

Preparing for the Next Influenza Pandemic

Lessons from Multinational Data

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Background: In the past decade, avian influenza has made several incursions of increasing scope and virulence into humans. The likelihood of another pandemic is increasing with time. In work recently published, influenza was found to be the principal cause of the increase in mortality in the United States during the winter months. In a companion report, the U.S. national vaccination program was shown to have increased coverage of high risk groups 5-fold from 1980 to 1999, but excess mortality did not decline in any elderly age group. The Multinational Influenza Seasonal Mortality Study has assembled and has begun to mine mortality data from many countries. Early results indicate that the U.S. results extend to other economically developed countries and probably worldwide.

Results: The Multinational Influenza Seasonal Mortality Study data extend the observations of others that there were heralding events that provided advance warning for all of the pandemics of the 20th century. Moreover, in the first year of emergence of A(H3N2) viruses, the 1968–1969 pandemic produced little excess mortality outside of North America. It appears that there were at least 2 variants of the pandemic virus, differing at 1 or more internal gene loci, and that the more virulent form emerged as dominant in the second pandemic season.

Conclusions: Integrating these findings, it seems clear that the influenza control strategy now used in about 50 countries is less than optimal. While it is likely that there will be more time to react in the pandemic season than previously imagined, an enhancement of the historical strategy is clearly indicated. Furthermore, the vaccine shortage that is presently inevitable suggests that a departure from the historical strategy if calamitous ineffectiveness is to be avoided.

Key Words: pandemic planning, excess mortality, multinational data, national vaccination program effectiveness

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The next influenza pandemic is fast approaching. While this statement might have been true in, or in the interim between, any epidemic season(s) in the past, the present circumstance is unique in the history of the man-influenza

relationship. It has been a relatively long time (37 years) since the last pandemic. More importantly, a global surveillance and viral isolation capability, while still fragmentary, is in place. With the advance information this quasiglobal network provides, various “brushfires” associated with limited excursions of influenza viruses from the avian reservoir into the human population have been detected and documented, incompletely to be sure, but nevertheless to a far greater extent than ever before.

Arising in a similar timescale, the economically developed countries of the world have generated electronically readable versions of the record of mortality within their borders. In some cases, the entire mortality record after some date (most commonly about 1968) has become available. In most such countries, extractions of interval mortality are available, often by major disease class and occasionally by age group. These mortality records have been the subject of many analyses, usually limited to a single country’s data, but sometimes extending over a few closely related countries and several years. In 2001, in association with 2 branches of the U.S. National Institutes of Health, the National Institute of Allergy and Infectious Diseases and the Fogarty International Center, the Entropy Research Institute undertook the development of a multinational database, spanning 10–12 countries in detail and as many as 75 countries in a more limited sense. This database is intended to obtain and maintain all electronically available mortality data on a defined set of diseases comprising the majority of mortality from the enlisted countries. The guiding protocol for this effort was entitled the Multinational Influenza Seasonal Mortality Study (MISMS), and accession began in 2002.¹ The ultimate objective of this research is to generate a high quality estimate of the mortality burden produced by influenza in every country of the world.

In economically developed countries with a temperate climate, mortality peaks in midwinter. The area below this peak appears to vary according to a global pattern, at least one determinant of which is related to the midwinter mean temperature in the capital city of the country.² In the United States, during the period of 1959–1999, the winter rise in mortality was principally caused by the influenza virus.³ An analysis of the effectiveness of the national influenza vaccination program⁴ reported that, despite an increase in vaccine coverage of US elderly from 15–20% before 1980 to 65% in 2001, there was no decrease in mortality. These findings suggest that the global mortality effects of influenza may be much greater than one might expect from viewing single-country reports and data analyses limited to mortality directly attributable to influenza. Thus, the current strategy for influ-

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enza control now deployed in more than 50 countries may be inadequate.

In addition, Simonsen et al^{4,5} recently summarized the multinational data on the 3 influenza pandemics of the 20th century. The principal finding was that, preceding the seasons of elevated mortality historically associated with the emergence of each genetically shifted influenza A virus, several heralding events provided advance notice of the disasters to come. More recently, the emergence of the currently circulating A(H3N2) virus was analyzed, for which the heralding event was a season of severe mortality only within North America.^{6,7}

Early MISMS study results from several countries are presented in this publication. Many of these results are currently under review. These results validate and extend the findings of the U.S. studies referenced above and provide an opportunity for data synthesis that should be useful in preparing for the pandemic inevitability.

MATERIALS AND METHODS

The MISMS database consists of monthly mortality data for several major disease classes from about 10 countries. Mortality information is available by selected age groups at monthly intervals for all economically developed countries in the database. Each country's database also contains extractions from laboratory surveillance data identifying the influenza viruses dominant in circulation in each season. Additionally, the doses of influenza vaccine distributed in each country and season are tabulated. All mortality information is derived from public-use files.

In the work summarized here, excess mortality was estimated using either a Serfling-type algorithm⁴ or a digital filtering procedure.³ In the latter procedure, a 13-month moving average of mortality centered on each month weighted using a Hamming data window was subtracted from each observed mortality value. The sum of positive values of this difference for nonsummer months was taken as the estimate of excess mortality for each influenza season.

RESULTS

Influenza Is the Principal Cause of the Winter Excess in Mortality. The proposition that influenza is the principal cause of the wintertime excess of mortality was tested using data from Australia, Canada and France from 1968 to 1999. (Reichert TA, Sharma A, Pardo SA, et al. The winter increase in mortality in economically developed countries: the role of influenza submitted for publication.) The validation exercise followed the template developed for U.S. data.³ For each country, monthly mortality data for ischemic heart disease, cerebrovascular disease, diabetes, pneumonia and all-causes were subjected to the H-ZLS digital filtering procedure. In all 3 countries, monthly mortality for each disease class was transformed into a time series that seemed highly similar to the transformed time series for every other disease class in that country, including death due to all-causes.

The peak of mortality for the 3 vascular diseases lagged the peak in mortality attributed to pneumonia (about 3 months in 4), as expected, in each country.

Time series analysis of the digital-filter-transformed series for all disease classes and countries everywhere suggested an autoregressive model of order 2. With an exception for the very low mortality levels attributed to diabetes in Australia and Canada, the coefficients of these models were indistinguishable, not only within a specific country but also across countries. These findings confirm and extend the U.S. findings.³

Surveillance data indicated which influenza virus subtype was dominant in a particular country in each season. This information was used to separate the 31 seasons into 2 categories, high versus low excess mortality, in all but a very small number of seasons.

In all 3 countries, the age distribution of mortality was shifted to younger age groups only in the season of emergence of the A(H3N2) virus and in the seasons dominated by these viruses in the decade immediately after.

The first 2 findings indicate that the cause of the winter excess of mortality in these countries was singular and the same as that in the United States. The other findings, however, demonstrate that it is very unlikely that the cause can be anything other than influenza.

Effectiveness of the Conventional Strategy for the Control of Influenza. Validation of the observation that a 4- to 5-fold increase in the influenza vaccine coverage of the U.S. elderly between 1980 and 1999 produced no decrease in excess mortality in any elderly age group proceeded similarly to the above procedure. Excess all-cause and pneumonia and influenza mortality were determined for the period of 1968–1999 for Australia, Canada and France. Data on the dominant influenza virus subtype and influenza vaccine distribution were obtained. No middle-aged or elderly age group had experienced a decline in excess mortality in any of these 3 countries with 3 different trajectories in increasing influenza vaccine use. [Reichert TA, Hampson A, Tam T, et al. National vaccination programs for the control of influenza: no evidence of a reduction in excess mortality in 4 countries (a report from the MISMS study), manuscript in preparation.]

Herald Events for the Pandemics of the 20th Century. For each pandemic of the previous century, conventionally designated as occurring in 1918, 1957–1958, and 1968–1969, locations have been identified and influenza infections have been documented that occurred in advance of the putative pandemic season.⁵ “Herald waves” occurred in several locations in the spring of 1918 and 1957. In the winter of 1968–1969, the A(H3N2) virus, as well as other viruses, was documented to be in circulation at multiple locations in the northern hemisphere.⁸ Where detailed surveillance was available, the A(H3N2) epidemic proceeded in fits and starts, and the label “smoldering” was applied. Excess mortality was noted to be severe in the first season only in the northern United States and Canada. However, for elderly individuals in North America older than 77 years of age, excess mortality fell below that for the precedent season, which was dominated by the A(H2N2) virus. In the 1968–1969 season outside of North America, there was no consistent shift to younger age groups in the age distribution of influenza-related mortality. Therefore, it can be hypothesized that influenza-related mortality in that region was caused by viruses co-

circulating during that season. In locations outside of North America in the 1969–1970 season, however, excess mortality was exceptionally severe. The age shift was classic for a pandemic, with little evidence of sparing the very elderly. For example, individuals 45–64 years of age in France elevated excess all-cause mortality 5.5 times the average for that group, whereas the excess mortality for the group >85 years of age was increased <60% above that age group's average.

DISCUSSION

In a series of recent reports, data from widely separated economically developed countries were used to validate the following findings on U.S. data. Influenza is the principal cause of the winter excess in mortality, at least in countries with a developed economy and a four-season climate, probably everywhere (Reichert TA, Sharma A, Pardo SA, et al, submitted for publication).

Control strategies from 4 developed countries involving the deployment of inactivated influenza virus vaccine toward high risk groups (primarily the elderly) over 4 different time courses have all failed to produce a reduction in excess mortality in any elderly age group. [Reichert TA, Hampson A, Tam T, et al. National vaccination programs for the control of influenza: No evidence of a reduction in excess mortality in 4 countries (a report from the MISMS study), manuscript in preparation].

In addition, in all of the most recent pandemics, herald events have provided significant advance warning of the disaster to come.⁵ A recent study reported that there was a genetic drift in the neuraminidase gene between 1968–1969 and 1969–1970. The drifted variant came to dominate circulation in the second season after the emergence of the A(H3N2) virus.⁹ This drift has also been cited as the most likely basis for the difference between the North American excess mortality experience and that elsewhere.⁶ The first neuraminidase variant was universally dominant in the first season and the second variant was universally dominant in the second season. The basis for difference cannot lie in the neuraminidase gene. Furthermore the elderly in North America were equally protected in both the first and second pandemic seasons. There must have been 2 variants of the emergent A(H3N2) virus circulating in the first season. However, since they did not differ in either the hemagglutinin or neuraminidase genes, they must have differed in the sequence of one or more internal genes. This difference made one variant virulent and the other much less so. The first variant circulated in North America, accumulated the drifted neuraminidase gene and emerged as universally dominant in 1969–1970 and thereafter.⁷ The second variant circulated elsewhere. This hypothesis suggests that the emergence of the last pandemic virus, A(H3N2), may have been similar to the evolution of the A(H5N1) viruses now unfolding in southeast Asia,¹⁰ wherein a progressively more virulent form of the virus has emerged from multiple reassortment events within the avian reservoir with multiple trial excursions into humans. Although A(H5N1) is not the only candidate for the next human pandemic virus, it is widely regarded as having the greatest and most lethal potential.

The results discussed here have implications for pandemic preparedness. Most of the emerging genotypes of A(H5N1) are resistant to adamantane derivatives, the commonly available antiviral drugs amantadine and rimantadine.¹¹ It is of more concern that initial attempts at development of an effective vaccine were not successful¹² and the generation of rapidly growing seed strains, essential to the conventional process for the manufacture of inactivated virus vaccine, has been problematic.¹³ Similar issues are likely to beset vaccine development for any of the other viruses now being followed within the avian reservoir. Except for small populations of individuals with a history of close contact with poultry, it is unlikely that any humans will have an immunologic history with any of these viruses. Therefore, unlike A(H3N2), no age group will be spared, and all persons are likely to require a full dose (or possibly 2 doses) of conventional vaccine to achieve a protective state. Except for Canada, the only country to have attained a full dose per capita state of utilization (>333 doses per 1000 population), no nation currently has a level of vaccine use that would allow a seamless transition to universal pandemic vaccination.¹⁴ Furthermore, since the influenza vaccine is produced in only 12 countries worldwide, political vulnerabilities may further inhibit most countries from acquiring sufficient pandemic virus vaccine to protect a substantial portion of their populations. Vaccine and antiviral drug shortages are also likely.

The implications of the body of work summarized here (influenza is the principal cause of the winter excess of mortality, probably everywhere) is that the global mortality impact of influenza will be highly coordinated, especially given the rise in the volume and frequency of air travel since the last pandemic. While completely inadequate in many ways, the current best guess as to relative mortality impact is provided by the proposed global model that uses mean midwinter temperature in the capital city as the determinant of the influenza mortality impact for a country.² This model suggests that nations located either very near or well away from the equator will experience significantly lower excess mortality than those located such that mean midwinter temperatures are in the range of 4–10°C.

What should be done to best accommodate the virtually certain shortages in control agents and the likely disparate geographical effects? Nearly every country currently uses a control strategy that focuses on the delivery of influenza vaccine to a defined high risk population, the largest segment of which is the group of persons of an above-a-threshold age.¹⁵ The implications of the current research (that increasing the level of application of this control strategy has not led to a demonstrable reduction in the mortality effect of influenza in any of the 4 widely separated countries studied thus far) are profound. Research findings by Fedson¹⁴ suggested that all countries must increase their interpandemic usage of vaccine to at least 333 doses per 1000 population, and every country must complete negotiations with vaccine producers located in the 12 vaccine-producing nations to ensure vaccine availability in the event of a pandemic.

Fedson also suggested that, in the event of a pandemic, "health officials in many countries will want to vaccinate large segments, if not most, of their populations."¹⁵ The drive toward

increased interpandemic usage to a level at which a change from a trivalent vaccine to a monovalent vaccine might provide sufficient vaccine for universal coverage is laudable and reasonable. However, most countries will not have a domestic capability for the production of the influenza vaccine. Therefore it is highly likely that most countries will have to face the question of the most appropriate pandemic strategy given a limited availability of vaccine and antiviral drug supplies.

As noted above, in 1969–1970 in France, the first year of appreciable excess mortality after the emergence of the A(H3N2) virus, the relative increase in excess mortality was in the age group 45–64 years was almost 10-fold greater than the increase in those older than 75 years of age. In the United States, in both of the pandemics of 1918 and 1968–1969, individuals over the age of 75 experienced excess mortality that was the same absolute level or less than that of the precedent season.^{5,16} In the United States in 1957–1958, the relative increase in excess mortality for individuals over the age of 75 was again about 60% over the average excess mortality for this age grouping, whereas the relative increase for middle-aged groups (45–64 years of age) was ~2.5-fold their average (data not shown). Thus, the relative increase in mortality risk for middle-aged individuals as compared with the very elderly can reasonably be estimated at 4- to 10-fold for the case in which the pandemic virus is not one with which humans have had previous immunologic experience (eg, H5N1). The new work summarized here suggests that, even if scarce vaccine resources were deployed on very elderly age groups, it is unlikely that mortality would be reduced; it would be easiest simply to expand vaccine coverage beyond the groups for which it is currently recommended. However, data from the Tecumseh experience,¹⁷ modeling,¹⁸ epidemiology¹⁹ and recent clinical experience²⁰ suggest that extension of vaccine resource to schoolchildren would most efficiently limit the extent and slow the pace of a pandemic. Still, it would require great intellectual courage for a national vaccine program administrator to initiate a diversion of vaccine resource to schoolchildren and away from recommendation-denoted, high risk groups in the event of a pandemic, without direct clinical evidence of increased effectiveness. Therefore, it is important that a demonstration extension of vaccine coverage to schoolchildren be made in the interpandemic setting in a country or large region in which adherence to recommended guidelines is already largely in place. The exact basis for the lack of a reduction in elderly excess mortality remains unknown. However, based on the Japanese experience with schoolchildren,¹⁹ an appreciable likelihood exists that extending vaccine resource to schoolchildren may provide protection for the very elderly. While this may already be happening in Canada, with the drive in that country toward universal vaccination, modeling studies suggest that a programmatic focus on schoolchildren is required to achieve the desired coverage level ($\geq 70\%$). It was suggested recently that community-based studies be performed in the United States.²¹ However, such an experiment would have the greatest likelihood for demonstration of effect in countries in which the a priori expected impact rate is high. Among developed countries, these are as follows: Japan, New Zealand, and, in Europe, Portugal, the United

Kingdom, Italy, Spain and Greece. It is essential that a mechanism for international cooperation be established that could facilitate the acquisition of this important information.

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