How Will Physicians Respond to the Next Influenza Pandemic?

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The emergence of the H7N9 virus in China is another reminder of the threat of a global influenza pandemic. Many believe we could confront a pandemic by expanding our capacity to provide timely supplies of affordable pandemic vaccines and antiviral agents. Experience in 2009 demonstrated that this cannot and will not be done. Consequently, physicians may have little more to offer their patients than they had in the 1918 pandemic. Fortunately, several modern drugs (eg, statins, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors) can modify the host response to inflammatory illness, and laboratory and clinical studies suggest they might be used to treat pandemic patients. Unfortunately, little attention has been given to the research needed to support their use in patient care. There is no guarantee these drugs will work, but physicians will never know unless those responsible for pandemic preparedness recognize and act on the extraordinary possibility that they might save lives.

Keywords. pandemic influenza; statins; immunomodulatory agents; public health.

The recent emergence of the influenza A(H7N9) virus in China has led to a limited outbreak of disease that has been associated with an overall mortality of approximately 30% [1–3]. The impact has been especially severe among the elderly. It is widely known that influenza viruses can modify or exchange their genes, and these changes often yield new viruses with altered virulence and/or transmissibility. An experiment published in 1974 showed that infecting turkeys with 2 different influenza viruses generated a new reassortant virus that killed all of the infected birds and all of their contacts—a 100% population collapse [4]. The influenza pandemic of 1918 killed between 50–100 million people worldwide, and epidemiologists estimate that a similar pandemic today could kill 62 million people [5], almost twice the number that have ever died of AIDS. Since 1997 there has been deep concern about the high mortality (≥50%) seen in human infection with the avian influenza A(H5N1) virus, and recent controversy over H5N1 gain-of-function research has heightened this concern [6]. Billions of dollars have been spent preparing for an H5N1 pandemic. It is no wonder that scientists and health officials are worried about the H7N9 virus [7].

Several commentators writing in journals that target practicing physicians in the United States have expressed concern that the H7N9 virus could evolve to become easily transmissible and lead to a devastating global pandemic [8–10]. Many believe that the most effective way to respond to the next pandemic would be to greatly expand our capacity to rapidly produce influenza vaccines. They have been encouraged by new developments in influenza vaccinology, especially those based on antibodies and cytotoxic T lymphocytes that mediate heterotypic protection against influenza virus infection [11]. Targets for these new vaccines include the stem cell region of the hemagglutinin molecule and several internal proteins (eg, M2e, NP, M1, and NA). Many believe that research on these targets could lead to a universal influenza vaccine that would obviate the need for annual immunization and provide a foundation of protection against the next pandemic. Other developments in influenza vaccinology include (1) rapid

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preparation of seed strains for vaccine production using reverse genetics; (2) expanded cell culture vaccine production facilities; (3) recombinant glycoprotein HA antigens produced in pharmaceutical bioreactors; (4) antigen-sparing adjuvants that increase the number of vaccine doses that could be produced; and (5) monovalent live attenuated pandemic vaccines [12]. However, enthusiasm for these new developments in influenza vaccinology must be tempered by recognizing that they alone will not guarantee the success of pandemic vaccination.

If vaccination against a global pandemic is to succeed, other measures will be required [12]. New facilities for vaccine formulation and filling will be needed, experienced production technicians must be trained, supplies of syringes and needles for administering inactivated vaccines must be secured, clinical trials of candidate vaccines must be supported, procedures for rapid regulatory certification must be put in place, commercial arrangements between vaccine companies and patent holders must be worked out, advanced purchasing agreements and prices must be negotiated between companies and governments, the logistics of vaccine distribution must be set up, and a human infrastructure for vaccination programs must be established. In each country, the cumulative impact of these factors will directly affect the ability of vaccination programs to successfully confront the next pandemic [12].

The most important factor that will determine the global success of pandemic vaccination will be the level of expansion of seasonal influenza vaccination programs, especially in countries that currently use little vaccine [12]. This will require better understanding of the burden of influenza disease and the effectiveness of influenza vaccination. Remarkably, in recent years the global production capacity for seasonal influenza vaccines has increased to the point where it exceeds world demand, yet there is little evidence that demand will soon match production capacity [13]. In all likelihood, expansion of seasonal vaccination will depend on whether governments in low-use countries recommend and purchase influenza vaccines. In the absence of such decisions, implementing new advances in influenza vaccinology "will depend on company assessments of their individual scientific, technical and commercial advantages. These assessments will be viewed within the context of seasonal not pandemic vaccination" [12].

The global vaccination response to the influenza A(H1N1) pandemic in 2009 offers little encouragement that things will be much better for the next pandemic [14]. In the United States, because pandemic vaccines were not available in time, vaccination affected only 2%–4% of all pandemic cases, hospitalizations, and deaths (see Tables 3–5 of [15]). Consequently, health officials had to advise people to wash their hands and limit social contacts, a throwback to 19th-century public health "technologies." Although the vaccine and antiviral response in the United States was minimally effective, for most of the world it was a comprehensive failure: >90% of the world's people had no access to timely supplies of affordable pandemic vaccines [16].

The threat of another influenza pandemic, H7N9 or otherwise, is real [4–10]. If it is severe, hospitals and intensive care units will be swamped with patients. Extracorporeal membrane oxygenation treatment will help only a few. Even if excellent medical care (including antiviral agents) is available, experience with H7N9 and H5N1 influenza has shown that mortality rates could still be high. Wherever such care is not available, especially in low- and middle-income countries, the mortality impact of a global pandemic could be devastating. Although physicians in most countries will find themselves in healthcare settings much different from those in 1918, their experiences and those of their patients could be much the same [17]. Given this possibility, physicians everywhere need to ask whether agents they already know and use in the routine care of their patients might also be used to treat those who become seriously ill with pandemic influenza.

Until now, health officials have relied on influenza scientists—primarily virologists and epidemiologists—to guide pandemic preparedness efforts. Virologists who have adopted a systems approach to discovery have made important contributions to explaining influenza virus–host interactions and the consequences of these interactions for the pathogenesis of disease [18]. Nonetheless, they have yet to suggest agents that would be available to physicians who will be called upon to manage severely ill pandemic patients. Fortunately, investigators in other fields, especially cardiovascular and metabolic diseases, have developed several groups of drugs whose "pleiotropic" activities modify the innate and adaptive immune response to acute inflammatory illness. These drugs might be used for pandemic treatment and prophylaxis. Statins were the first group suggested [19], and since then angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, peroxisome proliferator-activated receptor (PPAR) γ and PPARα agonists (glitazones and fibrates, respectively), and adenosine monophosphate–activated kinase agonists (eg, metformin) have emerged as additional candidate agents. These developments have been comprehensively reviewed in a recent publication [16]. Laboratory studies of acute lung injury, sepsis, and other forms of acute systemic inflammation have shown that these drugs control damaging inflammation, promote its resolution, and improve survival [16, 20, 21]. The benefits of treatment may have little to do with the effects of these drugs on influenza virus–infected cells [16]. Instead, they might improve survival by maintaining or restoring pulmonary microvascular barrier integrity [22], accelerating the early return of mitochondrial biogenesis [23], and/or promoting beneficial changes in immunometabolism [24–26]. Laboratory and clinical research on these agents might help us understand why influenza mortality rates are lower in children

than in adults [16], and perhaps show that "disease tolerance" in children with influenza is a defense strategy that reflects the heritage of human evolution [16, 27–29].

Clinical studies support laboratory findings on the effectiveness of inpatient treatment with 3 groups of these agents (reviewed in [16]). For example, an observational study of 3043 patients hospitalized with laboratory-confirmed seasonal influenza showed that statin treatment was associated with a 41% reduction in 30-day mortality [30]. This reduction was in addition to any that might have been attributable to previous vaccination and antiviral treatment. Another observational study showed that inpatient treatment with ARBs, ACE inhibitors, and statins reduced 30-day pneumonia mortality by 53%, 42%, and 32%, respectively [31]. Importantly, a randomized controlled trial in 100 statin-naive patients (untreated for at least 2 weeks) who were hospitalized with sepsis showed that inpatient atorvastatin (40 mg per day) reduced progression to severe sepsis by 83% (24% in control patients vs 4% in treated patients; $P = .007$) [32].

Statins and other immunomodulatory agents that might benefit influenza patients are used by physicians every day to treat millions of patients with cardiovascular diseases and diabetes. For statins, long-term treatment is safe and effective in improving cardiovascular outcomes, and the benefits greatly outweigh the modestly increased risks of statin-associated diabetes, elevated liver enzymes, and myopathy [33], adverse events that are easily managed. Cases of severe liver injury or rhabdomyolysis are rare. For short-term inpatient treatment, cardiologists routinely initiate statin treatment in patients hospitalized with acute coronary syndrome (ACS), and such treatment has shown to be safe and effective in reducing hospital and 30-day ACS mortality (reviewed in [16]). This experience suggests that studies of treating influenza patients with statins and other immunomodulatory agents should focus on those with illness serious enough to require hospitalization, and an agenda for such research has recently been presented [16]. This research will allow physicians to carefully assess the clinical and immunological effects of treatment while monitoring patients for any signs of adverse events or drug–drug interactions. Special attention will have to be given to the safety of treating pregnant women and children.

Several small-scale studies of statin treatment in humans with experimental acute lung injury, sepsis, and pneumonia have been published (reviewed in [16]). Although these studies were too small to show evidence of clinical benefit, no adverse reactions were noted and several parameters associated with immune dysregulation showed improvement. If statins or other immunomodulatory agents could be shown to be safe and effective, treatment for most patients (especially those who are not older adults) would probably be limited to the duration of the hospital stay and would not need to be continued after hospital discharge. For hospitalized patients who have previously received outpatient treatment with any of these agents, continued treatment after hospital admission would probably be indicated, just as it is for ACS patients who have received outpatient statins [16].

All of the immunomodulatory agents discussed above are now produced as inexpensive generics in developing countries, and global supplies are huge [16]. If 1 or more of them were shown to be safe and clinically effective in treating severe influenza (or in the syndromic treatment of acute critical illness due to other causes such as pneumococcal pneumonia [34]), they would be immediately available to physicians in any country with a basic healthcare system. The cost of treating an individual patient would probably be less than $1.00 [16]. Nonetheless, the laboratory and clinical research needed to justify using these agents to treat influenza patients must be initiated and supported by governments and/or nongovernmental institutions; it cannot be left to pharmaceutical companies because the drugs are no longer of commercial interest.

In the United States, the Assistant Secretary for Preparedness and Response (ASPR), Department of Health and Human Services, joined by the directors of the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health, recently published a set of key components for a research response to public health emergencies [35]. After listing the research failures during the influenza A(H1N1) pandemic in 2009, the authors called for several actions to be taken before the next emergency event. These actions include (1) identifying potential knowledge gaps and research questions; (2) developing and preapproving generic study protocols; (3) obtaining approval for these protocols from institutional review boards; (4) using prefunded research networks and preawarded just-in-time research contracts; and (5) developing an on-call "ready reserve" of clinicians, scientists, and other experts to undertake this research. The essential elements of ASPR's research response plan as they might apply to influenza pandemic preparedness were outlined in an article published in 2009 [36]. Unfortunately, none of ASPR's proposed actions has been implemented, and no plans have been made to study immunomodulatory agents (D.S. Fedson, unpublished observation).

The statins/influenza study mentioned earlier [30] was conducted by the CDC's Emerging Infections Program, but CDC's Influenza Division has not initiated studies to confirm or extend its findings (D.S. Fedson, unpublished observation). In September 2012, the Infectious Diseases Society of America (IDSA) published its US action plan for pandemic and seasonal influenza [10, 37]. The plan focuses on vaccines, antiviral agents, better diagnostics, improved surveillance, and more effective risk communication. The IDSA report briefly mentions

immunomodulatory treatment, but a careful reading indicates that research on these agents is not central to the IDSA's action plan. At the global level, the pandemic preparedness efforts of the World Health Organization (WHO) remain focused on vaccines and antiviral agents [38]. WHO has paid no attention to immunomodulatory treatment, and it was not discussed at the World Health Assembly meeting this past May [39].

George Orwell once wrote that "to see what is front of one's nose needs a constant struggle" [40]. Physicians inevitably will be called upon to care for patients in the next pandemic. They need to ask why influenza scientists and health officials who support their work have not undertaken pragmatically focused laboratory and clinical research to see if statins and other promising immunomodulatory agents could be used to reduce influenza-related mortality. There is no guarantee that any of these drugs will work, but physicians will never know unless those responsible for pandemic preparedness recognize and act on the extraordinary possibility that these agents might save lives.

Note

Potential conflicts of interest. The author has previously received honoraria and travel expenses from Sanofi Pasteur, Sanofi Pasteur MSD, and Merck, Inc, for speaking engagements on influenza and pneumococcal vaccination.

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