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Avian Flu

A NextGen *Free-Standing Perspective* Article

Following the Katrina disaster and the US federal government's mismanagement of the relief efforts, the question of the government's ability to respond to and handle disasters has occupied the minds of many people. With the media's constant coverage of avian influenza's frighteningly quick expansion in worldwide bird populations, it is no wonder that the public is concerned. The question of whether or not our global society is prepared for a potential avian influenza pandemic is thus not only of great importance medically, but also socially and politically.

The current viral strain under scrutiny is the H5N1 virus, which refers to the fact that this is an influenza A virus bearing a subtype 5 hemagglutinin and a subtype 1 neuraminidase on its surface. This avian virus differs from the human H1N1 and H3N2 influenza A strains, which are typically responsible for human infection and are found in current trivalent flu vaccines (along with an influenza B strain). These viruses show sharply different pathogenicity as Dr. Frederick Hayden, Professor of Internal Medicine and Pathology at the University of Virginia School of Medicine, Charlottesville, explains: "Human influenza has a high rate of infectivity...a fact that translates into significant portions of the population being infected each year. While the CDC estimates that about 36,000 deaths per year can be attributed to influenza and its complications, this tragic figure is just the tip of the iceberg when it comes to the total population infected, most of who typically suffer from minor consequences. In contrast, sporadic human H5N1 infections have been few in number but in the documented cases of H5N1 in humans, there is a high mortality rate in excess of 50%."

In the medical community, such a high mortality rate immediately brings to mind the 1918 Spanish Flu pandemic, which, as Hayden points out, "was particularly notable because of its high mortality rate in young and middle-aged adults." An estimated 1% of the population of the developed world died from it. More recently, it has been possible to reconstruct the 1918 virus from RNA samples preserved in fixed or frozen tissue specimens, allowing a determination, as Dr. Hayden explains, "that it was of bird origin [and] underwent some sort of mutational changes allowing it to infect human populations." This risk of a viral species jump into humans is of particular concern with the H5N1 virus, a virus that has, thus far, been documented primarily in humans who have come in close contact with infected poultry and rarely with other infected humans. Hayden notes, "There are two methods that H5N1 could reach pandemic status. It can occur through the virus acquiring mutations which allow it to be easily transmissible from person-to-person (i.e. through air droplets, as in the case of human influenza viruses). It can also occur through dual infection with a mammalian influenza virus of a host (i.e. pig or human), that allows the viruses to swap gene segments to generate a novel virus containing the H5 that is infectious for human populations."

With close contact between bird populations and humans (i.e. on poultry farms) facilitating the first, and the relative ease of the second, many experts believe that it is only a matter of time before the H5N1 virus jumps the species barrier on a sustained basis. As Dr. Michael T. Osterholm, director of the Center for Infection Disease Research and Policy and a member of the National Science Advisory Board on Biosecurity, notes, "There are many reasons given as to why it would happen, and many as to why it wouldn't. I happen to give more weight to the 'it would happen' argument, especially from the perspective of public health planning. What we need to understand is that there have been ten pandemics in the last three hundred years, and that having a pandemic at some point will be inevitable, and that even a moderately sized pandemic is a very big and serious issue." This has led some to tout the importance of eradicating the disease in bird populations before it affects humans. Dr. Osterholm,

however, believes this idea is foolish: "The idea that we can control the threat by eradicating the disease in birds is like saying that we can control the wind. Nothing we can do now can alter the course of an H5N1 pandemic at this point. If it's going to happen, it will happen."

If attempts to control the infection in birds are doomed to fail, the obvious next question revolves around the status of the medical preventions and treatments that exist. Sadly, although annual vaccines for influenza viral strains are reasonably available in the developed world, the prospect of controlling the spread of the virus with mass vaccination campaigns appears to be bleak. Regarding Dr. John Treanor's recently published findings in a clinical trial on a possible H5N1 vaccine in the *New England Journal of Medicine* (1), Dr. Osterholm states, "While promising, there are still serious reasons to be concerned. The dose used in the study is about twelve times higher than the typical flu dose, and was effective only in a little over half the receiving population." This is particularly problematic, as Dr. Hayden explains, "This takes a great deal of antigen, enough such that the production of the vaccine becomes a major limiting factor."

Work is currently being done on improving the immunogenicity of the vaccine by adding adjuvants and experimenting with different routes of administration. Sadly, as Dr. Osterholm sums it up, "What we have here is just nibbling at the edges." To Dr. Osterholm, the problem is a systemic one: "There are two important things to consider. First, we are currently still employing a basically 1950's technology with some very limited changes...The second thing is that pandemics, in today's era of the global just-in-time-economy, would be catastrophic events, especially for the world economy. Even if we had the capability to vaccinate most Americans...there would be serious collateral effects around the world to take into consideration. For example, a vast majority of the supplies and drugs that we would use to deal with a pandemic are manufactured offshore. In a pandemic, it is unclear if those production facilities would still be operational, if there would be people to fly and drive the planes and trucks to deliver them, and if there would even be proper staffing to administer the vaccines."

While there are two classes of antivirals which exist to treat influenza, these too have serious limitations. The first class, the amantadanes (amantadine and rimantadine), have been in existence for decades, but have limited applicability. Dr. Hayden explains, "The CDC recently issued a statement asking doctors not to use the amantadanes because of high frequencies of antiviral resistance, over 90% of the influenza strains isolated between October and December of 2005 showed resistance to amantadanes. It is also known that many H5N1 viruses also show resistance," a problem which restricts the applicability of the amantadanes in dealing with an H5N1 pandemic. The second class of antivirals used for flu are the neuraminidase inhibitors. While two neuraminidase inhibitors exist in the form of zanamivir (Relenza) and oseltamivir (Tamiflu), there is such little use and production of zanamivir that Dr. Hayden states, "Functionally, we really are restricted to just oseltamivir at present."

Luckily, resistance to oseltamivir in viruses seems to be accompanied by a reduced ability to replicate, making it a useful drug to stockpile. However, Dr. Osterholm points out that there is a serious problem of quantity as "we probably will need to treat patients for a longer period at a higher dose than the current regimen. Hoffman-La Roche can produce (along with all the sublicensing organizations which produce the drugs under its auspices) enough drug to treat 7–8% of the world population in four years [under the current regimen]. We would probably need to at least double the dose for twice the duration, which would mean possibly only a 2% coverage." These drugs, too, are only effective if given early. In the case of avian influenza, which replicates very quickly, the drugs must be given almost at the time of infection, a problem which to Dr. Osterholm is very difficult to solve because, "as far as I know, there is no feasible way to provide this sort of delivery system even if we did have enough drug for everyone." Additionally, even if a system of distribution were identified, serious work needs to be done in answering the ethically difficult question of which groups of people would be given the limited supply of drugs.

With the specter of pandemic hanging over the world, the obvious question is "what can be done?" The answer, however, is contextual, as Osterholm points out, "What we need to do depends a great deal on when the epidemic happens. If it happens in ten years, then the use of vaccines can play a big role. If it happens tonight, we're somewhat screwed with regards to the vaccine." To Osterholm, the critical thing, beyond the obvious stockpiling of drugs and vaccines, needs to take place on a global level, "Much of the world just doesn't understand the seriousness of the problem and hasn't given enough attention or resources into properly planning for a pandemic." This is an oversight which is particularly fatal when dealing with a disease which pays no attention to political borders, and, to Dr. Osterholm, can only be dealt with if a unified and worldwide effort is made at surveillance and towards production and testing of a universal vaccine.

When asked the same question, Dr. Hayden focused a good deal on the issue of "surge capacity," the ability of a health infrastructure to cope with a sudden increase in the need for critical healthcare. On the subject, Dr. Hayden noted, "one dilemma that we face in the United States is the great focus on cost efficiency to the point where there is very little surge capacity in hospitals in terms of beds and staffing.

We have a quarter of the hospital beds per capita that Japan and Switzerland have, most of which are occupied, creating doubt in what would happen if many more people required hospital care." To Dr. Hayden, this same problem existed also in our drug and vaccine manufacturing technology: "[Our] goal is to develop a [vaccine] production technology that can be quickly and effectively ramped up to full capacity."

Currently in the United States, as Dr. Hayden puts it, "Many groups of experts are working with government officials on how we plan to deal with an avian flu pandemic. There are many non-pharmacological strategies being actively discussed such as closing schools, preventing mass public gatherings, house quarantines, isolation of the sick, and on whether or not to use masks, and so on and so forth." Osterholm, too, notes, "Communities...must learn to depend on themselves and their own preparation...every region is going to be affected by this at the same time, and unlike a natural disaster, they won't be able to wait for the national guard or volunteer forces or federal aid to deploy."

It was no surprise, then, when asked what individuals and families could do that Dr. Osterholm replied "Go to city council and find out what's going on. Go to your county administrator, to all areas of local government and ask if planning is being undertaken, if funding is being allocated, and so on. Put pressure on the people who can make a big impact and who have the responsibility and the ability to direct the necessary changes. □

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» Back to Current Issue
