

The Threat of an Avian Influenza Pandemic

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There have been three influenza pandemics during the past century — in 1918, 1957, and 1968. Although the severity of the epidemics and the primary age groups affected varied, each was caused by a novel type A virus of avian origin. In 1957 and 1968, the new viruses had components of previous human viruses as well as avian viruses. The genome of the influenzavirus is made up of eight segments of RNA, and it was determined retrospectively that in both cases, there had been a reassortment of avian and human genes — most likely the result of the coinfection of a host by two different viruses. The origin of the lethal 1918 virus appears to have been different: recent data suggest that it resulted not from reassortment, but from the mutation of the genes of what was originally a purely avian virus.

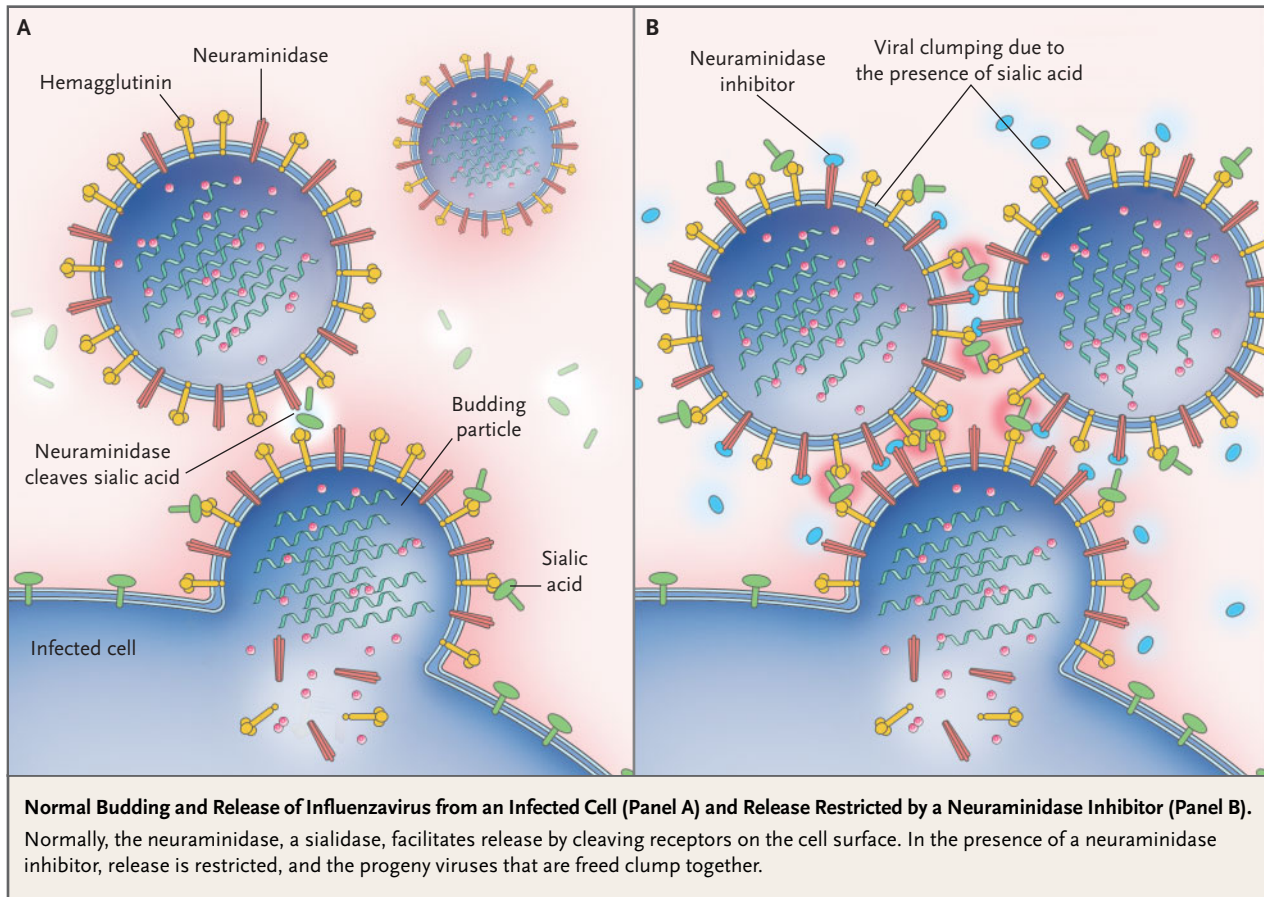
Although attention has recently been directed to the highly pathogenic avian influenzaviruses, most avian strains are of low pathogenicity. Ordinary avian influenzaviruses vary greatly, owing to their 15 hemagglutinins and 9 neuraminidases, and are widespread in migratory birds and water fowl. It was originally thought that these avian viruses could not directly infect humans, because humans have receptors for human viruses, and birds for avian viruses. Therefore, it was hypothesized that an intermediate host was required in which coinfection and reassortment could take place and that this host was the pig, which possessed receptors for both kinds of viruses.

The highly pathogenic avian influenzaviruses have appeared only occasionally, causing economic losses in the form of a reduced supply of poultry; the current widespread dissemination of these avian influenzaviruses is unprecedented. Also unprecedented is disease caused by the spread of these

highly pathogenic viruses from chickens directly to humans. The type A (H5N1) viruses spread in this way in Hong Kong in 1997, resulting in six deaths among 18 people with documented clinical cases; a smaller number of cases also occurred in this manner in Hong Kong and Fujian Province, China, in early 2003, and at least one death resulted. In addition, confusingly enough, there was a massive outbreak of another highly pathogenic avian influenzavirus — type A (H7N7) — in the Netherlands in 2003, in which bird-to-human transmission resulted in the death of an infected person. The antiviral drug oseltamivir was used extensively to help control and limit the spread. However, it is the A (H5N1) virus that represents an increasing global concern. Changes in the virus in 2003 resulted in the generation of what is termed the Z strain, which spread to at least nine countries in East Asia and Southeast Asia.¹ This strain was characterized by pathogenicity in a larger number of animal species than are affected by other strains and by resistance to the older class of antiviral drugs represented by amantadine and rimantadine. Bird-to-human transmission has continued, and it has now been documented as the cause of 32 deaths in 44 patients with confirmed cases.

Although the direct transmission of the virus from birds to humans is itself cause for concern, the greatest worry is that human-to-human transmission may begin to occur if there is a change in the viral genome. Even without genetic change, some inefficient spread among humans may now be expected. Such events occurred in 1997 in Hong Kong as well as during the outbreak in the Netherlands, but only asymptomatic infection caused by such transmission was documented. The report by Ungchusak et al. in this issue of the *Journal* (pages 333–340), however, clearly suggests the occurrence of person-to-person transmission through close contact with an infected child, leading to both clin-

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ical illness and death. No further spread occurred — a fact that is in keeping with the genetic characterization of the virus as still completely avian; neither mutation nor the sharing of genetic material with a human virus had taken place. The question, though, given the continued spread of this virus in Asia, is when such changes will happen. More important, what, if anything, can be done to limit early, albeit perhaps inefficient, human-to-human transmission?

Our newfound ability, facilitated by improving surveillance, to observe all these events, including occasional spread among humans, has led to the belief that it might be possible to restrict early spread and perhaps even to prevent a pandemic. The use of conventional vaccine in persons who come into contact with the virus, such as health care workers or those who kill infected chickens, has been recommended. Vaccination to prevent human influenza would also reduce the likelihood that a person would become coinfecting with the bird vi-

rus and the human virus, allowing for possible genetic reassortment.

But what if recognized transmission does begin to occur in a limited geographic area? Isolation and quarantine, which have proved effective against the severe acute respiratory syndrome (SARS), will probably not be sufficient to stop the spread of such an infection. Vaccine specific for the new strain will not be available for months after its appearance in humans, although studies of the necessary characteristics of such vaccines are ongoing, mainly under the sponsorship of the National Institutes of Health, and will provide essential information on their use should a pandemic begin.

We know that the neuraminidase inhibitor oseltamivir inhibits the type A (H5N1) viruses (see diagram).² It might be possible to achieve local control of an incipient outbreak among humans by using oseltamivir for prophylaxis in the contacts of patients as well as for treatment in the infected persons themselves.³ Treatment of patients alone

would not prevent further spread, but it might reduce the shedding of the virus and would, in any event, be required for ethical reasons. All these actions rely on early recognition through good surveillance and the ability to deliver the antiviral drug at a time when transmission might still be inefficient.

The logistic hurdles are formidable. A mobile stockpile of the drug would have to exist and be made available in the affected country. Oseltamivir is now being stockpiled by a number of developed countries for use once a pandemic virus becomes established and begins to spread rapidly around the globe. Developing a stockpile in an attempt to restrict the spread of the new virus at its source might mean diverting drugs from other national stockpiles. However, this diversion must happen. The notion of trying to control a pandemic at its source would have been considered laughable just a few years ago — but that was before SARS transmission was controlled by public health measures. We have no idea whether a type A (H5N1) virus that

was fully adapted to humans would continue to be highly lethal, but it is nevertheless incumbent on the global community to try to contain it.

The avian origin of previous pandemic viruses was recognized only after the fact; this time, we have been given a warning. We really are not sure when, or whether, the type A (H5N1) virus will start to spread among humans, but we must be ready to stop it if we can — and, if we cannot, at least to mitigate its effects through the use of stockpiled antiviral drugs and, eventually, strain-specific vaccine.

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2. Govorkova EA, Leneva IA, Goloubeva OG, Bush K, Webster RG. Comparison of efficacies of RWJ-270201, zanamivir, and oseltamivir against H5N1, H9N2, and other avian influenza viruses. *Antimicrob Agents Chemother* 2001;45:2723-32.
3. Monto AS. The role of antivirals in the control of influenza. *Vaccine* 2003;21:1796-800.

To Inform or Persuade? Direct-to-Consumer Advertising of Prescription Drugs

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Merck's withdrawal of rofecoxib from the market last September and Pfizer's announcement in December of possible cardiac risks associated with high doses of celecoxib reignited long-simmering controversies regarding drug promotion, in part because both cyclooxygenase-2 inhibitors have been heavily marketed directly to consumers. Indeed, after discussion with the Food and Drug Administration (FDA), Pfizer suspended all direct-to-consumer advertising of celecoxib. Adding fuel to the fire is class-action litigation filed against AstraZeneca alleging that its direct-to-consumer advertising misrepresents the superiority of its proton-pump inhibitor esomeprazole over less expensive alternatives.

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Although the information made public in these cases is probably incomplete, these events offer an opportunity to step back and consider the appropriate role of drug promotion in general and direct-to-consumer advertising of prescription drugs in particular. What are its effects on physician-patient relationships? How might FDA oversight of such advertising of prescription drugs (and now also of prescribed medical devices) and the content of industry advertising be improved through evidence-based policy changes?

Advertising has long been controversial. Although Thomas Jefferson once claimed that "advertisements contain the only truth to be relied on in a newspaper," F. Scott Fitzgerald voiced a more common view when he opined that "advertising is a racket . . . its constructive contribution to humanity is exactly minus zero." In the context of pre-