

To Kill a Mocking Bird Flu?

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Why devote an entire issue of the *Annals* to pandemic influenza when there are so many other pressing health needs around us? With a potential mortality comparable to tuberculosis, malaria or HIV/AIDS but occurring within a much shorter timeframe, pandemic influenza remains a real possibility. Even if no pandemic materialises in the foreseeable future, the increase in global public health capacity and preparedness for emerging and re-emerging infectious diseases will still be a major positive outcome of the “hype” surrounding pandemic influenza.¹

Since 1997, highly virulent H5N1 avian influenza A viruses have caused periodic outbreaks in poultry and in humans with unusually high mortality rates. The rapid spread of H5N1 from Asia to the Middle East, Europe and Africa has enabled these viruses to be deeply entrenched in the ecosystem. Three hundred and eighty-five human cases of H5N1 infection have been reported in 14 countries since 2003, with the highest number in Indonesia. As at 19 June 2008, there have been 243 H5N1-related deaths, giving a case fatality rate of 63%. No one knows when, and what virus strain, will ignite the next influenza pandemic, but H5N1 is currently the prime contender, the most likely pandemic strain. H5N1 has already fulfilled the first two out of the following three criteria required for a pandemic: it is highly pathogenic; humans are immunologically naïve to the virus; and efficient human-to-human transmission occurs. Most human infections are caused by direct viral transmission from infected chickens or poultry products, and hitherto there is no evidence of efficient transmission between humans. However, if the current H5N1 strains (or other strains such as H7N7 and H9N2 that have crossed the species barrier to cause human disease) mutate and acquire the ability to spread easily among humans, they may trigger a severe pandemic. The changing behaviour of the virus, the acquisition of adaptive mutations, the expansion of host range, the emerging transmissibility among humans, and the potential for re-assortment events are raising concerns.²

Influenza pandemic preparedness plans include boosting biosecurity; stockpiling existing antiviral drugs, the cost-effective and timely use of these drugs; and the rapid development of pre-pandemic and pandemic flu vaccines. Vaccination is generally effective in prevention of influenza, and can reduce complications and the amount of virus in

circulation. The cost benefits of investing in vaccine development and production may far outweigh the potential health, economic and social catastrophic consequences of a pandemic. Because of the nature of global vaccine supply, there is real concern that it may not be possible to get vaccines to Asia and other regions in time, or in affordable and adequate quantities. The World Health Organization (WHO) is actively working with member nations and the pharmaceutical industry to address the demand to produce vastly increased quantities of vaccine to counter a potential pandemic.

At a WHO Meeting held on 25 April 2007, it was agreed that there is a need to develop mechanisms to ensure greater access to pandemic influenza vaccine for developing countries, and that it is feasible to create a stockpile of H5N1 vaccine. WHO Director-General Dr Margaret Chan declared “We have taken another crucial step forward in ensuring that all countries have access to the benefits of international influenza virus sharing and pandemic vaccine production”.³

Should a pandemic erupt, it may strike in two waves. It may be possible to attenuate the first wave of infections by initially deploying antiviral agents. If the pandemic strain can be rushed into an emergency plan to manufacture and administer vaccines quickly enough, the second wave of infections and deaths may be significantly decreased. Instead of using the outmoded egg-based vaccine process, a better strategy is cell-based vaccine production which is easier to handle, and involves culturing the virus for producing vaccines in human or mammalian cell lines. This may require manufacturing capacity at Biosafety level-3 if whole virus is used to generate vaccines.⁴ Alternatively, using reverse genetics, batches of vaccines have been produced as a hybrid consisting of a standard flu vaccine strain that incorporates genes derived from H5N1 strains belonging to clades 1 and 2.

Since 2005, many clinical trials to test such “pre-pandemic” vaccines have been initiated in advance of the possible mutation of H5N1 into a lethal pandemic version. Trials involving healthy adult volunteers aged under and above 65 years, who were injected with two vaccine doses, suggest that such candidate vaccines are safe, well-tolerated, and stimulate immune responses potent enough to neutralise

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H5N1 strains. In April 2007, the US Food and Drug Administration approved the first H5N1 influenza vaccine, which was purchased by the US government for their national stockpile.^{5,6}

Despite this preliminary optimism, more studies are required to compare the efficacy of prototype H5N1 vaccine candidates and of adjuvants, including antigen-sparing strategies. WHO has reported that the highest fatality rate of 73% was among patients aged between 10 and 25 years. Importantly, candidate vaccines must be able to protect the high-risk groups, i.e. children, the elderly, immunocompromised persons, and patients with chronic diseases.

Many questions remain unanswered. What is the actual post-vaccination antibody level in humans needed for protection against challenge with a live virus? Do current human influenza vaccines containing the N1 subtype confer partial cross-protection against H5N1? What are the roles of other vaccines (e.g. pneumococcal), modern antibiotics, and intensive care in reducing pandemic influenza morbidity and mortality? It is unclear whether vaccines now being developed would be effective against an emergent pandemic strain. What is the extent of cross-protection of current vaccine-induced immune responses to multiple virus clades of circulating and evolving highly pathogenic avian influenza H5N1 virus?

The ongoing evolution of H5N1, which is transmitting in diverse avian species, and at the avian-human interface, necessitates the continuous surveillance of evolving wild-type H5N1 strains in animals and humans. Indeed, different genetic sublineages have been isolated in Asia since 1997, i.e. clades 1, 2, 3 etc.⁷⁻¹⁰ Towards this end, the WHO launched the H5N1 Influenza Virus Tracking System in late 2007 as part of its Global Influenza Surveillance Network. Antigenic drift and shift, that allow influenza viruses to escape immunological or drug targeting, pose tremendous challenges to clinical practice. For example, there are increasing reports of the emergence of resistance or diminished sensitivity of influenza strains to the antiviral drug oseltamivir in several countries.^{11,12} Also urgently needed is research on vaccines that confer better protection against drift variants or that may not require regular updating.¹³

Lethal outcomes in patients with severe influenza pneumonitis may be attributed to acute respiratory distress syndrome, sepsis syndrome, or multiorgan failure, or any combination thereof.¹⁴ Influenza viruses that caused previous pandemics were avian-related viruses which acquired the ability to propagate competently in the human lung. Although genetic drift and shift are well-known mechanisms for heightened virulence, virus adaptation is less well-established. To better understand the molecular and pathological changes that occur during viral adaptation

in different host species, suitable animal models are required for studying the cross-species adaptation of the influenza A virus, a phenomenon of profound relevance to the emergence of future pandemic strains.^{15,16}

Perhaps even more significant than the capacity to build vaccine manufacturing plants or Biosafety level-3 laboratories, the prevailing anxiety over a potential influenza pandemic caused by the persistence of H5N1 in avian populations, together with sporadic human cases, has forced the world to seriously examine the social justice issue of global access to healthcare.¹⁷ The world is quite far from achieving the noble goals of the Alma-Ata declaration of 1978 by WHO, which recognised health as a fundamental human right of all countries and not just of the wealthy ones.¹⁸

Moving beyond the global perspective of avian influenza by the WHO leadership¹⁹ are complementary articles from Singapore^{20,21} and Hong Kong²² about preparations for pandemic influenza. The SARS crisis affected both cities drastically, and many valuable lessons have been learnt from that episode.

Another article that stems from the SARS outbreak is the commentary on risk communications by Menon²³ of the Singapore's Ministry of Information, Communications and the Arts. Some of the worst damage from a pandemic arises not from the virus or its complications, but from the fear and panic often instigated by certain sensationalistic aspects from the media and other sources. The paper illustrates some important principles in preparedness that go beyond the health sector to the wider realm of public communications.

This issue also features contributions on the scientific, epidemiological and clinical aspects of influenza. Lee et al²⁴ document the pattern of influenza pandemics in Singapore based on a historic review of multiple data sources. Relevant not just to historians, epidemiologists and public health physicians but also to policy makers, this paper clearly reveals that most influenza pandemics in Singapore were over within a few weeks during a period well before the rapid urbanisation of the 1970s. Sugrue and colleagues²⁵ review the role of antiviral drugs in the control of influenza from the perspective of research virologists. Hampson²⁶ provides an authoritative overview of the status of vaccines for pandemic influenza. As with most scientific innovations, getting the science to the bedside is often the greatest challenge as illustrated by the observational study of Kheok et al.²⁷ To lend useful insights from the veterinary angle, there is a document on the prevention and control of avian influenza in Singapore.²⁸

The articles in this issue thus aim to address the major fields of scientific research and endeavour from virology to immunology, epidemiology, therapeutics and public policy relating to pandemic influenza.

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