

Swine Flu

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In an earlier column, I commented on the poor general state of preparation for natural and unnatural disasters, particularly those involving diseases (1). Since then, a virulent influenzavirus strain has emerged in the Northern Hemisphere, now is spreading world-wide, and has been declared by the World Health Organization (WHO) as the cause of a Phase Six global pandemic, based on the sustained worldwide spread of this H1N1 virus, not based on the severity of illness caused by this virus.

This emergence and the attendant media frenzy accompanying this emergence caused me to re-examine my earlier thoughts and expressions. I believe now that those comments were superficial, only in part due to space constraints for this column. What I neglected to discuss were the media responses to disease emergence. I apologize for this sociological oversight.

The final sentence of that column was "Perhaps John Lennon had it right: "Life is what happens when you are making other plans." That philosophy still is correct. While we have been making (very expensive) plans to forecast, detect, and prevent disease outbreaks, which we justifiably continue to fund, we have not done what always is necessary in disease control – educate the public. During the past days, I have been inundated with e-mails, telephone calls, and people stopping me in the hall asking for "my view" on this latest potential disaster, "swine flu." I certainly am no expert on influenzaviruses, swine, or clinical medicine, so merely by asking me for advice, wisdom and insights, these people demonstrate just how bad the situation is. They might as well ask me about the best fertilizers to spread on their gardens (I know that fertilizer should be spread, to wit these columns), what the name of the capital city of the Democratic Republic of Timor-Leste is (I am sure it must have a capital city; most countries do), or why the Palestinians keep bombing Israel and then ask why Israel keeps bombing them back (they do). Here is the problem: laypeople look to people they consider ex-

perts to answer their uneducated questions. The reason they have questions in the first place is that they have seen something on TV, read something on a blog, in a newspaper or other non-scientific publications, heard a neighbor say something in a bar, or have heard the calm and soothing voices of politicians saying that there is no need for panic. Panic? Was there some tendency to panic before they said that? Is there panic now that they have said there is no need for panic?

The media are trying to sell their products, not trying to educate anyone. Governments are trying to show that they are on top of things, that they are competent to provide safety and security for the citizens of their country. The Obama administration certainly does not want to be seen as responding to a disaster as incompetently as the previous administration responded to the Hurricane Katrina disaster. Sometimes that adds up to people stirring an un-stirred pot to show they can handle a stirred pot. There are more examples of this than I could possibly include in this or in hundreds of columns.

"SWINE FLU," "PIG FLU," "HOG FLU": Any of these terms sends chills up the spines of people in the pig-rearing business. Indeed, on April 29, 2009 Egypt announced that all 300 000 pigs in Egypt would be slaughtered to prevent transmission of this virus to people. Great idea but there is no evidence that the virus had reached Egypt or, somewhat more importantly, that transmission of this virus from pigs to humans is important, although it probably is. This act likely pleased some in Egyptian society but it impoverished others.

Early on I was wondering how long it would take for countries which consider pigs "unclean" to have their say in naming this virus. It didn't take long to get an answer: Israel has announced that it would not call this virus "swine flu," it would call it "Mexican flu." Moslem countries have not said anything as yet, as far as I know. In any case, it wasn't

“Mexican” for very long. A paper by the Editorial Team of “Eurosurveillance” made helpful suggestions as to a proper name for this virus (2).

DISCOVERY: Influenza has been recognized for hundreds of years, but the cause was unknown for most of that time. In 1892, the German bacteriologist Richard Pfeiffer isolated a bacterium which he considered the causative agent of this disease (3). In 1921, however, Peter Olitsky and Frederick Gates of the Rockefeller Foundation published their filtration results, which demonstrated that nasal secretions from patients infected with the 1918 influenza virus (influenza A H1N1, *vide infra*), and passed it through a filter that excluded bacteria, still caused pneumonia in rabbits (4,5). Olitsky and Gates had isolated the etiologic agent of this disease but did not recognize that and subsequent studies by others minimized their discovery. Paul Lewis and Richard Shope, also of the Rockefeller Foundation, later did similar filtration work and discovered that the bacterium they found, which they called *Bacillus influenzae suis*, was similar to that which Pfeiffer had isolated. That bacterium did not cause disease in pigs (6); the filtrate, however, did. When the disease they could cause in pigs was found to be more mild than the natural disease, they added their *B. influenzae suis* to the filtrate and reproduced the severe form of the disease (7).

DEFINITION AND CHARACTERISTICS: To understand this disease, let us start at a reasonable beginning – the word “influenza,” first used in English in 1743 when the disease was recognized in Europe. This word originated with the Italian word *influenza*, meaning “influence” (Latin: *influentia*), named so because the disease was considered to be caused by unfavorable astrological conditions. The disease also is known as *epidemic catarrh*, *grippe* (from the French), *sweating sickness*, and *Spanish fever* (particularly for the 1918 pandemic strain). Hippocrates had clearly defined this disease about 2400 years ago but he lacked laboratory confirmation (8,9).

According to one web site “The disease is caused by certain strains of the influenza virus.” As are other, if not most, web sites about many other topics, this is incorrect. There is no such thing as “the influenza virus,” any more than there is “the encephalitis virus” or “the hantavirus” or “the elephant,” unless you are writing a novel. Within the virus family *Orthomyxoviridae* are 5 genera: *Influenzavirus A*, *Influenzavirus B*, *Influenzavirus C*, *Thogotovirus*, and *Isavirus*. Within the former 3 genera are viruses that cause influenza; the thogotoviruses are transmitted to vertebrates by ticks but

do not cause influenza, and the single isavirus, infectious salmon anemia virus, is transmitted to fish through water. Influenza A virus (FLUAV), influenza B virus (FLUBV), and infectious salmon anemia virus contain 8 linear, negative sense single-stranded RNAs (viral RNAs, vRNA). Influenza C virus (FLUCV) and Dhori virus (a thogotovirus) contain 7 vRNAs and Thogoto virus contains 6 vRNAs. Superinfections of cells with, for example, 2 different FLUAVs allows for reassortment of vRNAs, which can result in progeny viruses with characteristics of each parent. For example, if one parental virus contains genes specifying high pathogenicity and low transmission potential and the other parental virus contains genes specifying low pathogenicity and high transmission, the progeny might have high pathogenicity and high transmission potential. This is not a good thing.

The 8 vRNAs of the influenzavirus A genome produce: PB2 (cap binding transcriptase), PB1 (elongation transcriptase), PA (protease activity [uncertain] transcriptase), HA (hemagglutinin; viral surface projections), NP (nucleoprotein that binds RNA and transports vRNA nucleoprotein), NA (neuraminidase that functions to release virus from the cell; viral surface projections), M1/M2 (matrix proteins), and NS1/NS2 (non-structural proteins; NS1 functions in RNA transport, translation, and splicing; the function of the NS2 is unknown). Obviously this is a complex virus, but the major problem we have dealing with it is that the reassortants that can and do occur can cause trouble for humans and for our livestock and wild friends. Influenzavirus A isolates from birds have provided us with evidence for the presence of 16 hemagglutinins and 9 neuraminidases in various combinations. The subtypes are noted as H1N1, H1N2, etc., based on these characteristic proteins. Pigs, horses, and humans have a much narrower range of subtypes but multiple variants may circulate enzootically among birds and among mammals of certain species, ie, H5N1, H7N7, and H7N3 in birds; H3N8 in dogs; H7N7 and H3N8 in horses, etc. Some have been documented to jump species to humans, some have not. In addition to reassortment of genes (genetic shift), small but significant mutations in the nucleotide sequence (genetic drift) can suddenly, or cumulatively over time, bring about alterations in the virus phenotype. The fun never stops!

Colloquial expressions such as swine flu, canine flu, equine flu, bird flu, etc. are used, but these terms are neither accurate nor sufficiently descriptive. If those to whom swine represents something forbidden, what about elephant flu (might make you gain weight), dog flu (might make you turn around 3 times before you lie down), or ad-

ministrator flu (makes you want to lock doors, kick people out of parking spaces, and write more rules)? The virus is the virus, the host is (not so simply) a vehicle.

The proper expression for a particular strain of an influenza virus, according to the International Committee on Taxonomy of Viruses, should include the name of the virus, the source, the location, the laboratory isolate number, and the year of collection (10). An isolate from the current outbreak in Mexico might be named influenza A virus/human/TM/123/2009 (H1N1). In other words, it is an influenza virus A from a human in Tamaulipas State, Mexico, it was the 123rd isolate from the laboratory which isolated it, and was collected in 2009. The term "swine flu" may be useful for rapid and vulgar communications but it is not correct. In the current outbreak in Mexico, or anywhere else, pigs were not even the first vertebrate hosts shown to be infected.

It likely will be difficult to convince newspapers, TV talking heads, and government spokespeople to say anything but "H1N1," which is good enough and a great deal more accurate than is "Mexican flu" or "swine flu."

EPIDEMIOLOGY: Previous experiences with influenza epidemics indicate that many of them appear as outbreaks at the end of the expected influenza "season," disappear for the summer and then reappear at epidemic rates after that, when people spend more time indoors, people such as school children (who also are people, although they sometimes appear to be something else). Therefore, even if this particular strain disappears over the Northern Hemisphere summer of 2009, surveillance still must be maintained. This virus might disappear altogether or it might resurface to cause considerable human misery.

VACCINES: Determination of the required composition of influenza virus vaccines is done annually by a committee of W.H.O. experts. The difficult task these people have is to provide informed deduction as to which of the currently epidemiologically significant circulating strains should be included in the next year's vaccine. Under current procedures, they only have a 6-month lead time to do this, and even then they cannot be 100% certain that the viruses they judge should be in the vaccine are the ones that will be circulating in the next year or in this or that hemisphere. Composition of next year's vaccine was determined more than a month ago and now these people must decide whether to modify the plans to include the new H1N1 virus. Fortunately, certain drugs which block neuraminidases appear to be effective against this virus.

All this might be old news by the time you read it. From 1993 to 2003, the average number of deaths due to influenza (all influenzaviruses) in the US was 36 171. In 2005, there were 63 000 and in 2006 there were 56 000. As of early May 2009, the number of deaths due to influenza A viruses in the United States was slightly lower than average (11). As I write this, the number of cases in Mexico has peaked, perhaps due to individual and governmental actions, perhaps to a lack of epidemic potential on the part of the virus. Perhaps everyone there already was exposed to this virus or everyone in Mexico has at least partial protection acquired by previous infections with closely related viruses.

WHAT'S NEXT?: The bottom line in this tale is that a huge amount of money has been spent since the false fright days of fall 2001 and the SARS outbreak. National, state, and local laboratories have been improved, detection systems have been enhanced, more laboratory workers have been trained and hired, emphasis has been placed on early and automatic reporting, meetings have been held, symposia organized, and education upgraded. Still, as pointed out in the Washington Post (12), the so-called swine flu in Mexico was being investigated by Mexican authorities on April 6, 2009 but the public did not receive reports of this until April 24. Could it be that the WHO was not properly informed within a useful period of time? Even a regional warning from the Pan-American Health Organization (WHO's representative in the Americas) would have been informative and, perhaps, useful.

"Life is what happens when you are making other plans." Perhaps public health authorities were making other plans, for the weekend, a few days at the beach, or for the Spring holidays. Whatever the answer is, it isn't good enough.

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