The Clinical Newsletter
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Western Maryland Health System
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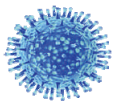
The Influenza Pandemic: What will it be?



The present influenza virus epidemic of A(H1N1)2009 [AH1N1], aka swine flu, novel A(H1N1), S-OIV (Swine-Origin Influenza Virus), and officially identified as A/California/4/09(H1N1), has been classified by the World Health Organization as a Stage 5 outbreak. Staging is based on the degree to which an infection has spread around the globe rather than the virulence of the involved organism.

There may be several issues/questions that arise at present and retrospectively. Among them are:

● Virulence: It appears to be difficult, if not impossible, to define the case fatality rate (CFR) of the circulating strain. In the absence of an accurate number of confirmed cases and total number of asymptomatic, mildly symptomatic and severely symptomatic cases to serve as the denominator, together with the number of deaths for the numerator, the CFR is not available. An early estimate places the CFR in Mexico at ~0.4% (range 0.3 to 1.5%).

● Cause of fatalities: It is not known whether the deaths identified as being caused by AH1N1 are due to respiratory failure, multiple organ failure (as is the case with the present avian influenza virus), a "cytokine-storm", or secondary bacterial pneumonia. The CDC has reported that many hospitalized patients have a viral pneumonia with fewer having a bacterial etiology. However, it is pointed out that most hospitalized patients have received antimicrobial therapy.

● Vaccine production: The choice of influenza A and B strains for the seasonal flu vaccine is usually made in February or March. The decision is generally based on influenza strains circulating in China. The question arises as to what strains will be used for the 2009-2010 Northern Hemisphere vaccine. There are a few possibilities. Among them are that the vaccine will be composed of:

○ the AH1N1 strain presently in circulation as the sole vaccine antigen. The 1918 influenza pandemic began as a mild infection in the Spring, was relatively quiescent during the Summer, and returned in a more virulent form in the Fall. Were this to occur this time the basis for the increased virulence may be of importance. If there is a change in the hemagglutinin (H) or neuraminidase (N) epitopes we may end up with a vaccine that is less protective, as was the case with the 2007-2008 flu vaccine.

○ the AH1N1 strain presently in circulation added to the vaccine components already in production based on the WHO and CDC decisions earlier this year. This would require a larger amount of viral antigen of each strain as the same volume of vaccine would be maintained per dose. Hence, the number of available doses of vaccine may have to be decreased.

○ an adjuvant added to either the single strain vaccine or to the combined vaccine to elicit a better immune response per dose.

○ the previously planned components of the 2009-2010 vaccine without the AH1N1 strain presently in circulation . This could be due to production problems, e.g., growth rate of the novel strain, or its antigenicity.

○ two vaccines, the original 2009-2010 preparation and two doses of the vaccine containing the AH1N1 antigen.

● Basis of virulence: Virulence of the 1918 pandemic flu virus was due to its ability to replicate in the absence of trypsin and a high growth rate in human bronchial epithelial cells. The strain was also readily transmitted from person-to-person. It seems that the AH1N1 strain is transmitted readily too. An early estimate of the reproductive number (the average number of secondary infections caused by each individual), R_o, was 1.4-1.6, which is higher than seasonal flu. More recent estimates gave values for R_o for Mexican cases between 2.2 and 3.1; and for students of the St Francis Preparatory School in NYC 2.69 to 3.45. If the strain gains some property to add to its ease or rate of growth in humans a similar increase in virulence may occur. Some studies suggest that social distancing may only be effective if R_o = <2.

It is known that the present virus is a reassortant of genetic material of avian, porcine and human origin. Genetic shift or reassortment may be more apt to occur in pigs. There has been a recent report of AH1N1 being transmitted from human-to-pig in Canada. This may increase the possibility of an altered strain by Fall.

● Immunity: By sequencing the genomes of more than 50 samples of the AH1N1 virus, researchers have found that it is distantly related to its nearest relatives, indicating that its genes have been circulating undetected for an extended period. At the present time we do not know what percentage of the population will have been exposed to AH1N1 by the time the present wave of infection subsides. If there is no significant drift of the H and A antigens these people will have at least partial immunity and should have a milder infection, if any, later. Additionally, it has been seen that the average age of AH1N1 cases is <20 years. If this holds true the "older" population (such things are relative) may be less affected. This is being seen with the H5N1 avian influenza strain that has been of concern. The vast majority of those infected have been <40 years of age. One possibility for both situations is that the "older" population has either been naturally exposed to sufficiently similar strains in the past or has been immunologically challenged by previous vaccination. A recent CDC study supports this possibility. There may be a sufficient anamnestic response to afford some level of protection so that when exposed the patient is asymptomatic or presents with a mild case.

● Different virus strain: The British Columbia Centre for Disease Control virology laboratory has described some H3N2 strains from recent travelers to Mexico. They are suggesting that some of the infections in Mexico may have been caused by this strain rather than AH1N1 as initially thought. The strain has been identified as being very similar to A/Brisbane/10/07(H3N2) that was part of the 2008-2009 vaccine and is expected to be in the 2009-2010 version. They have identified at least two gene mutations at the hemagglutinin B antigen site that change its amino acid sequence. This may be an early sign of genetic drift in a strain expected to circulate in the Northern Hemisphere in the coming flu season. Such a drift might occur in AH1N1 too.

● Multiple waves: Past influenza pandemics have come in multiple waves, with a higher CFR in a second or third one. If there is a second outbreak the interwave period may offer the opportunity to produce an effective vaccine, increase the supply of antivirals for all nations, and better prepare for the base(s) for mortality, e.g., if deaths are primarily due to secondary bacterial pneumonia sufficient antibiotics can be at the ready; if they are similar to the "cytokine-storm", as was the case in the 1918 pandemic, measures can be taken to address this.

● Testing: Commercially available influernza screening test kits were initially thought to be able to detect all, or at least the vast majority of, cases of AH1N1. It quickly became apparent that the assays were far from approaching 100% sensitivity and specificity. Manufacturers are reviewing their tests but it may be unlikely that all of them will be able to get FDA approval before October 2009. The CDC has since supplied RT-PCR reagents to all of the states which allows faster TATs than initially.

● The near future: Several questions remain:

○ How long will this wave of AH1N1 persist? Will there be additional ones? If so, what will be the severity re: symptoms, R_o, and CFR?

○ Are all or at least the majority of cases seen now necessarily going to be AH1N1? Since seasonal flu appeared to be almost over by early April it is possible that the majority of patients meeting the case definition will have been infected with AH1N1.

○ Will the pandemic influenza strain develop resistance to the neuraminidase inhibitors?

○ If there is a significant outbreak in the Fall will it be a pandemic? If yes, caused by which virus - Novel A(H1N1), the mutated A/Brisbane/10/07(H3N2) found in Canada, the A(H5N1) avian strain that has gained an increased R_o an A(H7) or A(H9) that has been reported in recent years in humans, or?