International Congress Series 1263 (2004) 3–11

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Global burden of influenza: what we know and what we need to know

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Abstract. While influenza morbidity and mortality are now recognized as a major concern in temperate climates, this has not been the case until recently in the tropics and subtropics. Pandemics represent a special situation. Historically, the United States and Western Europe have been following influenza mortality systematically since the influenza pandemic starting in 1889. High mortality in the 1918 pandemic was well documented in these countries, but also in much of the developing world. This was also true during the 1957 pandemic, though with lower mortality. A problem for tropical countries in quantifying interpandemic influenza is the differing seasonality of outbreaks in these areas. Seasonality has been a necessary tool in such quantification. Recently, following better definition of seasonal occurrence, data have been developing on the burden of influenza in many parts of the tropics and subtropics, indicating that mortality and morbidity are likely to be similar to that identified elsewhere. Further confirmation of the impact of influenza, often underestimated in the past globally, is still needed. Selected studies need to be carried out to define health burden where this has not been done in the past. Data from these studies can be used to determine economic impact in different health care systems.

Keywords: Influenza illness; Pneumonia and influenza deaths; Influenza vaccine; Tropical disease

1. Introduction

Unlike many of the infections we deal with today, influenza has a long history, with a name that has been used for centuries and outbreaks, which may go back to antiquity. In spite of its long history, its continuing activity and occasional dramatic pandemics, the quantifiable impact of influenza is something that is still a matter for discussion and study. This is particularly the case for those parts of the globe where most of the world's population live, regions where influenza does not exhibit winter seasonality, making recognition of outbreaks more difficult.

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0531-5131/
doi:10.1016/j.ics.2004.02.049

There are a number of issues, which have made quantification of influenza occurrence challenging. First is the existence of two types of influenza, A and B, as well as subtypes of the type A virus, which behave differently. Then, there are the periodic shifts in the subtypes of the type A viruses resulting in pandemics. Not only do pandemics produce greater morbidity and mortality than annual interpandemic outbreaks, they also may be recognized in regions of the world in which annual outbreaks go unnoticed.

In regions in the temperate zone, seasonality has been used as an aid in defining the impact of influenza viruses. Seasonality has been a useful analytic tool, given the problem in accurately assessing influenza mortality and morbidity because of difficulty in virologic confirmation of outcomes. The problem, briefly stated, is that specific diagnosis of influenza is not possible in the large numbers needed for epidemiologic analyses. For mortality, the traditional criterion, deaths recorded by physicians as caused by pneumonia and influenza (P&I), is not very sensitive, missing many influenza-related deaths, and is applicable only in a defined influenza season. Morbidity has been extremely difficult to quantify, with the possible exception of severe morbidity requiring hospitalization, but again with reference to the defined influenza season. Throughout these determinations, both in terms of logistics and biologic issues, diagnosis of more than a few cases by viral identification has not been possible. Therefore, methods used to differentiate influenza from other conditions with similar illness characteristics have compared occurrence in the defined seasons with occurrence in other seasons. For this reason, it has been more difficult to quantify influenza mortality and morbidity in those more tropical regions where influenza seasonality is less profound than in the North and South temperate zones.

A variety of specific techniques have been used to quantify the impact of influenza; some have been more successful than others. While the different methodologies have sometimes resulted in varying estimates, there has been a reasonable similarity in the pattern of results, which allows, if not exact estimation, some reasonable degree of recognition of the overall impact, especially in terms of mortality and severe morbidity.

2. Early identification of influenza mortality

Pandemics prior to 1889 produced qualitative information on the relation of this periodic phenomenon to mortality in Europe and elsewhere in the world. However, it was the pandemic starting in that year that provides the first clear evidence of the usual pattern of mortality, with greatest impact among those at extremes of age. This was most clearly demonstrated in Massachusetts where deaths from pneumonia and influenza increased markedly from approximately age 50 years onward to age 90, with approximately 250 deaths per 100,000 in those of advanced age. Higher mortality frequency was also seen in the very young, producing the U-shaped curve [1].

During the same pandemic in the United Kingdom, it has surprisingly been reported that many of the deaths were in those aged 20–40. It has even been said that review of primary data shows little difference in mortality patterns between that pandemic and that of 1918 [2]. The age-specific mortality rates seen in the infamous 1918 pandemic were derived in the United States from national vital statistics, and resulted in the W-shaped curved with high mortality not only in very young children and the elderly, but also in 20–40-year-olds [1,3]. Contemporaneous studies in the United States examined age-specific

death rates in different occupational groups and found all were involved. Data from insurance companies suggest that older individuals might have been spared, while white males aged 25–45 in some defined occupations died at a higher frequency of 62 per thousand [4].

Because of the unusually high mortality rates, it was possible during the 1918 pandemic to identify the impact of influenza in many countries which do not ordinarily report the disease. In Asia, excess deaths were observed in Iran, Singapore and Indonesia; it was estimated that three million died in several countries in Asia, while in India, one source reported 12.5 million deaths [5]. Interestingly, based on the recent experience in Madagascar, that island was one of the few places in sub-Saharan Africa where a large outbreak was well documented with 114,000 deaths out of a population of 3,250,000. Thus, the worldwide distribution of these reports indicates that under conditions where high mortality was clustered in time and place, the global impact of influenza could easily be recognized. This assessment of impact took place more than 80 years ago and even in parts of the world where, at that time, healthcare was poor and collection of vital statistics was limited.

Global mortality was also reported, albeit with lower death rates, during the next major pandemic when the A (H2N2) viruses arrived in 1957. Most countries in Europe had 17–30% increases in deaths. In tropical countries in the Americas, increases ranged from 9% to 68% with the greatest increase reported in Costa Rica [1]. In parts of India, the increase was 19%. Thus, as in the 1918 pandemic, the sharp increase in mortality allowed recognition of influenza transmission globally. During such a period, it may be assumed that all respiratory, or more typically, pneumonia and influenza deaths can be attributed to the pandemic. A major difference between this pandemic, that of 1918 and perhaps also the 1889–1892 period was the age-specific pattern of death. The mortality curve was again U-shaped, high in the very young and the old, with relative sparing of older children and younger adults. This has since become the expected pattern of interpandemic influenza. The subsequent 1968–1969 A (H3N2) pandemic was of still lesser magnitude, and the major impact was delayed in Europe and mitigated by prior experience with the neuraminidase of the type A (H2N2) virus. Interestingly, one of the more dramatic tropical country influenza experiences was recorded again in India, where there was a known introduction into the seaport of Madras; in the subsequent outbreak, 8.4% of the population had documented, medically attended illnesses [6]. Little specific information on mortality in this pandemic is available from the tropical world, although respiratory mortality did increase in some countries.

3. Methodologic developments in developed countries in the A (H2N2 and H3N2) eras

Pneumonia and influenza (P&I) deaths were identified in the early part of the last century as the most sensitive way to evaluate the impact of influenza on mortality. Data were analyzed using this measure in the 1918 and subsequent pandemics. Attributing all deaths with these diagnoses to influenza during the peak weeks of transmission is probably reasonably accurate in a pandemic. That is the case because of the extreme nature of the outbreak, with likely replacement by influenza of other pathogens, which produce respiratory deaths. However, during other periods, when mortality is not as extreme and sharp, another approach must be used. The reason is that other viruses and bacteria co-

circulate with influenza and the diagnosis of P&I, while reasonably specific, is not so specific that only deaths caused by influenza viruses are identified. Thus, particularly in interpandemic periods, only excess deaths above a baseline could reliably be related to influenza. Use of the "excess" methodology actually dates back to William Farr, the Registrar General of England and Wales, who first used it in the mid-19th century. It was refined and given necessary methodologic expression by the work of Serfling at the US Center for Disease Control and Prevention (CDC) [7]. This method has served as the basis of determining the impact of influenza on mortality for many years in the United States; the model dealing with reported mortality from major cities in the United States was slightly modified to deal with certain issues, such as temporary lack of information during the Christmas holidays. These modifications involved time-series methodology and were not without their own problems.

It was realized in the days of Farr that deaths, in addition to those recorded as caused by pneumonia and influenza diagnoses, increased during major influenza outbreaks and this observation has resurfaced periodically [1]. In 1974, Housworth and Langmuir reanalyzed data on excess mortality from 1957–1966 [8]. They previously had concluded that using P&I diagnoses was not as appropriate of a measure to track mortality as all respiratory causes. Their analysis of seven influenza outbreaks, caused by types A and B viruses, and one heat wave demonstrated that in the influenza outbreaks, only 22% to 38% of the excess illnesses were assigned to respiratory causes (in a heat wave, the value was even lower, at 13%), but in the influenza periods, 44% to 70% of excess illness were assigned to heart, circulatory and nervous causes. This indicated how much all respiratory outcomes underestimate the total influenza burden.

Liu and Kendal carried the approach further by developing a more refined, cyclical regression model, which attempted to examine not only the question of causes other than P&I during an influenza outbreak, but also the fact that typically only the peak periods were included in the counts. For a country as large as the United States, influenza is not synchronous in occurrence and there are weeks of influenza-related mortality outside the peak periods [9]. Therefore, two periods were calculated, first the traditional one showing the peak in mortality above the baseline, and the other extending a month on either side. In addition, besides the traditional excess P&I mortality, all cause mortality was calculated as a somewhat less specific but more comprehensive indicator of influenza mortality burden. An excerpt of these results is shown below in Table 1.

Table 1
Estimates of excess pneumonia and influenza (P&I) and all cause mortality in the US, 1973–1981

Influenza-associated period	Virus strain	Range of excess P&I deaths	Range of excess deaths from all causes
Jan. 1973–Feb. 1973	A/England/42/72 (H3N2)	6200–6500	20,700–22,100
Jan. 1975–Feb. 1975	A/Pt. Chalmers/1/73 (H3N2)	4800–5400	9800–5400
Feb. 1976–Apr. 1976	A/Victoria/3/75 (H3N2)	11,300–10,800	32,400–23,900
Dec. 1977–Feb. 1978	A/Texas/1/77 (H3N2)	8400–8900	49,800–56,100
Jan. 1980–Mar. 1980	B/Singapore/222/79	4800–5000	31,900–36,400
Dec. 1980–Feb. 1981	A/Bangkok/1/79 (H3N2)	9700–10,100	45,300–47,600

Modified from Ref. [9].

The calculated range reflects a shorter peak period of influenza activity and a longer extended period encompassing additional weeks around the peak period. As can be seen, the all cause mortality is considerably higher than the traditional P&I mortality with the magnitude of differences varying greatly from year to year. Simonsen et al. [10] further extended these observations, and were able to conclude over a period of 20 years that all cause mortality was approximately 3.8-fold higher than P&I mortality. A problem with all cause mortality was that it was less stable compared to P&I, and sometimes was not statistically significant because of a broad range in estimates. Also, some causes of death, including cardiovascular disease, are likely related to influenza infection, but others such as, in the extreme, accidents are clearly not; an intermediate measure of mortality impact is currently being considered.

4. Severe morbidity in children: a global concern

Death is an indicator of influenza impact, which can be measured in many healthcare systems, using data routinely collected. However, it is most relevant for older individuals and those with defined high-risk conditions. Children without underlying chronic conditions now rarely die of influenza, at least in the developed country environment, and thus another indicator of severe disease expression must be used to quantify the impact of influenza in this important group. Hospitalizations are very costly to the health care system and have now been used as an indicator of burden of influenza in young children. In Tennessee, data are available from a 19-year-old Medicaid database, and have been used to determine hospitalizations by time in children without underlying chronic conditions [11]. Also available, from a single site in Tennessee, are long-term data on times of influenza and respiratory syncytial virus (RSV) prevalence that could be used to determine periods for analysis. As has been done with mortality data, the influenza period was compared with another period to determine excess hospitalizations, either the peri-influenza period, which might include the transmission period of the parainfluenza viruses, or the summer, generally the lowest period of respiratory viral spread. Excess hospitalizations annualized over the entire period were found to be 104 per 10,000 children under 6 months of age, 50 per 100,000 in the 6–11-month-olds, and 17 per 10,000 in those 1 to 3 years of age.

The frequency of hospitalization in the Tennessee study did not seem much changed where periods of RSV prevalence were excluded. However, there was concern that over a long period and in an area of a large US state, RSV might not have been sufficiently excluded and might have inflated hospitalization frequency, especially in the youngest children. Therefore, Izurieta et al. carefully identified 3 years in two California managed care organizations in which the timing of RSV circulation was temporally removed from periods different from influenza transmission. Using the database of the organizations, hospitalizations were identified on a person–month basis for children without those underlying conditions, which would make them subject to standard recommendations for influenza vaccination [12]. To annualize these rates so they can be compared to those calculated by Neuzil et al., a factor recommended by the authors of 1.67 was employed. The adjusted annual rates for the under 2-year-olds ranged from 14 to 25 per 10,000. While similar in that there was little excess risk in those above 2 years of age and none above 5

years of age, they are substantially lower than the Tennessee data. A number of reasons can be advanced for these differences, such as the nature of the population, the assumptions used and the particular years examined. However, it is clear that this independent observation in a different population confirmed that healthy young children are at excess risk for hospitalization and are appropriately targeted for influenza prevention.

Is this excess risk limited to those parts of the world where most of the past work on influenza transmission has taken place, or is it more universal? A study conducted using methodology similar to those described above was conducted by Chiu et al. [13] in the Hong Kong Special Administrative Region (SAR) of China. Seasonality of influenza in the area is quite different from that seen in the temperate zone with two periods of transmission, one usually greater than the other. The excess hospitalizations of all children, including the small numbers with underlying conditions, were calculated for the major peaks in 2 years in which influenza and RSV transmission were separate. Excess frequencies were calculated by comparing hospitalizations during the peak period with those during baseline periods. Excess hospitalizations were found in those under 2 years of age, similar to that found in the US data. Unlike the situation in the US, excess hospitalizations continued in those under 5 years of age, but at a considerably lower frequency than those younger. One major hospital had comprehensive data on the contribution of influenza to hospitalizations as defined by systematic viral isolation of admitted cases. Therefore, an adjustment was carried out to correct what appeared to be too conservative estimates. This adjustment increased the frequency of hospitalizations by factors of 3.9 in 1 year and 2.3 in the second. The adjusted rates were substantially higher than those from the United States, especially the Izurieta study. Such adjustments may be particularly justified and necessary when working in regions where the influenza season or seasons are prolonged. Just examining the peak period, limited to only a few weeks, will substantially underestimate the actual burden. Overall, these results give guidance to a methodology that might be tried elsewhere.

5. Estimates of influenza morbidity

There is an increasing difficulty in assessing the impact of influenza as the illnesses under consideration become less severe. Yet, morbidity is so extensive in major influenza outbreaks that it exerts an enormous burden on the health care system in terms of both direct

Table 2
Average annual number of influenza-associated respiratory illnesses per 1000 per year, Tecumseh and Houston

Age group	Tecumseh			Houston
	Observed illness	Estimated illnesses[a]		Estimates
		Lower	Upper	
<5	103	109	113	349
5–14.9	155	164	171	375
15–24.9	40	42	44	218
25–59.9	19	20	21	153
60+	35	37	39	100
Overall	70	74	83	205

Modified from Ref. [14].

[a] Based on two different estimates of the accuracy of laboratory tests.

and indirect costs; disruptions in services may also occur. Two different methods were used to develop estimates of influenza illness occurrence, in community-based studies conducted in Tecumseh, Michigan and Houston, Texas; results are shown in Table 2 [14].

In Houston, data from primary pediatric care suggested that the majority of illnesses during the influenza season were influenza, with few other viruses being identified in these periods; thus, all respiratory illnesses during those times were directly attributed to influenza. In Tecumseh, it has been observed that other viruses circulated during such periods. Therefore, paired sera collected to bracket outbreaks were used to assess infection rates. Hemagglutination-inhibition (HAI) tests were carried out to identify those pairs with rises in titer, indicating infection with influenza viruses, as well as to identify those without infection. Illnesses in the influenza period in persons without infection were subtracted from illnesses in persons with documented infection, thus creating an "excess illness" rate. The conservative assumption in the calculation is that an influenza illness does not actually replace respiratory illnesses of other etiologies during that period, but occurs in addition to such illness. The results, shown in Table 2, include the observed illnesses plus higher estimates based on differing assumptions based on the lack of total sensitivity of the serologic tests in defining the infected population. These results can be contrasted with the estimates from Houston; the likely frequency of influenza illnesses are somewhere in between. What is clear from other data in the Tecumseh study is that influenza is the respiratory infection, which produces the illness of greatest health impact with 38% of episodes resulting in physician consultation and with considerable bed disability [15].

Most estimates of morbidity rely on use of medical care. This can provide a valuable estimate of a portion of morbidity, which results in physicians' visits, which can be used in economic models. However, there are limitations to these sorts of data, given differences in health care systems, some of which attempt to restrict physician visits for acute illnesses. The result, for example, is differences in physician visits associated with influenza isolation seen in the UK compared to the Netherlands, with the Netherlands consistently reporting more events [16]. Such differences in patterns of care might need to be considered if new interventions in treatment are under consideration.

Morbidity studies have begun in tropical areas, following realizations that severe illnesses are taking place in these regions as well as in developed areas, and that milder illnesses are putting a burden on the healthcare system. For example, situated almost on the equator, Singapore is thought to have influenza transmission taking place throughout the year. However, as in Hong Kong, transmission increases during certain months of the year. Respiratory illnesses in the community have been enumerated by several methods during that period and occur at a very high frequency [17]. Even if all of them cannot truly be influenza, still such frequent occurrence confirms the importance of influenza morbidity in a tropical environment.

6. Vaccine probes for determining morbidity

There is often difficulty in determining the extent of influenza morbidity in the community, and estimates will vary, sometimes widely, according to methods used to identify those illnesses, which are truly influenza in etiology. A technique that has been used for other infectious agents in which there have been problems in establishing etiology

is that of the vaccine probe. Simply stated, the approach is ideally conducted as a randomized trial of a particular vaccine; those illnesses that are prevented are presumed to be those which would have been caused by the agent in question. Such studies have, for example, indicated that *Haemophilus influenzae* Type B is responsible for cases of pneumonia in children living in developing countries; such etiology was hard to establish in observational studies because of the difficulty in collecting appropriate specimens [18]. Similarly, trials with influenza vaccine in the United States have suggested that the attack rate of influenza in otherwise healthy adults is much higher than had previously been estimated [19]. A study that illustrates the use of influenza vaccine to demonstrate the impact of influenza on residents of a developing country is one, which was conducted among Pakistani pilgrims participating in the Haj to Saudi Arabia [20]. The original plan was to randomize individuals to receive vaccine or placebo, but that was not possible. This demonstrates a problem with the probe design; like any intervention study, there are often ethical and practical considerations. In assessing the results, the authors calculated both the apparent efficacy of the vaccine, and then, factoring in this efficacy, the number of cases of influenza that truly would have occurred had vaccine not been used. In this population coming from Pakistan, the estimated number of cases of influenza, depending on the endpoint chosen, ranged from 17 to 24 per 100. This study did not use a true randomized design; in such a case, adjustment for potential confounding must be considered. In many observational studies of vaccine effectiveness, controlling for potential confounding is absolutely necessary, since a person's choosing to be vaccinated may relate to the likelihood of infection and illness.

7. Conclusions

Much needs to be done to increase awareness of the importance of influenza globally. The basics are to improve influenza illness surveillance as contrasted with just identification of circulating viruses and to identify disease periodicity on a regular, annual basis. This should be carried out in as many parts of the tropical and subtropical world as possible, but may, in some areas, be limited to certain health care facilities. In all cases, overall identification of the occurrence of influenza-like illnesses in the population under study, with calculation of rates, should be attempted and virus isolation carried out in a subset of the population.

In many areas, detection and enumeration of severe outcomes, such as pneumonia and influenza, can be established. Mortality and hospitalization data will be available by age group, as will population data. The process may need to be carried out in certain administrative areas, rather than in whole countries. In contrast, morbidity studies may be possible only in limited areas, since they will require more extensive virology. These investigations should be tied to utilization of health care and economic consequences. Vaccine probes may be involved. Throughout, it should be remembered that health effects are generalizable, so studies do not have to be carried out everywhere. However, economic consequences are specific to healthcare systems, but can often be calculated based on the magnitude of the health effects and the local costs and benefits.

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