MAJOR ARTICLE

Influenza-Associated Mortality in Hong Kong

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Background. The impact of influenza on mortality in countries in subtropical and tropical regions is poorly quantified. Estimation of influenza-related illness in warm-climate regions is more difficult, because the seasonality of virus circulation is less well-defined. Partly as a result of these factors, influenza vaccine is grossly underutilized in the tropics, even for individuals ⩾65 years of age.

Methods. Weekly numbers of deaths were modeled by Poisson regression, and excess deaths attributable to influenza in Hong Kong were estimated for 1996–1999. Comparison of weekly mortality during periods of influenza predominance and periods of low influenza activity was used to derive an alternative estimate of influenza-associated mortality.

Results. Estimates derived from the Poisson model indicated that influenza resulted in 7.3 deaths per 100,000 population per year (95% confidence interval [CI], 3.1–11.4) from cardiorespiratory disease among individuals aged 40–65 years and 102.0 deaths per 100,000 per population per year (95% CI, 61.2–142.7) among individuals aged ⩾65 years. Although respiratory diseases accounted for the majority of influenza-related deaths, influenza also contributed to 13.8% (95% CI, 4.8%– 22.7%) and 5.3% (95% CI, 1.2%–9.3%) of deaths related to ischemic heart disease.

Conclusion. Influenza is associated with deaths due to ischemic heart disease as well from respiratory diseases. Overall influenza-associated mortality in a region with a warm climate, such as Hong Kong, is comparable with that documented in temperate regions. The need for influenza vaccination in tropical regions needs to be reassessed.

Influenza is a vaccine-preventable disease that is associated with significant morbidity and mortality. There is a need for reliable data on the influenza-associated clinical disease burden on which national and global policy decisions on influenza vaccine can be based [1]. The morbidity and mortality caused by influenza is often attributed to secondary bacterial infection, and the primary viral illness goes unrecognized [2]. A virological diagnosis of influenza is often not sought, and even when it is, influenza viruses may no longer be detectable after secondary bacterial infection has supervened [3, 4]. It is now recognized that influenza contributes to excess morbidity for conditions not previously thought to be associated with infection, such as congestive heart failure [5].

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Statistical models have been used to predict seasonally adjusted baseline trends in mortality, with the assumption that the number of deaths that exceed the expected baseline number during an influenza epidemic is related to influenza [6, 7]. However, the reliable estimation of disease burden is dependent on a well-defined population denominator. The assumption—in studies based on nationwide data—that influenza activity is uniform in the area under study may not be valid [8]. Furthermore, it is also recognized that respiratory syncytial virus (RSV) can contribute to disease morbidity in adults and older persons, with clinical syndromes very similar to those of influenza [2, 9, 10]. Because the seasonality of infection due to influenza virus and to RSV often overlaps in temperate regions, it is difficult to differentiate the contribution of these 2 viruses to excess mortality.

Although estimates of the influenza disease burden are available for temperate regions of the developed world [2, 11, 12], there are no valid estimates for tropical and subtropical regions [13]. There are several reasons for the lack of information from the tropics. Virus circulation tends to be less seasonal and, in some regions, may continue year-round [14]. The focused winter seasonality of influenza in temperate regions makes

the impact of influenza obvious (e.g., through the increased demand for hospitalization). On the other hand, the more diffuse seasonality of virus activity in the tropics results in the clinical impact of the disease being less obvious, leading to the perception that influenza is a less important cause of serious illness and mortality. The lack of well-defined data on the seasonality of influenza also makes it more difficult to apply commonly used models for estimating the excess influenza-associated disease [13].

Hong Kong, with a latitude of 21°45′ North and mean temperature of 24°C, is geographically situated in the tropics and has a subtropical climate. It lies in the region considered to be the hypothetical epicenter for the emergence of influenza pandemics [15]. However, apart from the recent outbreaks of avian influenza [16], influenza is not currently recognized as a major health problem in Hong Kong. Recent studies, based on clinical case definitions of "influenza-like illness," failed to document significant influenza-associated morbidity and mortality [17, 18]. However, without virological validation, such clinical case definitions are often poor indicators of influenza when applied outside periods of peak influenza activity [19], particularly in the context of year-round influenza circulation. In this study, we examined the impact of influenza on mortality by use of 2 different methodologies.

METHODS

Data Collection

Weekly numbers of deaths over a 4-year period (1996–1999) were obtained from the Hong Kong Census and Statistics Department for 4 underlying causes of death—cardiovascular and respiratory (cardiorespiratory) disease (*International Classification of Diseases, Ninth Revision [ICD-9]*, codes 390–519), pneumonia and influenza (*ICD-9* codes 480–487), chronic obstructive pulmonary disease (COPD) (*ICD-9* codes 490–496), and ischemic heart disease (IHD) (*ICD-9* codes 410–414)—as well as for all-cause death [20]. Weekly records of mean temperature and relative humidity were derived from the Hong Kong Observatory [21]. Weekly numbers of positive isolations of influenza A and influenza B (hereafter, "influenza") virus and RSV, as well as the total number of specimens tested, were obtained from the Department of Microbiology, Queen Mary Hospital (Hong Kong). The laboratory in this department receives 6000–7000 clinical specimens annually.

Statistical Analysis

Comparison between influenza predominance and baseline periods. We defined influenza predominance as the period of ⩾2 consecutive weeks in which the weekly isolation of influenza virus accounted for at least 4% (i.e., twice the weekly average) of the annual total number of influenza virus isolations and <2% of the annual total number of RSV isolations. Baseline was defined as the period of ⩾2 consecutive weeks during which both influenza virus and RSV weekly isolations were <2% of the annual total number of isolations of each virus [22]. The remaining weeks in each study year were classified as intermediate periods. We estimated excess deaths by taking the difference in number of deaths per week between the influenza predominance and baseline periods and multiplying the result by the total number of predominance weeks [22]. The possible confounding effect of RSV on influenza virus–associated mortality was minimized by restricting the analysis to weeks in which diagnosis of RSV infection was <2% of the annual total of RSV isolations.

Poisson regression modeling. We applied Poisson regression [23, 24] to the weekly number of each of the health outcomes under study, including as covariates weekly mean temperature and relative humidity, as well as 4 separate dummy variables for the years 1996–1999 and 2 pairs of seasonality variables. For additional control of seasonal variation in the amplitude of deaths in each year, we defined the year-by-seasonality variables as the multiplicative product of the dummy variable for each year and the 2 pairs of seasonality variables. These year-by-seasonality variables were then entered into the model.

The proportions of laboratory specimens that tested positive for influenza virus and RSV each week were entered into the model to assess the impact of influenza virus, with adjustment for RSV. The delayed impact (i.e., lag effect) of influenza virus and RSV on outcome was assessed by adding the virological data from 0–3 weeks preceding the deaths into the model. For each virus and outcome, we selected as the best lag effect the one with the most significant association with mortality. The difference between the total number of observed deaths and the total number of expected deaths (when the proportion of specimens that tested positive for influenza or RSV in the model was set to 0), divided by the total number of observed deaths, yielded the fraction of deaths associated with influenza [25]. The excess number of deaths attributable to influenza was estimated by multiplying the total number of deaths by the influenza-associated fraction of deaths. The statistical package Splus (StatSci) was used for analysis [26]. Detailed data and results statistical analysis are available as supplementary information from the authors.

RESULTS

In the categories studied, the group aged ⩾65 years contributed ~70% to 90% of all deaths. Over the 4-year study period, all outcomes under study were relatively constant, except that deaths due to pneumonia and influenza showed a decreasing trend (data not shown). Influenza virus activity during the period under study is shown in figure 1.

In a comparison of weekly mortality between the influenza predominance and baseline periods, we estimated that ~1% to

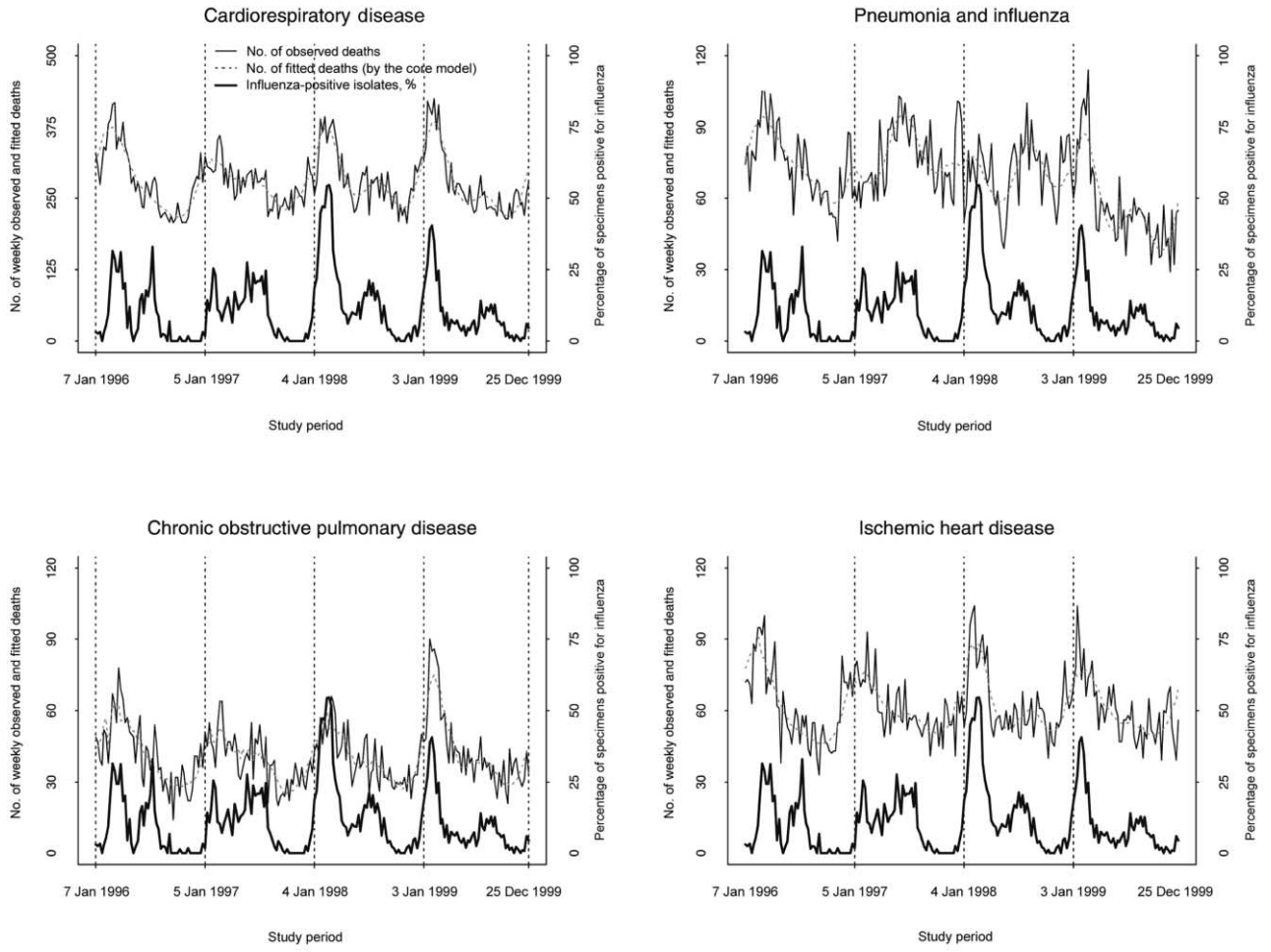

Figure 1. Weekly number of influenza-associated death per 4 causes, observed and fitted according to the core model (with control for seasonal patterns), and the proportion of influenza-positive isolates used in laboratory diagnosis for the all-ages group.

8% of the health outcomes under study were due to influenza. During the 4-year period, ~2400 deaths due to cardiorespiratory conditions and ~500 deaths due to IHD in the all ages group were attributable to influenza (table 1). RSV activity and the concentrations of air pollutants during these 2 periods were comparable (data not shown). During periods of influenza predominance, the mean temperature was lower (18°C vs. 22°C) and the relative humidity was higher (78% vs. 73%) than during the baseline period. Because there were no definable weeks of influenza predominance in 1997, there are no estimates of influenza-associated excess mortality for this year.

The weekly time series plots of mortality in the all-ages group show that each of the 4 health outcomes had 1 main cycle and 2 subcycles each year, a pattern similar to that seen with influenza activity (figure 1). The Poisson model fitted the data adequately, as indicated by the absence of any discernible patterns and by auto-correlation (i.e., correlation between successive measurements) in the residuals (supplementary data are available from the authors). For all health outcomes in the group aged ⩾65 years and the all ages group, there were significant associations with influenza, with the maximum effect seen at a best lag of 2 weeks for death due to cardiorespiratory conditions, pneumonia and influenza, and COPD and a best lag of 1 week for all-cause and IHD-attributed death. For all health outcomes in the group aged 40–64 years, the best lag effects were shown at a longer lag period of 2–3 weeks. No significant association between RSV infection and mortality was seen for any lag periods between 0–3 weeks (except for mortality attributable to pneumonia and influenza in the group aged ⩾65 years), and no lag period was assumed for RSV infection (data not shown).

The weekly proportions of laboratory-based virological diagnoses of influenza showed a significant association with all health outcomes under study, except for death due to pneumonia and influenza in the group aged 40–64 years, which only accounted for 7% of all deaths attributed to this diagnosis. The proportion of influenza-associated deaths throughout the study period was 3%–16%. Over the 4-year period under study, ~800

Table 1. Excess deaths during influenza predominance periods over baseline periods during 1996–1999.

Characteristic	Study year				No. of excess deaths	
	1996	1997[a]	1998	1999	Per year	Per 100,000 population per year (95% CI)[b]
No. of predominance weeks (n = 19)	5	0	7	7	…	…
No. of baseline weeks (n = 78)	25	24	16	13	…	…
No. of excess deaths per age group, by cause						
All cause						
40–64 years	53	0	46	89	47	2.4 (1.0–3.9)
⩾65 years	603	0	816	1137	639	93.2 (78.4–107.7)
All ages[c]	650	0	897	1233	695	10.6 (8.9–12.3)
Cardiorespiratory disease (*ICD-9* codes 390–519)						
40–64 years	77	0	63	121	65	3.4 (2.5–4.3)
⩾65 years	492	0	685	963	535	78.1 (67.2–89.0)
All ages[c]	568	0	759	1090	604	9.2 (8.0–10.5)
Pneumonia and influenza (*ICD-9* codes 480–487)						
40–64 years	12	0	0	17	7	0.4 (0.0–0.7)
⩾65 years	126	0	25	308	115	16.7 (9.8–23.7)
All ages[c]	138	0	29	335	126	1.9 (1.1–2.7)
Chronic obstructive pulmonary disease (*ICD-9* codes 490–496)						
40–64 years	11	0	18	37	16	0.8 (0.6–1.1)
⩾65 years	119	0	122	258	125	18.2 (13.8–22.7)
All ages[c]	129	0	140	293	140	2.1 (1.6–2.7)
Ischemic heart disease (*ICD-9* codes 410–414)						
40–64 years	19	0	19	30	17	0.9 (0.4–1.3)
⩾65 years	93	0	207	168	117	17.1 (12.8–21.3)
All ages[c]	113	0	230	196	135	2.1 (1.6–2.5)

NOTE. The annual number of excess deaths is obtained by multiplying the difference in the observed weekly number of deaths between periods of influenza predominance and at baseline by the number of weeks of influenza predominance. *ICD-9, International Classification of Diseases, Ninth Revision.*

[a] The number of influenza-associated excess deaths for 1997 could not be estimated because of substantial cocirculation of influenza virus and respiratory syncytial virus during this period, which precluded the identification of periods of influenza predominance.

[b] Calculation based on population in corresponding age groups

[c] The number of excess deaths was estimated from a model developed according to data for each age group and was independent of those for the other age groups. As a result, the number of excess deaths in the all-ages group is not a total sum of excess deaths for each of the age groups.

annual deaths due to cardiorespiratory conditions and ~200 annual deaths due to IHD in the all ages group were attributable to influenza (table 2).

The excess deaths at lag 0 for the group aged ⩾65 years and for the all ages group were, in general, lower than those estimated at the best lag week, but the effects were statistically significant ($P < .05$) for all mortality outcomes, except for death due to pneumonia and influenza. But for the group aged 40–64 years, only death from cardiorespiratory diseases and from IHD showed a significant effect at lag 0 (data not shown).

DISCUSSION

Previous estimations, using statistical models, of morbidity and mortality attributable to influenza have been criticized on the grounds that winter baseline periods may not be free of influenza activity [8] and because other viruses (such as RSV) that are known to contribute to respiratory mortality among older adults may confound these estimates [2]. Recent studies have addressed this problem by comparing periods of influenza predominance with periods during which neither influenza virus nor RSV circulated, to avoid the confounding effect of RSV infection on hospitalization [22, 27, 28]. Alternatively, regression modeling of the number of deaths associated with pneumonia and influenza has taken into account both influenza virus and RSV [2, 7, 29]. We used both of these approaches in parallel to estimate influenza-related excess mortality in Hong Kong, with broadly comparable results indicating that, each year, influenza was responsible for ~78.1 to 102.0 excess deaths

Table 2. Influenza-associated excess deaths in 1996–1999 estimated by Poisson modeling after adjustment for covariates, including respiratory syncytial virus infection (1996–1999).

Cause of death, age group	Lag period, weeks	Percentage of deaths associated with influenza (95% CI)[a]	No. of excess deaths per year (95% CI)	No. of excess deaths per 100,000 population per year (95% CI)[b]
All cause				
40–64 years	3	3.4 (1.1–5.8)	227 (73–387)	11.8 (3.8–20.1)
⩾65 years	1	3.9 (2.4–5.4)	933 (574–1291)	136.1 (83.7–188.4)
All ages[c]	1	3.3 (1.9–4.7)	1073 (618–1528)	16.4 (9.4–23.3)
Cardiorespiratory conditions (*ICD-9* codes 390–519)				
40–64 years	2	7.7 (3.3–12.0)	140 (60–219)	7.3 (3.1–11.4)
⩾65 years	2	5.5 (3.3–7.7)	699 (419–978)	102.0 (61.2–142.7)
All ages[c]	2	5.5 (3.4–7.6)	813 (503–1124)	12.4 (7.7–17.1)
Pneumonia and influenza (*ICD-9* codes 480–487)				
40–64 years	0	5.9 (−6.8 to 18.6)	16 (−19 to 51)	0.8 (−1.0 to 2.6)
⩾65 years	2	8.1 (4.4–11.8)	270 (146–393)	39.3 (21.4–57.3)
All ages[c]	2	7.4 (3.7–11.1)	272 (136–408)	4.1 (2.1–6.2)
Chronic obstructive pulmonary disease (*ICD-9* codes 490–496)				
40–64 years	2	15.9 (2.5–29.1)	33 (5–61)	1.7 (0.3–3.2)
⩾65 years	2	8.7 (4.1–13.4)	169 (79–260)	24.6 (11.6–37.9)
All ages[c]	2	9.4 (4.8–13.9)	204 (104–301)	3.1 (1.6–4.6)
Ischemic heart disease (*ICD-9* codes 410–414)				
40–64 years	2	13.8 (4.8–22.7)	63 (22–104)	3.3 (1.1–5.4)
⩾65 years	1	5.3 (1.2–9.3)	147 (33–259)	21.5 (4.9–37.7)
All ages[c]	1	6.1 (2.4–9.8)	200 (79–321)	3.0 (1.2–4.9)

NOTE. *ICD-9, International Classification of Diseases, Ninth Revision.*

[a] Estimated by taking total observed number minus the total expected number (when influenza proportions are set to 0 in the Poisson regression model) and dividing by the total observed number expressed as a percentage.

[b] Based on population in corresponding age groups.

[c] The number of excess deaths was estimated from a model developed according to data for each age group and was independent of those for the other age groups. As a result, the number of excess deaths in the all-ages group is not a total sum of excess deaths for each of the age groups.

due to cardiorespiratory conditions and for 17.1 to 21.5 excess deaths due to IHD per 100,000 population aged ⩾65 years.

The age-specific influenza-attributable mortality rates derived by Poisson regression were higher than influenza-associated death derived from the comparison of baseline and predominance periods. Rates derived from the latter will underestimate the impact of influenza in those years in which there is substantial cocirculation of influenza virus and RSV, which precludes the identification of periods of influenza predominance that are free of RSV. In our study, this happened in 1997, and this analysis clearly fails to estimate influenza-associated mortality during this year.

Another potential criticism of the method of comparison of baseline and influenza predominance periods is that the periods being compared may differ because of seasonal and other factors that may contribute to mortality. Both baseline and influenza predominance periods occurred in the cool season, when levels of air pollutants are higher, but there was no difference between the periods with respect to the mean levels of all 4 pollutants (e.g., nitrogen dioxide, sulphur dioxide, respirable particulates, and ozone) (data not shown).

The alternative method of Poisson modeling allows adjustment for the impact of seasonal and climatological factors and also allows the impact of influenza to be estimated, with adjustment for potential confounding factors. In our study, the weekly variation of each mortality outcome was modeled with the seasonal amplitude specific to each year of the study, with adjustment for temperature, humidity, and RSV activity. Influenza was significantly associated with mortality in each of the health outcomes studied, with the exception of the smaller number of deaths due to pneumonia and influenza in the group aged 40–64 years, in which the wider 95% CIs precluded demonstration of a significant effect.

The Poisson regression estimates of influenza-associated pneumonia and influenza-associated mortality per 100,000 population per year in Hong Kong were 39.3 for the group aged

⩾65 years and 4.1 for the all-ages group, which are similar to the figures of 22.1 and 3.1 per 100,000 population per year, respectively, estimated by this method in the United States [23]. Influenza-associated mortality in the United States for all respiratory and circulatory deaths per 100,000 population per year in the group aged ⩾65 years was 98.3 and in the all-ages group was 13.8, which is closely comparable to the rates of 102.0 and 12.4 per 100,000 population per year, respectively, we obtained for Hong Kong. In the United States, the greatest number of influenza-associated deaths was associated, in descending order, with influenza A subtype H3N2, followed by influenza B and influenza A subtype H1N1 [23, 29]. In Hong Kong, during the 4-year period we studied, subtype H3N2 viruses accounted for 77% (range, 65%–94%) of all influenza viruses isolated (data not shown). Both the causes and magnitude of influenza-associated mortality are similar in Hong Kong and the United States, especially in the group aged ⩾65 years, for whom vaccination is strongly recommended.

There is little additional data on influenza-associated mortality in the tropics or subtropics [13]. One study from Singapore estimated that ~265 such deaths per 100,000 population ⩾65 years of age occur annually. However, this estimate was derived from the total number of deaths that were coded "pneumonia and influenza," based on the assumption that 40% of these deaths were associated with influenza [30].

Interestingly, both the Poisson analysis (table 2) and the comparison of periods of influenza predominance with baseline periods (table 1) reveal a significant association between IHD-attributed death and influenza. Poisson analysis indicates that influenza was associated with 13.8% and 5.3% of IHD-attributed deaths in the groups aged 40–64 and ⩾65 years, respectively (table 2). The influenza-associated excess IHD-attributed mortality in the group aged ⩾65 years was 21.5 deaths per 100,000 population per year and accounted for a significant component of the overall mortality associated with influenza. In our analyses, influenza was associated with 4%–6% of all deaths from IHD annually.

There is accumulating evidence suggesting that influenza plays a role in triggering IHD. Much of these data come from studies showing that influenza vaccine exerts a protective effect against IHD during hospitalization or against recurrences of IHD [31–34], although other studies have failed to demonstrate such an association [35]. Influenza and other acute infections may predispose to increased risk of IHD through alterations in circulating clotting factors, platelet aggregation and lysis and through alterations in concentrations of inflammatory-response proteins and cytokines [36]. In a mouse model, it was found that influenza infection promotes inflammation, smooth muscle cell proliferation, and fibrin deposition in atherosclerotic plaques [37]. Our conclusions, which are based on weekly data on mortality and influenza virus activity, show that influenza is significantly associated with IHD-attributed mortality and supports the concept that IHD is, in part, a vaccine-preventable disease.

Meta-analysis of the efficacy of influenza vaccine in older persons indicates that it reduces influenza-like illness by 35%, hospitalization due to pneumonia and influenza by 47%, and all-cause mortality by 50% [35]. However, worldwide, influenza vaccine is grossly underutilized, particularly in tropical and subtropical regions, in part because its clinical impact is not recognized [13] and influenza is perceived to be a less important disease in warmer climates [17, 18]. Thus, influenza vaccination is not accorded high priority, even for individuals aged ⩾65 years [36]. Our findings suggest that this perception is incorrect and indicate that vaccination, especially for individuals >65 years of age, is as relevant in warm climates as it is in temperate regions.

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