It's Not about Smoldering or Neuraminidase: There Were 2 Variants of the A(H3N2) Pandemic Virus Differing in Internal Genes

To the Editor—Viboud et al. [1] found:
1. The A(H3N2) pandemic (winter 1968/1969, United States and Canada, and 1969, Southern Hemisphere) was marked by widespread seeding; however, outside North America, substantial excess mortality did not occur. The “Eurasian smoldering pattern” was further characterized as low-level excess mortality during the first pandemic season but as substantial excess mortality during the second (winter, 1969/1970 and 1970, respectively, by hemisphere).
2. In the United States and Canada, excess mortality was greater, substantially so in the United States, during the first pandemic season.
3. Total mortality for the first 2 pandemic seasons was 2–5-fold lower in the United States and Canada than in the other countries studied and 2–3-fold higher in the United Kingdom and France than elsewhere.

For “smoldering” locations, the first season was dominated by the pandemic virus, but it produced little mortality. The evidence for this is
4. The pandemic virus was detected by surveillance in all 4 countries.
5. Cocirculation of other viruses was not documented.
6. A shift in age distribution of excess mortality to younger age was found in 3 countries.
7. The increase in mortality in “smoldering” locations during the second pandemic season was explained by a genetic drift in the neuraminidase gene and by preexisting differences in immunity.

Unexplained issues remain:
8. The significant mortality seen in the United States and Canada during the first pandemic season.
9. The 3 different mortality levels seen: United States and Canada < (Australia and Japan) < (United Kingdom and France).

We believe that the article by Viboud et al. [1] contains 3 kinds of errors: in analysis, in selection of evidence, and in reasoning.

Points 1–3: The term “smoldering” has been consistently used in both the literature and textbooks (e.g., [2]) to describe a slow spread from multiple epicenters within countries, including the United States, during the first pandemic season; it has only secondarily been applied to the phenomenon of a 1-season delay in mortality.

Point 5 is contradicted by references that have documented cocirculating influenza B viruses [3–5] suggesting that influenza A(H2N2) may have continued to circulate during that season [6], and others that have suggested that 2 distinct variants of A(H3N2) viruses circulated during the first pandemic season [7, 8].

Point 6 is an error in analysis. Viboud et al. [1] used an ad hoc and unvalidated modification of the original Serfling model to estimate excess mortality for the age groupings “all ages” and “age <65 years.” This entire class of algorithms is neither consistent nor additive—that is, the estimate for any season depends on which other seasons are included (inconsistency), and the estimates for age groups do not sum to the estimate for all age groups (or for combinations of age groups).

Instead of estimating excess mortality from age-adjusted mortality series, Viboud et al. [1] presented the age-adjusted nonadditive estimates for 6 age groups, summing these to obtain, at best, an approximate value for all-age, age-adjusted excess mortality. Estimates for the group age <65 years are usually small numbers, and Serfling estimates can even be negative during years for seasons of low excess mortality. The ratio of Serfling estimates to an approximate estimate for all ages is an unstable estimate of age shift.

Points 7–9 are errors in reasoning: We applied a consistent and additive algorithm to mortality series to estimate excess mortality for each age group [9]. For each country, season, and age group, we plotted the relative excess mortality ratio of excess mortality for that season to the excess mortality for that age group, averaged over all study years. For 1968/1969 in the United Kingdom (figure 1A), excess mortality in all age groups was lower than that for the season before. This pattern was similar to that for the mild 1964/1965 season, and it should not be cited as an age shift signifying a pandemic season. For 1968/1969 in France, all age groups had essentially the same relative excess mortality (data not shown). Therefore, in these countries, most excess mortality during the first season was caused by cocirculating viruses. During the second season in both the United States (figure 1B) and Canada (data not shown), excess mortality declined substantially in all elderly persons age <77 years (see [10]), and it was unchanged for older age groups. Therefore, the drift in neuraminidase, which occurred everywhere, cannot explain any of the differences (in the United States and Canada and elsewhere) during the second season.

Viboud et al. [1] were apparently unaware that more vaccine was distributed in Australia during the first pandemic season than during any season since (A.
Figure 1. Relative excess all-cause mortality (excess mortality for any season:average excess mortality for that age group over all study seasons) for 42 seasons, 1959–2000, for the United Kingdom (A) and 46 seasons, 1953–1999, for the United States (B). During 1968/1969 in the United Kingdom, all age groups exhibited a decrease in excess mortality from the previous season, similar to that in 1964/1965. In the United States, age groups >77 years old exhibited a dramatic increase in excess mortality, whereas that in age groups <77 years old decreased. During the next season, 1969/1970, excess mortality decreased further for all age groups in the United States. In the United Kingdom, it increased strongly for all groups >77 years old and less strongly for older persons.

Hampson, World Health Organisation Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia, private communication). Excess mortality was reduced, and the observed age distribution was not that of a pandemic shift (data not shown). Viboud et al. [1] invoked “preexisting immunity to neuraminidase” (p. 241) from the A(H2N2) era as an additional effect. However, the only evidence of protection that they cited was from the United States. They also noted that the season preceding the first pandemic season was one of large excess mortality everywhere. Therefore, the evidence that they presented is negative, in that both influenza genetics and precedent exposure were the same everywhere. Why, then, should the mortality impact differ?

The likely answer is that, during the first pandemic season, other influenza viruses did cocirculate with the pandemic virus, which caused widespread infection but little observable mortality and no age shift in excess mortality outside North America (the pattern of mortality in Mexico was similar to that in the United States and Canada). The following hypothesis is consistent with all assembled data.

The historical exposure (before 1891) to the recycling A(H3N2) virus differed in North America and Europe. (1) In the first pandemic season, 2 variants of the A(H3N2) virus circulated that differed in ≥1 internal gene, such that the North American variant was more virulent than the variant that circulated elsewhere. (2) In the second pandemic season, reassortment had occurred, such that the drifted neuraminidase gene, the makeup of the North American variant, and, possibly, other changes were combined in the dominant circulating species. (3) Outside North America, the doubly altered strain produced an extraordinary increase in excess mortality with an age distribution that showed only modest evidence of historical exposure. (4) The relative levels of excess mortality seen in the 6 countries studied by Viboud et al. [1] are concordant with observations that meteorologic and, possibly, other variables combine to produce a global pattern of consistent
differences in the mortality impact of influenza [11]. This hypothesis can be tested by comparing complete genetic sequences from samples from North America with those obtained elsewhere during the first season.

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References

Reply to Reichert and Christensen

To the Editor—Our recent study described variations in influenza-related mortality patterns in 6 countries during the first 2 years of the A(H3N2) influenza pandemic (1968/1969 and 1969/1970) and offered a hypothesis to explain them [1]. Reichert and Christensen [2] have raised several issues about our work, to which we respond in turn.

Reichert and Christensen state that cocirculation of influenza A(H2N2), influenza B, and 2 variants of the emerging A(H3N2) subtype may explain the observed 1968/1969 influenza mortality patterns. We emphatically disagree. Their evidence for the cocirculation of an A(H2N2) virus during the 1968/1969 season is based on a single figure legend that is unsupported by accompanying text, from a study that took place in Italy [3]. We suspect the legitimacy of this evidence, in that the viral circulation of A(H2N2) was not verified in a similar article by the same authors [4]. Moreover, there was no mention of the cocirculation of A(H2N2) in World Health Organization reports of worldwide virus surveillance from that period [5]. Reichert and Christensen further cite articles [6, 7] concerning 2 periods [5]. Reichert and Christensen further cite articles [6, 7] concerning 2 A(H3N2) variants, but only one [6] suggests the possibility of 2 A(H3N2) variants, despite no accompanying data, whereas the other [7] makes no mention of 2 cocirculating A(H3N2) variants during the time of our study. As for the cocirculation of B and A(H3N2) viruses both in the United States and in Japan during 1968/1969, this fact alone is insufficient to explain the differences in influenza mortality patterns between these 2 countries.

We also disagree with Reichert and Christensen’s suggestion that our modeling approach has not been validated. Our excess mortality approach, a variation of the Serfling model that has been used by the Centers for Disease Control and Prevention since 1963, is by no means new [8]. In fact, the exact same excess mortality and age-adjustment approach to US mortality data was applied to a study in which Reichert recently collaborated [9]. As for their criticism that our model is not “additive,” we found that, during the pandemic period under study, the maximum difference was only 2.5% between excess pneumonia and influenza (P&I) mortality estimates summed across age groups and estimates obtained by applying the model to all age groups combined.

Reichert and Christensen suggest in their letter that an alternative “Z-like score” (ZLS) modeling approach would be better, as described in Reichert et al. [10]. Again, we disagree. Although ZLS modeling can be useful for the study of synchronicity in mortality time series [10], the model baseline is a 13-month moving average of observed mortality, which is not at all appropriate for estimating P&I excess mortality. Indeed, when mortality shifts suddenly, as during a pandemic, the ZLS winter baseline becomes considerably distorted around the severe season. This approach, therefore, cannot be used to accurately quantify the age shift in pandemic mortality during 1968/1969. We demonstrate this by comparing the ZLS and Serfling approaches applied to P&I mortality data from England and Wales (figure 1). As can be seen, the ZLS winter baseline varies by as much as 50% during the pandemic years 1968–1970, whereas the Serfling baseline varies by ≤4%.

Reichert and Christensen also suggest that our findings may have been confounded by high vaccination coverage during the first A(H3N2) season in Australia. However, vaccination coverage is reported to have been ~35%–40% during both A(H3N2) seasons in Australia [11, 12], and vaccination rates were negligible in the other countries studied [6, 13, 14]. We therefore do not believe that differences in vaccination rates provide a viable alternative explanation for the “smoldering” pandemic pattern in Europe and Asia, in which mortality was delayed until the second season of A(H3N2) circulation.

Reichert and Christensen also discuss

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the large intercountry differences observed in absolute excess mortality rates. We and others have already commented on these interesting differences, which were not limited to the 1968 pandemic period [1]. This point is irrelevant to the conclusions of our article, which were based on a comparison of relative changes in excess mortality to surrounding influenza seasons in each country.

Finally, Reichert and Christensen propose an alternative and rather complex hypothesis to explain the smoldering pandemic pattern that we found in Europe and Asia but not in North America. Their alternative hypothesis—that 2 variants of A(H3N2) virus circulated during 1968/1969, each of which had different internal genes—conflicts with the only study of internal gene sequences from that time, which found the same genetic makeup in viruses from North America and elsewhere during 1968/1969 [15]. We believe that our neuraminidase hypothesis is more consistent with the limited data available; indeed, we were pleased to find that a second study, which appeared in the same issue of the Journal of Infectious Diseases as ours, further supported the role of neuraminidase variations on the severity of influenza outcome [16].

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