unvaccinated (per 1000)	Poisson	1502.5 (rate parameter = 1502.5)	321.2 (rate parameter = 321.2)
Relative rate of impaired work productivity among vaccinated vs. unvaccinated persons	Normal on log scale	0.82 (mean ln 0.82; 95% CI = ln 0.74, ln 0.91)	0.75 (mean ln 0.75; 95% CI = ln 0.65, ln 0.88)
Productivity level during days of impaired productivity (%)	Triangular	50 (min = 20, max = 100)	Same

[a] See Nichol et al. (2003) for a detailed description of the primary cost–benefit model and analysis.

Table 4
Results of the cost–benefit analyses: comparison of the scenarios using more sensitive vs. specific clinical case definitions

Cost category	Mean costs per person vaccinated[a]	
	Primary model (based on events due to any symptom for entire outcome period)	Alternate model (based only on events due to febrile URI for peak outcome period)
Costs incurred due to vaccination		
Direct costs of vaccine and administration	Unknown	Unknown
Indirect costs of vaccination (US$)	4.58	4.58
Direct costs of side effects (US$)	0.61	0.61
Indirect costs of side effects (US$)	1.47	1.47
Total vaccination costs incurred (US$)	6.66 (+costs of vaccine and administration)	6.66 (+costs of vaccine and administration)
Costs prevented by vaccination		
Direct costs of medical care prevented (US$)	5.39	2.00
Indirect costs of work loss prevented (US$)	27.16	6.17
Indirect costs of impaired work productivity prevented (US$)	17.18	5.07
Total costs prevented by to vaccination (US$)	49.73	13.24
Break even costs for vaccine and its administration		
Mean break even cost for vaccine and administration, 5th–95th percentile (US$)	43.07, 25.72–58.92	6.58, 1.45–10.53

[a] Costs have been adjusted to US$ 1998 using the appropriate component of the consumer price index. Shown are the mean costs for each category. The 5th and 95th percentiles were estimated from the Monte Carlo simulation analysis. If the actual costs for vaccine and administration are less than the break even costs, then vaccination would generate net savings to society. If the costs for vaccine and administration are greater than the break even costs, then vaccination would generate net costs to society. The scenario based on events due to any symptom for the entire outcome period was the most sensitive for identifying influenza-associated morbidity and benefits of vaccination. See Nichol et al. (2003) for a detailed description of the primary cost–benefit model and analysis.

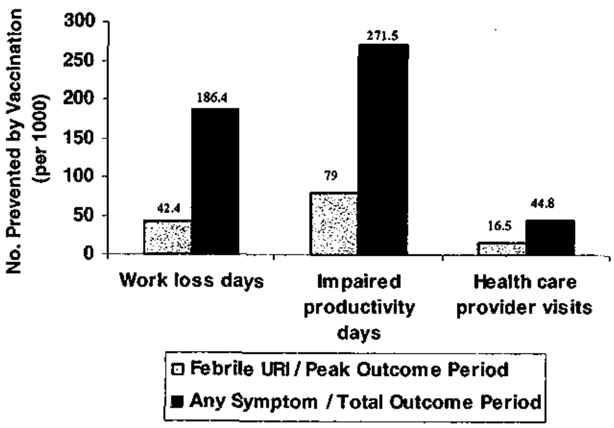

Fig. 1. Influence of clinical case definition and outcome period on the identification of the number of events prevented by vaccination. URI denotes upper respiratory tract infection.

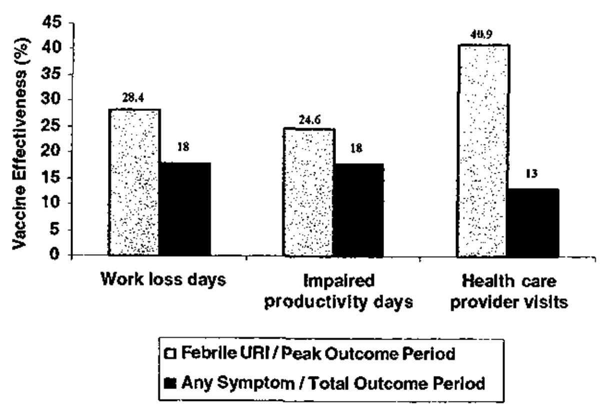

Fig. 2. Influence of clinical case definition and outcome period on estimates of the effectiveness of vaccination as a percentage reduction in outcome events. URI denotes upper respiratory tract infection.