



## Perspective

### The Signature Features of Influenza Pandemics — Implications for Policy

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Vast amounts of time and resources are being invested in planning for the next influenza pandemic, and one may indeed have already begun. Data from past pandemics can provide useful

insights for current and future planning. Having conducted archeo-epidemiologic research, we can clarify certain “signature features” of three previous influenza pandemics — A/H1N1 from 1918 through 1919, A/H2N2 from 1957 through 1963, and A/H3N2 from 1968 through 1970 — that should inform both national plans for pandemic preparedness and required international collaborations.

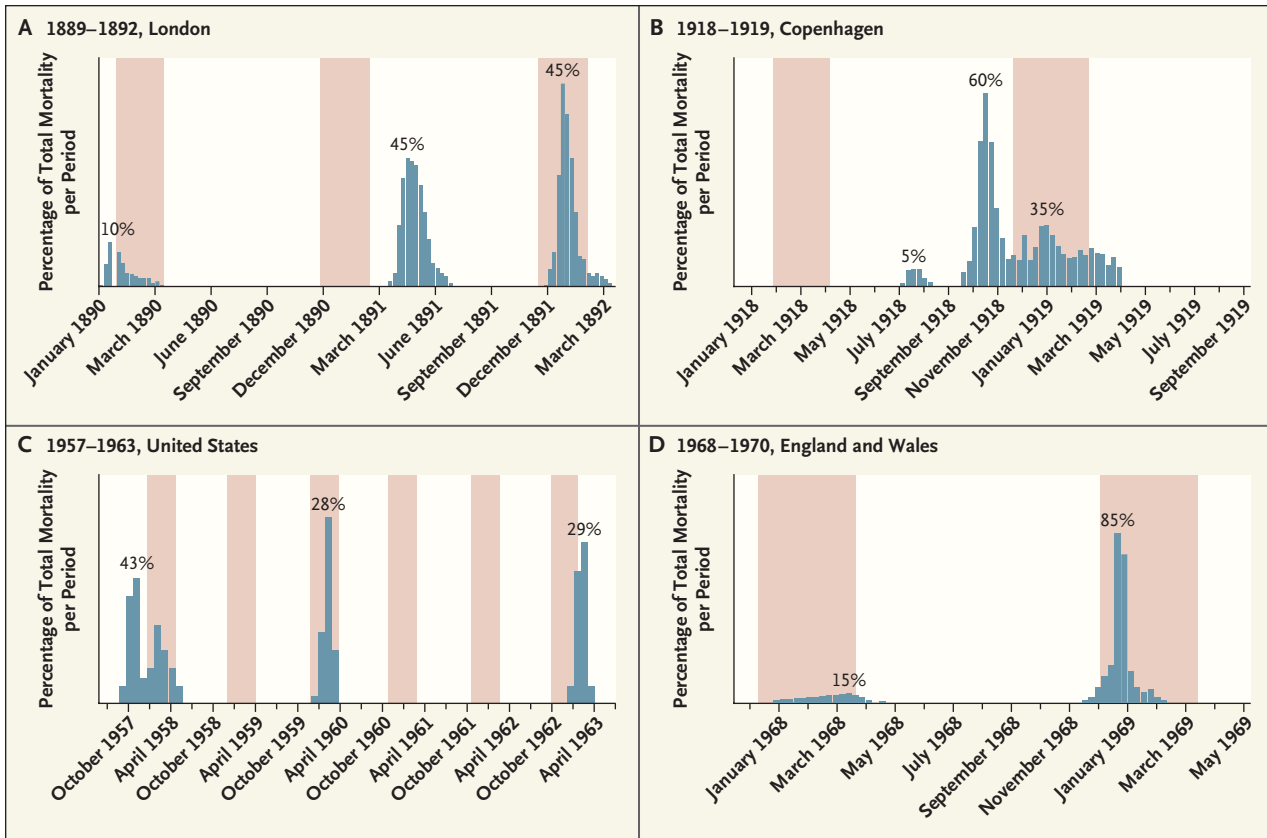
Past pandemics were characterized by a shift in the virus subtype, shifts of the highest death rates to younger populations, successive pandemic waves, higher transmissibility than that of seasonal influenza, and differences in impact in different geographic

regions. Although influenza pandemics are classically defined by the first of these features, the other four characteristics are frequently not considered in response plans.

Yet the second feature, the shift in mortality toward younger age groups, was the most striking characteristic of the 20th-century pandemics.<sup>1,2</sup> Exposure to influenza A/H1 subtypes before 1873 may have offered some protection to adults over 45 years of age during the pandemic of 1918 and 1919. A similar mechanism of antigen recycling might explain the partial protection against influenza-related death that was observed among people over 77 years of age during the 1968–1970

pandemic — a possibility supported by the prepandemic presence of antibodies to H3, which were isolated in people born before 1892.<sup>1</sup> Another possible mechanism is immune potentiation, leading to an increased likelihood of lethal outcomes after influenza infection in specific age groups. Still other hypotheses include the possibility of bacterial superinfection due to asymmetric carriage rates, given that higher rates were found among young people in 1918 and 1919.<sup>1,2</sup> Although the elderly frequently have the highest death rates during seasonal epidemics, their relative sparing during pandemics has not been generally appreciated. Advance knowledge of which subpopulations are most likely to be at increased risk for death can shape the optimization of control strategies.

The third feature, a pattern of multiple waves, characterized all



**Mortality Distributions and Timing of Waves of Previous Influenza Pandemics.**

Proportion of the total influenza-associated mortality burden in each wave for each of four previous pandemics is shown above the blue bars. Mortality waves indicate the timing of the deaths during each pandemic. The 1918 pandemic (Panel B) had a mild first wave during the summer, followed by two severe waves the following winter. The 1957 pandemic (Panel C) had three winter waves during the first 5 years. The 1968 pandemic (Panel D) had a mild first wave in Britain, followed by a severe second wave the following winter. The shaded columns indicate normal seasonal patterns of influenza.

three 20th-century pandemics, each of which caused increased mortality for 2 to 5 years (see chart).<sup>1</sup> The lethal wave in the autumn of 1918 was preceded by a first wave in the summer that led to substantial morbidity but relatively low mortality in both the United States and Europe. Recent studies suggest that these early mild outbreaks partially immunized the population, decreasing the mortality impact of the main pandemic wave in the fall of 1918.<sup>2</sup> In the United States, the 1957 influenza A/H2 pandemic had three waves in the United States, with notable excess mortality in the

nonsuccessive winter seasons of 1959 and 1962 — the latter being 5 years after the initial emergence of the pandemic strain.<sup>1</sup> From 1968 through 1970, Eurasia had a mild first influenza season, with the full effects on morbidity and mortality occurring in the second season of pandemic-virus circulation. The reasons for multiple waves of varying impact are not precisely understood, but they probably include adaptation of the virus to its new host, demographic or geographic variation, seasonality, and the overall immunity of the population.<sup>1,2</sup> The occurrence of multiple waves po-

tentially provides time for health authorities to implement control strategies for successive waves.

Increased transmissibility of influenza because of high susceptibility of the population, the fourth feature, has also been documented for all the past pandemics, although estimates of reproductive numbers — a measure of the average number of secondary infections caused by each individual case — vary considerably among studies and pandemics.<sup>2,3</sup> Recent studies suggest that during the early mild wave of the 1918–1919 pandemic, the reproductive number (i.e., the number of new cases attributable to a

single established case) may have ranged between 2 and 5,<sup>2,3</sup> as compared with the average of 1.3 for seasonal influenza. Since models of containment and pandemic control assumed lower reproductive numbers for the current epidemic than those that have been historically observed, they are likely to be overly optimistic regarding the success of containment strategies.

Great heterogeneity among regions in terms of incidence and mortality is also a characteristic of pandemics. This variability is probably explained by the complex heterogeneity in the degree of immunity in local populations to the circulating influenza strains, as well as by transmission factors such as geographic conditions, social mixing, degree of viral infectiousness, and “seasonal forcing” (small seasonal changes in the effective transmission rate).<sup>4</sup> The benefits of sharing data on all these variables provide major incentives for international collaboration.

Although the A/H5N1 influenza subtype has spread to avian populations in more than 30 countries and infected nearly 400 persons, with a case fatality rate above 50%, scientists disagree about its pandemic potential. Such a highly pathogenic virus does not usually adapt well to its host, since it tends to kill faster than it can be transmitted. Other avian subtypes are also considered to be pandemic threats. Although avian viruses have a different tropism for respiratory cellular receptors in birds than for those in humans, gradual viral mutations or gene-segment reassortments in a mammal “mixing vessel” could result in a novel viral clade or subtype that spreads rapidly in a population that has

largely not previously been exposed to it. Such changes may have occurred in the current swine H1N1 circulating strain.

The death toll of a future pandemic depends not only on the virulence of the virus in question but also on the rapidity with which we are able to introduce effective preventive and therapeutic measures. Although A/H5N1 has been associated with a “cytokine-storm” phenomenon reminiscent of that observed in 1918 and 1919, new methods for the timely manufacture and administration of antiviral agents and influenza and pneumococcal vaccines could mitigate the effects of a pandemic.

The evidence of multiple waves in the 20th-century pandemics underlines the importance of active real-time viral surveillance on a global scale. Transnational collaborations are crucial for the effective exchange of genomic, clinical, and epidemiologic data that will make possible the development of vaccines and treatment protocols and the identification of the best population-based strategies. Although our ability to produce a vaccine in sufficient quantities to cover people who are exposed in a first pandemic wave is very limited with today’s technology, an interwave period would provide time to increase the production of biomedical tools and to vaccinate populations, thereby mitigating the morbidity and mortality associated with successive and potentially more lethal waves. This possibility, too, is a powerful incentive for international collaboration, since all would potentially share the benefits. If an effective vaccine had been available and used even a year after the emergence of the

A/H3N2 viruses in 1968, most of the deaths in Europe and Asia could probably have been prevented.

The signature pandemic feature of shifts in age-specific mortality patterns should influence vaccination priorities.<sup>5</sup> Given that the supplies of vaccine and antiviral agents are likely to be constrained, the efficient allocation necessary for reducing mortality will require consideration of local demography, expected shifts in age-specific incidence, direct and herd effects of vaccination in various age groups, and ethical issues regarding life expectancies and potential years of life saved in various groups. The indirect effects of reducing transmission also warrant further consideration. The role of preexisting antibodies in the elderly, their reduced immune response because of immune senescence, and greater transmission among children should prompt the targeting of younger age groups as the soundest policy in a 1918-like scenario. However, these attributes do not necessarily apply to other pandemics to the same extent.<sup>5</sup>

Nonmedical interventions — primarily social distancing — could be useful in staving off transmission. Simulation models suggest that such interventions would considerably decrease the incidence of infection only if the basic reproductive number was less than 2, a rate that is lower than that observed in past pandemics.<sup>3</sup>

Though the rapidity of transmission of influenza virus during pandemics necessitates immediate action, it can be hoped that close collaborations and lessons drawn from previous pandemics will contribute to reducing national and global mortality. The

documented relevant signature features can help health authorities prioritize national strategies and aid international collaborators in addressing the initial and successive waves of illnesses and deaths.

Dr. Miller reports being named on a pending patent held by the National Institutes of Health on a novel influenza vaccine; and Dr. Simonsen, receiving consulting fees from Merck and research support from Wyeth. No other potential conflict of interest relevant to this article was reported.

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