INFLUENZA-ASSOCIATED MORTALITY IN TROPICAL SINGAPORE

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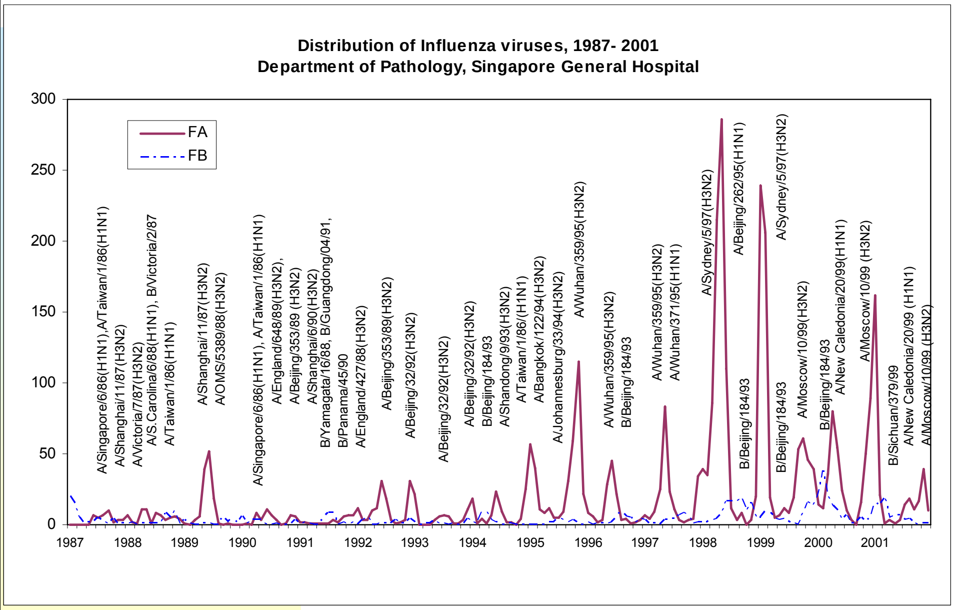
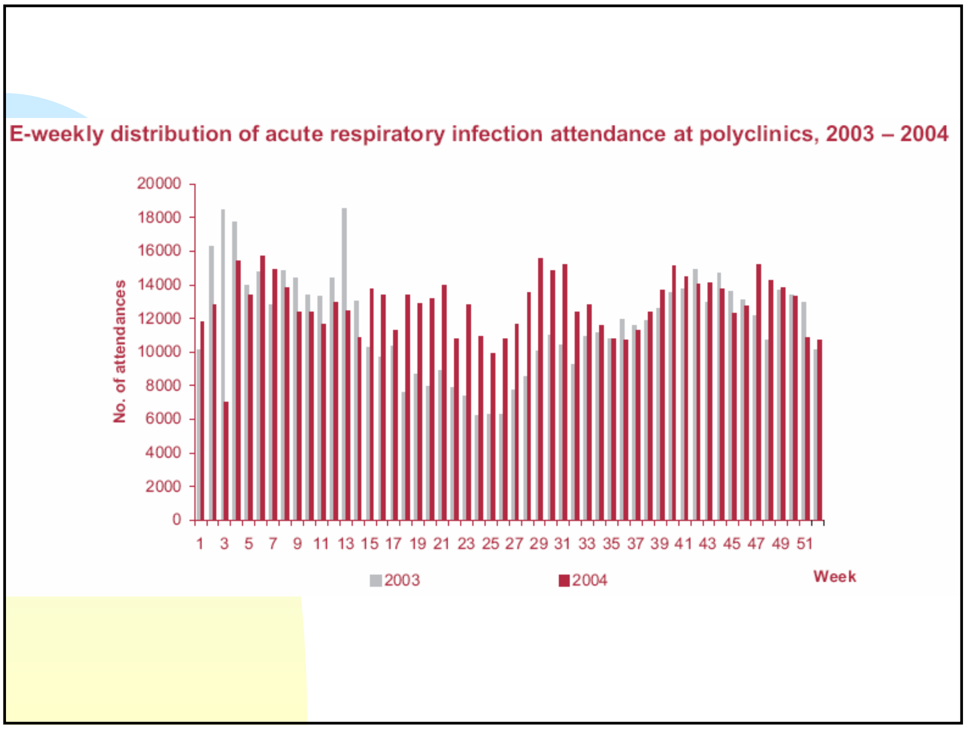
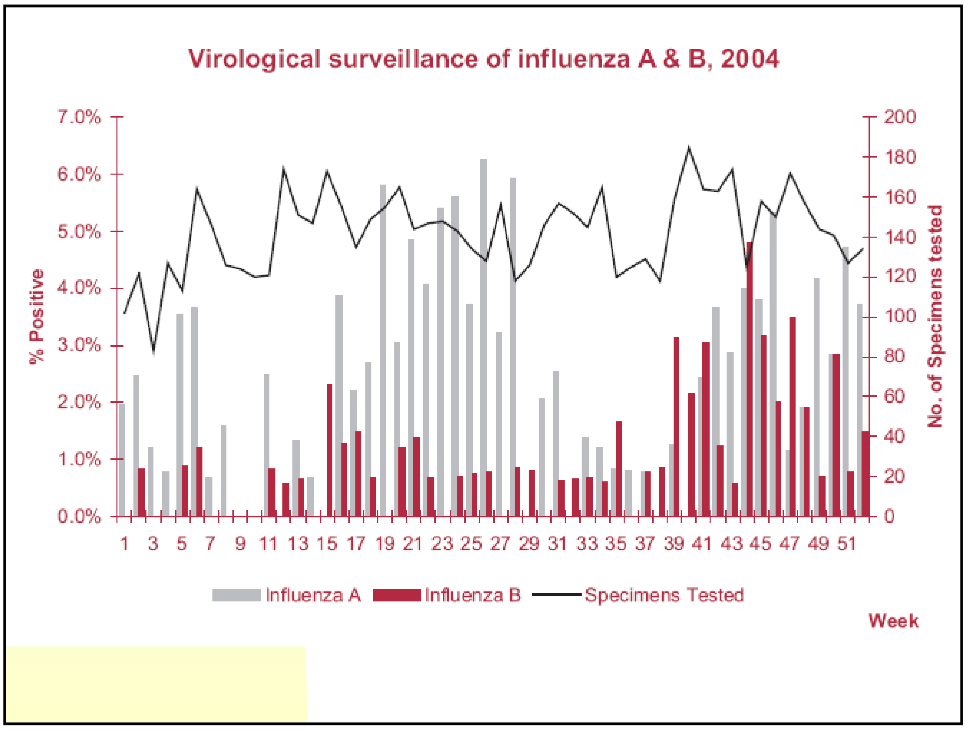
Influenza activities in Singapore

Land area
692 sq km
Four million people
Chinese (76%)
Malays (14%)
Asian Indians (7%)
Others (3%)

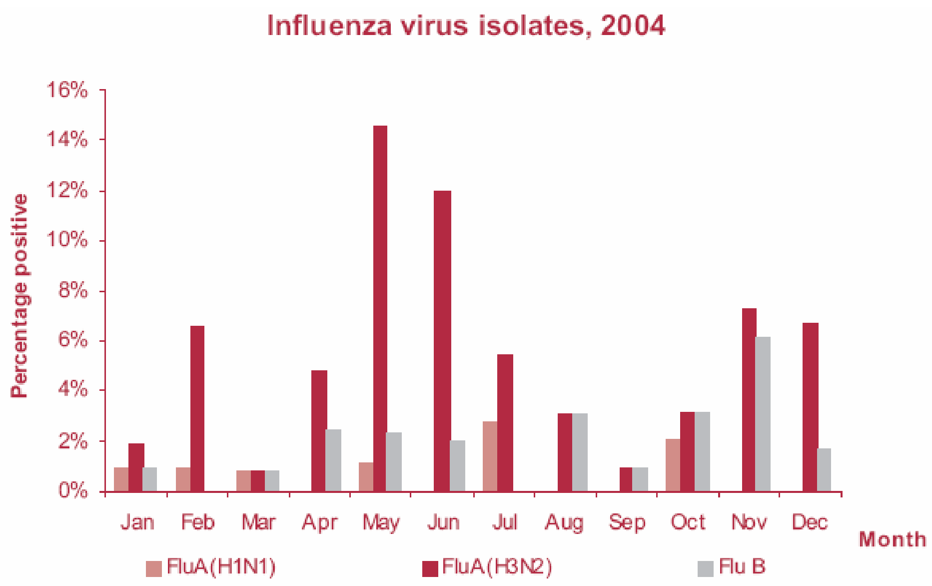




E-weekly distribution of acute respiratory infection attendance at polyclinics, 2003 – 2004
No. of attendances
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51
2003
2004
Week



Virological surveillance of influenza A & B, 2004
% Positive
7.0%
6.0%
5.0%
4.0%
3.0%
2.0%
1.0%
0.0%
No. of Specimens tested
200
180
160
140
120
100
80
60
40
20
0
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51
Influenza A
Influenza B
Specimens Tested
Week



Background of this study

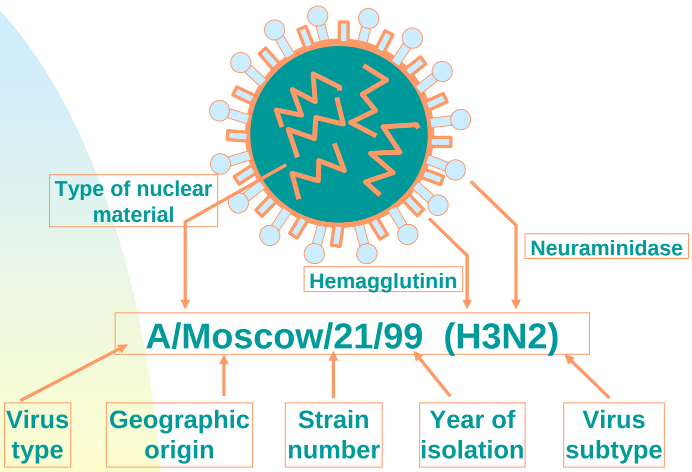
Motivations of this study

- Influenza virus infections cause excess morbidity and mortality in temperate countries.
- In the Northern and Southern Hemisphere, influenza epidemics occur nearly every winter, leading to an increase in hospitalization and mortality.
- However, little is known about the disease burden of influenza in tropical regions, e.g. Singapore, where the effect of influenza is thought to be less.

Epidemiology of Influenza

- Highly infectious viral illness
- Epidemics reported since at least 1510
- At least 4 pandemics in 19th century
- Estimated 21 million deaths worldwide in pandemic of 1918-1919
- Virus first isolated in 1933

Influenza Virus



Influenza Virus

- Single-stranded RNA virus
- Family Orthomyxoviridae
- 3 types: A, B, C
- Subtypes of type A determined by hemagglutinin and neuraminidase

Influenza Virus Strains

- Type A- moderate to severe illness
  - all age groups
  - humans and other animals
- Type B- milder epidemics
  - humans only
  - primarily affects children
- Type C- rarely reported in humans
  - no epidemics

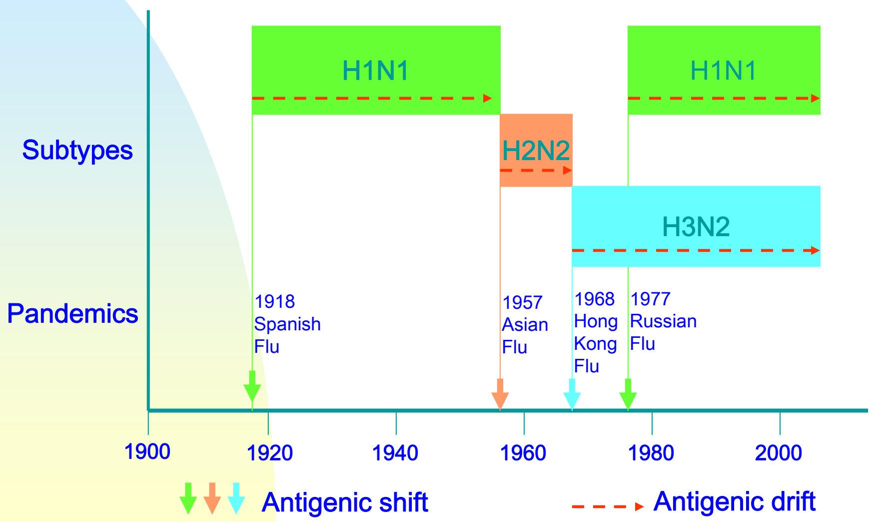
Influenza Antigenic Changes

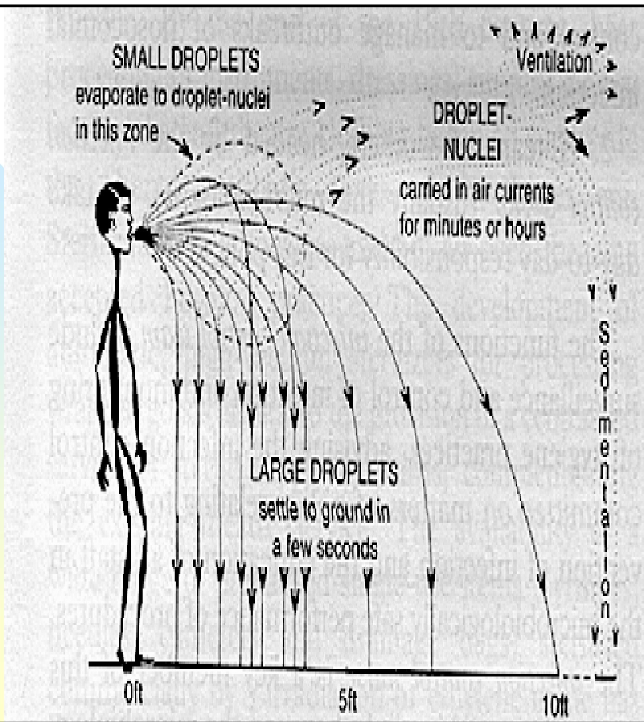
- Structure of hemagglutinin (H) and neuraminidase (N) periodically change
- Shift
  Major change, new subtype
  Exchange of gene segment
  May result in pandemic
- Drift
  Minor change, same subtype
  Point mutations in gene
  May result in epidemic

Examples of Influenza Antigenic Changes

- Antigenic shift:
  - H2N2 circulated in 1957-1967
  - H3N2 appeared in 1968 and completely replaced H2N2
- Antigenic drift
  - In 1997, A/Wuhan/359/95 (H3N2) virus was dominant
  - A/Sydney/5/97 (H3N2) appeared in late 1997 and became the dominant virus in 1998

Influenza A virus of the 20th century pandemics





Objectives

- To examine the influenza-associated mortality in tropical Singapore using time-series regression approach

Problems encountered

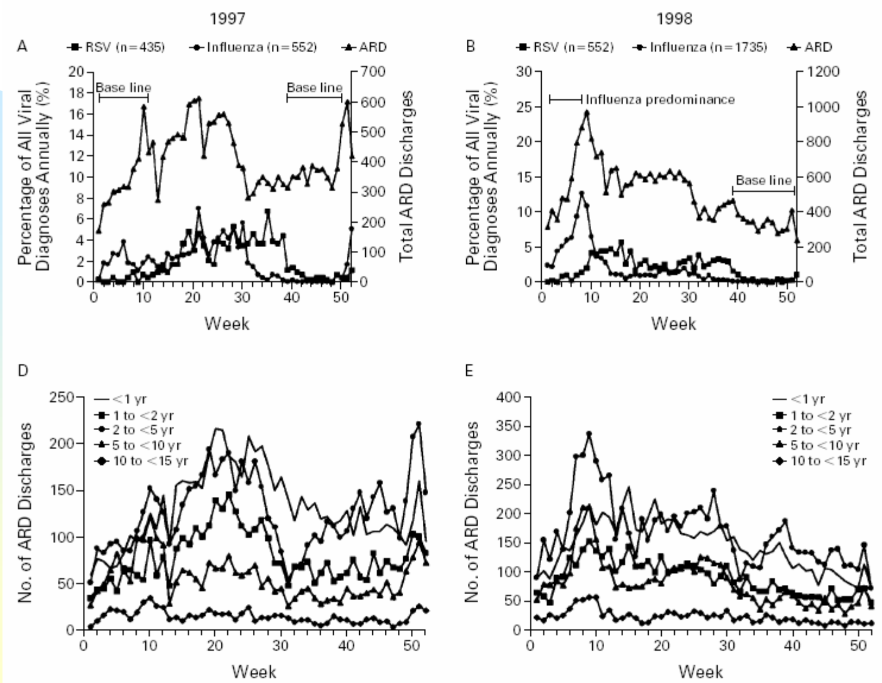
- But, all these exposure data are measured at the individual levels that are collected using individual-based study design.
- There is problem in studying impacts of influenza in human setting!
  - Because of no individual exposure data available.

Possible solution

- Epidemiological time-series data using regression approach could help?!

Two State-of-the-art methods:

1. Comparative method:
   - The average numbers of deaths or hospital admissions during the months assumed to have low or no influenza virus circulation are defined, followed by calculation of the excess mortality or hospitalization by subtracting this baseline from the observed numbers of deaths or hospital admissions during influenza epidemics.



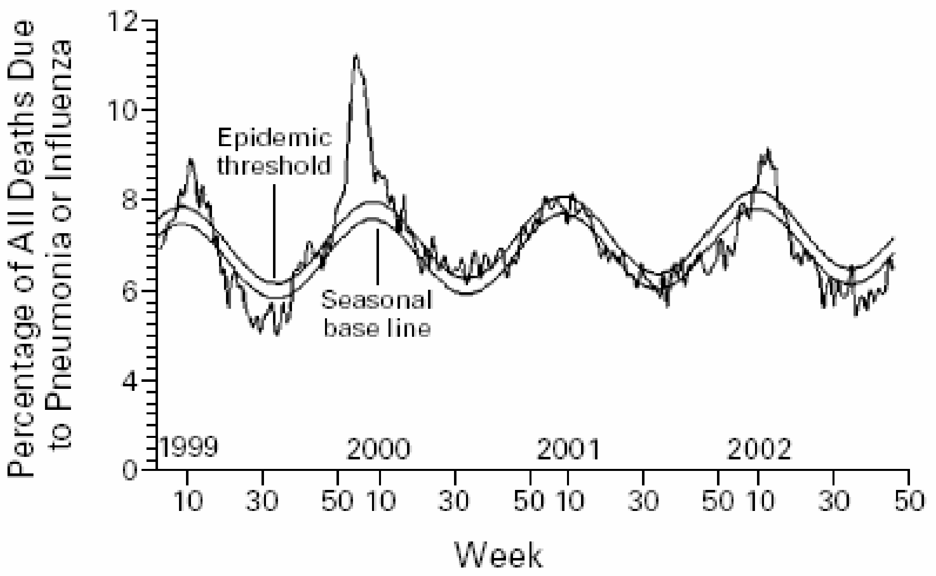
Source: Chiu et al. NEJM 2002;347:2097-103.

Two State-of-the-art methods:

2. Regression method developed by Serfling:
   - First sets a baseline for excess numbers of events by fitting a linear regression function to the data of the period assumed to have a low virus circulation, after taking into consideration the confounding factors such as seasonality and meteorological condition without including influenza virus data in the model.

Two State-of-the-art methods:

2. Regression method developed by Serfling (cont'd):
   - used to assess impact on hospitalization, but only in temperate countries where there are well-established and clear seasonal patterns of influenza.



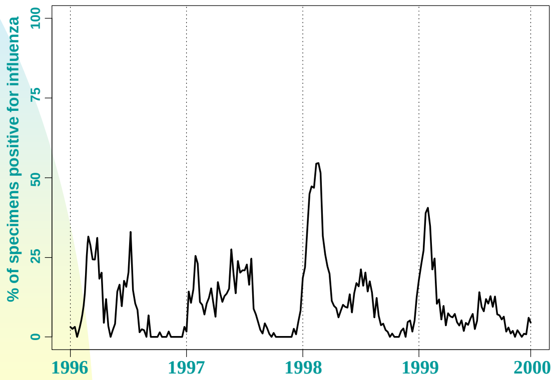
Source: Griffin and Neuzil. NEJM 2002;347:2159-61..

Short-coming of these 2 methods:

- Application of either comparative or Serfling methods requires a well-defined seasonal pattern of non-influenza period.
- Required alternative approach!

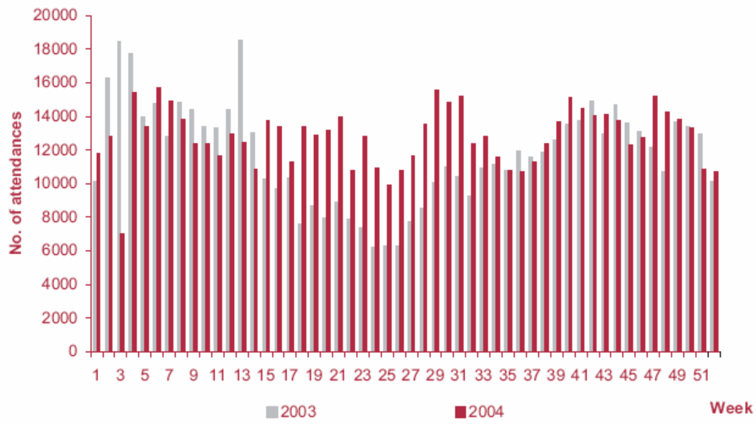
Human influenza epidemics occur almost every year

Weekly percentages of specimen positive for influenza in Hong Kong



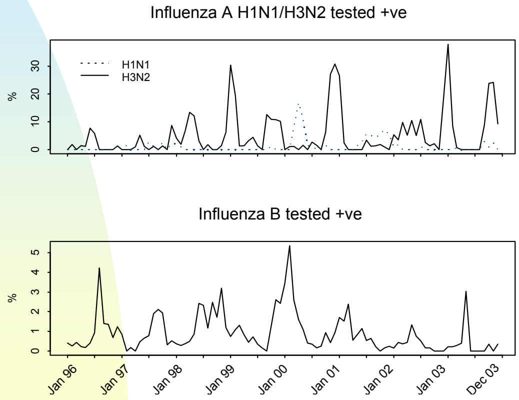
Source: Wong et al. CID 2004;39:1161-7.

E-weekly distribution of acute respiratory infection attendance at polyclinics, 2003 – 2004

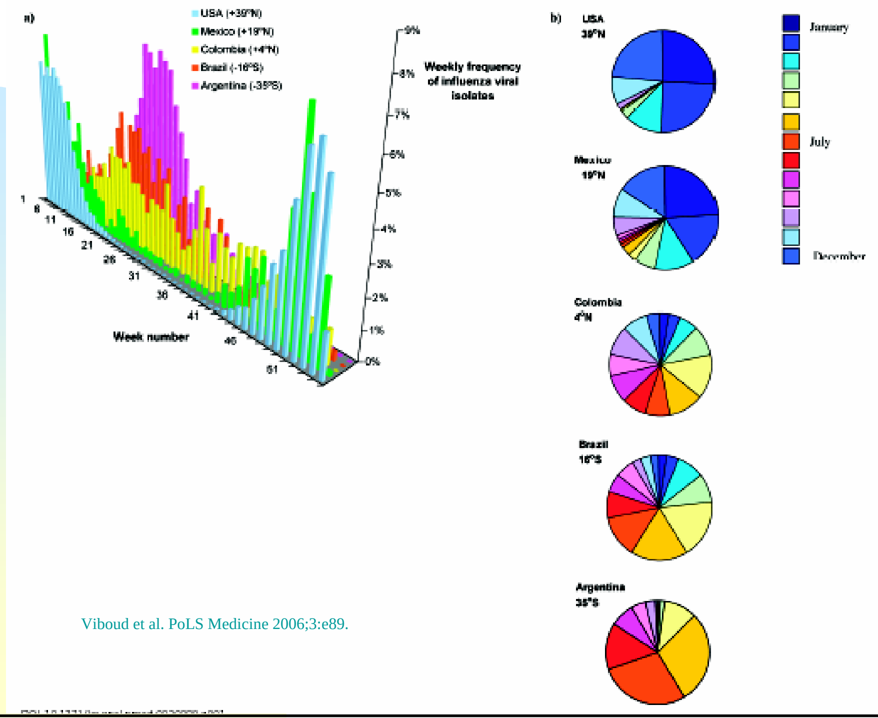


Influenza in the Tropics and Subtropics

- *Lack of well-defined seasonality*: influenza peaks usually appear during winter and spring



Influenza virus isolation rates in Singapore during 1998-2003



Viboud et al. PoLS Medicine 2006;3:e89.

Methods and Materials

- Monthly counts of all-cause mortality, underlying cause-specific deaths for cardiovascular & respiratory (C&R) and pneumonia & influenza (P&I) occurred in Singapore during 1996—2003 were studied.
- Monthly percentages of influenza A sub-types (H1N1, H3N2), influenza B and respiratory syncytial virus positive tested in the same period were also used for analysis.
- The impact of influenza on mortality adjusted for number of days for each month, trends, seasonal patterns, temperature and relative humidity and over-dispersion were estimated from negative binomial regression models.

Statistical models

$$\log E(D_t) = \beta_0 + \beta_1 t + \beta_2 t^2 + \sum_i^{3,4}\left(\beta_{3i}\sin(\frac{2t\pi k_i}{12}) + \beta_{4i}\cos(\frac{2t\pi k_i}{12})\right)$$
$$+ \beta_5 temp_t + \beta_6 humid_t + \beta_6 RSV_t$$

$$\log E(D_t) = \beta_0 + \beta_1 t + \beta_2 t^2 + \sum_i^{3,4}\left(\beta_{3i}\sin(\frac{2t\pi k_i}{12}) + \beta_{4i}\cos(\frac{2t\pi k_i}{12})\right)$$
$$+ \beta_5 temp_t + \beta_6 humid_t + \beta_7 RSV_t + \beta_8 Flu_t$$

$$D_t \sim Poisson(\mu_t)$$
$$D_t \sim NB(\alpha_t, \beta)$$

Epidemic models

$$I_t \propto \beta S_t^{\alpha} I_{t-1}^{\gamma}$$

Mass-action assumption

α and γ are the mixing parameters

$$\log(I_t) = \log(\beta) + \alpha \log(S_t) + \gamma \log(I_{t-1})$$

Statistical models

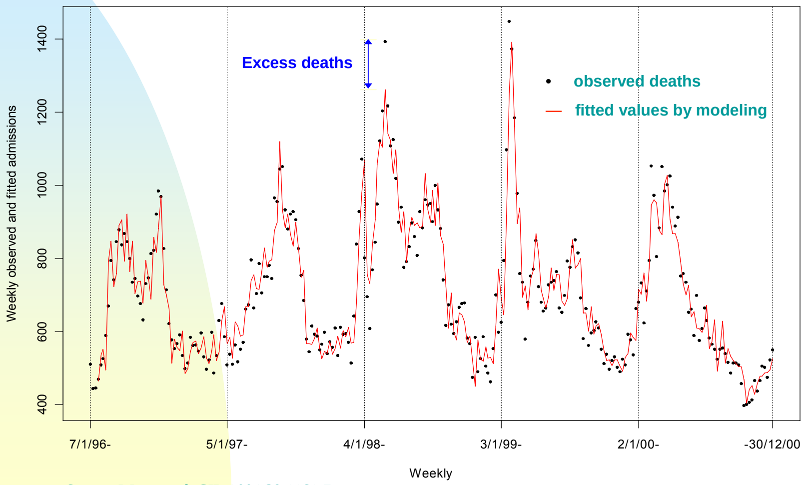
$$excess(\%) = \frac{\sum_{t=1}^{96} (D_t - E(D_t \mid Flu_t = 0))}{\sum_{t=1}^{96} D_t} \times 100\%$$

In statistics, excess risk is the increase of risk relative to some baseline risk.
excess risk = (1 - relative risk) * 100 %

Statistical models

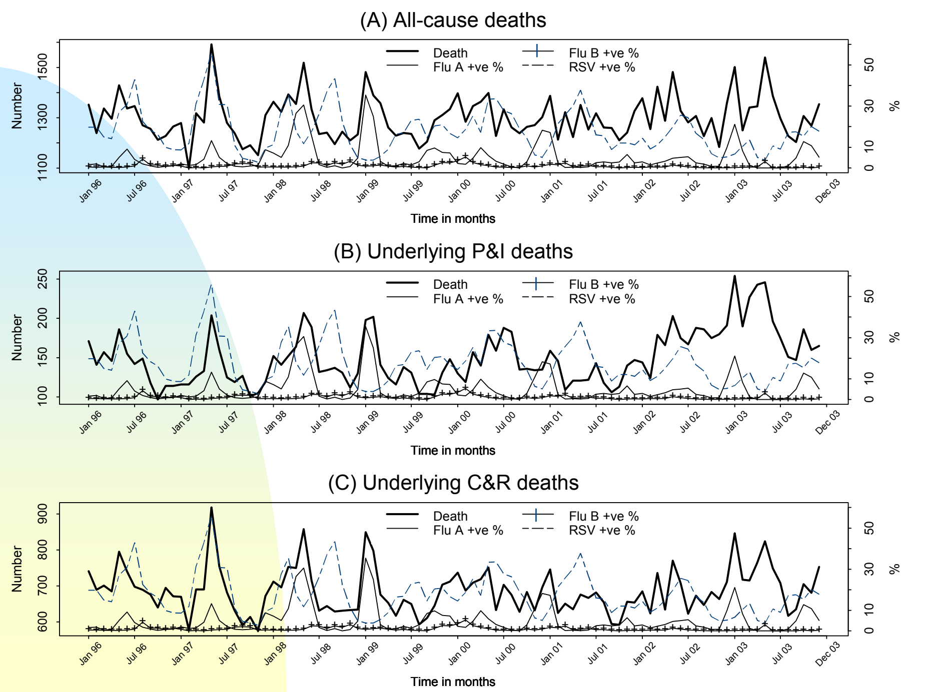
$$\textit{excess numbers per } 100{,}000 \textit{ population} = \frac{excess(\%) \times \textit{ average deaths per year}}{\textit{average population per year}} \times 100{,}000$$

Excess deaths were estimated by difference between observed and predicted deaths



Source: Wong et al. CID 2004;39:1161-7.

Results


(A) All-cause deaths
Death
Flu A +ve %
Flu B +ve %
RSV +ve %
Number
%
Time in months
(B) Underlying P&I deaths
Death
Flu A +ve %
Flu B +ve %
RSV +ve %
Number
%
Time in months
(C) Underlying C&R deaths
Death
Flu A +ve %
Flu B +ve %
RSV +ve %
Number
%
Time in months

Annual influenza viruses and respiratory syncytial virus (RSV) surveillance data in Singapore, 1996-2003

Year	Influenza viruses: Influenza type[*]: Number of specimens tested	Influenza A positive tests (%)	Influenza B positive tests (%)	Influenza A sub-type†: Number of specimens tested	A(H1N1) positive isolates (%)	A(H3N2) positive isolates (%)	RSV: Number of specimens tested	Total positive tests (%)
1996	5140	132 (2.6)	47 (0.9)	924	1 (0.1)	15 (1.6)	4249	868 (20.4)
1997	5255	208 (4.0)	39 (0.7)	1041	9 (0.9)	17 (1.6)	4441	902 (20.3)
1998	8934	817 (9.1)	120 (1.3)	941	3 (0.3)	40 (4.3)	7573	1683 (22.2)
1999	7548	714 (9.5)	74 (1.0)	1001	1 (0.1)	99 (9.9)	6915	1004 (14.5)
2000	7716	397 (5.1)	122 (1.6)	974	34 (3.5)	61 (6.3)	7094	1425 (20.1)
2001	8171	300 (3.7)	76 (0.9)	1023	33 (3.2)	44 (4.3)	7445	1415 (19.0)
2002	8317	274 (3.3)	34 (0.4)	897	3 (0.3)	58 (6.5)	7840	1128 (14.4)
2003	5979	454 (7.9)	21 (0.4)	1130	6 (0.5)	121 (10.7)	5813	678 (11.7)
Mean	7133	412 (5.8)	67 (0.9)	991	11 (1.1)	57 (5.7)	6421	1138 (17.8)

Annual mortality in Singapore, 1996-2003

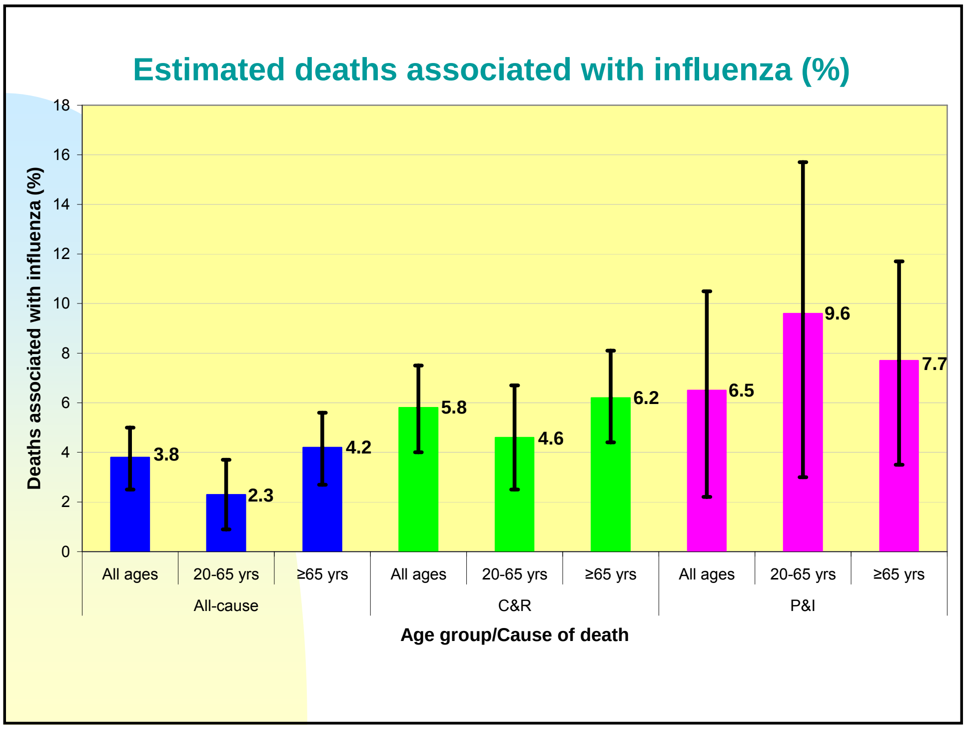
Year	Number of deaths: Pneumonia and influenza (*ICD-9*: 480-487)	Circulatory and respiratory (*ICD-9*: 390-519)	All-cause (*ICD-9*: 000-999)
1996	1 690	8 420	15 569
1997	1 551	8 065	15 301
1998	1 781	8 286	15 649
1999	1 640	8 169	15 513
2000	1 795	8 253	15 691
2001	1 545	7 833	15 368
2002	2 077	8 158	15 811
2003	2 340	8 715	16 024

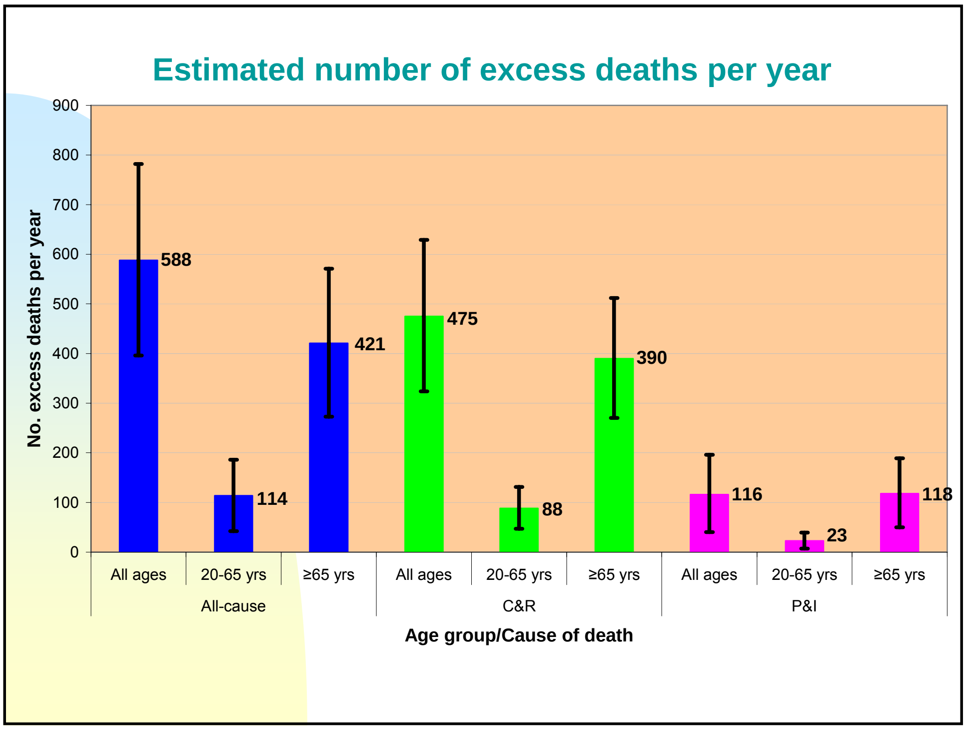
Adjusted risk ratios* (95% confidence intervals) and p-values for each 10% change in positive influenza A and RSV tests, and for each 1% change in positive influenza B† tests respectively, estimated by negative binomial regression model, 1996-2003 (regardless of testing method for respiratory specimens)

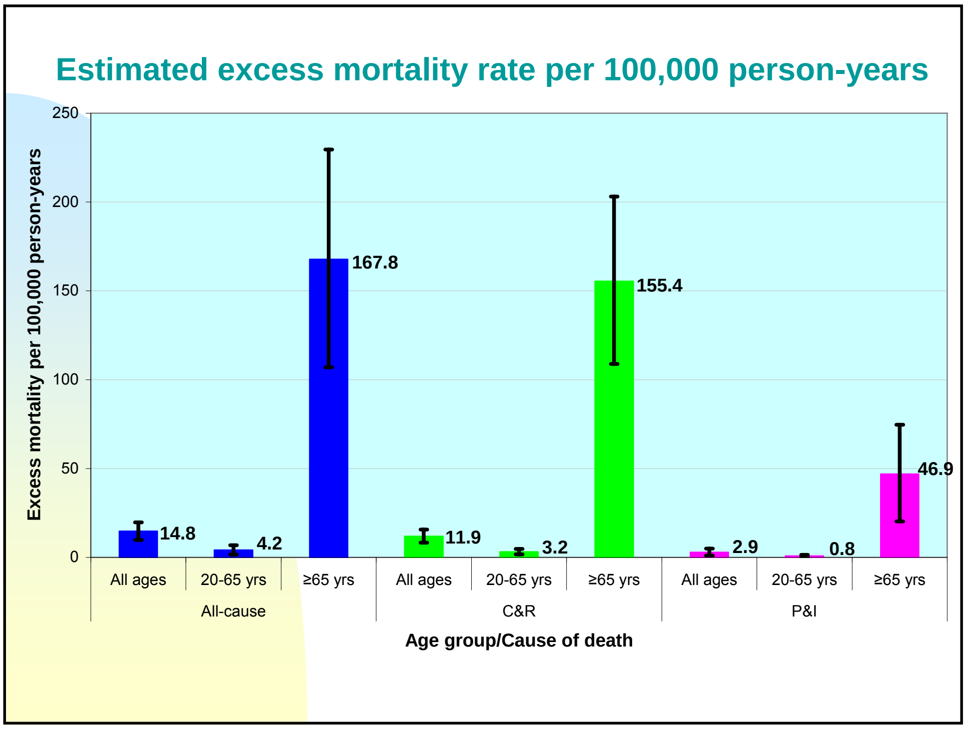
Mortality outcome/ Risk factor	Model 1‡	Model 2‡	Model 3‡	Model 4‡	Model 5‡	Model 6‡
All-Cause						
Influenza A	1.05 (1.04-1.06) 0.000	-	-	1.05 (1.04-1.06) 0.000	1.05 (1.04-1.06) 0.000	1.05 (1.04-1.06) 0.000
Influenza B	-	1.01 (1.00-1.02) 0.173	-	1.01 (1.01-1.02) 0.001	-	1.01 (1.01-1.02) 0.001
RSV	-	-	1.00 (0.99,1.00) 0.810	-	1.00 (1.00-1.01) 0.254	1.00 (1.00-1.01) 0.159
Underlying Pneumonia and Influenza						
Influenza A	1.12 (1.08-1.16) 0.000	-	-	1.12 (1.08-1.16) 0.000	1.13 (1.09-1.17) 0.000	1.13 (1.09-1.17) 0.000
Influenza B	-	0.99 (0.96-1.02) 0.389	-	1.00 (0.94-1.03) 0.994	-	1.00 (0.98-1.03) 0.872
RSV	-	-	1.01 (0.99,1.02) 0.342	-	1.03 (1.00-1.02) 0.022	1.01 (1.00-1.02) 0.021
Underlying Circulatory and Respiratory						
Influenza A	1.08 (1.06-1.10) 0.000	-	-	1.08 (1.07-1.10) 0.000	1.08 (1.06-1.11) 0.000	1.09 (1.07-1.11) 0.000
Influenza B	-	1.01 (0.99-1.02) 0.360	-	1.02 (1.01-1.03) 0.004	-	1.02 (1.01-1.03) 0.002
RSV	-	-	1.00 (0.99-1.01) 0.686	-	1.01 (1.00-1.01) 0.025	1.01 (1.00-1.01) 0.011

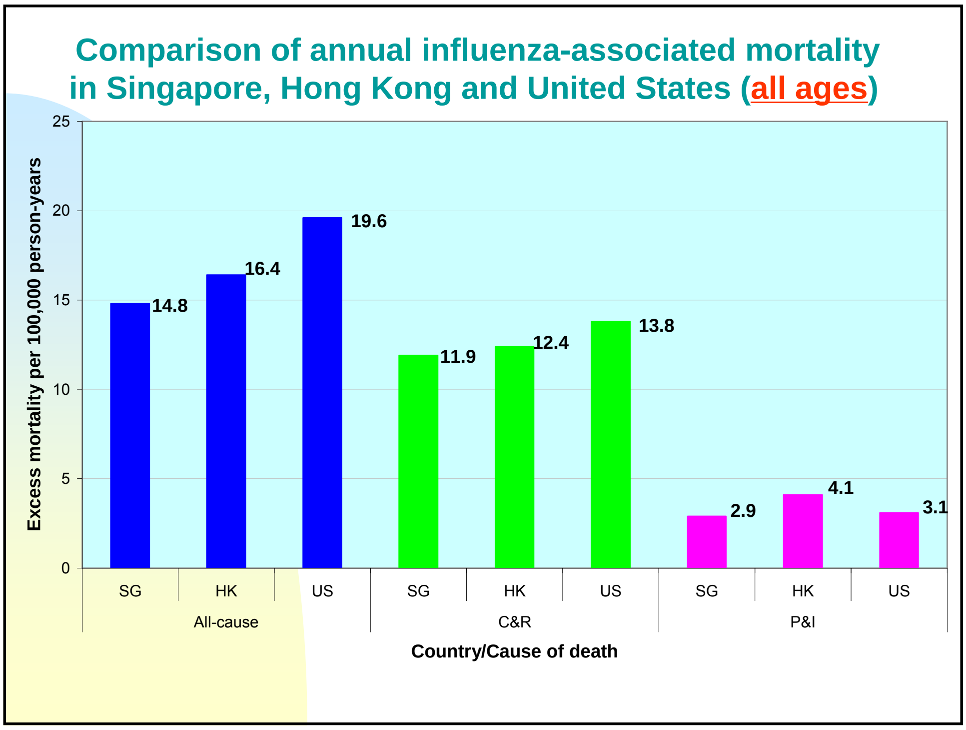
Adjusted risk ratios* (95% confidence intervals) and p-values for each 10% change in positive influenza A and RSV tests, and for each 1% change in positive influenza B† tests respectively, estimated by negative binomial regression model, 1996-2003

Model 6‡	Influenza viruses			
Mortality outcome	Influenza A(H1N1)	Influenza A(H3N2)	Influenza B	RSV
All-Cause	1.00 (0.96-1.04) 0.928	-	1.01 (1.00-1.02) 0.178	1.00 (0.97-1.00) 0.824
	-	1.04 (1.02-1.05) 0.000	1.01 (1.00-1.02) 0.008	1.00 (1.00-1.01) 0.484
Underlying Pneumonia and Influenza	1.00 (0.88-1.13) 0.993	-	0.99 (0.96-1.02) 0.409	1.01 (0.99-1.02) 0.369
	-	1.08 (1.04-1.12) 0.000	1.00 (0.97-1.03) 0.878	1.01 (1.00-1.02) 0.099
Underlying Circulatory and Respiratory	1.01 (0.95-1.08) 0.771	-	1.01 (0.99-1.02) 0.343	1.00 (0.99-1.01) 0.626
	-	1.05 (1.04-1.07) 0.000	1.01 (1.00-1.03) 0.037	1.00 (1.00-1.01) 0.166

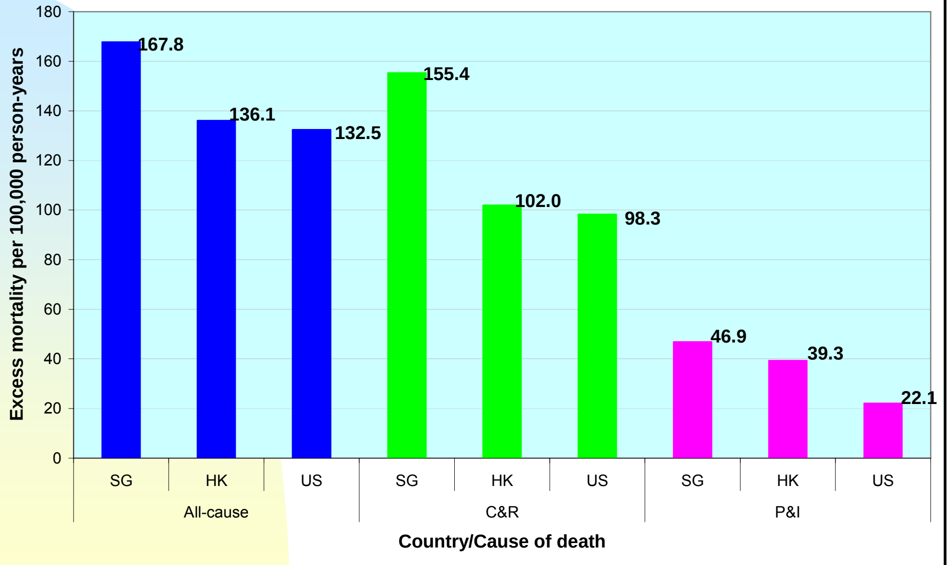

Estimated deaths associated with influenza (%)
Deaths associated with influenza (%)
18
16
14
12
10
8
6
4
2
0
3.8
2.3
4.2
5.8
4.6
6.2
6.5
9.6
7.7
All ages
20-65 yrs
≥65 yrs
All-cause
C&R
P&I
Age group/Cause of death


Estimated number of excess deaths per year
No. excess deaths per year
900
800
700
600
500
400
300
200
100
0
588
114
421
475
88
390
116
23
118
All ages
20-65 yrs
≥65 yrs
All-cause
C&R
P&I
Age group/Cause of death

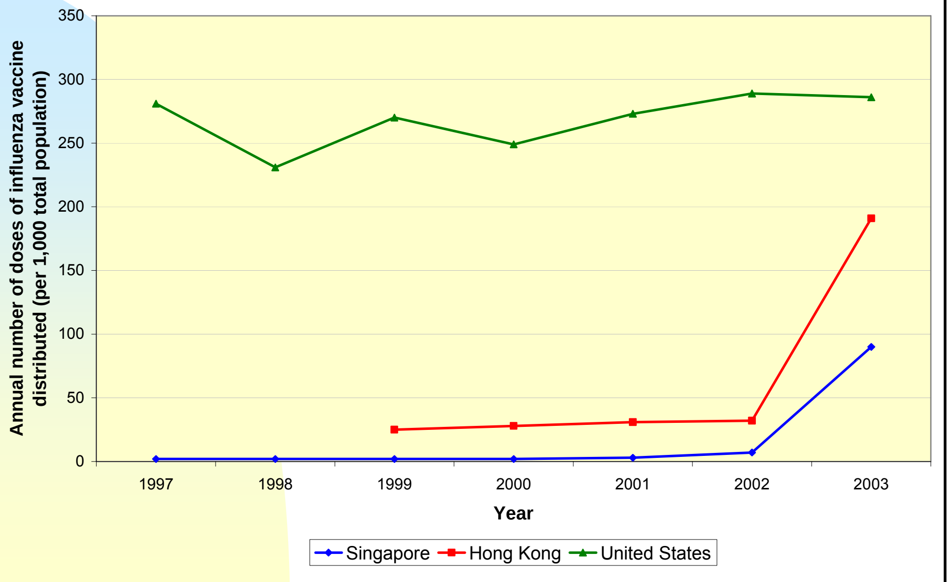

Estimated excess mortality rate per 100,000 person-years
Excess mortality per 100,000 person-years
250
200
150
100
50
0
14.8
4.2
167.8
11.9
3.2
155.4
2.9
0.8
46.9
All ages
20-65 yrs
≥65 yrs
All-cause
C&R
P&I
Age group/Cause of death


Comparison of annual influenza-associated mortality in Singapore, Hong Kong and United States (all ages)
Excess mortality per 100,000 person-years
25
20
15
10
5
0
14.8
16.4
19.6
11.9
12.4
13.8
2.9
4.1
3.1
SG
HK
US
All-cause
C&R
P&I
Country/Cause of death

Comparison of annual influenza-associated mortality in Singapore, Hong Kong and United States (Aged ≥65)



Annual number of doses of influenza vaccine distributed per 1,000 total population



Source: MIV Study Group. Vaccine 2005;23:5133-43

Summary of the findings

- Influenza A (H3N2) was the predominant circulating influenza virus subtype, with consistently significant and robust effect on mortality.
- Influenza was associated with an annual mortality from all causes, from underlying P&I, and from underlying C&R conditions of 14.8 (95% confidence interval 9.8–19.8), 2.9 (1.0–5.0), and 11.9 (8.3–15.7) per 100,000 person-years, respectively.
- These results are comparable with observations in the United States and subtropical Hong Kong.
- An estimated 6.5% of underlying P&I deaths was attributable to influenza. The proportion of influenza-associated mortality was 11.3 times higher in persons age >65 years than in the general population

Conclusions

- Time-series regression approach is a good alternative compared with two current methods.
- In our study, significant burden associated with influenza activities was showed using this alternative approach.
- Our findings support the need for influenza surveillance and annual influenza vaccination for at risk population in tropical countries


Be Flu Free
Practise good personal hygiene and be socially responsible
Wash your hands regularly with soap and water.
Cover your mouth and nose with a tissue when coughing or sneezing.
Wear a surgical mask, see a doctor and do not go to school or work when you are ill.
Never spit in public places.
When sharing food at meal times, use a serving spoon.
soap
Be careful when you travel overseas
Check with your doctor if any vaccinations are required.
If you are travelling to a country affected by bird flu, avoid:
contact with chickens, ducks, pigeons and wild birds
handling or eating raw or undercooked poultry and eggs
contact with anyone who appears unwell.
Lead a healthy lifestyle
Eat a balanced diet with plenty of fruits and vegetables.
Do 30 minutes of physical activity at least 5 days a week.
Have enough sleep and rest.
Keep stress levels low.
Do not smoke.
For more information:
MOH Hotline: 1800-3339999 • HealthLine: 1800-2231313
or visit:
www.flu.gov.sg • www.moh.gov.sg • www.hpb.gov.sg
Health Promotion Board

Thank you