Letter from the Desk of David Challinor
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During the years 1918-19, just before I was born, the world suffered from a pandemic (an epidemic that affects the global population). It was called Spanish flu because of the early affliction and large mortalities in Spain where it allegedly killed eight million people in May 1918. While growing up in the 1920's, I heard stories from my parents and their friends about the Spanish flu, particularly how lethal it was and how many soldiers succumbed to it in the trenches of WWI. A typical example of the illness was that experienced by my late father-in-law. He was a healthy man in his 30's, and when he came home one evening from work, he remarked to his wife that he did not feel well and was going to take a nap before dinner. Without knowing it, he had been struck by the flu and did not awaken for seven days! This month's letter is about pandemics, their effect on the global economy and what tools are available today to fight such disasters.

The rapid spread of Spanish flu was astounding and it is hard to imagine today how many it killed; although it was fatal to only two percent of those infected, it was believed to have been the primary cause of death for somewhere between 40 and 100 million people. Scientists believe that the virus responsible for this flu was an avian one (H1N1) similar to the current virus infecting poultry in Southeast Asia (H5N1).

It appears that the present avian flu is spread among crowded chickens in commercial operations by physical contact between birds. Most of the human cases so far have been among poultry workers and their immediate families. Interestingly, the World Health Organization reported after an intensive study of 200 human cases that the victims were skewed towards the young. The average age for the group studied was only 20, with the greatest death rate (73%) among those between 10 and 19. This mortality pattern fits that of the Spanish flu pandemic. The common annual flu, by contrast, mostly kills infants and the aged, frequently from subsequent bacterial pneumonia.

Only recently have scientists proposed a hypothesis to explain why the young are disproportionately vulnerable. Blood tests from people living near recent avian flu outbreaks in Southeast Asia indicate that very few individuals have antibodies to the H5N1 virus, with the result that no large group of survivors of even mild avian flu exists. Public health experts believe that the many young people who succumbed to both the Spanish flu and to the current avian flu fell victim to what is called a "cytokine storm." This medical condition occurs because the unusually vigorous immune system of most young people goes into "overdrive" during cell division to produce new white blood cells to fight the infection—so much cytoplasm (protoplasmic liquid within the cell, but outside the cell nucleus) is produced that the lungs are flooded.

The H5N1 virus that had been confined to Southeast Asia has now spread throughout Europe and into several African countries. Fatalities, however, are three times greater this year than last, with most new cases cropping up in Indonesia where 39 have died so far. Indonesia is thus approaching Vietnam's total mortality of 42 (the country hardest hit so far). Interestingly, Vietnam has not had either a human death or poultry outbreak of infection this year.

Although no wild birds infected with the virus have yet been found in the New World, health officials are on high alert. The crowded breeding grounds of alcids (auks and their close relatives) would seem to be prone to the rapid spread of avian flu once infected, but these Arctic birds are still widely separated from current infected areas. Wild birds from Asia frequently appear in North America far outside their normal range, generally being driven off course by strong winds. Fortunately, such vagrants are relatively rare and widely scattered, making the odds of any one individual carrying the virus exceedingly remote.

A greater threat to New World infection comes from the international pet bird trade. An estimated 47,000 pet birds were imported legally into the United States last year. Although the Customs Service insists that each legally imported bird has been tested for avian influenza, one wonders whether each such bird is truly free of infection. An even greater threat arises from smuggled birds, whose total numbers may match the legally imported ones. Another threat exists in the huge commercial poultry trade, which includes not only the birds themselves but also their byproducts and processing machinery. So little is known about H5N1 that defensive measures are hard to plan. Nonetheless, vaccines against bird flu are being developed.

In May, eight people in a Sumatran family came down with bird flu and seven of them died. What was especially significant about this large cluster of cases was that all but one of the victims appears to have caught the disease from other family members. This is the first known incident of human-to-human transmission, and apparently resulted from the crowded room where they all slept. Although there is no solid evidence yet that the H5N1 virus has mutated to spread easily through human populations, virologists tend to fear that the virus may eventually do so. Because of this threat, scientists and pharmaceutical companies are seeking a vaccine to inoculate people before a pandemic hits. Such a vaccine should have a long-term effect and be able to counter any mutant form the virus might take. To illustrate recent advances in virology, inoculants soon to be tested in humans contain adjuvants—immunity stimulating chemicals. Other vaccines to be tested are made from DNA rather than from the virus itself. The ultimate goal is to find a vaccine that will be effective against all kinds of flu. Until such a vaccine is developed, it makes sense to have available the best vaccine researchers can make now. Even though the vaccine might not yet be 100 percent effective in stopping avian flu infection, it should at least drastically lower the current high death rate.

Several problems must be resolved before any vaccine against pandemic bird flu can be stockpiled. The first is that most big pharmaceutical companies are presently concentrating on proven vaccines to protect against ordinary flu. Producing this vaccine is very profitable so there is scant economic incentive to gear up production of a new specialized vaccine. Unfortunately, once a pandemic starts spreading, there would not be time to speed up production, distribute the vaccine globally and inoculate the endangered. Sadly, the manufacturers were "burned" in 1976 when it was predicted that swine flu would become a human pandemic. The United States government vaccinated millions of people, but the pandemic never transpired. Compounding the problem was that a scattering of those inoculated became ill and sued the government.

I remember an embarrassing consequence of the swine flu epidemic. When I was in Cuba in 1983, I paid a courtesy visit to the Cuban Minister of Agriculture, an elderly revolutionary who berated the United States for introducing swine flu into Cuba surreptitiously from night-flying CIA planes. The island had historically been free of this disease. I listened in silence and finally responded by shifting to the mutual benefits of the proposed joint projects between the Smithsonian and the Cuban Academy of Sciences for which I had come to negotiate. What else could I do?

Vaccines also have development problems. Although adjuvants, when combined with vaccines improve potency, some of the powerful adjuvants tend to be toxic. New techniques involving a skin patch placed over the vaccine injection site allow the adjuvant to enter the skin's dendritic cells (which are a type of immune cell) and thus never (or hardly ever) enter the bloodstream. Using this procedure on mice has proved successful in avoiding toxic reaction to the adjuvant.

I have used these examples to show that the development of a successful vaccine is indeed a complicated and time-consuming process. Whether avian flu ever becomes pandemic is hard to predict, yet the consequences of failing to take appropriate countermeasures early on would be devastating. The Smithsonian has already prepared defensive protocols to protect The National Zoo's people, birds and animals from infection. Disinfectant shoe sole baths have been installed at all facilities where keepers enter for hands-on care to animals. A website has been established for current information on emergencies and to provide basic protection procedures such as regular hand washing and the use of protective equipment—these are as effective against a pandemic virus as against any flu virus. Over the past 500 years there have been two or three flu pandemics each century; whether one will arrive in the USA as a mutation of H5N1 virus or from some other kind of flu, an eventual outbreak is undoubtedly inevitable. The good news is that conscientious public health professionals recognize the threat and are already reacting to it. The obverse is the reality that many high

government officials are unwilling to assign the necessary priority to develop adequate protective measures until the pandemic has already hit. Do not give up! There is always hope that action will trump inaction.

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P.S. Background information for this letter came from Debora Mackenzie's article "Today's bird flu vaccines will do." *New Scientist*, 17 June 2006, pp. 10-4, Donald G. McNeil Jr.'s piece in *The New York Times*, 7/2/06 "Avian Flu Tends to Kill Youths as in 1918 Wave, Study Finds" and Colleen Perlman's article "SI prepares for potential pandemic flu" in the *TORCH*, No. 06 June 6, 2006. Comments from Peter Marra of the Zoo's Department of Conservation Biology were much appreciated.