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The global impact of influenza on morbidity and mortality

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1. Background

1.1. Global pattern of influenza epidemics and pandemics

Influenza in zones with a temperate climate is characterized by the occurrence of one annual epidemic during the winter months. In the northern hemisphere, the influenza season falls in November through April, while in the southern hemisphere influenza occurs during May through September [1]. In contrast, in countries with a tropical climate, the timing of periods of influenza epidemics is less distinct, and significant amounts of influenza virus are isolated throughout the year. In several tropical countries, a biannual pattern has been reported, with epidemics occurring both in spring and autumn, in between the seasons of influenza epidemics in temperate zones (Fig. 1).

The virological basis for recurrent epidemics is continual antigenic drift among circulating influenza viruses [1,2]. Worldwide pandemics of influenza occur infrequently, in association with the unpredictable emergence of new influenza A virus subtypes [1–4]. Pandemics have occurred three times this century (Fig. 1): The 1918 'Spanish flu' A(H1N1) pandemic was particularly severe, causing about 20 million deaths worldwide, while the more recent pandemics, A(H2N2) 'Asian flu' in 1957 and A(H3N2) 'Hong Kong flu' in 1968, were associated with moderately increased mortality [1]. Since 1968, strains of influenza A(H1N1), A(H3N2) and B viruses have co-circulated and caused discrete or overlapping epidemics each season.

The recent outbreak of 18 human cases of avian A(H5N1) influenza in Hong Kong and the high fatality were a reminder that another pandemic with heavy global morbidity and mortality is a very real possibility. Indeed, as the pattern of recurrence of pandemics since the mid-eighteenth century indicates that pandemics occur every 30 years or so [1], it may be only a few years before the next pandemic occurs.

How the world community chooses to respond to the annual recurrence of influenza epidemics and to the infrequent threat of pandemics depends in large part on the perceived disease burden. The burden of influenza has not been well established in tropical countries, in contrast to temperate countries. In some tropical countries, no significant disease burden appears to be associated with influenza epidemics, but only with pandemics. Further, as many tropical countries are also in the process of developing, influenza epidemics may be considered of little significance in relation to the severe burden of other infectious diseases and the economic issues of survival.

Nevertheless, as witnessed by several of the contributions to these proceedings, many Asian countries are in fact conducting surveillance of influenza viruses and are documenting the annual activity, thus assisting the world community in the early identification of new viruses with pandemic potential. The challenge lies in documenting and quantifying severe morbidity and mortality due to influenza in these countries—within the context of the pattern of year-round influenza activity and biannual epidemics in tropical countries.

1.2. Methods for quantifying the burden of influenza

Assessment of the burden of influenza is not straightforward because severe complications triggered

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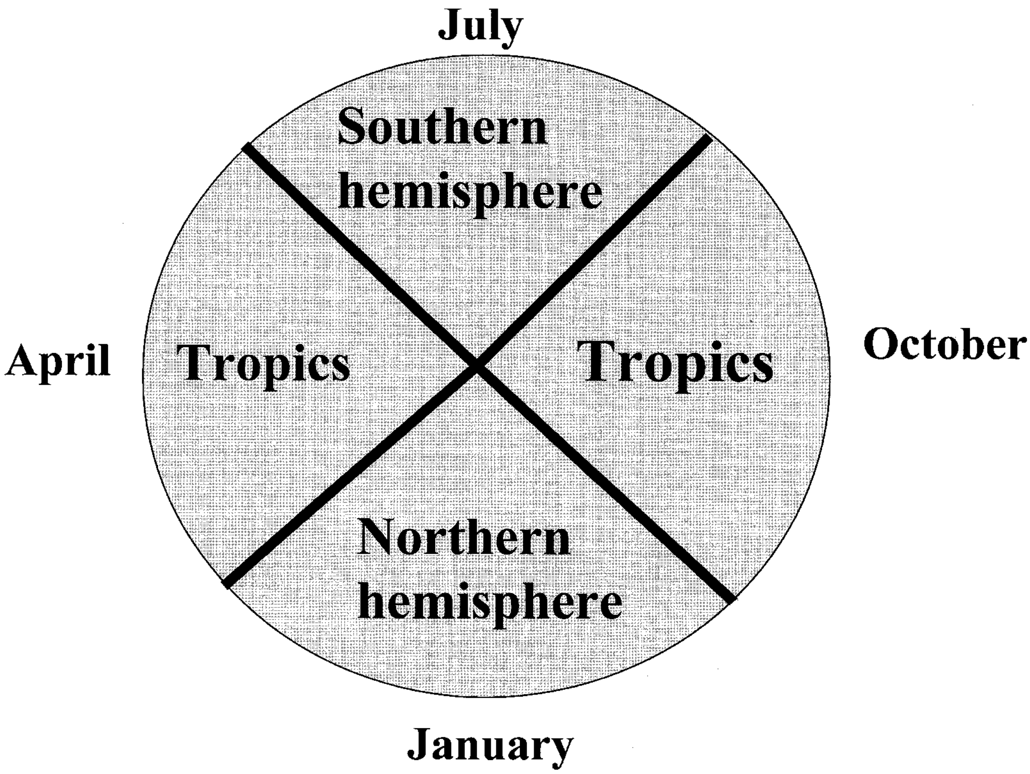

Fig. 1. General pattern of an annual influenza season in zones with a temperate climate and bi-annual influenza seasons in the tropics.

by influenza infection, such as bacterial pneumonia, are often diagnosed well after the influenza infection has been cleared. As a result, the virus can no longer be demonstrated, and many influenza-related hospitalizations and deaths are incompletely ascertained [5]. In order to assess the contribution of influenza to mortality rates, there is therefore a long tradition of calculating national excess mortality during influenza seasons [1,6–10]. Excess mortality is typically estimated as the sum of deaths during the influenza season that exceeds a baseline of expected deaths in the absence of influenza (Fig. 2(A)). Excess mortality from pneumonia and influenza (P & I) has long been used as an index of the relative severity of epidemics. However, as P & I excess deaths (based on statistics for underlying cause of death) account for only about 25% of all influenza-related deaths, the excess in deaths from all causes is used as a measure of the total impact of influenza on mortality, (although these seasonal estimates lack precision) [9] the excess approach can be applied to weekly or monthly numbers of hospitalizations (Fig. 2), outpatient visits or school and workplace absenteeism in order to calculate the influenza-attributable portion of any of these outcomes.

2. Burden of influenza in temperate countries

2.1. Non-pandemic influenza

2.1.1. Epidemiology of influenza

In most European and North American countries surveillance systems are used to document the circulation and impact of influenza on morbidity. Typically, influenza surveillance systems include some or all of the following components: weekly surveillance for the number of influenza virus isolates and/or the percentage of all respiratory isolates that are influenza, weekly numbers or percentage of outpatient visits due to influenza-like illness or acute respiratory infections; regional reports of the degree of epidemic activity; weekly average numbers of work absenteeisms, emergency house calls, home visits or drug prescriptions filled; reports of individual influenza outbreaks; and an index of weekly drug use. Such surveillance data are typically markedly increased during influenza epidemics, and a general impression of an increase in some or all of these parameters has long been used to identify the onset of annual epidemic influenza periods [11–13]. A formal algorithm is being developed for use of surveillance data in identifying periods of epidemic

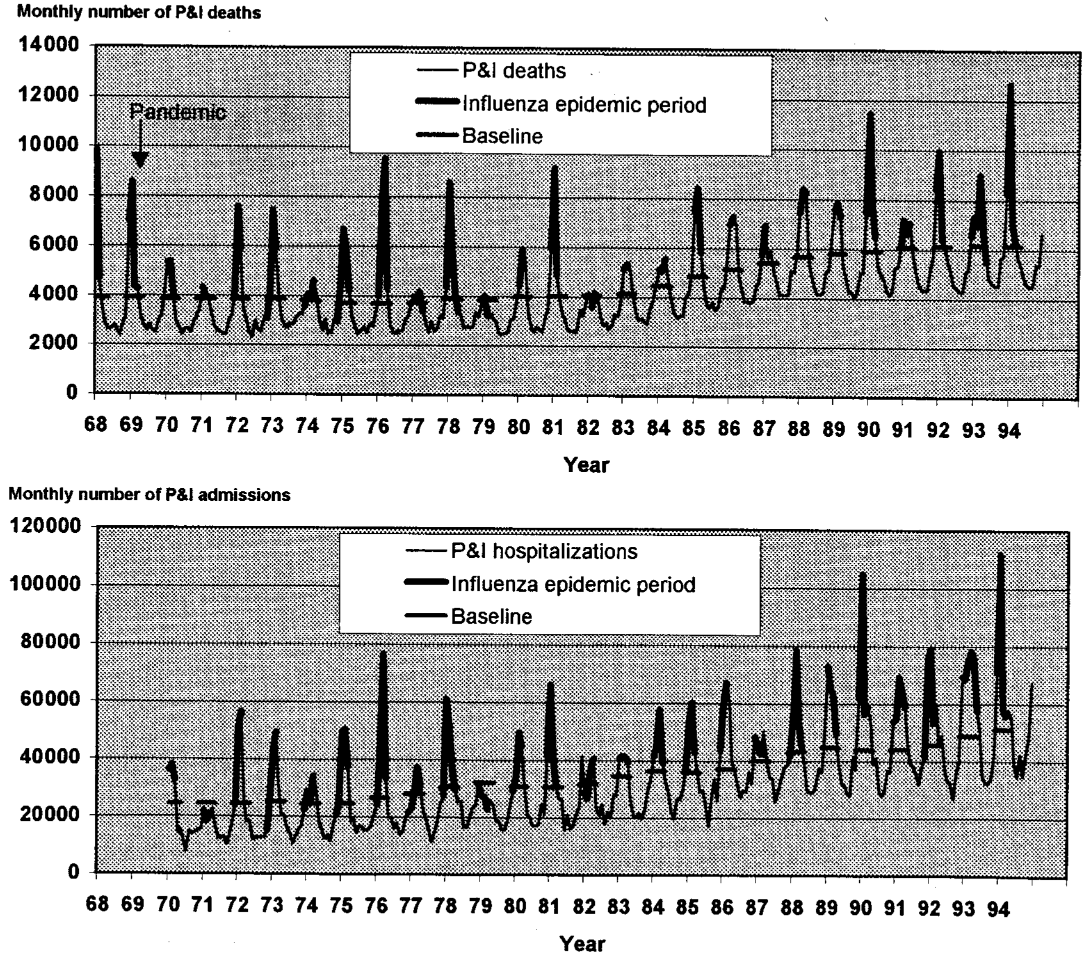

Fig. 2. Seasonal impact of influenza in temperate climates during epidemic influenza periods: monthly numbers of deaths (A) and hospitalizations (B) associated with pneumonia and influenza (P&I) among persons over 65 years of age in the United States, 1970–94 [9].

influenza in a systematic fashion [14]. Typically, such data lack a denominator and are therefore not suitable for generating quantitative information about the burden of influenza.

2.1.2. Impact of influenza on mortality

Through the excess mortality approach, influenza epidemics have been associated with a significant rate of mortality in the United States (Fig. 2) and in other

Table 1
Average age-specific seasonal incidence of influenza-related mortality and hospitalizations per 100,000 population, United States, 1972–92

	Age (years)				
Outcome	< 65	> 65	> 75	> 85	All
Excess mortality from pneumonia and influenza	0.3	18	40	100	2.3
Total influenza-related deaths[a]	1.3	73	160	400	9.1
Excess hospitalizations for pneumonia and influenza[b]	30	160	NA[c]	NA[c]	50

[a] All estimates of excess mortality are based on analyses of weekly numbers of deaths from pneumonia and influenza and all causes using cyclical regression modelling [9] [1]. Total influenza-related deaths among persons aged > 75 and > 85 were calculated proportionally, using the observed relationship of 1:4 between the excess of deaths from pneumonia and influenza and all causes for the other two age groups and all ages.

[b] Rounded estimates based on analyses of data on monthly hospitalizations from the National Hospital Discharge Survey (L. Simonsen et al., unpublished observations) for the period 1972–92.

[c] Data not available.

countries with a temperate climate [1,6–10]. The average seasonal incidence of influenza-related deaths was 9.1 per 100,000 Americans during the years 1972–92 (Table 1 and [8]), which represents about 1% of all deaths in the United States. Mortality from influenza was characterized by large seasonal variations during these years, ranging from 0 to more than twice the average incidence. Most of the deaths occurred during seasons dominated by influenza A(H3N2) viruses. During the inter-pandemic years, over 90% of influenza-related deaths occurred among persons 65 years of age or older; consequently, the incidence of influenza-related mortality was 100-fold higher for these age groups than among younger persons (Table 1) [1].

In one study of the burden of influenza among people over 75 years of age in France during 1980–90 [10], the estimated average seasonal total of influenza-related deaths was 216 per 100,000 persons. This estimate is similar to an estimated rate of 160 per 100,000 Americans in that age group (Table 1). In contrast, the number of excess deaths from pneumonia and influenza was 22 per 100,000 population, or about half the rate observed in the United States (Table 1). Since excess deaths from pneumonia and influenza in the French study accounted for 18% of all influenza-related deaths, however, in comparison with 30% in the United States, the discrepancy probably reflects a difference in the coding of mortality from these causes in the two countries and not a true difference in the impact of influenza.

2.1.3. Impact of influenza on hospitalizations

A similar seasonal pattern in the number of hospitalizations for pneumonia and influenza during influenza epidemics has been observed in the United States (Fig. 2) and in other countries with a temperate climate [15,16]. The seasonal excess in hospitalizations for these causes accounted for the majority of all influenza-related hospitalizations [16]. During the influenza seasons of 1972–92, the average seasonal burden of influenza was estimated to be about 50 hospitalizations per 100,000 Americans per season; half of these hospitalizations were of persons under 65 years of age (Table 1) [2].

2.1.4. Influenza epidemic severity index

Because mortality data from surveillance programmes are readily available, the impact of influenza on mortality from pneumonia and influenza has long been used as the index of seasonal severity in the United States. Recently, each influenza season occurring in 1969–97 has been classified in an influenza epidemic severity index and ranked in one of the severity categories 1 (mild) to 6 (severe). In general, the seasons involving A(H3N2) were ranked in categories 4–6, while those involving A(H1N1) and influenza B were ranked in categories 1–3. In comparison, the 1968 A(H3N2) pandemic was ranked as 7– 8 and the 1957 A(H2N2) pandemic in category 10 [9].

Concern has been expressed that this index does not accurately describe the impact of influenza on morbidity, as some seasons with no excess mortality have been shown to be associated with excess influenza-related hospitalizations in studies of regional populations [11]. The seasonal impacts of influenza on hospitalizations and deaths are in fact proportional, with the greatest excesses in influenza-related hospitalizations and deaths in the influenza A(H3N2) seasons and smaller excesses during the A(H1N1) and influenza B seasons [2]. Thus, the mortality-based influenza epidemic severity index [9] also captures the impact of influenza on severe morbidity. While this severity index is currently limited to the United States, it may be worthwhile to develop the concept for international use. If such a mortality index was available in several countries worldwide, each providing a timely severity assessment on the basis of surveillance data [17], it might eventually be possible to produce a timely assessment of the severity of current influenza epidemics for use in public health planning globally, as a new virus variant sweeps the planet.

2.1.5. Paediatric influenza

Although only a small proportion of all influenza-related deaths occur in children, they have the highest morbidity rates during influenza outbreaks and are major disseminators of the virus. In one study in the United States, vaccination of school-age children resulted in a three-fold reduction in the overall rate of illness in all age groups [18]. Infants have been shown to be at increased risk for influenza and for serious consequences of infection. In one recent study, about 30% of infants in a family study in the United States had been infected during their first year of life [19]. At particularly high risk for infection were infants who had several older siblings, with an infection rate of 60% during their first year of life. The highest rate of serious influenza-related illness occurred among infants 6–12 months of age, most often as a result of A(H3N2) viral infection. On this basis, immunization of infants from six months of age has been proposed in the United States [19].

2.2. Pandemic influenza

For reasons yet to be fully understood, the 1918 A(H1N1) pandemic was particularly severe and caused a much higher death toll than the A(H2N2) pandemic in 1957 and the A(H3N2) pandemic in 1968 [1]. The impact on mortality of each of the three pandemics of this century was higher than those recorded in all subsequent epidemics caused by influenza viruses of the

Table 2
Relative age-specific risk of dying from pneumonia or influenza (P&I) during the two most recent pandemics in the United States in comparison with later[a] severe seasons dominated by the same influenza A virus subtype

	Persons aged <65			Persons aged ≥65		
	Excess deaths per 100,000 population		Relative risk[b]	Excess deaths per 100,000 population		Relative risk[b]
Season and dominant viruses	P&I	All causes		P&I	All causes	
1957–58 A(H2N2) pandemic		15.5			273	
1967–68 A(H2N2) epidemic		0.56			113	
Pandemic versus epidemic A(H2N2) season			28:1			24:1
1968–69 A(H3N2) pandemic	4.2			44		
1980–81 A(H3N2) epidemic	0.48			32		
1989–90 A(H3N2) epidemic	0.20			31		
Pandemic versus epidemic A(H3N2) seasons:						
1980–81			9:1	(1980–82)		1:4:1
1989–90			21:1	(1989–90)		1:4:1

[a] Any influenza season that occurred after one decade and was ranked in severity category 6 of the influenza severity index (most severe non-pandemic category) were included [1,20].
[b] The relative risk for a person in each age group of dying of influenza in the pandemic versus the non-pandemic season was calculated by dividing the excess mortality rate from pneumonia and influenza or all causes during the pandemic by the estimate for the non-pandemic season [20].

same subtypes, but not dramatically so for the last two pandemics. For example, the 1968 pandemic in the United States caused an excess of about 16,000 deaths due to pneumonia and influenza, while several of the following A(H3N2) epidemics resulted in up to 12,000 excess deaths, or about 75% of the pandemic level [9].

While the absolute number of pandemic deaths does not always distinguish a pandemic from severe non-pandemic seasons, the age distribution of influenza-related deaths has been shown to be dramatically different during pandemics and the non-pandemic seasons immediately preceding them [20]. In an analysis of vital statistics for the United States, persons under 65 years of age accounted for half of the influenza-related deaths during the 1968–69 A(H3N2) influenza pandemic but for decrementally smaller proportions after the first decade following each pandemic. A similar pattern was seen for all pandemics of this century in the United States. As a consequence, the elderly were at approximately the same risk for dying of influenza during a pandemic as they were during later severe non-pandemic seasons dominated by the same virus subtype. In contrast, younger persons were on average at a 20-fold elevated risk for influenza-related mortality during pandemics, relative to later severe epidemics (Table 2).

Most of the deaths among younger persons occurred among adults aged 45–65, half of whom had no comorbid condition listed on their death certificate, indicating that specific consideration should be given to general vaccination of people in this age group at the time of the next pandemic [20].

2.3. Influenza vaccination as a highly cost-effective public health intervention

A complete assessment of the burden of influenza would include the total impact, ranging from the most severe (mortality, hospitalizations, disabilities) to mild morbidity (outpatient visits) and absenteeism from work and schools related to influenza. In one study, the total annual cost to influenza in the United States was estimated to be US$ 3–5 billion [21].

In several other studies, a large avoidable disease burden was shown each season among both the elderly [22,23] and healthy young adults [24]. Thus, in the United States and several other countries with a temperate climate, influenza vaccination in now considered one of the most cost-effective medical interventions possible for the older adult population and for other high-risk populations [3,22,23].

3. Burden of influenza in tropical countries

3.1. Epidemiology of influenza

While there appears to be a general biannual pattern of influenza epidemics during the spring and autumn

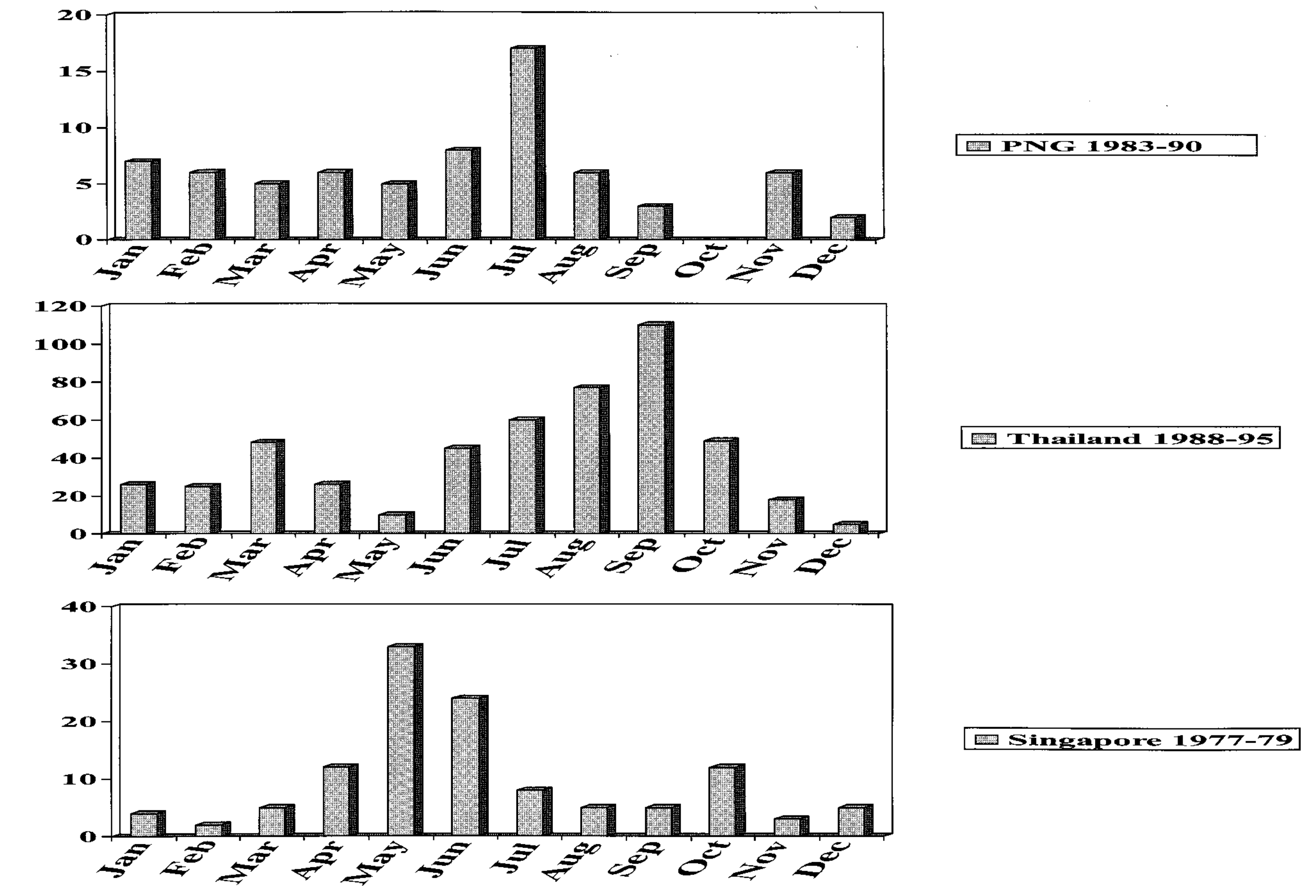

Fig. 3. Seasonality of influenza in the tropics: Combined monthly distribution of influenza isolates over several years in Papua New Guinea, Singapore and Thailand.

months in the tropics, there is considerable background activity in between these epidemic periods and also considerable variation in the timing of biannual influenza epidemics (Fig. 3) [25–27] (see also other contributions in these proceedings). Assessment of the actual timing of each epidemic may be complicated by the limited number of influenza virus isolates typically obtained in any country during a season. In the situation of considerable background activity, variable timing of biannual epidemics and limited ability to time each influenza epidemic from virus surveillance data, it would be difficult to implement the excess approach successfully to data for tropical countries on a routine basis; however, for investigations of individual outbreaks, with increased emphasis on virus surveillance and collection of data on impact, it might be possible to document and quantify influenza-related morbidity and mortality.

3.2. Pandemic influenza

The existence of a disease burden associated with influenza in the tropics is evidenced by documentation of excess mortality during the 1957 and 1968 pandemics in Taiwan and Manila, with attack rates and rates of influenza-related mortality similar to that observed in the United States (Table 3) [28]. Influenza can have a significant impact on mortality, as evident in the data from Taiwan, where 7% of all deaths in 1957 were related to the A(H2N2) pandemic. Further, during the 1968 pandemic, about 50% of the influenza-related deaths in Taiwan were among persons under 65 years of age, similar to the observed age distribution of deaths observed in the United States during the 1968 pandemic [20].

3.3. Non-pandemic influenza

The existence of a disease burden associated with non-pandemic influenza in the tropics is clear in the data from a few investigations of outbreaks. In one study of the 1963 outbreak of influenza A(H2N2) on a military base in Panama, a large influenza-related disease burden was documented; it was shown that the military influenza vaccine was highly protective in this tropical setting [29]. In a study of an outbreak of influenza A(H3N2) in Papua New Guinea in 1982–83, a marked increase in the number of outpatient visits for

Table 3
Rates of attack and mortality associated with pandemic influenza in countries with a temperate climate and in the tropics

Geographic region	1957–58 A(H2N2) pandemic		1968–69 A(H3N2) pandemic	
	Serological attack rate (% population)	Total influenza-related deaths per 100,000 population	Serological attack rate (% population)	Total influenza-related deaths 100,000 population
Tropics				
Taiwan[a]	42	64		21
Manila[a]		80		
Temparate				
USA (Cleveland, Seattle)[a]	55	39	41–57	17–26
Australia (Melbourne)[a]	45		52	
Spain (Barcelona)[b]			30–40	

[a] Data for Taiwan and Manila from [28] and for the USA from [1].
[b] Data from [34] for the first pandemic wave, 1957–58, only; numbers calculated as the difference between reported pre- and post-pandemic seropositive rates.

influenza-like illnesses at the local hospital and a significant increase in the number of adult hospitalizations for pneumonia were documented during the epidemic [30].

Although the impact of pandemic influenza was very similar in Taiwan and the United States, no excess mortality was found in Taiwan during any of the non-pandemic seasons studied [28]. This should not be taken as evidence that no influenza-related deaths occurred, however, for the following reasons: the excess in mortality from all causes was considered, resulting in difficulty in detecting small or moderate excesses in the death rates [9]; the statistical method used to estimate excess mortality probably included influenza-related deaths at the baseline level; and, as previously discussed, the significant background influenza activity all year round probably prevented detection of small to moderate increases in influenza-related mortality.

3.4. Alternative methods for detecting the burden of influenza in tropical countries

The unique pattern of year-round influenza activity and a biannual epidemic pattern in tropical Asian countries complicates routine assessment of the related disease burden. Special studies of influenza epidemics are needed, which include influenza virus surveillance to help identify the influenza epidemic period and a very specific indicator of influenza-related disease burden, such as adult hospitalizations or deaths from pneumonia (pneumonia and influenza). Few such studies have been done, and this may be the reason for the general belief that there is no significant influenza burden in Asia and consequently for the very low influenza vaccine uptake in this region.

In the absence of data on disease burden, since the pandemic mortality rates appear to be similar in Taiwan and the United States and since influenza epidemics occur each year in Asia, it could be argued that the disease burden associated with non-pandemic seasons is also similar, although this is difficult or impossible to document.

Perhaps the best use of the limited resources of individual countries for documentation and quantification of the burden of influenza in Asia would be to conduct a prospective vaccine probe [31], in which the efficacy of a known vaccine is assumed and the difference in disease burden between vaccinated and unvaccinated populations is attributed to influenza. Are such vaccine-probe studies ethical when the influenza vaccine is known to prevent severe outcomes of influenza infection? If public health authorities believe that there is no influenza-related disease burden in a country, the effectiveness of influenza vaccine is presumed to be zero, despite the known efficacy of the influenza vaccine (as there would be no disease to prevent). It may therefore be argued that using a placebo-controlled study design in not unethical, until such a study has proven the existence of a preventable disease burden in that country.

It has been shown in several studies that infants are at elevated risk for infection with influenza and may suffer severe consequences [18,19]. If these findings can be extrapolated to tropical countries, influenza may well be a common childhood infection that leads to substantial numbers of severe outcomes. A vaccination probe study of the impact of influenza among children in low-income tropical countries, that includes an assessment of the contribution of malnutrition is needed. Currently, no consideration appears to be given to influenza among infants in developing countries—even though influenza infection is a preventable disease that may trigger a significant proportion of acute respiratory infections among infants, a leading cause of morbidity and mortality [32].

Alternatively, retrospective case-control studies considering the influenza vaccination status of persons hospitalized with pneumonia can be used to demonstrate the influenza-related disease burden. One such study showed that a large proportion of all hospitalizations of elderly persons for pneumonia could be prevented by use of influenza vaccine, and this observation supported the implementation of a national vaccine programme in Argentina [33]. As the burden of influenza has been shown to vary widely between seasons and with different circulating influenza viruses, the impact of several epidemics must be studied in order to quantify the burden of influenza in the tropics.

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