

Multinational Impact of the 1968 Hong Kong Influenza Pandemic: Evidence for a Smoldering Pandemic

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Background. The first pandemic season of A/H3N2 influenza virus (1968/1969) resulted in significant mortality in the United States, but it was the second pandemic season of A/H3N2 influenza virus (1969/1970) that caused the majority of deaths in England. We further explored the global pattern of mortality caused by the pandemic during this period.

Methods. We estimated the influenza-related excess mortality in 6 countries (United States, Canada, England and Wales, France, Japan, and Australia) using national vital statistics by age for 1967–1978. Geographical and temporal pandemic patterns in mortality were compared with the genetic drift of the influenza viruses by analyzing hemagglutinin and neuraminidase sequences from GenBank.

Results. In North America, the majority of influenza-related deaths in 1968/1969 and 1969/1970 occurred during the first pandemic season (United States, 70%; Canada, 54%). Conversely, in Europe and Asia, the pattern was reversed: 70% of deaths occurred during the second pandemic season. The second pandemic season coincided with a drift in the neuraminidase antigen.

Conclusion. We found a consistent pattern of mortality being delayed until the second pandemic season of A/H3N2 circulation in Europe and Asia. We hypothesize that this phenomenon may be explained by higher pre-existing neuraminidase immunity (from the A/H2N2 era) in Europe and Asia than in North America, combined with a subsequent drift in the neuraminidase antigen during 1969/1970.

Annual influenza epidemics are sustained in the human population through gradual mutations in hemagglutinin and neuraminidase, the surface antigens of the virus. The genetic makeup of the influenza virus allows frequent minor drifts every 2–5 years in response to selection pressure to evade human immunity [1]. Rarely, reassortment between human and nonhuman viruses results in larger shifts, in which a new virus subtype emerges and replaces the previously circulating one [2]. A new pandemic virus rapidly invades the human population with partial or no immunity and may cause severe illness

worldwide [3, 4]. Although the impact of influenza is not always higher during pandemics than during inter-pandemic periods, a shift in the age distribution of mortality toward younger age groups distinguishes pandemic from epidemic impact [5, 6].

The influenza virus responsible for the last pandemic, A/Hong Kong/68 (A/H3N2), was first isolated in Hong Kong in July 1968 [7]. The new A/H3N2 virus exhibited a shift in hemagglutinin but not in neuraminidase; it replaced A/H2N2 viruses that had been circulating in all countries since 1957. Despite rapid and extensive spread by international air travel [7, 8], the impact of the new virus was not the same in all geographical regions. A marked increase in mortality occurred in the United States during the first pandemic season (1968/1969), especially in persons <65 years old, but was not seen elsewhere [7]. Conversely, in England, the second pandemic season (1969/1970) of A/H3N2 virus proved to be more severe than the first [9, 10].

The reasons for the delayed severe impact in England are still not understood [4, 11]. Such a delay is coun-

Received 19 October 2004; accepted 31 January 2005; electronically published 15 June 2005.

Financial support: National Institutes of Health.

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The Journal of Infectious Diseases 2005;192:233–48

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0022-1899/2005/19202-0007

terintuitive, since a novel virus introduced in a susceptible population should demonstrate decreasing impact over time as immunity increases [9, 12]. Here, we analyze monthly mortality data on 6 countries (on 4 continents) and review published morbidity and virological studies to extend the current understanding of the Hong Kong A/H3N2 pandemic. To explain the epidemiological patterns, we investigate the genetic sequences of influenza surface antigens. Finally, we discuss the implications of these patterns for pandemic preparedness.

METHODS

A detailed description of the data sources and analytic approach is given in the Appendix.

Data Sources

Mortality and population data. Monthly age-specific data on pneumonia and influenza (P&I) and all-cause mortality were compiled from vital statistics on the United States, Canada, England and Wales (referred to as “England” for simplicity), France, Japan, and Australia for 1967–1979, which includes the 2 pandemic seasons, 1968/1969 and 1969/1970. No details on age were available for Japan. Before analysis, we calculated the monthly incidence per 100,000 persons for both mortality outcomes.

Review of the literature for virological surveillance and morbidity data. We compiled literature reports, mostly from World Health Organization sources, to compare the date of the first isolation of the pandemic strain and the timing of the 2 pandemic seasons in each country [13–19] (figure 1). To compare influenza morbidity patterns, we analyzed published weekly time series of influenza virological isolates and summary estimates of morbidity. We restricted the analysis to follow-up studies that covered both pandemic seasons [9, 17, 20–23]. We also searched the available published literature for general-population influenza seroepidemiological surveys that reported the prevalence of new influenza infections [9, 20–24].

Influenza genetic sequences. Temporal and/or geographical differences in the antigens of circulating viruses may explain intercountry differences in patterns of mortality. For viruses collected during 1966–1975, we analyzed all hemagglutinin and neuraminidase genetic sequences published in GenBank (<http://www.ncbi.nlm.nih.gov/GenBank/>) and in the Influenza Sequence Database (<http://www.flu.lanl.gov>) [25]. We chose this period in order to include strains that circulated just before the pandemic until the first major postpandemic antigenic change (A/Victoria/75) [11]. We analyzed 38 sequences for the hemagglutinin H3 gene and 53 sequences for the neuraminidase N2 gene.

Analytic Approach

To evaluate the impact of the 2 pandemic seasons in the 6 countries, we calculated P&I and all-cause seasonal excess mortality and adjusted for age and nondemographic factors.

Estimating P&I and all-cause seasonal excess mortality. P&I and all-cause seasonal excess mortality were computed for 2 age categories (all ages and <65 years old) as the increase in mortality above a seasonal baseline, during epidemic months, for both the 1968/1969 and the 1969/1970 pandemic seasons. We used a Serfling-type regression model [26] and identified influenza epidemic months from the time series of deaths specifically attributed to influenza.

We adjusted excess mortality using the mid-1969 population of England as the reference population, to account for differences in age structure between countries. To compensate for nondemographic differences (e.g., access to health care and coding for underlying cause of death [27, 28]), we calculated the percentage increase in mortality as the excess mortality divided by the baseline mortality during winter (expected mortality) for both P&I and all-cause seasonal excess mortality. This measure was introduced by Serfling, for comparison of influenza mortality in different age groups [29].

Exposure to influenza during the last A/H2N2 epidemic season (1967/1968) may have reduced the impact of the A/H3N2 pandemic by granting protection against neuraminidase [3, 11]. We also analyzed the age-standardized excess mortality and corresponding percentage increase for this epidemic season.

Proportion of deaths, illnesses, and infections during each pandemic season (1968/1969 and 1969/1970). To estimate the relative mortality during each pandemic season, we summed the excess mortality for 1968/1969 and 1969/1970 and computed the proportion occurring during each pandemic season separately for each country. We compared the resulting estimates with those of previous studies of mortality [5, 9, 24, 30–35]. Similarly, we computed the proportion of clinical illnesses and infections identified by serologic tests during each pandemic season from the available published literature [9, 17, 20–24].

RESULTS

Timing of the First 2 A/H3N2 Pandemic Seasons

In most countries, the pandemic strain was isolated shortly after its appearance in Hong Kong in July 1968 (figure 1), with several months of sporadic activity before the epidemic took off. There was no documented cocirculation of A/H3N2 and A/H2N2 viruses in the same geographical area; the last reported isolation of A/H2N2 was in August 1968 in Australia [14, 36].

Mortality

Epidemic pattern and impact of the first 2 A/H3N2 pandemic seasons (all ages). The epidemic patterns of the 2 pandemic seasons were different in the 6 countries studied (figure 2). The P&I mortality time series reveals a large epidemic in the United States in 1968/1969, followed by a milder one in 1969/1970, late in the winter season. In Canada, the 2 epidemic patterns were similar in amplitude and timing. In the other 4

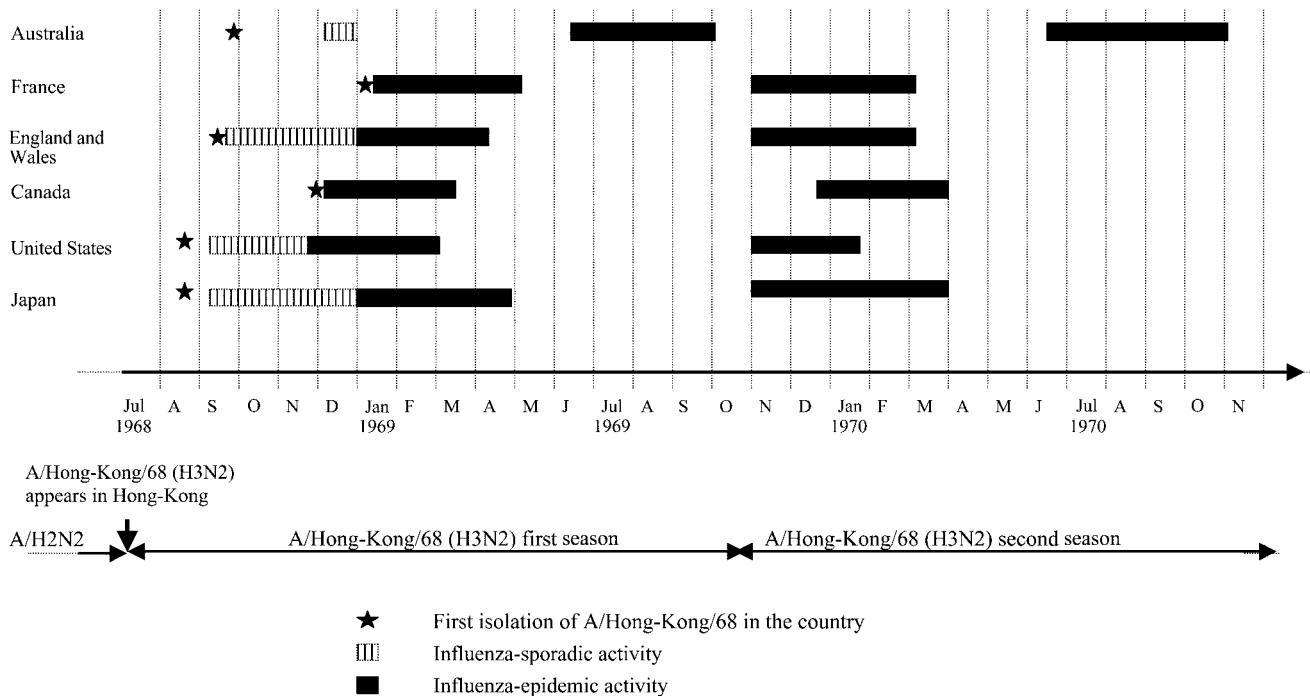


Figure 1. Timing of the first 2 pandemic seasons of A/H3N2 influenza virus in 6 countries. Shown are isolation, sporadic, and epidemic activities, as defined by virus surveillance reports [13–19].

countries, entirely different patterns emerged. The first epidemic was mild, followed by a much more intense epidemic the next season. Similar patterns were observed from all-cause mortality time series (data not shown).

Of the sum of P&I excess deaths that occurred during 1968/1969 and 1969/1970, in the United States, 70% occurred during the first pandemic season; in Canada, 54%; in Japan, 32%; in England, 23%; in Australia, 22%; and, in France, 15% (table 1). The same trend was obtained for all-cause excess mortality, which supports a 1-year delay in the major impact in England, France, Japan, and Australia.

Age standardization and computation of the percentage increase reduced but did not eliminate the intercountry differences in the sum of excess deaths that occurred during 1968/1969 and 1969/1970, for both P&I and all causes (table 1). For instance, P&I excess mortality was 2–3-fold higher in England and France than elsewhere. All-cause excess mortality was 2–5-fold lower in North America than elsewhere, and the corresponding percentage increase remained lower, suggesting that the total pandemic mortality was substantially lower in North America than in other countries.

Last epidemic season of the A/H2N2 era (1967/1968). Similar intercountry differences were found for the last A/H2N2 epidemic season (table 1). P&I excess mortality was 2–3-fold higher in England and France than elsewhere. All-cause excess mortality was lower in North America than in other countries. The percentage increase in P&I and all-cause mortality was

consistently lower in North America than elsewhere, supporting a lower impact for the last A/H2N2 epidemic season in this region. Interestingly, in all countries, all-cause excess mortality during the last A/H2N2 epidemic season was greater than or equal to that during the major A/H3N2 pandemic season.

Pandemic “age shift” and impact in persons <65 years old (1968/1969 and 1969/1970). For all countries studied, the proportion of excess P&I mortality in persons <65 years old increased substantially (by 2.2–4.6-fold) during the first A/H3N2 pandemic season, compared with that during the last A/H2N2 epidemic season (table 1). This signature age shift of a novel virus subtype, taken together with virus surveillance data that indicated exclusive A/H3N2 circulation, clearly supports pandemic virus activity in all countries throughout the first A/H3N2 season.

Intercountry differences in the relative impact of each pandemic season reported for all ages also existed for persons <65 years old (table 2). In this age group, the majority of P&I and all-cause mortality occurred during the first pandemic season in North America but during the second pandemic season in England, France, and Australia. Regarding the sum of deaths during the 2 pandemic seasons, all of our mortality measures showed a lower impact in North America in persons <65 years old than in Europe and Asia.

Geographically distinct pandemic patterns. For the Hong Kong A/H3N2 pandemic, 2 geographically distinct mortality patterns emerged. The North American pattern (United States

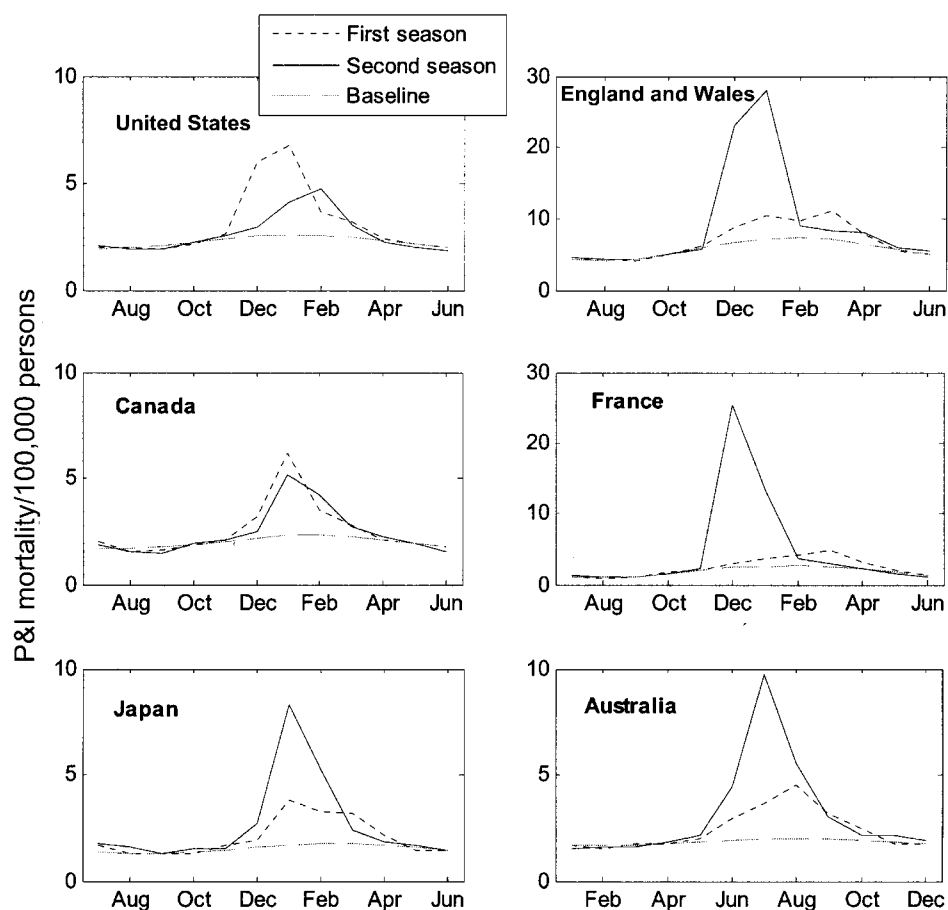


Figure 2. Influenza epidemic mortality curves for the first 2 pandemic seasons of A/H3N2 virus in 6 countries. Pneumonia and influenza (P&I) monthly mortality time series/100,000 persons are represented for the United States, England and Wales, Canada, France, Japan, and Australia. Note the geographical differences in the relative mortality of each pandemic season. First pandemic season, 1968/1969; second pandemic season, 1969/1970. In Australia, the first pandemic season was in 1969, and the second pandemic season was in 1970 (figure 1).

and Canada) was characterized by a first pandemic season that was more severe than the second, although, the impact of each pandemic season was more balanced in Canada than in the United States. There were minimal geographical variations in local pandemic patterns across the United States (Appendix). By contrast, local pandemic patterns were heterogeneous in Canada, which explains the more-balanced impact in the national analysis.

The “smoldering” pattern in Europe and Asia (England, France, Japan, and Australia) was characterized by a second pandemic season 2–5 times more severe than the first. The last A/H2N2 epidemic season was less severe in North America than elsewhere.

Review of the Literature for Proportion of Deaths, Illnesses, and Infections during Each Pandemic Season (1968/1969 and 1969/1970)

On average, across all mortality studies, including the present one, in the United States, an estimated 70% of influenza-related

deaths occurred during the first pandemic season; in Canada, 57%; in England, 30%; and, in Australia, 31% (table 3). These studies gave fairly consistent estimates, although they did not use the same approach for estimating excess mortality. No study other than ours included France and Japan.

Morbidity time-series analysis revealed a pattern similar to the mortality time series in the United States, England, and Australia, in terms of amplitude and timing (figure 3A–3C). In these 3 countries, the relative morbidity and mortality of each pandemic season were very close (table 3), ruling out potential differences in case fatalities. In all countries, high morbidity was associated with high mortality.

General-population seroepidemiological surveys reported that the majority of influenza infections occurred during the first pandemic season in the United States and Canada, closely matching the pattern of deaths and clinical illnesses (table 3). Conversely, in England, patterns of serological infections were discordant with mortality and morbidity patterns. Infections during the first pandemic season were nearly as frequent as were those

Table 1. Influenza mortality impact of the last A/H2N2 epidemic season and the first 2 A/H3N2 pandemic seasons.

Season, parameter	United States (205 million ^a)		Canada (21 million ^a)		England and Wales (48 million ^a)		France (50 million ^a)		Japan (103 million ^a)		Australia (13 million ^a)	
	P&I	All cause	P&I	All cause	P&I	All cause	P&I	All cause	P&I	All cause	P&I	All cause
Last A/H2N2 epidemic season (1967/1968)												
Excess mortality ^b	7.3	25.5	7.1	11.9	29.6	85.4	16.6	58.9	6.6	45.4	9.0	64.8
Percentage increase in mortality ^c	41	7.5	38	6.3	57	19.5	67	17.0	50	18.3	56	15.2
Percentage of deaths in persons <65 years old ^d	17		5		9		11		NA		13	
First A/H3N2 pandemic season (1968/1969)												
Excess mortality ^b	11.0	27.2	7.8	11.9	11.9	43.0	6.2	21.8	5.4	27.0	4.0	23.5
Percentage increase in mortality ^c	51	8.2	42	5.7	30	10.6	41	5.2	44	13.3	33	5.6
Percentage of deaths in persons <65 years old ^d	38		23		20		18		NA		33	
Second A/H3N2 pandemic season (1969/1970)												
Excess mortality ^b	4.7	11.0	6.6	11.0	39.3	77.0	35.3	71.5	11.3	49.1	14.1	63.8
Percentage increase in mortality ^c	33	3.3	37	5.3	63	19.7	84	20.9	65	20.3	61	15.6
Percentage of deaths in persons <65 years old ^d	37		20		25		25		NA		28	
Sum of the 2 pandemic seasons (1968/1969 and 1969/1970)												
Excess mortality ^b	15.7	38.1	14.4	22.9	51.2	120.0	41.5	93.3	16.7	76.1	18.1	87.3
Percentage increase in mortality ^c	44	5.8	40	5.5	52	15.4	74	13.8	57	16.9	51	10.8
Relative impact of each pandemic season ^e	70:30	71:29	54:46	52:48	23:77	36:64	15:85	23:77	32:68	36:64	22:78	27:73

NOTE. Pneumonia and influenza (P&I) and all-cause excess mortality are age adjusted and given per 100,000 persons. In Australia, the last A/H2N2 epidemic season was in 1968, and the first and second pandemic seasons of A/H3N2 were in 1969 and 1970, respectively (see figure 1 for exact timing). NA, not applicable.

^a Estimate of the population in mid-1969.

^b Excess mortality was age adjusted by use of the population of England and Wales in mid-1969 as the reference population. No age adjustment was available for Japan. The age-adjusted excess mortality was higher than the crude excess mortality by 20%–30% in the United States, Canada, and Australia and by 2%–5% in France. The demographics of the Japanese population in 1969 were similar to those of the Canadian population at the same time; therefore, age adjustment would increase crude excess mortality by ~30% (reinforcing our conclusions).

^c Excess mortality expressed as percentage increase over the winter baseline (ratio of excess deaths during epidemic months divided by the baseline deaths from the seasonal model).

^d Proportion of P&I excess mortality in persons <65 years old among total P&I excess mortality (age adjusted to the population of England and Wales in mid-1969).

^e Relative mortality impact is presented as deaths during the first A/H3N2 pandemic season:deaths during the second pandemic season (%) (e.g., in the United States, 70% of P&I excess deaths occurred during the first pandemic season, and 30% occurred during the second pandemic season).

Table 2. Influenza mortality of the first 2 A/H3N2 pandemic seasons in persons <65 years old.

Season, parameter	United States (183.7 million ^a)		Canada (19.2 million ^a)		England and Wales (42.4 million ^a)		France (43.5 million ^a)		Australia (12.0 million ^a)	
	P&I	All cause	P&I	All cause	P&I	All cause	P&I	All cause	P&I	All cause
First A/H3N2 pandemic season (1968/1969)										
Excess mortality	4.2	10.4	2.0	4.2	2.8	9.2	1.4	4.6	1.7	4.4
Percentage increase in mortality ^b	54	9.1	47	4.3	37	8.0	46	3.2	43	4.5
Second A/H3N2 pandemic season (1969/1970)										
Excess mortality	1.7	4.2	1.4	3.1	11.3	20.4	9.6	21.8	4.9	13.9
Percentage increase in mortality ^b	35	4.0	39	2.9	74	16.8	89	19.0	67	13.3
Sum of the 2 pandemic seasons (1968/1969 and 1969/1970)										
Excess mortality	5.9	14.6	3.4	7.3	14.1	29.6	11.0	26.4	6.6	18.3
Percentage increase in mortality ^b	47	6.6	43	3.6	63	13.0	82	11.9	59	9.1
Relative impact of each pandemic season ^c	71:29	71:29	57:43	58:42	20:80	31:69	13:87	17:83	26:74	24:76

NOTE. Pneumonia and influenza (P&I) and all-cause excess mortality are given per 100,000 persons. In Australia, the first and second pandemic seasons of A/H3N2 virus were in 1969 and 1970, respectively (see figure 1 for exact timing).

^a Estimate of the population <65 years old in mid-1969.

^b Excess mortality expressed as percentage increase over the winter baseline (ratio of excess deaths during epidemic months divided by the baseline deaths from the seasonal model).

^c Relative mortality impact is presented as deaths during the first A/H3N2 pandemic season:deaths during the second pandemic season (%) (e.g., in the United States, in persons <65 years old, 71% of P&I deaths occurred during the first pandemic season, and 29% occurred during the second pandemic season).

Table 3. Relative impact of the first 2 influenza A/H3N2 pandemic seasons on mortality, morbidity, and serological infections in the United States, Canada, England, and Australia.

Parameter	United States		Canada		England		Australia	
	Source	Relative impact	Source	Relative impact	Source	Relative impact	Source	Relative impact
Mortality ^a	Average from this study and [5, 30–34]	70:30	Average from this study and [24]	57:43	Average from this study and [9, 31, 35]	30:70	This study	31:69
Morbidity	[22]	74:26		NA	Average from [9, 35]	32:68	Average from 3 studies in [51]	31:69
Infections ^b	[20]	75:25	[24]	55:45	Average from 2 studies in [9]	47:53		NA

NOTE. The relative impact is presented as mortality during the first pandemic season:mortality during the second pandemic season (%). Estimates are based on published follow-up studies that cover the 2 pandemic seasons. No comparable data were available for France and Japan. NA, not applicable.

^a Based on all-cause excess mortality, except for [24] (influenza excess mortality) and [32] (pneumonia and influenza excess mortality).

^b From seroepidemiological surveys of the general population; infection is defined by a ≥ 4 -fold increase in antibody titers to hemagglutinin H3 during the influenza season (serological conversion).

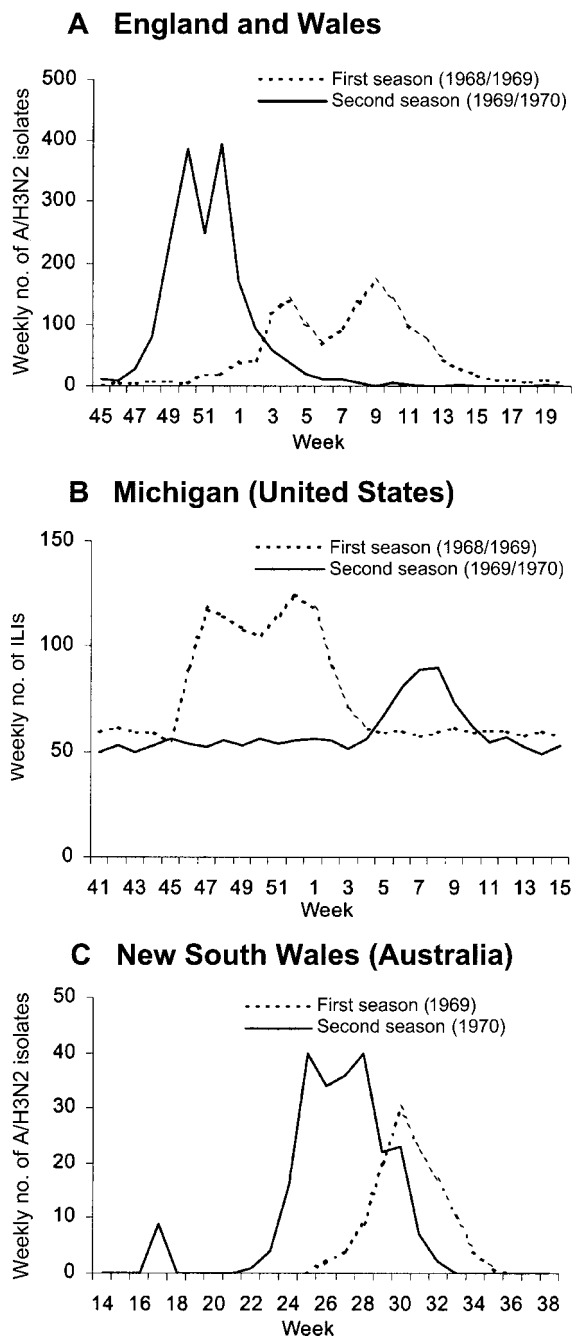


Figure 3. Influenza epidemic morbidity curves for the first 2 pandemic seasons of A/H3N2 virus. A, Weekly no. of influenza A isolates in England [9]. B, Weekly no. of influenza-like illnesses (ILIs) in Michigan [20–23]. C, Weekly no. of influenza A isolates in New South Wales, Australia [17].

during the second pandemic season, whereas the large majority of deaths and clinical illnesses occurred during the second pandemic season. These discordances imply that asymptomatic (sub-clinical) infections were frequent during the first pandemic season in England. Similarly, in the other countries in Europe and Asia that were studied, high rates of asymptomatic infections during the first pandemic season were reported [15, 17, 37].

From the combined analysis of mortality, morbidity, and serological studies, we concluded that asymptomatic infections were frequent during the first pandemic season in Europe and Asia and were less frequent in North America.

Phylogenetic Studies

We searched for temporal and/or geographical differences in the genes of influenza surface antigens. The hemagglutinin H3 gene sequences available from the 2 pandemic seasons clustered in a single group in the hemagglutinin tree ($n = 13$ for 1968/1969–1969/1970) (figure 4A). A drift in this gene appeared in 1971/1972, which was later than our period of interest. Taken together with the single antigenic cluster defined by Smith et al. for the hemagglutinin between July 1968 and late 1970 [1], the single genetic cluster found here suggests that there was no significant evolution in this antigen during the 2 pandemic seasons.

Phylogenetic analysis of the neuraminidase N2 gene highlighted similarities in this gene between late A/H2N2 and early A/H3N2 viruses (figure 4B). The neuraminidase gene of A/H2N2 viruses from 1967/1968 formed 2 distinct clusters (clusters I and II in figure 4B). The neuraminidase gene of A/H3N2 viruses from 1968/1969 formed a single cluster, genetically close to the A/H2N2 cluster I. Although few sequences were available for A/H3N2 viruses from 1969/1970, they all formed a distinct cluster comprising strains from England and Canada, genetically close to the A/H2N2 cluster II. For A/H3N2 viruses, the 1968/1969 genetic cluster differed from the 1969/1970 genetic cluster by 29 nt. The clusters were supported by bootstrap values >90%. The neuraminidase genes of more-recent A/H3N2 viruses were derived from the 1969/1970 genetic cluster. In addition, we predicted and compared the protein sequence of neuraminidase. Similar to the nucleotide analysis, the protein analysis revealed 2 distinct clusters for 1968/1969 and 1969/1970. The clusters differed by 11 amino acid changes, 3 of them located in characterized antigenic sites [38]. These findings are in agreement with those of a recent study showing that neuraminidase had an increased rate of change immediately after the emergence of A/H3N2 viruses, compared with that during the more-recent inter-pandemic period [38]. These results highlight temporal differences in the neuraminidases of influenza viruses circulating during the 2 pandemic seasons, whereas the hemagglutinins remained unchanged.

DISCUSSION

The present study is based on data from 6 countries and demonstrates distinct differences in mortality patterns for the Hong Kong A/H3N2 pandemic. The United States and Canada displayed the expected pattern—high mortality during the first pandemic season (1968/1969), when the emerging virus first circulated, followed by a relatively mild second pandemic season (1969/1970). This pattern was observed only in North

America. For the 4 other countries in Europe and Asia that were studied, we identified an opposite mortality pattern: more than two-thirds of all influenza-related deaths that occurred during 1968/1969–1969/1970 occurred during the second pandemic season. Although this smoldering pattern had previously been reported for England [9], the present study is the first multinational study to carefully compare and quantify the mortality and temporal pattern of the Hong Kong A/H3N2 pandemic. Published mortality time series for at least 8 additional countries in Europe and elsewhere support the idea that the 1-year delay in mortality might be the most common experience in continents other than North America [7, 31, 39–41].

We next entertained a possible hypothesis to explain the unexpected smoldering pattern in Europe and Asia (figure 5) that combines (1) the effect of geographical differences in preexisting immunity to neuraminidase at the time of emergence of A/H3N2 (remaining from the A/H2N2 era) and (2) the effect of genetic drift in the neuraminidase antigen during 1969/1970. Preexisting immunity to the neuraminidase N2 gene may have contributed to the differential impact of the first pandemic season in the 2 regions. It is believed that exposure to A/H2N2 viruses during 1967/1968 attenuated the impact of the 1968 pandemic [3, 11]. A study showed that individuals infected by A/H2N2 during 1967/1968 were protected against influenza infection during the first A/H3N2 pandemic season, and infections in persons with prior antineuraminidase antibodies were more frequently asymptomatic, compared with those in persons without prior antineuraminidase antibodies [20].

The smoldering pattern in Europe and Asia is consistent with high preexisting immunity to neuraminidase. The greater mortality of the last A/H2N2 epidemic season in this region suggests greater exposure to late A/H2N2 viruses (figure 5). Hence, immunity to neuraminidase may have been greater in Europe and Asia during the fall of 1968, when the A/H3N2 virus started to circulate. Furthermore, the neuraminidase of late A/H2N2 viruses circulating in Europe and Asia may have been closer to that of early A/H3N2 viruses [14, 16, 42].

A drift in the neuraminidase antigen found in our phylogenetic analysis coincided with the severe second A/H3N2 pandemic season in Europe and Asia (figure 5). This analysis is in agreement with antigenic studies conducted by the World Influenza Center (London, UK) in Europe and Japan. In 1968/1969, influenza viruses were antigenically similar to the first A/H3N2 virus identified in Hong Kong, in both hemagglutinin and neuraminidase [42, 43]. In 1969/1970, the neuraminidase antigen had changed, but the hemagglutinin antigen had not [41–43]. Accordingly, Lindstrom et al. recently found that 2 distinct neuraminidase lineages circulated during 1968/1969 and 1969/1970 and hypothesized that such genetic diversity could be due to multiple reassortments with A/H2N2 viruses [38].

We were unfortunately unable to study geographical hetero-

geneity in the neuraminidase gene, since very few North American viral sequences from 1968/1969 to 1969/1970 were available in the public domain. Rapid fluxes in international populations [8] and the available sequences would suggest that the same viruses circulated in North America and in Europe and Asia.

Assuming that the same viruses circulated in all continents studied, differences in prior immunity followed by a drift in the neuraminidase antigen could explain the intercountry differences in mortality patterns. What sets North America apart epidemiologically is the severity of the first pandemic season, which included frequent influenza illness and death (figure 5). Hence, at the end of the first pandemic season, a substantial proportion of the North American population had antibodies to the novel hemagglutinin H3 gene. Since the hemagglutinin did not change between the 2 pandemic seasons, these antibodies would have protected this population during the second pandemic season.

One of the other factors we considered was immunity to the hemagglutinin H3 gene in the very elderly, which remained from childhood exposure to H3-like viruses before 1892 [10, 32, 44–46]. However, such immunity would not account for the intercountry differences in mortality found in persons <65 years old. Furthermore, influenza vaccination coverage was too limited during this time to explain these differences [9]. Finally, environmental differences and weather could have played a role—but this explanation is unlikely, given the geographical heterogeneity of the countries studied [47]. The A/H3N2 pandemic strain appeared early during the winter season in all countries. Certainly, weather did not hamper the full potential for causing widespread epidemics and mortality in every country during the 1968/1969 pandemic season.

Despite the geographical differences in the timing of the major mortality, the A/H3N2 pandemic was relatively mild in all countries, compared with surrounding severe epidemics [48], including the last A/H2N2 epidemic season. The mildness of the 1968 pandemic is perhaps not entirely unexpected, considering preexisting immunity to the neuraminidase antigen in all age groups [3, 11] and to the hemagglutinin antigen in the elderly [10, 32, 44–46].

It has been reported that, for the 1950s and 1960s, both P&I excess mortality and all-cause crude excess mortality (unadjusted) were systematically 2–3-fold higher in Europe than in North America [27, 28, 31]. Adjusting for differences in age structure and mortality outside influenza periods (data not shown) reduced but did not eliminate these differences. Therefore, we studied the percentage increase in mortality above the winter baseline, which further reduced intercountry differences [29]. A more thorough investigation of the intercountry differences in absolute mortality was beyond the scope of the present study; factors such as population density, demographics, climate, country size, and health care systems could affect influenza transmission and disease out-

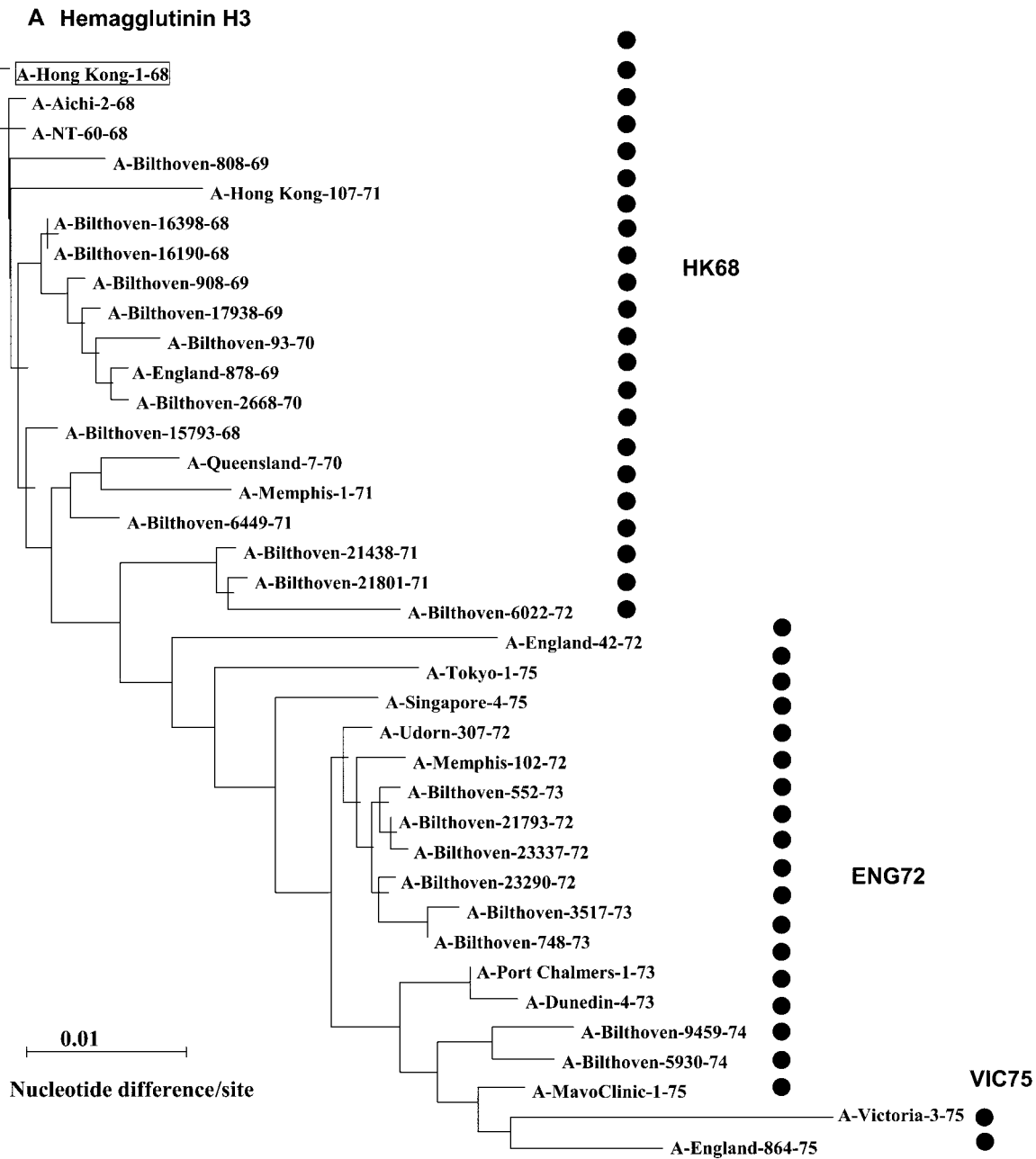


Figure 4. Phylogenetic relationships of the hemagglutinin H3 gene (1968–75) (*A*) and the neuraminidase N2 gene (1967–72) (*B*) of influenza virus. For the hemagglutinin gene, black dots indicate the antigenic clusters (*A*), as defined elsewhere [1]. For the neuraminidase gene, black dots denote the genetic clusters corresponding to the 1968/1969 and 1969/1970 sequences (*B*); clusters were supported by bootstrap values >90%. Braces indicate earlier or later clusters. Italic font indicates neuraminidase genes from A/H2N2 viruses; boldface font indicates neuraminidase genes from A/H3N2 viruses. Hemagglutinin and neuraminidase sequences (nt 49–960 and 1–1310, respectively) were aligned by use of the Clustal W program of MacVector (version 7.2.2). Phylogenetic analysis was performed by use of the neighbor-joining method, with Kimura's 2-parameter distance (1000 bootstrap replicates). A/Hong-Kong/1/68 was used as the root for the hemagglutinin tree, and A/Singapore/1/57 was used as the root for the neuraminidase tree. The first A/H3N2 virus isolated was A/Hong Kong/1/68.

come and, in turn, mortality [27, 28, 31, 49]. In the present study, the smoldering pattern relies on the unbiased comparison of the relative impact of each pandemic season.

The present study was based on analysis of both P&I (as an underlying cause of death) and all-cause mortality. Analysis of P&I

data could potentially have been biased as a result of intercountry differences in coding of the underlying cause of death and the transition to a new system of classification of deaths around 1968 (Appendix). However, because our analysis of all-cause mortality data was not affected by such possible bias and be-

B Neuraminidase N2

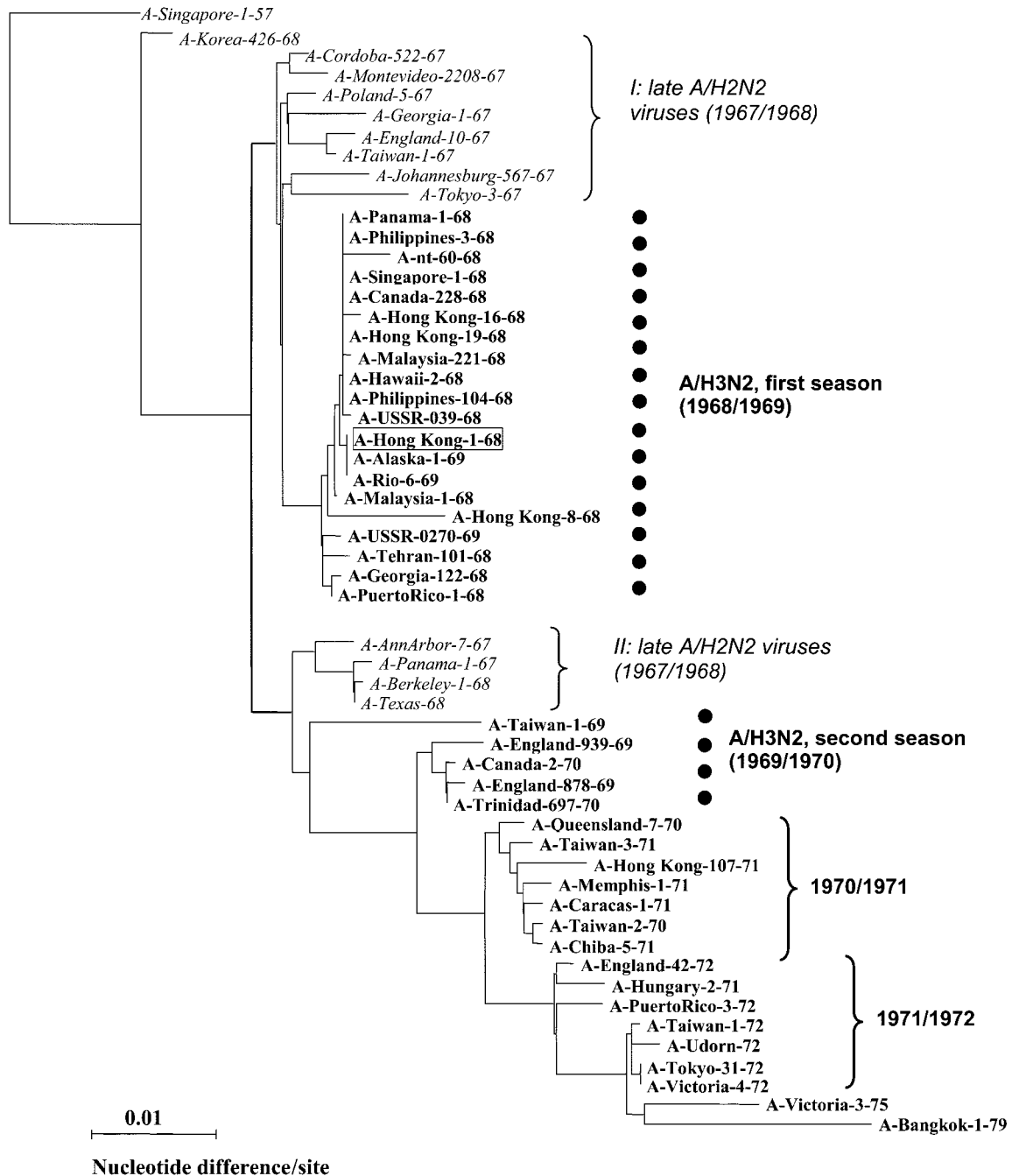


Figure 4. (Continued.)

cause it produced similar results in terms of temporal and geographical differences in patterns, nosological bias was not an issue in the present study.

Another limitation of the present study was the poor temporal and geographical resolution of influenza genetic sequences from this pandemic, both in terms of the overall number of sequences and the lack of systematic sampling (outliers were

preferentially sequenced [1]). This bias tends to preclude the use of phylogenetic studies to derive the epidemiological importance of each strain. However, in this work, analyses at the amino acid level and antigenic studies support the significance of the drift in the neuraminidase antigen [38, 41–43].

Why should we care about studying the geographical and temporal impact of pandemic influenza? The pattern in Europe

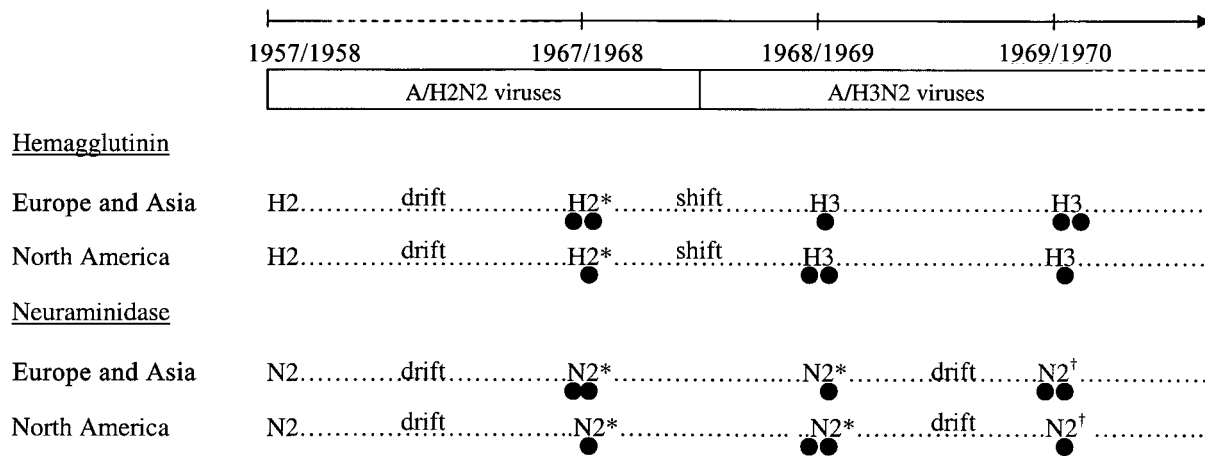


Figure 5. Hypotheses for explaining the differences in influenza pandemic patterns between Europe and Asia and North America. The genetic evolution of hemagglutinin and neuraminidase are indicated from the first pandemic season of A/H2N2 viruses (1957/1958) to the second pandemic season of A/H3N2 viruses (1969/1970). * and †, successive drifts; ●, virus circulation and impact in each region (●, low; ●●, high).

and Asia during the 1968/1969–1969/1970 period suggests a possible favorable opportunity for pandemic response should a future pandemic be like the one in 1968. The smoldering first pandemic season observed in 4 of the 6 countries suggests that a pandemic vaccine available 1 year after the emergence of the new subtype could have prevented the majority of deaths and illnesses associated with the emerging pandemic strain. The exact role that neuraminidase played in driving the mortality of the 1968 pandemic remains to be confirmed, but it seems that the 1968 pattern, unique in its conservation of the neuraminidase antigen, allowed ample time to produce and distribute a pandemic vaccine. In the meantime, vaccination targeted against neuraminidase could be complementary to treatment and prophylaxis by antiviral agents, which would probably be available in short supply in most countries during a pandemic situation [50]. Unfortunately, given our limited experience with pandemic influenza—only 3 pandemics occurred during the 20th century—our ability to predict the likelihood of a 1968-like pandemic in the future is quite limited.

MULTINATIONAL INFLUENZA SEASONAL MORTALITY STUDY (MISMS) GROUP

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Acknowledgments

We thank O. T. Bjørnstad, B. T. Grenfell, D. L. Smith, F. E. McKenzie, and J. Dushoff for fruitful discussions on this study.

APPENDIX

DATA

Mortality data. The monthly number of deaths due to pneumonia and influenza (P&I) and all causes were compiled from death certificates collected by national agencies for vital statistics in 6 countries for 1967–1979 (United States, National Center for Health Statistics; Australia, Australian Bureau for Statistics; France, Institut National de la Santé et de la Recherche Médicale, Service Commun 8; England and Wales, Office for National Statistics; Japan, Ministry of Health and Welfare; and Canada, Statistics Canada). This period was chosen in order to cover the first 2 A/H3N2 pandemic seasons (1968/1969 and 1969/1970) as well as the surrounding seasons, to provide a good fit to our mortality model. To select P&I deaths, we used the underlying cause of death from the *International Classification of Diseases* (ICD) (codes 490–493 and 480–483 from ICD-7 and codes 480–486 and 470–474 from ICD-8).

To compute mortality rates, population censuses and interim annual estimates for the study period were obtained from the national census agencies. In 1968, the population size was 205 million in the United States, 103 million in Japan, 50 million in France, 48 million in England and Wales, 21 million in Canada, and 13 million in Australia.

Morbidity data. In the United States, a weekly follow-up of influenza-like illnesses was conducted during the 2 pandemic seasons in Michigan, with parallel identification of periods of

influenza circulation [20, 21, 23]. In England and Australia, influenza A isolates were collected on a weekly basis during the 2 pandemic seasons by national surveillance networks [9, 17, 51]. In the latter countries, summary data on insurance claims and influenza surveillance by general practitioners were also available [9]. Serological studies in the adult population spanning both pandemic seasons were available for the United States, England, and Canada [9, 20–24].

We also searched the available published literature for general-population influenza seroepidemiological surveys that reported the prevalence of influenza infections by testing the rise in antihemagglutinin H3 antibodies (available for the United States, Canada, and England) [9, 20–24].

Influenza genetic sequences data. We searched and analyzed all hemagglutinin and neuraminidase genetic sequences published in the Influenza Sequence Database and GenBank for viruses collected during 1966–1975 [25]. We retrieved 50 sequences for the hemagglutinin H3 gene, including the precursor strain isolated in Hong Kong in July 1968 and strains isolated in the United States, England, Australia, and Japan. We retrieved 60 sequences for the neuraminidase N2 gene, including the Hong Kong precursor strain and strains isolated in the United States, Canada, England, and Japan. We discarded 12 sequences for the hemagglutinin H3 gene and 7 sequences for the neuraminidase N2 gene because they were too short or redundant. For each sequence, the year of isolation was indicated, and, when it was ambiguous, we determined the winter of isolation by a search of the literature.

INFLUENZA MORTALITY, 1967–1979

Identification of influenza epidemic periods. For both A/H3N2 pandemic seasons of interest (1968/1969 and 1969/1970), the month of the peak number of deaths attributed specifically to influenza (ICD-7 codes 480–483 and ICD-8 codes 470–474) matched the month of peak influenza activity reported by virological surveillance systems in all countries [18, 19], which is consistent with an expected delay of only 2 weeks between morbidity and mortality. Epidemic months were defined by fitting a seasonal linear regression model to the influenza monthly mortality time series (all ages), excluding values reported between December and April [26, 52]. The model gave the expected baseline number of influenza deaths in the absence of epidemic activity, as well as an epidemic threshold (i.e., the upper limit of the 95% confidence interval). Months in which observed influenza mortality was above the threshold were considered to be epidemic months.

Estimation of P&I and all-cause excess mortality each winter. Baseline nonepidemic mortality was estimated by fitting a seasonal regression model to P&I and all-cause monthly mortality time series, as described elsewhere [52]. The model allowed for

linear and quadratic trends and was fitted separately for each country and each age group (see below). Values between December and April were excluded before model fitting. For each influenza season (December–May in the Northern Hemisphere and May–September in Australia), we measured the excess mortality by subtracting the expected baseline mortality from the observed mortality and determined the algebraic sum over influenza-epidemic months. To reduce nonstationarity in the time series that displayed changes in the summer baseline, we first normalized each series by (1) fitting a smooth monthly trend through observed summer values (July–September) using a spline function and (2) normalizing observed monthly values by (dividing by) the spline monthly values. Then we fitted a seasonal model, as described above, on normalized time series and transformed excess mortality values back to their original scale. The same procedure was used to estimate all-age and age-specific excess mortality.

Age standardization. The data was broken down into 6 age groups (<65, 65–69, 70–74, 75–79, 80–84, and >85 years) to allow calculation of age-specific P&I and all-cause excess mortality. Then we applied these age-specific mortality estimates to a reference population, the population of England and Wales in mid-1969, and summed the resulting number of deaths across all age groups to give an overall age-standardized measure of pandemic impact.

Percentage increase in mortality. It has been reported that P&I appeared as an underlying cause of death more frequently in England and Wales than in other countries [27, 28, 31]. These differences were not specifically related to influenza, because they were present year round, in particular in the summer when no or very low influenza activity was detected. In addition, inter-country differences in all-cause excess mortality during influenza epidemics have been reported [27, 28, 31] and were also found in the present study for the 1967–1979 period, even after adjustment for age. For the 12 seasons studied, P&I excess mortality was, on average, 2–3-fold higher in Europe than elsewhere. On average, all-cause excess mortality was ~2-fold higher in Europe, Australia, and Japan than in North America (table A1).

To compensate for these differences, we calculated the percentage increase in mortality as the excess mortality divided by the expected mortality (sum of excess mortality during epidemic months/sum of expected mortality during epidemic months) [29]. The expected mortality was taken to be the baseline from our seasonal model, and it also mirrored closely the observed mortality in winters without epidemic influenza activity. Indeed, the modeled baseline was equal to the observed mortality \pm 5% in the winters without epidemic influenza activity during 1967–1979 (1–3 such winters, depending on the country). To be comparable between different populations, the percentage increase needs to be estimated for a standard duration of the epidemic period [29]. We restricted the epidemic period to the 3 consec-

Table A1. Average intercountry differences in age-adjusted excess mortality related to influenza.

Country	P&I age-adjusted excess mortality/100,000 persons		All-cause age-adjusted excess mortality/100,000 persons	
	All ages	<65 years old	All ages	<65 years old
United States	4.6	1.4	11.9	3.2
Canada	4.3	0.7	9.2	2.5
England and Wales	13.5	2.7	29.3	5.6
France	9.4	1.8	21.5	5.3
Japan	5.0	NA	21.2	NA
Australia	3.9	1.0	20.0	3.4

NOTE. Data are average seasonal pneumonia and influenza (P&I) and all-cause excess mortality for 12 seasons, 1967/1968–1978/1979. NA, not applicable.

utive months surrounding the peak number of influenza deaths in each country. For the 3 influenza seasons of interest, 1967–1970, this captured the large majority of excess mortality during the epidemic (average [across 6 countries and 3 seasons] P&I and all-cause excess mortality, 96% [range, 89%–100%]).

TRANSITION FROM ICD-7 TO ICD-8

Because our study period includes the transition from ICD-7 to ICD-8, we checked that this transition did not affect the mortality estimates. The transition occurred in 1968 in all countries except for Canada, where it occurred in 1969. Both pneumonia and influenza codes changed with the new version of ICD.

This transition is unlikely to have had an impact on the mortality patterns evidenced in the present study, for 2 reasons. First, P&I mortality patterns in the summers before and after the transition were similar (i.e., within the range of usual year-to-year variations observed in other summers) (table A2). Hence, the effect of the change in coding P&I deaths was probably

minor or nonexistent. Second, all-cause mortality is free from such nosological bias, and the mortality patterns observed for P&I mortality were also observed for all-cause mortality.

LOCAL STUDIES OF PANDEMIC PATTERNS IN THE UNITED STATES AND CANADA

Local geographical disparities within countries may have existed during the Hong Kong A/H3N2 pandemic. We investigated this possibility for the United States and Canada, the outliers in this multinational study, by use of our own mortality data and by a search of the literature. Our US mortality data were available for the country's 9 geographically distinct administrative divisions. A Canadian study documented influenza-related mortality for the country's 9 administrative provinces [24].

Using the US mortality data, we found that the majority of influenza-related deaths in 1968/1969–1969/1970 occurred during the first pandemic season in the 9 administrative divisions (average, 70% [range, 60%–86%]). In the literature, only 1 local

Table A2. Change in summer pneumonia and influenza (P&I) mortality at the transition of *International Classification of Diseases* (ICD) and in later years, by country (1967–1978).

Country	Relative change in summer P&I mortality over the course of 2 consecutive years, %	
	Average change in years without ICD transition (1968–1978 ^a)	Change at the transition from ICD-7 to ICD-8 (1967 vs. 1968 ^b)
Australia	11.2	9.6
England and Wales	4.9	5.4
Japan	9.3	8.2
United States	5.4	0.5
France	9.5	10
Canada	7.5	7.4

NOTE. Summer is defined as July–September.

^a For Canada, the period was 1969–1978.

^b For Canada, the comparison was 1968 vs. 1969.

study, set in Seattle, documented an opposite pattern: the majority of deaths (60%) occurred during the second pandemic season [53]. In Canada, however, marked local differences were reported in serological tests, clinical illness, and mortality [24]. The mortality of the first pandemic season ranged from 26% to 86%, with 3 of the 9 administrative provinces experiencing a mild first pandemic season. This suggests that the A/H3N2 pandemic in Canada was a mixture of the smoldering pattern found in Europe and Asia and the expected pattern of decreasing impact found in the United States, explaining the nearly balanced impact of the 2 pandemic seasons in the national analysis. By contrast, the United States had minimal geographical variation.

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