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Planning for an influenza pandemic: thinking beyond the virus

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R. Théophile H. Laennec was the first to describe the pathology of pandemic influenza. The inventor of the stethoscope and of the technique of auscultation, Laennec published in the early 19th century a series of observations on diseases of the chest which remain relevant reading today. Among his many contributions to science was the recognition while practicing in Paris during the 1803 pandemic that pneumonia was a frequent, fatal complication of influenza [1]. He described an increase in expectoration of yellow to greenish-tinged sputum, increased frequency of "double" pneumonia, and noted that the lungs in most fatal cases were at the early pneumonic stage of "engorgement" when examined by autopsy.

This general pattern of increased incidence, increased mortality, but typical pathologic findings of bacterial pneumonia was repeated in virtually all of the generally recognized epidemics and pandemics through the modern era, when rigorous pathologic examination of fatal pneumonias fell out of use as a diagnostic modality. Indeed, Edwin O. Jordan, in his comprehensive survey of all literature relevant to the 1918 pandemic, argued that the general clinical and epidemiologic character of the pandemics of 1889–1890 and 1918–1919 were indistinguishable, including the disproportionately high attack rate in young adults which has been regarded to be pathognomonic of the 1918 pandemic [2] This contention runs counter to the prevailing view espoused in both the scientific and lay media that the 1918 pandemic strain was uniquely virulent, and that factors intrinsic to the behavior of the virus and the pathogenesis of the viral infection must account for the strikingly high worldwide mortality associated with this pandemic.

In this issue of *The Journal of Infectious Diseases*, Morens et al. review 118 published autopsy series from the 1918 pandemic and add new data from an additional 58 autopsies for which lung sections have been preserved [3]. Their findings are striking in the context of modern conceptions of the 1918 pandemic; the great majority of deaths could be attributed to secondary bacterial pneumonia caused by common respiratory pathogens, particularly pneumococci, group A streptococci, and staphylococci, and not to the virus itself. In fact, although evidence of severe viral bronchiolitis was found, often the primary viral insult appeared to be resolving at the time of the secondary infection responsible for the fatality. Their conclusions are strengthened by the remarkable consistency in theme if not details displayed across the many studies reviewed, and the inclusion in their review of not only gross pathologic findings but

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blood and lung culture data. In only 4% of the more than 8000 cases reviewed was no bacterial super-infection documented.

One insight offered by the authors is that this information is not new – we have simply lost this perspective over the last 50–60 years during the shift in modern medicine towards sophisticated imaging studies and molecular diagnostics and away from gross pathology. In similar fashion the design of the current study is itself not new; a reexamination of pathology from a past pandemic was undertaken by a German scientist during the 1918 pandemic [4] much as has been done by Morens et al. [3] Otto Lubarsch compared preserved autopsy specimens from the 1889–1890 pandemic to fresh autopsies from 1918–1919 and concluded the pathologic processes were nearly identical. This homogeneity in findings reinforces the idea that the end result, death from bacterial pneumonia, is a common feature of all pandemics in the pre-antibiotic era. If this supposition is correct, the virulence of the virus itself may not be the key predictor of mortality; the ability to interact with bacteria may be the more important factor [5]. In this light, study of virulence factors that increase the incidence or enhance the case fatality rate of secondary bacterial infections is as important as understanding the basic biology of influenza viruses with pandemic potential.

Current interest in the pathogenesis of deaths during the 1918 pandemic must be put into the context of concern over and preparation for the next pandemic, an occurrence that history tells us is inevitable, although unpredictable. An intense global effort to prepare for this potentiality has been ongoing for approximately 5 years following the reemergence in 2003 of highly pathogenic avian influenza viruses of the H5N1 subtype [6]. The majority of pandemic preparation has centered around prevention or treatment of the virus itself by developing vaccines against pandemic candidates and stockpiling antivirals [7]. Little to no attention has been paid to prevention and treatment of potential bacterial super-infections, which, as Morens et al. remind us, have historically caused the great majority of deaths during pandemics. Part of this failure can be traced to our collective amnesia regarding the 1918 pandemic as discussed above, and part can be attributed to assumptions about the clinical features of a theoretical H5N1 pandemic.

The clinico-pathologic syndrome suffered by persons infected with avian influenza viruses of the H5N1 subtype over the last 10 years does not closely resemble that reported during previous pandemics in the pre-antibiotic era. Instead, illness manifests as a severe, progressive pneumonia that rapidly acquires characteristics of the acute respiratory distress syndrome, leading in most cases to death [8]. Rather than wound healing and regeneration proceeding to resolution of viral disease with superimposed bacterial infection [3], the few pathologic examinations done after H5N1 infection show diffuse alveolar damage, necrosis, squamous metaplasia, and hemorrhage [8,9]. Bacterial infections have been shown to complicate H5N1 infections in a minority of cases, but have not been a prominent cause of death, likely due to modern intensive care and provision of broad-spectrum antimicrobial agents.

More important in the context of pandemic planning, however, is the difficulty inherent in extrapolating data from a limited series of zoonotic infections to the broader range of possibilities inherent in a full pandemic. Currently circulating influenza viruses of the H5N1 subtype are not fully adapted to humans; they lack the capacity to easily transmit from person to person. Because acquisition of this trait will require adaptation or reassortment with human influenza viruses, the pathogenesis of these theoretical pandemic strains cannot be predicted with any assurance. In addition, there is no guarantee that the next pandemic will be caused by viruses of the H5N1 subtype, and there is an equally compelling argument to be made for several other candidates [8]. The assumption implicit in some pandemic plans, that the disease course during the next pandemic will be similar to that seen in the limited clinical experience with H5N1 viruses in Eurasia, may be entirely wrong. Deaths due to the next pandemic strain,

even if it is an adapted H5N1, may follow precisely the pattern evident from history, and bacterial super-infections may be the predominant fatal events. Even if a clinical course similar to our recent H5N1 experience occurs in the next pandemic, our ability to provide modern intensive care and administer broad-spectrum antibiotics will certainly be compromised if clinical attack rates approach the 25–30% range seen in previous pandemics. In this scenario bacterial infections are likely to emerge as a major complication in survivors of the primary influenzal disease.

What is to be done? At this point pandemic planners have started to recognize the issue, but have not yet begun to deal with it. A shift in focus is required. Pandemic planning must take into account the possibility that secondary bacterial pneumonia will be a frequent complication of pandemic influenza. Basic research into the interactions between influenza viruses and bacteria is needed. Modeling studies extrapolating the breadth of potential risk should be undertaken. Planning for prevention of disease must include pneumococcal vaccines as well as influenza vaccines [10]. A comprehensive survey of the sources, supply, and surge capacity of important antibiotics should be undertaken. This should include analysis of distribution patterns as has been done for influenza vaccines [11]; it is likely that many of the countries in the developing world, where complications of pandemic influenza are likely to be worst, will have little to no access to appropriate antimicrobials in this scenario. Consideration of strengthening and diversifying these pipelines should be made – in the United States alone in the last 3 years more than a dozen antibiotics have been in shortage [12]. Included among these is vancomycin, an important drug used in the treatment of antibiotic resistant infections due to *Streptococcus pneumoniae* and *Staphylococcus aureus*, the two most common secondary pathogens following influenza. If these shortages are occurring in times of constant demand, it seems likely that worse will occur when there is a surge in demand.

Since the 1997 H5N1 outbreak in Hong Kong, a tremendous amount of work has been done to understand influenza viruses and prepare for the next pandemic. As Morens et al. have reminded us, however, the virus is only half of the story, and the bacterial super-infections may be the more deadly half [3]. Harry S. Truman may have summed it up best, “The only thing new in the world is the history you don't know.” This timely reminder of our past should act as an impetus to help prevent the history of the 1918 pandemic from repeating itself.

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