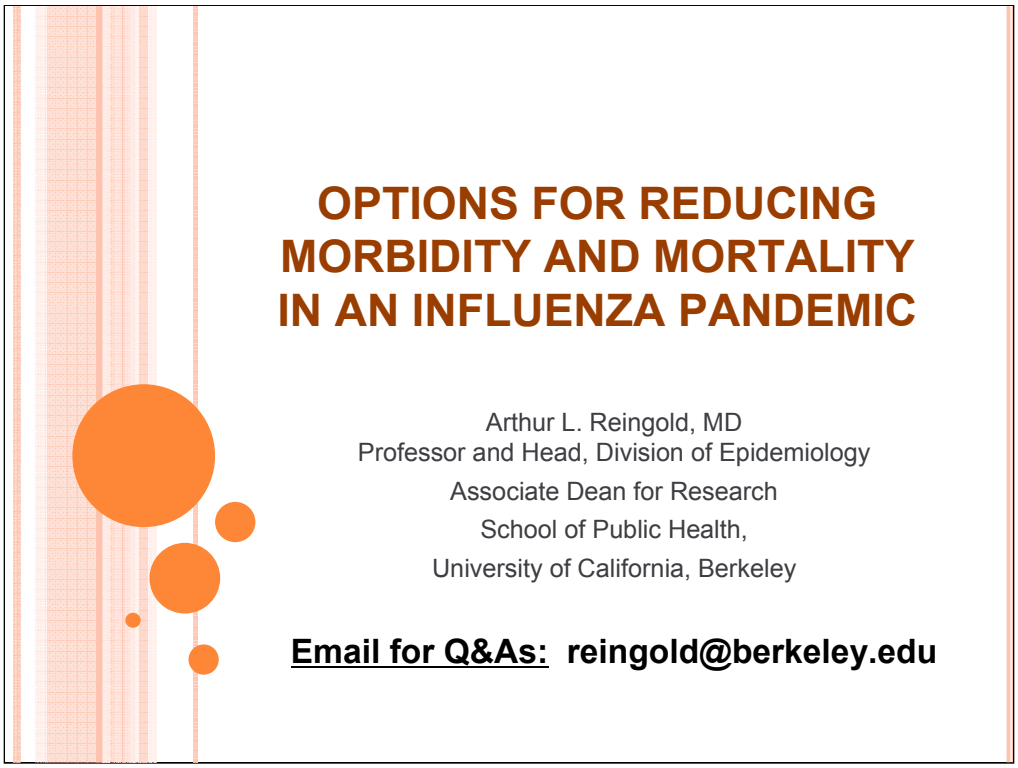
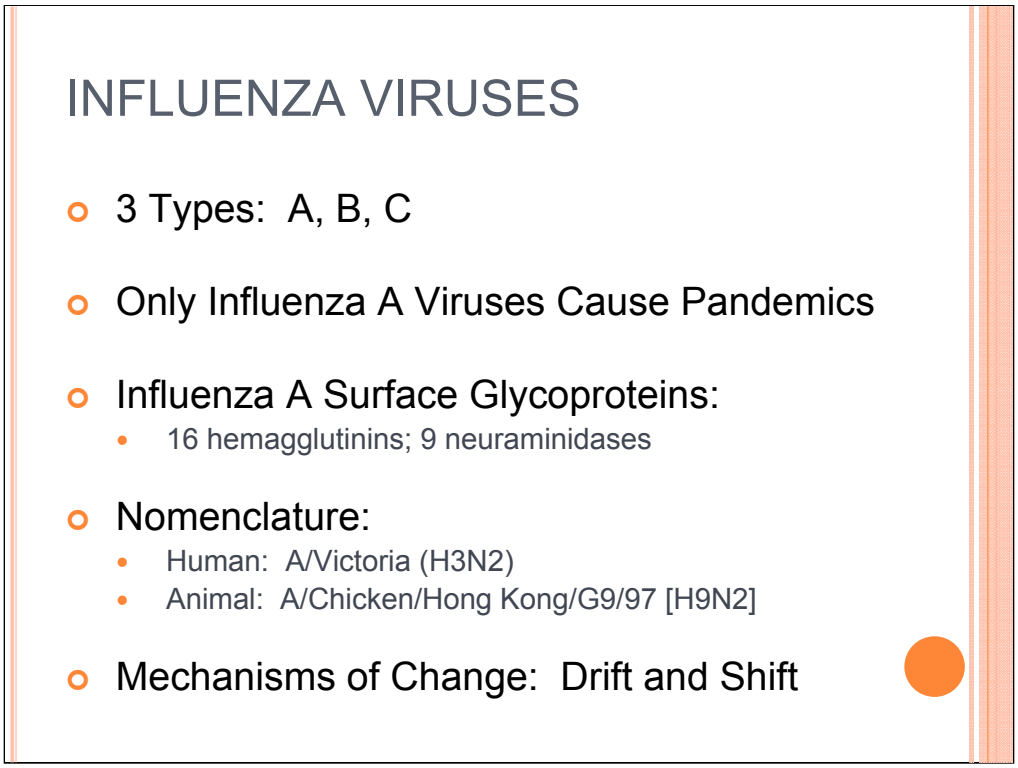


Good afternoon. First, let me thank you for inviting me to share some time with you to talk about influenza pandemics and how we can prevent morbidity and mortality associated with them and, second, let me apologize for not being there in person. Many of you may know that the original intention was that I would come to Singapore, which would have been a wonderful opportunity for me, but because of the H1N1 influenza epidemic which is currently occurring in the world, it appears that I would have been quarantined for a week if I had come to Singapore.

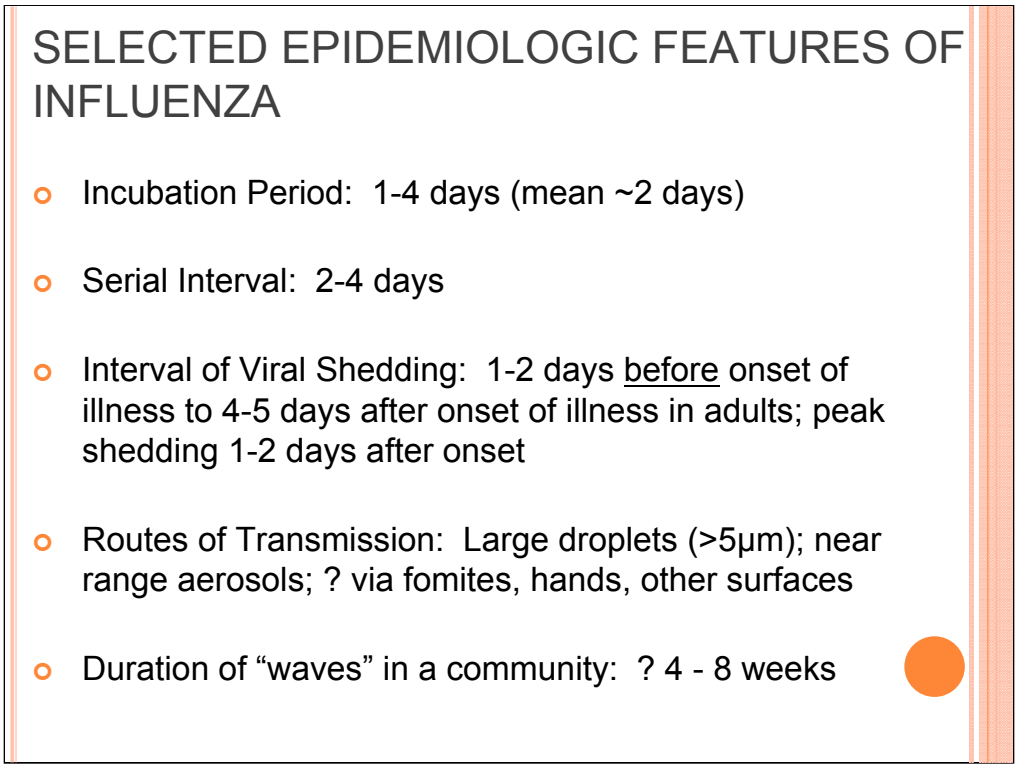
So the decision has been that I would give this talk via distance, share my slides with you, and then be available to take questions over the internet. Again, let me thank you for your kind invitation, and I look forward to interacting with many of you over the next week or two, in some discussion and interaction in trying to respond to your questions about my talk.

For next 45 or 50 minutes I'd like to just give some context in terms of what we know about influenza epidemics and pandemics, the role of pneumonia and secondary bacterial pneumonias in the morbidity and mortality associated with influenza, and then what some of the challenges and opportunities are that relate to reducing morbidity and mortality in the context of influenza.



I suspect that you all are very, very familiar with influenza viruses, but in this first slide, I would simply like to point out that while there are three known types of influenza viruses, A, B, and C, that only Influenza A viruses are capable of causing pandemics. For those who are not familiar with the nomenclature of influenza viruses, the A viruses are referred to in terms of their H and N antigens. H stands for hemagglutinin, N stands for neuraminidase, and so H1N1 virus, for example, means that it has the #1 hemagglutinin and the #1 neuraminidase.

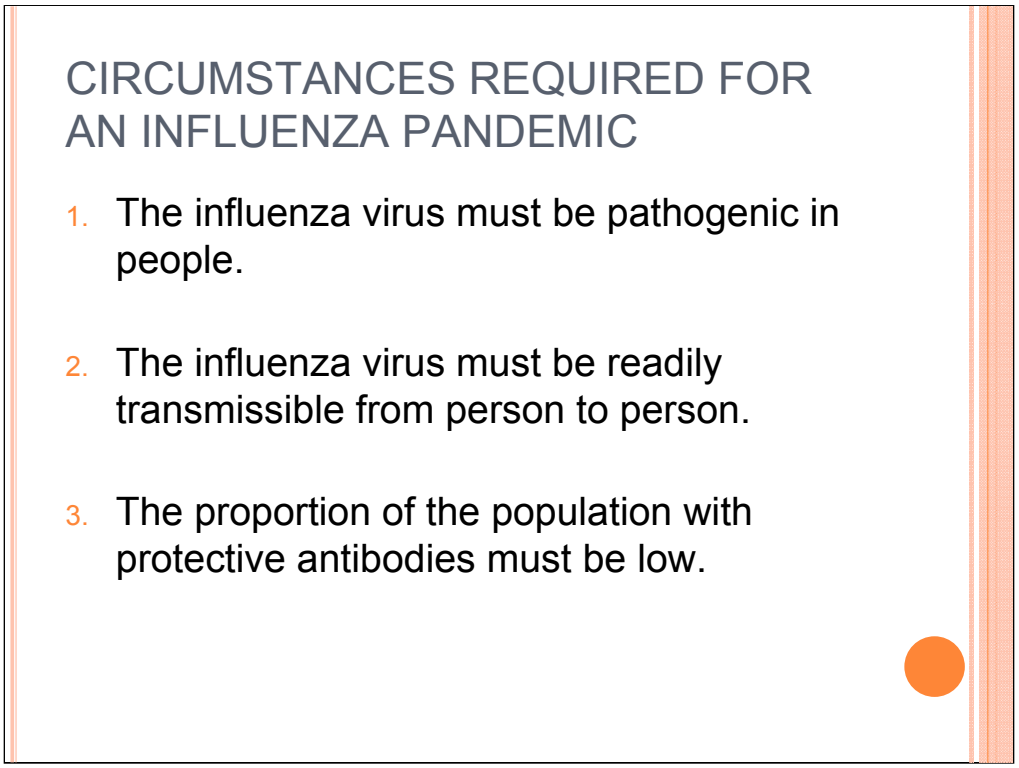
Influenza A viruses, as many of you will know, can undergo quite rapid changes in their genetic structure, and therefore in their antigenic structure. A slower form of change of influenza viruses is referred to as "antigenic drift," the change can be a much more rapid process referred to as "antigenic shift." Through these two processes, the Influenza A virus basically changes its antigens, and the result is, new viruses can arise to which the human population may not have durable immunity or any immunity at all.



This **slide** summarizes what we know about some of the important epidemiologic features of influenza. The incubation period is said to be in the range of 1 to 4 days, but I think in fact it is primarily more in the range of 1 to 2 days; 75 to 90% of people will develop illness within about two days.

One of the more challenging things about influenza is that people, once they become infected, will shed the virus in their nose and throat from the very beginning of their illness, and in fact can be shedding the virus even the day before they develop clinical symptoms, although typically we wouldn't expect them to be transmitting the virus to others except when they begin coughing and sneezing. This poses a challenge however, because, unlike some infections, people may still be walking around, may still be feeling well enough to be interacting in public, when they are in fact quite infectious to others. There is some controversy or perhaps some uncertainty about what the most important routes of transmission of the influenza virus are. That is, it's quite certain that large droplets play an important role. There is I'd say reasonably good evidence that smaller droplets also play a role. It's a little unclear what role very small droplets that may form aerosols play in the transmission of influenza and the extent to which hands and inanimate objects in the environment also contribute to the transmission of influenza. But, in general, the feeling is that all of these routes of transmission to one extent or another play a role in influenza transmission.

The other thing to point out is that in general when a new influenza virus enters a community, it basically moves through fairly quickly and in essence within about 6 to 8 or 10 weeks, people who are going to become infected and ill in that particular wave will do so, and then the outbreak of influenza is essentially over in that community for at least some period of time.



Now, I think what should be clear to everyone is that in order for an influenza virus to cause a pandemic, that virus needs three characteristics which are summarized in this slide:

The first characteristic is that the virus must be pathogenic in people--that is, capable of causing disease in people.

Second, the virus must be readily transmissible from one person to another.

And third, the proportion of the population with protective antibodies against that particular virus must be very low.

As we'll come back to in a few minutes, the H5N1, or bird flu virus, that many of you are familiar with, certainly fulfills two of these characteristics. It is certainly pathogenic in people, and very few people have antibodies to that virus, but so far that H5N1 bird flu virus has not developed the capability to be transmitted from one person to another.

In order for an influenza virus to cause a pandemic it must have all three of these features.

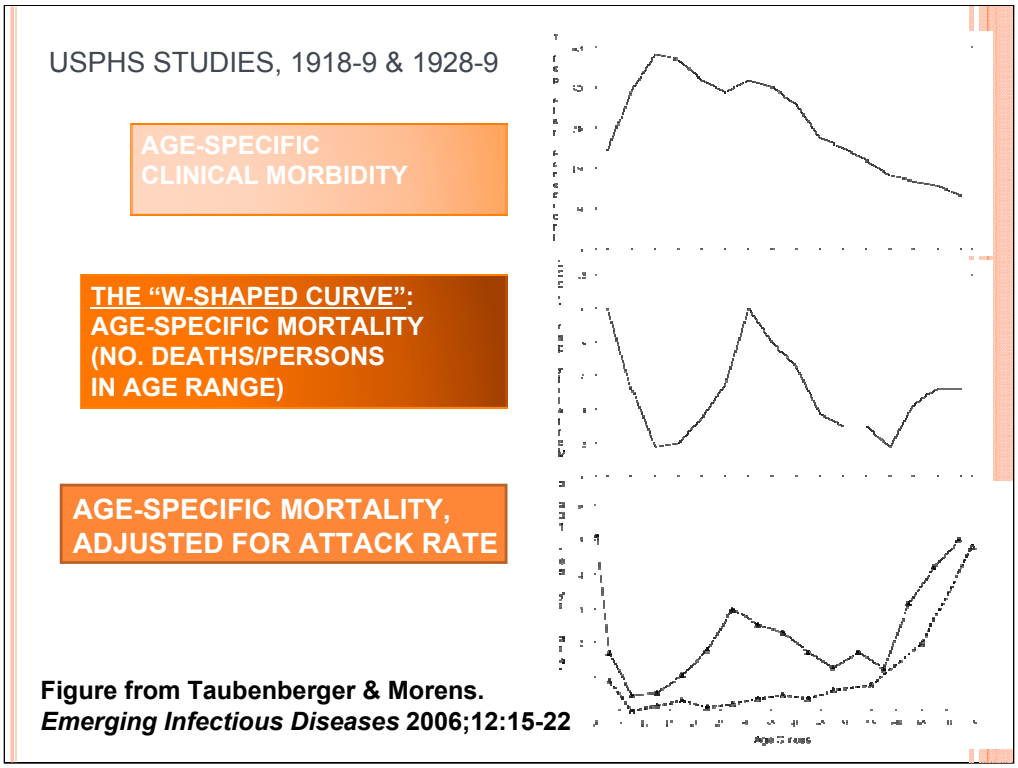
INFLUENZA PANDEMICS SINCE 1847

Year	Influenza A Subtype	Estimated Mortality Worldwide
1847	?	?
1889	H2N?	?
1918	H1N1 (“Swine” or “Spanish”)	~40-50 million
1957	H2N2 (“Asian”)	1-2 million
1968	H3N2 (“Hong Kong”)	~700,000
2009	H1N1 (“Swine”)	?

This slide summarizes a little bit of what we know about influenza pandemics going back about 150 years. The information about the pandemics in the 19th century is obviously largely inferential, and we really know relatively little, particularly about what virus caused those epidemics or pandemics. We know more now about the 1918 pandemic, the very famous Spanish flu of 1918-1919, which through very elegant virologic detective work has now shown to have been caused by an H1N1 or swine flu virus. That epidemic is conservatively estimated to have killed 40 to 50 million people worldwide and certainly is the epidemic that many people point to in an alarming way as an example of what an influenza pandemic might be capable of doing.

In 1957, we had an epidemic caused by the H2N2 virus or Asian influenza virus, and in 1968 we had another pandemic caused by the H3N2 or Hong Kong influenza virus.

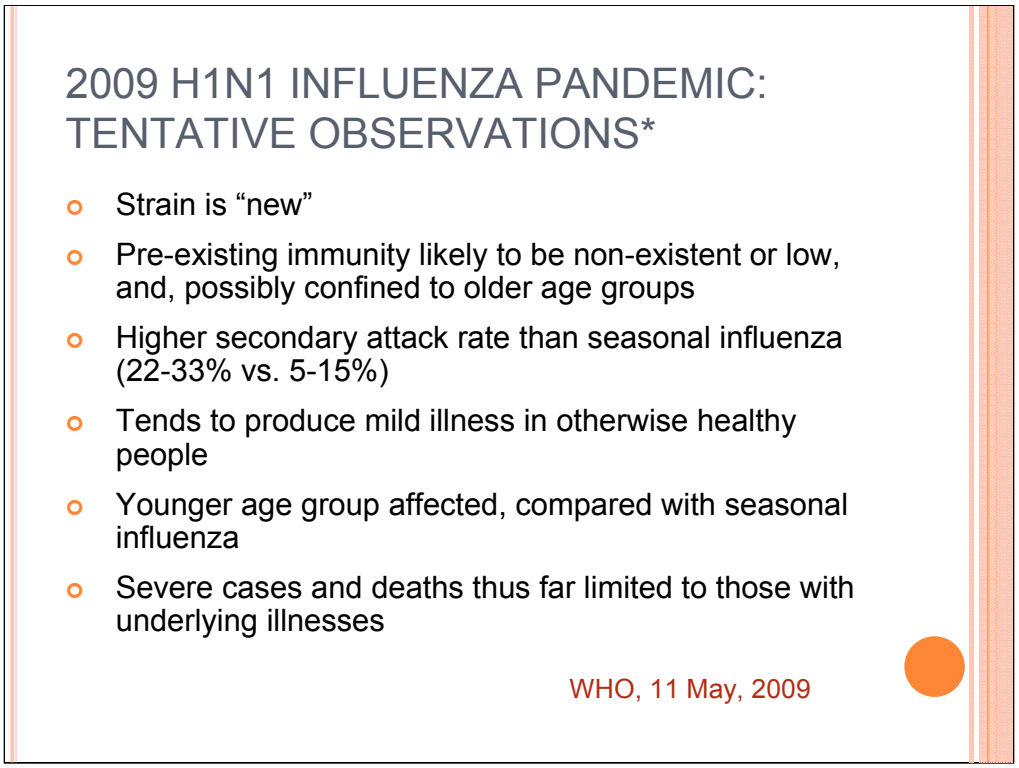
And as you obviously all know, we are currently in the midst of an H1N1 or swine influenza epidemic that is present now in many parts of the world that really just arose within the last two months or so. It remains to be seen exactly what that virus will do over the rest of this year and into next year, and no one can at this point talk about how much morbidity or how much mortality the current H1N1 virus is going to cause. And that uncertainty is the basis for many people's concerns going forward and a discussion about what we should do to be prepared for the H1N1 virus over the next 18 months or so.



Now this slide shows what, again, I suspect many of you are familiar with, which is that if you look at the curves in the lower graph, looking at the age-specific mortality, what you see in the lower line is the typical mortality seen with annual influenza epidemics, which is that mortality is largely concentrated in the very young and the very old. By the very young, I mean children under a year or a year and a half years of age, and by elderly I mean people my age or older, people over 55 or 60, in whom, with increasing age, we see increasing mortality. You can see the resulting "U"-shaped curve of influenza-related mortality.

What was unusual about the 1918 pandemic is illustrated, again, in that lower graph, but the upper curve, which is that in the influenza pandemic of 1918, a great deal more of the mortality occurred in people in their 20s, 30s and 40s. As a result, there were substantial socio-economic and other impacts.

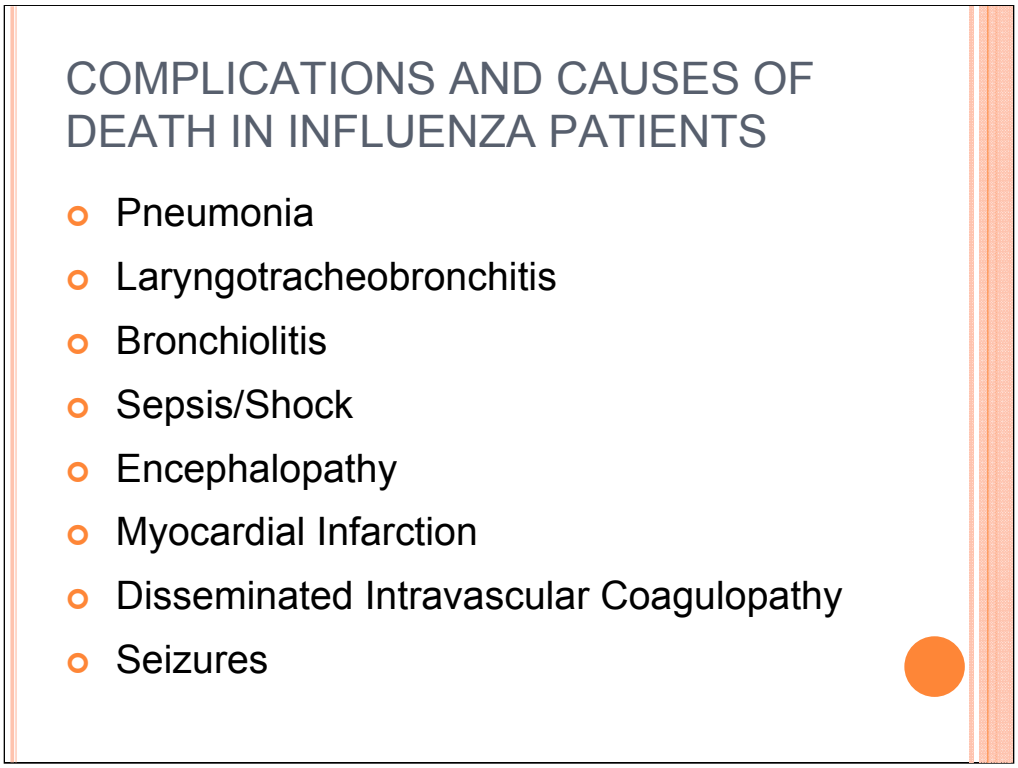
It's that "W"-shaped mortality pattern, which was seen in 1918, that would certainly be of concern if we experienced it again in another influenza pandemic.



What I've summarized here -- from the WHO website which is accessible at http://www.who.int/csr/disease/swineflu/en/index.html -- are some of the WHO observations about this new H1N1 influenza virus which is currently causing problems in many parts of the world. It's quite clear now that this is a new strain; it's also reasonably clear that younger people probably do not have pre-existing immunity to this virus. But based on some data released just today, it would appear that those of us who were alive in 1957, when H1N1 was still circulating widely, that is, people over the age of around 55 or 60, do have antibodies which may be partially or even more than partially protective against this new virus.

But people younger than that age may have little if any protective immunity to this new virus. The secondary attack rate which has been seen in households, and in close contacts with this new H1N1 virus, appears to be higher than what is seen in typical seasonal influenza, but the clinical illness that's being produced by this new virus so far appears to be more or less consistent with what we see with seasonal influenza epidemics: relatively mild illness in most people, particularly otherwise healthy people, with most of the severe illness and mortality being limited to people with underlying conditions of one kind or another.

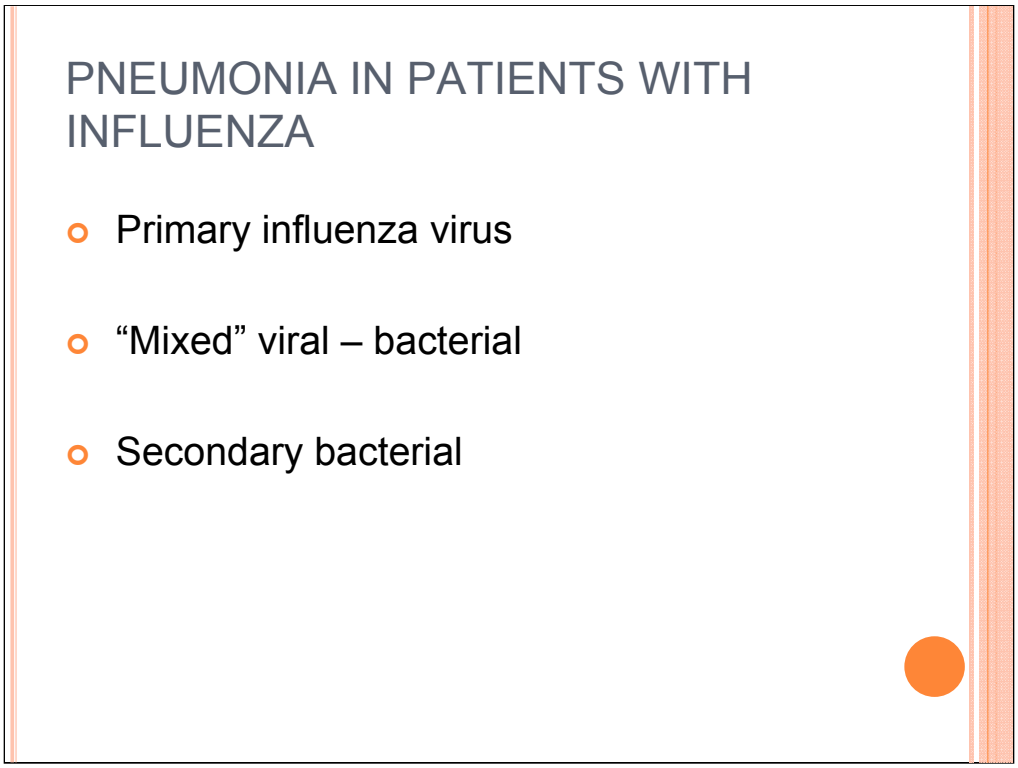
So that's pretty much what we know at the moment, but obviously there is still much work to be done in better understanding the current problem.



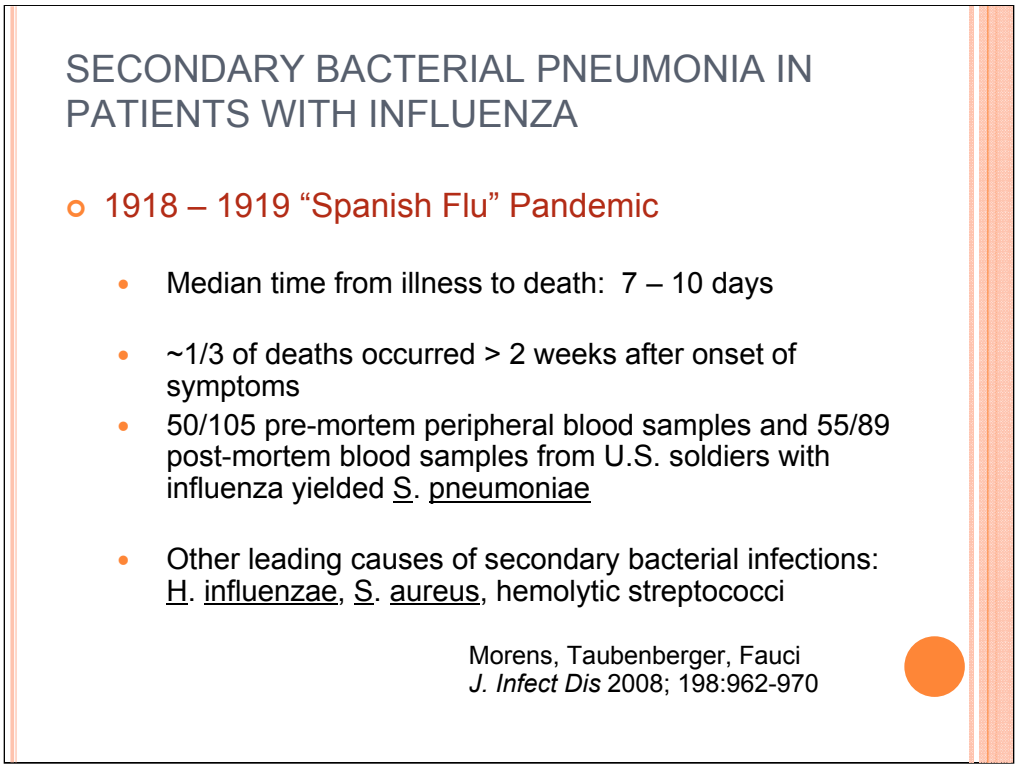
On this slide, I simply list the clinical features of influenza -- again, I suspect that many of you know more about these features than I do, because I don't see patients anymore -- but what I've listed here are some of the most important complications and causes of death that have been described for influenza patients.

There are clearly many, many other complications that can occur in individual patients. At the top of the list is pneumonia and other, if you will, severe respiratory complications, such as laryngotracheobronchitis and bronchiolitis.

But I would say that, for the most part, pneumonia belongs at the top of the list in terms of being one of the most important threats and complications causing severe illness and death in the context of influenza.



What I would like to do is spend a few minutes talking about what we know about pneumonia in the context of influenza infection. People have in essence divided these pneumonias into three types: Primary influenza virus pneumonia, what are referred to as "mixed" viral bacterial pneumonias, and then what are referred to as secondary bacterial pneumonias, where, in essence, the bacterial infection occurs somewhat later, a week or two into the influenza illness.

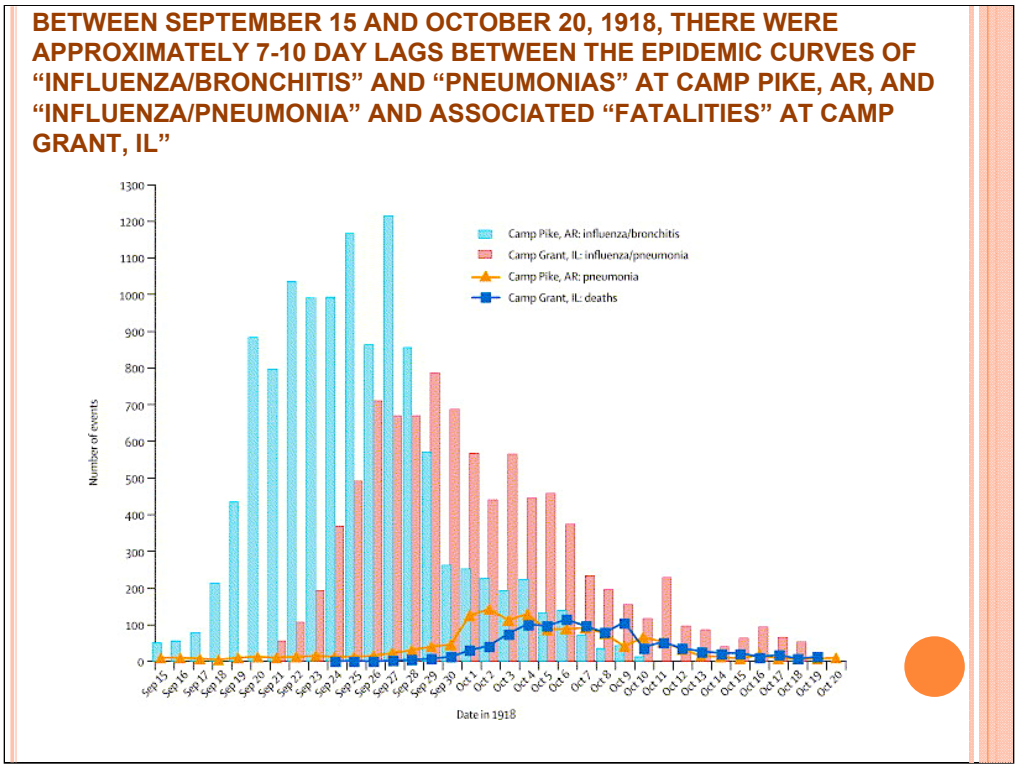


What I'm showing here are some data put together by David Morens, Jeffrey Taubenberger, and Anthony Fauci from the U.S. National Institutes of Health, going back and looking at findings from the 1918-1919 Spanish flu. It's important to point out here that the median time from onset of influenza illness to death during that pandemic was in the range of seven to 10 days, and that fully a third of the deaths occurred more than two weeks after the onset of symptoms.

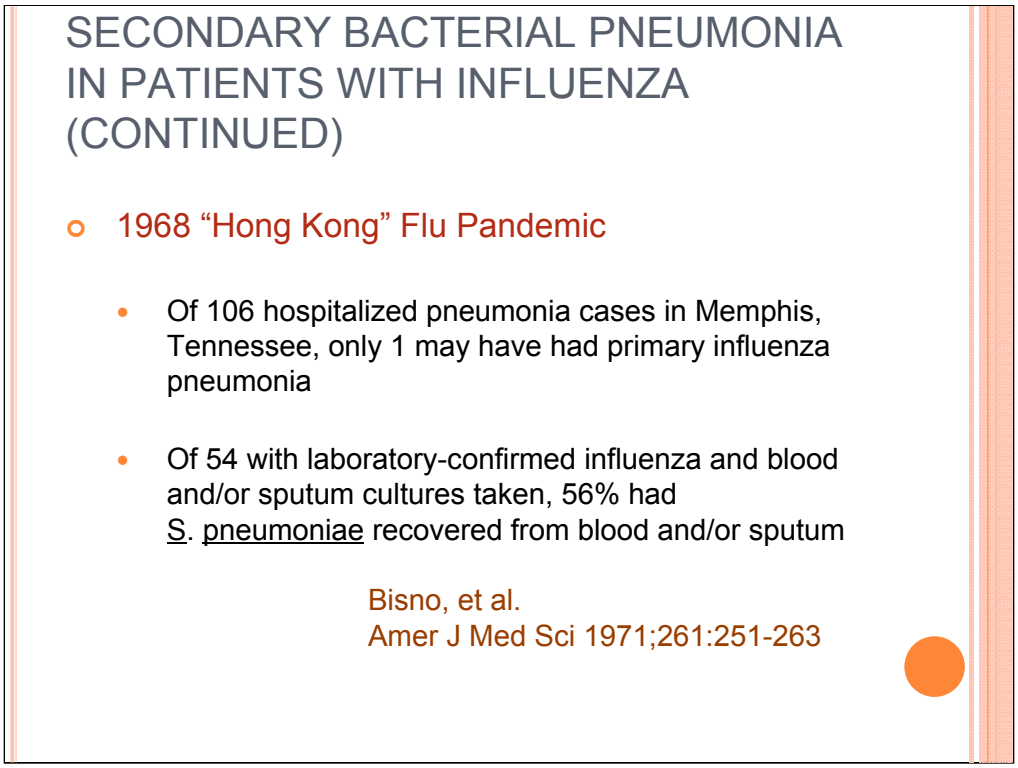
Going back and looking at studies that were done at the time, one can see that, in fact, a substantial proportion of the individuals who died or who had pre-mortem peripheral blood samples taken before they died, had *Streptococcus pneumoniae*, isolated either from their peripheral blood or from heart blood taken during the post-mortem. So, one of the important features of the 1918-1919 influenza pandemic was the very prominent role of the pneumococcus in producing secondary bacterial pneumonias in people with influenza.

The other leading causes of secondary bacterial infections in these patients were *Haemophilus influenzae*, *Staphylococcus aureus*, and *Hemolytic streptococci*.

So, in the 1918-1919 pandemic, secondary bacterial pneumonias were a very, very important cause of morbidity and mortality.



And what this graph illustrates -- again, these are very old data taken from that 1918-1919 pandemic -- is that the mortality lagged the onsets of illness by approximately two weeks, being most consistent with the fact that many, many of these patients did not die of primary influenza or primary influenza pneumonia, but in fact died from secondary bacterial infections, rather than from primary viral infections.

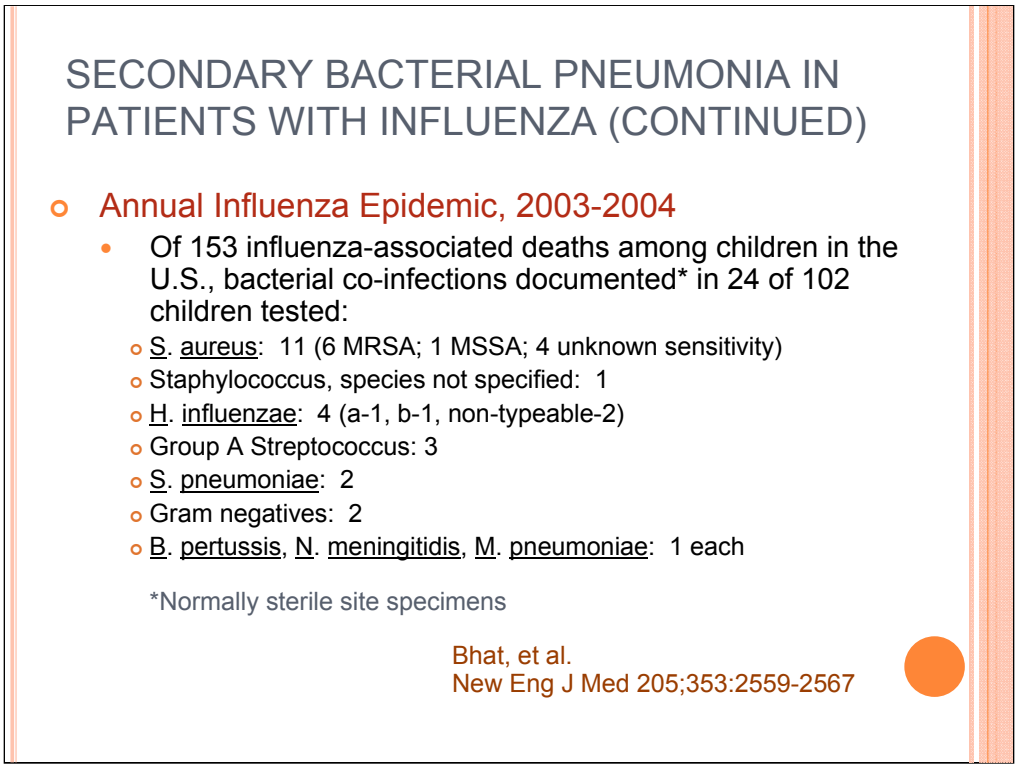


Now, moving forward to the 1968 Hong Kong flu pandemic--of course, there are many studies; here is a study done in Memphis, Tennessee, a very nice study that looked at 106 hospitalized pneumonia cases, all of whom had documented, laboratory-confirmed influenza. Only one of those individuals is thought to perhaps have had primary influenza pneumonia.

So a very, very small proportion, if any, of the hospitalized pneumonias during that pandemic were caused by primary influenza pneumonia and, again, among these hospitalized patients with pneumonia and laboratory-confirmed influenza infections, a substantial proportion of these individuals, in fact, had bacteriologic evidence of *Streptococcus pneumoniae* infection, in this instance recovered either from blood or from sputum.

We all know the problems of attributing pneumonia to something that is found in the sputum, but in many, many of these instances, the pneumococcus was recovered from the blood.

So, again, during the 1968 flu pandemic, there is very good evidence that primary influenza virus pneumonia was very uncommon and that secondary bacterial pneumonias were, in fact, quite common.

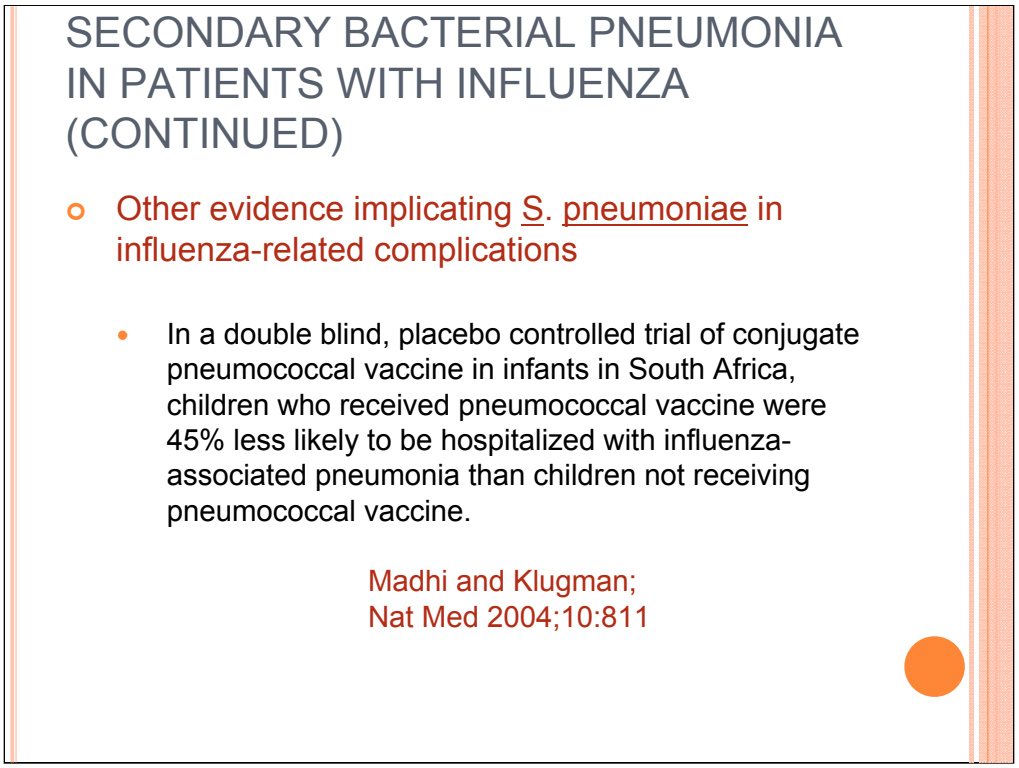


Here are also some data taken from a study that I participated in, a national study of influenza in the U.S. This would have been a typical year, if you will, or typical years, 2003 and 2004, of annual influenza here in the United States.

In this study we were looking at children rather than adults. In children it is also the case that many, many of the pneumonias and many of the deaths are attributable to secondary bacterial co-infections. So here you can see, this is now looking at fatal cases of influenza, that out of 153 fatal influenza cases among children in the United States during that time period, 24 of them had laboratory-confirmed bacterial infections.

And here I'm talking about bacteria isolated from normally sterile sites; I'm not talking about sputum cultures. So, in this case series, *Staph. aureus* was an important pathogen, as were *Haemophilus influenzae*, *Streptococcus pneumoniae*, a couple of different gram negatives and a small number of other organisms.

So this is a recurring pattern, that secondary bacterial infections in the context of influenza are frequently caused by the pneumococcus, by *Staphylococcus aureus* and by *Haemophilus*.



Another piece of evidence implicating the pneumococcus in influenza-related complications, came from a double blind, randomized, placebo-controlled trial of pneumococcal conjugate vaccine in infants in South Africa.

Obviously the vaccine did a very good job of preventing pneumococcal infections, but what this slide shows is that in these children, receipt of pneumococcal conjugate vaccine was associated with a 45% reduction in the likelihood of being hospitalized with influenza-associated pneumonia.

The results of this study again basically suggest that many of the serious influenza-associated pneumonias that occur in children may, in fact, be due to pneumococcal infection. So, just one more piece of evidence.

SECONDARY BACTERIAL PNEUMONIA IN PATIENTS WITH INFLUENZA (CONTINUED)

- Ecologic studies in Sweden and the U.S. suggest that 12-20% (Sweden) and 11-14% (U.S.) of invasive pneumococcal infections during "influenza season" can be attributed to influenza.

Grabowska, et al.
BMC Infect Dis 2006;6:58
and
Walter, et al.
Under review

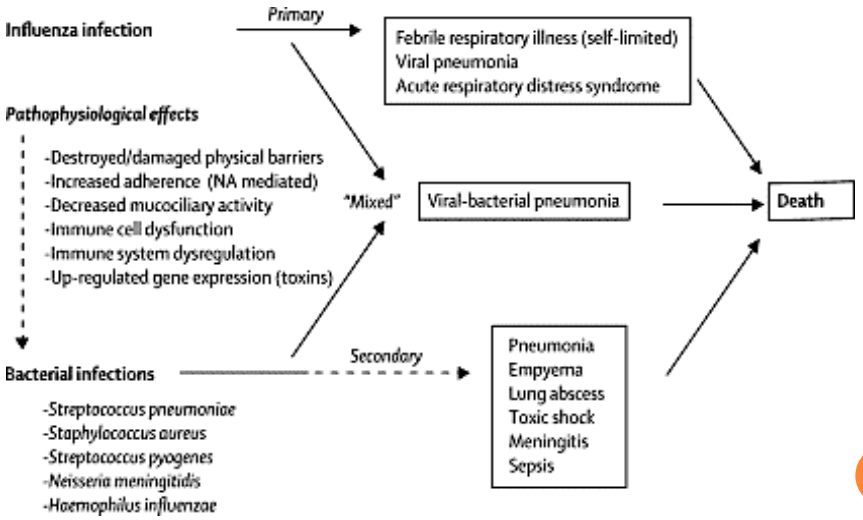
Now just a couple of other types of evidence about this relationship between influenza and pneumococcal infections:

Here you can see the results of two ecologic studies, one looking at data from Sweden, and the other looking at data from the United States that actually are remarkably consistent in estimating what proportion of invasive pneumococcal infections during influenza season can be attributed to influenza.

That is, during the influenza season, a substantial proportion of the pneumococcal infections, in essence, are the result of secondary infections in patients with influenza, over and above what we might expect if influenza virus were not there.

Both of these studies suggest that co-infection, if you will, between influenza and the pneumococcus is a very, very important ongoing feature of influenza epidemics.

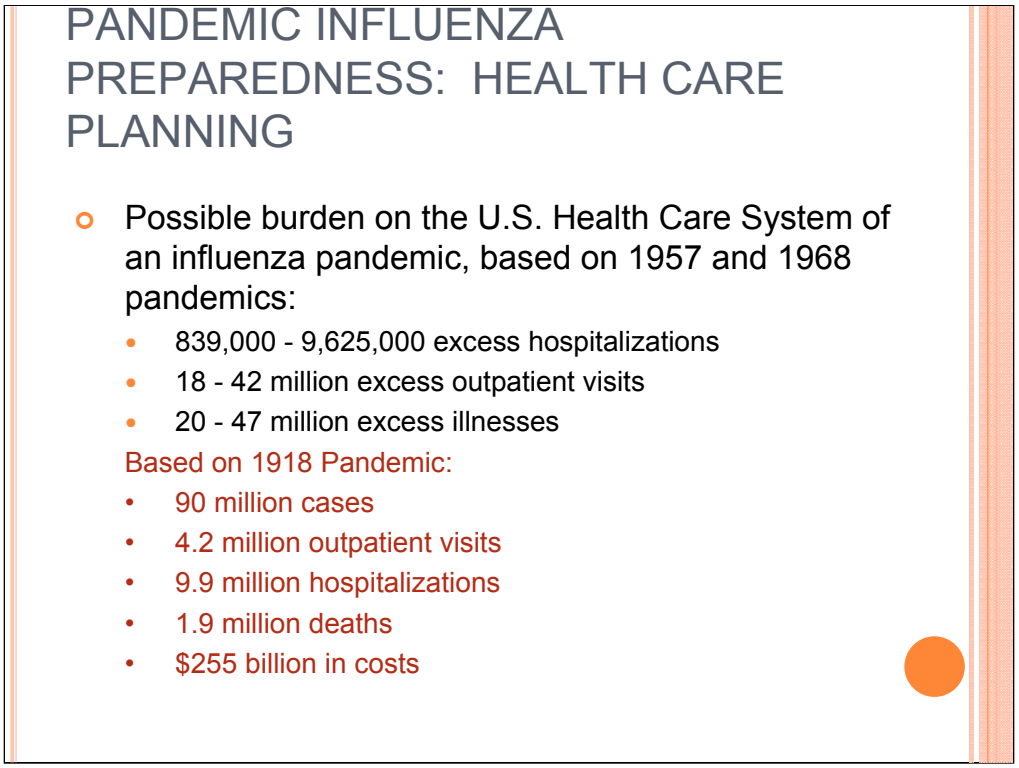
FIGURE 1 EXAMPLES OF PATHOPHYSIOLOGICAL INTERACTIONS BETWEEN INFLUENZA AND BACTERIAL RESPIRATORY PATHOGENS AND VARIOUS CLINICAL EXPRESSIONS



This slide points out some of the underlying pathophysiological interactions that might make this relationship between influenza and bacterial respiratory pathogens biologically plausible.

In fact, I am not an expert in this area, but I would say that one of the most important pieces of the influenza-pneumococcal puzzle, if you will, is that in some way the neuraminidase of the influenza virus does damage to the respiratory tract, and in essence increases the pathogenicity of the pneumococcus when it is present or allows the pneumococcus to be more pathogenic than it might be ordinarily.

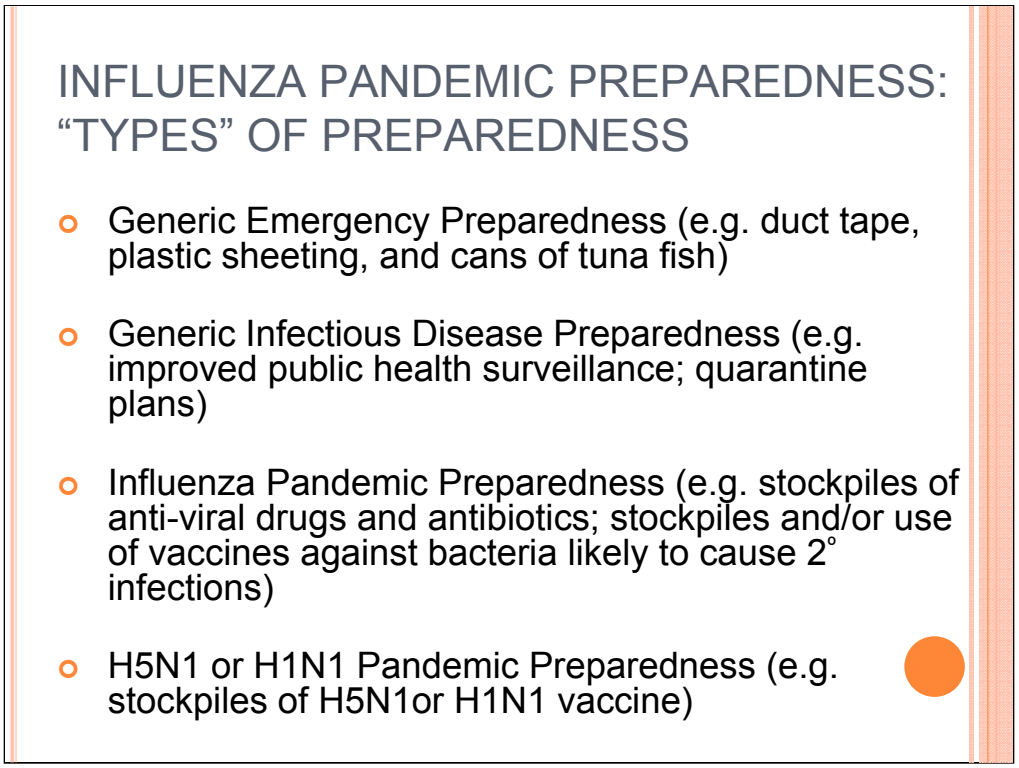
I think there is reasonable evidence that the neuraminidase of the influenza virus is one of the more important pieces of this puzzle, providing a biologically plausible explanation for the epidemiologic findings.



When we start thinking about how we can be better prepared for an influenza pandemic, and what the scope of such a pandemic might be, these are some of the projections that have been made for the United States, about what the burden might be on the U.S. health care system, if the next pandemic mirrors either the 1957 or the 1968 pandemic, or if it mirrors the 1918 pandemic.

I won't get into the details here, except to say that obviously there is real concern because of the very large number of cases that might occur, the substantial burden that would be placed on outpatient and hospital facilities, the substantial mortality, and the very, very substantial health care cost, not to mention the social and economic burden created by loss of work, loss of economic productivity, etc.

It's because of these concerns that people and their governments are obviously trying to be better prepared and see what they can do to reduce morbidity and mortality in the context of the next influenza pandemic.



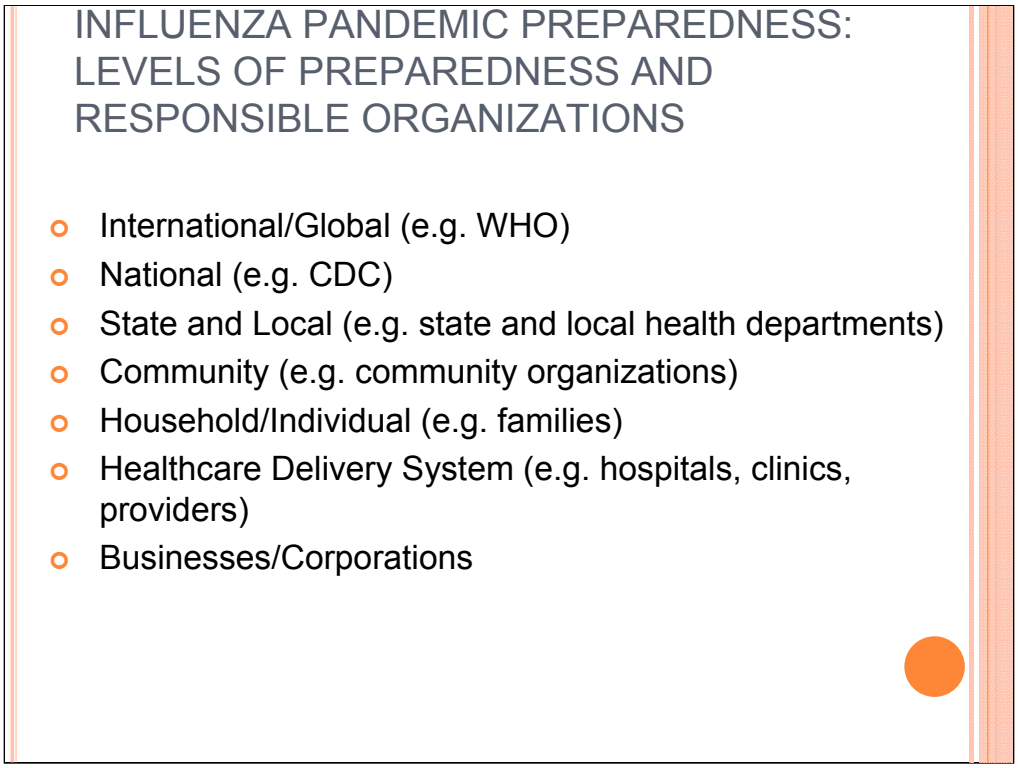
This slide illustrates that preparedness can come in several layers, if you will.

Generic emergency preparedness is the kind that those of us here in California who live in earthquake country might want to undertake, to be better prepared for any type of emergency. By generic infectious disease preparedness, I mean improvements to public health infectious disease surveillance and having quarantine plans and other plans in place. These approaches are relevant only to being better prepared for infectious disease, but might be relevant to a whole host of different infectious disease problems.

Next, one could think about influenza pandemic preparedness that might be helpful whatever influenza virus causes the next influenza pandemic and that might include stockpiles of antiviral drugs, stockpiles of antibiotics for treatment of secondary bacterial pneumonias and other secondary bacterial infections, and stockpiles or using in advance vaccines against the bacteria that are likely to cause secondary infections, particularly the *Haemophilus* influenza B, and the pneumococcal vaccines that we have available.

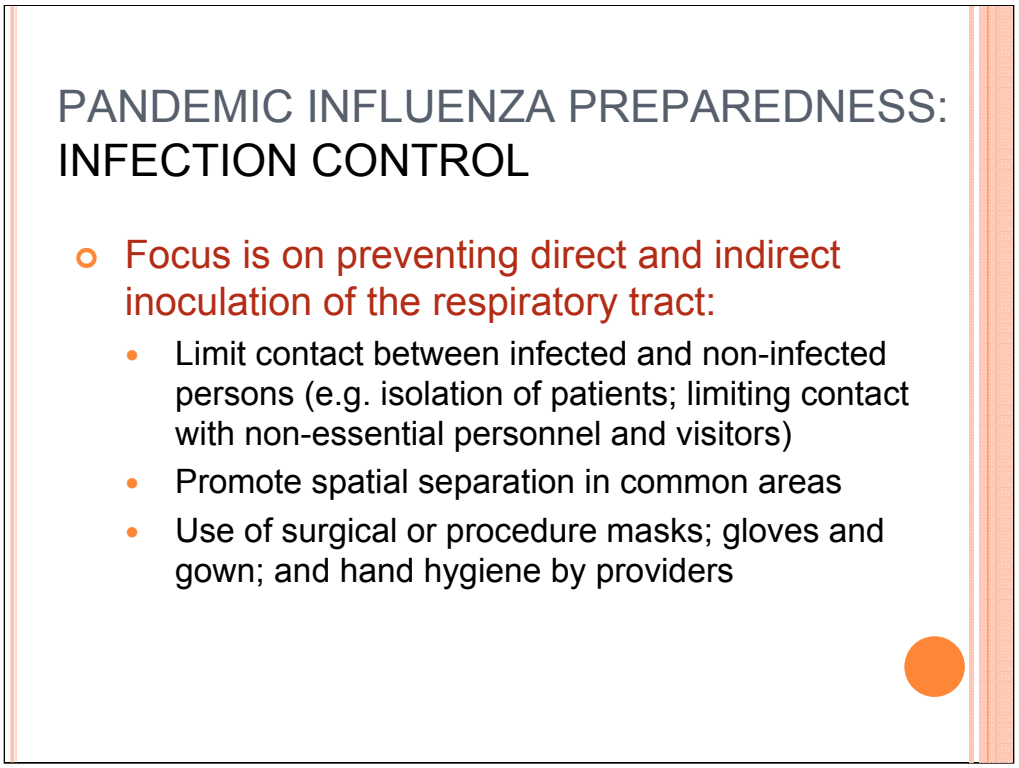
And then, last, there is preparedness that relates more specifically to a particular virus. Having a stockpile, a pre-pandemic stockpile, of an H5N1 vaccine or an H1N1 vaccine will only be helpful if the next pandemic is caused by that particular virus or a very closely related strain, a strain closely related to the one that's in that vaccine.

So, this just points out that there are different types or layers of preparedness.



Obviously, many types of organizations are responsible for trying to be better prepared for the next influenza pandemic, ranging from WHO at the global level; various organizations at the national level, such as Ministries of Health; state and local health departments here in the United States; community organizations; households; health care delivery systems; and businesses and corporations.

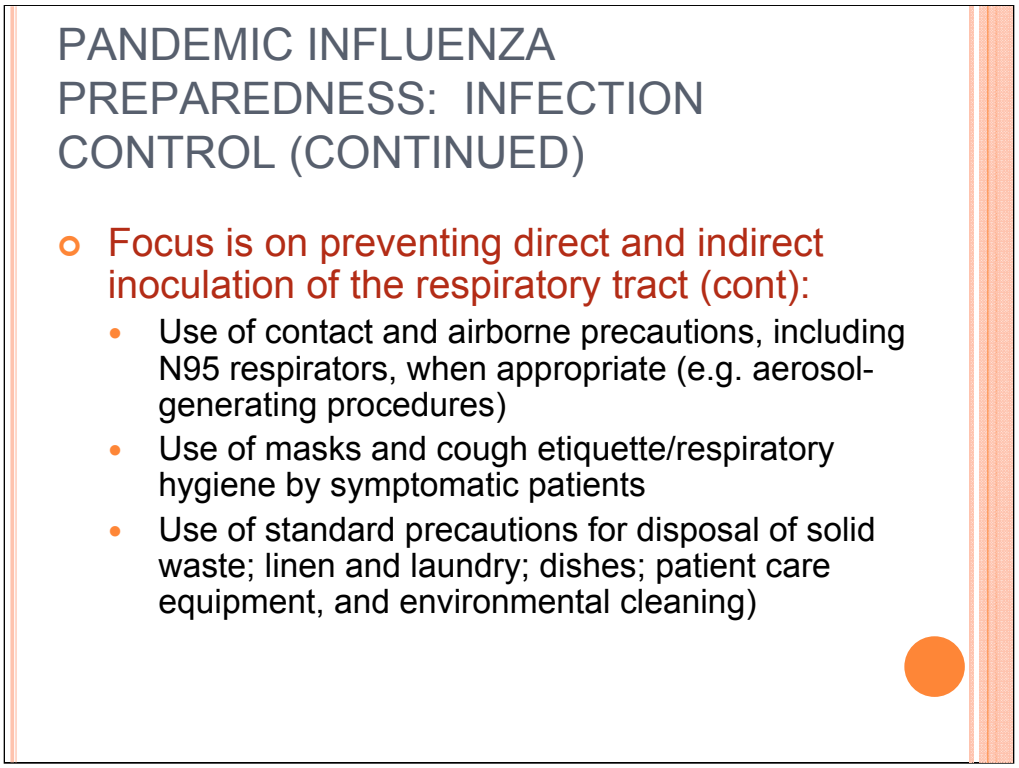
So, many, many organizations need to be and are thinking about pandemic preparedness.



One aspect of preparedness that I probably don't need to talk to you about is infection prevention, surveillance and control in a health care setting.

Obviously in the health care setting, when we have patients with influenza, the focus is on preventing direct and indirect inoculation of the respiratory tracts of others with the virus, and this is done through isolation of patients, limiting contact with non-essential personnel, promoting spatial separation, use of masks and gowns and gloves, and things of that type.

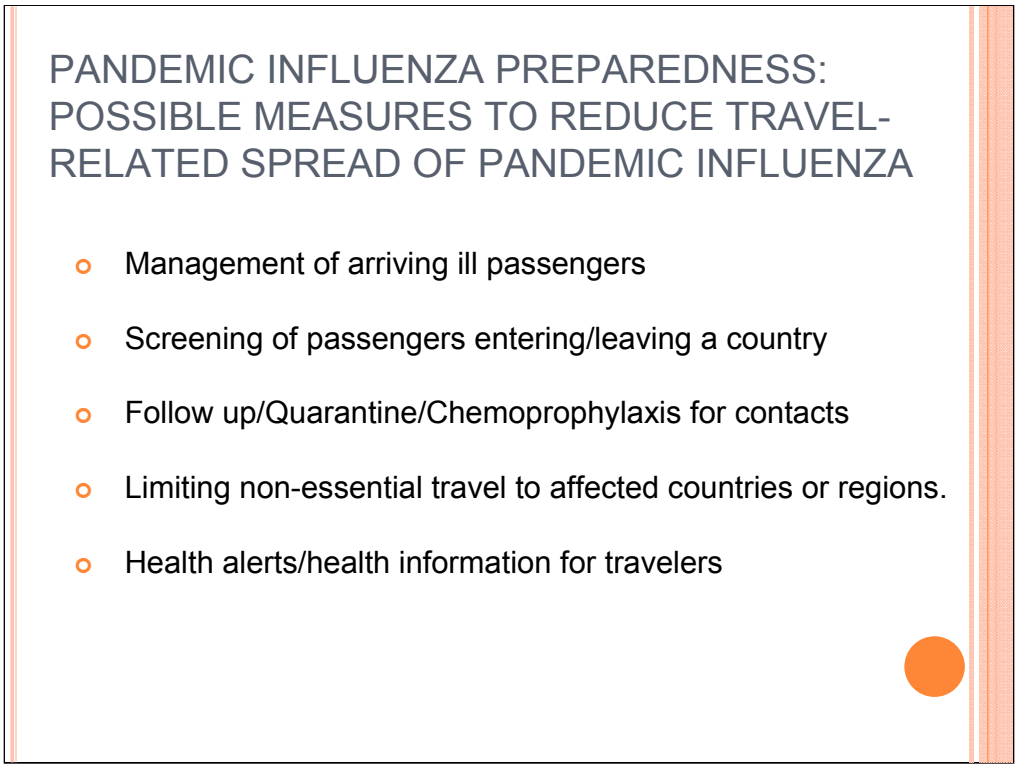
This approach is pretty well understood by anyone working in a hospital setting, particularly people involved in hospital infection control.



In health care facilities, the focus of preventing direct and indirect inoculation of the respiratory tract obviously can be quite challenging.

If we are talking about contact and airborne precautions, we might be talking about N95 respirators. If we are concerned about aerosol-generating procedures or viruses transmitted through an aerosol, we are talking about masks and cough etiquette, respiratory hygiene by symptomatic patients, and things of that type.

So these are things that I won't dwell on, because they are quite familiar to people working in a health care setting.



Another approach, another piece, if you will, of influenza preparedness, has to do with trying to reduce travel-related spread of influenza.

This can involve management of arriving ill passengers, screening of passengers entering or leaving a country, quarantine of individuals who might be incubating the disease, chemoprophylaxis of contacts, limiting non-essential travel, such as not letting me come to Singapore to give this talk, and asking that I do it through distance-based methods, health alerts, for travelers, etc.

Now, I'm going to point out in a minute that although all of these invariably are done in the context of a pandemic, it's questionable how effective some of these measures actually are.

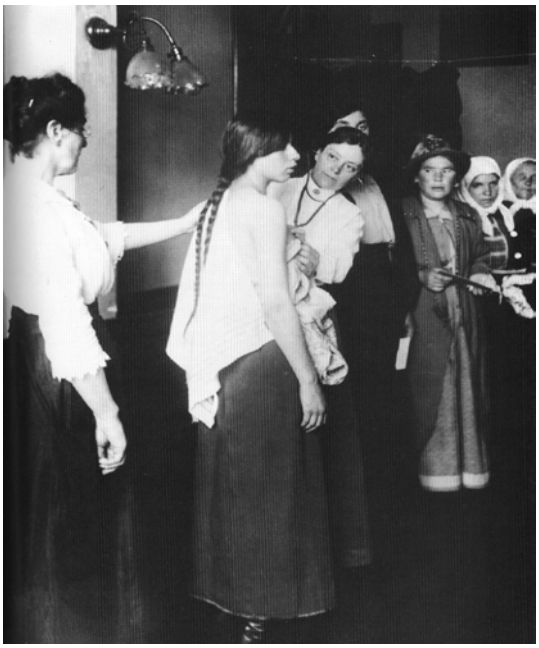
QUARANTINE AND ISOLATION

- *Quarantine* is the separation and restriction of movement of apparently healthy people or animals who may have been exposed to a microbial threat and therefore may become infectious (DGMQ, 2004). CDC quarantine stations and many of their public health partners have the legal authority to quarantine specific individuals and animals to protect the public's health. In addition, a CDC quarantine station may assure the *isolation* of specific individuals or animals that are reasonably believed to be carrying a communicable disease of public health significance. Through isolation, the infected persons or animals are separated from the population at large and their movement is restricted to prevent the microbial threat from spreading (DGMQ, 2004). Quarantine and isolation at national borders are non-medical components of the public health toolkit for limiting and containing the spread of microbial threats. Their utility varies, however, depending on the nature of the threat and the extent to which it has spread.

This slide points out the distinction between quarantine and isolation, that I suspect many of you understand, but that is frequently confused by the lay press.

Isolation refers to what we do to people who are ill and **quarantine** refers to what we do to people who are not themselves ill, they are asymptomatic, but who we are concerned are harboring the infection or incubating the disease, and whom we want to keep separate from others until we can be certain that they, in fact, are not about to become ill and symptomatic and infect others.

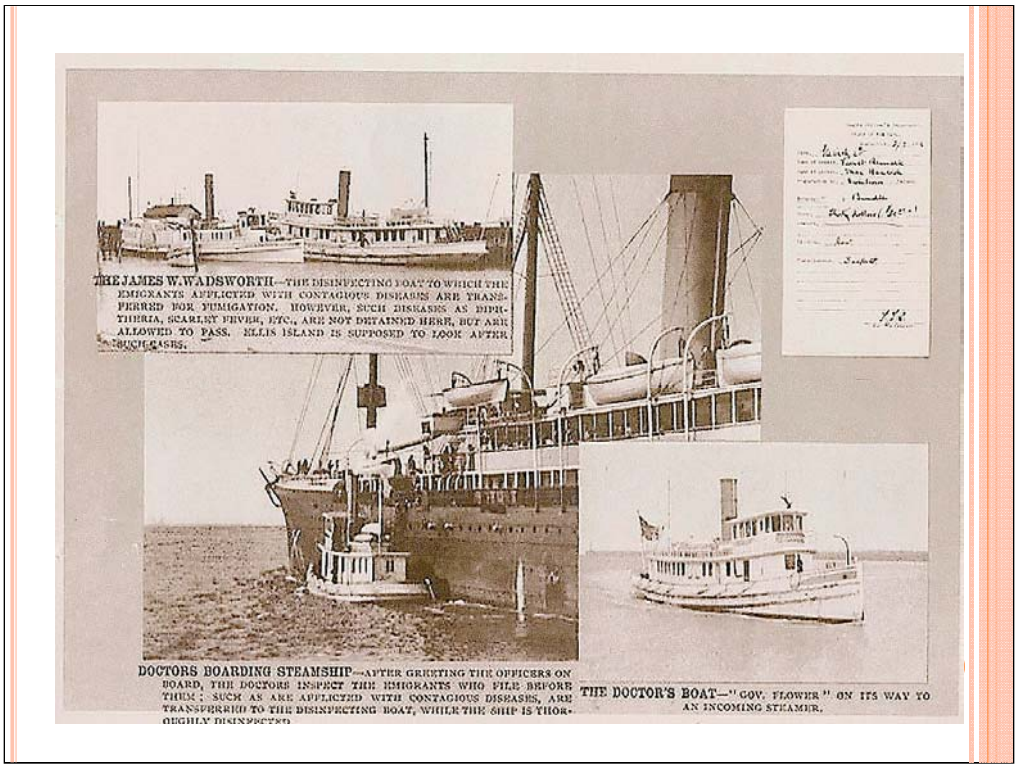
That's the distinction between the two.



And, of course, I think when many people think about quarantine, isolation, screening of travelers, things like that, at least in the United States, they have this mental image.

This is a picture going back to what we would call the days of Ellis Island, when immigrants coming to the United States underwent a physical examination as portrayed here, in an effort to detect various infectious diseases that might exclude them from entry into the United States.

I don't know about the situation in Singapore, but in the United States, we don't subject travelers to this type of disrobing and evaluation anymore.



In those days, if we detected people we thought might put others at risk, they might be put into quarantine.

Pictured here are old-time quarantine ships. People would actually be put on a ship out in the harbor until they passed a time period when we could be certain they were not, in fact, infectious to others.

We don't have ships like that anymore, so if we want to quarantine travelers, we have to have other types of facilities, hotel rooms or dormitories or other barracks types of facilities in which to put people.

You can imagine that quarantining substantial numbers of people is, in fact, a very, very expensive and labor-intensive thing to undertake.

Keystone/EPA/A.Rante

Indonesian Health Department officer setting up a body temperature scanner in May 2003 to detect fever in passengers at the height of the SARS crisis at Soekarno-Hatta Airport, Jakarta.

The scene illustrated here is perhaps much more familiar to those of you in the modern era.

This is the screening of arriving passengers for fever as was done in the case of the Jakarta airport in the context of SARS.

I suspect that if I were to land in Singapore this week, my fever--my temperature, rather--would be taken by someone with an infrared system of this kind.

Many, many places are using this type of equipment now.

BORDER SCREENING

Experience screening inbound and outbound air passengers for signs/symptoms suggestive of SARS; Toronto, Canada, 2003

Health Alert Notices (05/14 - 07/05/03)			
	Persons given notices	Persons referred	Final disposition
Outbound	495,492	411	All cleared
Inbound	349,754	1,264	All cleared

I have to tell you that a careful look at this type of screening of passengers in the SARS context was done by public health officials in Canada, and the results are very, very discouraging. In fact, their results, at least in the context of SARS, suggest that this type of screening is really not very effective, if effective at all.

Some of the data from careful evaluations are illustrated here.

Illustrated here is the approach of giving people a health alert notice and asking them if they have had any symptoms. These are outbound and inbound individuals, those going out and coming into Toronto during SARS. And you can see that, in essence, they did identify a fair number of people who reported one or more symptoms in the context of SARS.

But, none of those people with symptoms turned out to have SARS.

BORDER SCREENING (CONTINUED)

Thermal Imaging Scanner (05/16 - 07/05/03)

	Persons scanned	Persons referred	Final disposition
Outbound	281,959	94	All cleared
Inbound	355,532	83	All cleared

These are the results from thermal image scanning, again, for both outbound and inbound passengers.

You can see the results of screening in this case of about 630,000 people. A couple of hundred people were found to have fevers, none of whom turned out to have SARS.

So again, in this case, as they referred to it, they were all cleared, if you will, and didn't have the disease in question.

BORDER SCREENING (CONTINUED)

- Number of persons departing Canada in whom a SARS-like illness was subsequently diagnosed:
  11 (3 laboratory confirmed)
- Proportion who had symptoms at the time of travel:
  2 of 11
- Proportion who would have been "cleared" using criteria in the secondary screening protocol: 11 of 11

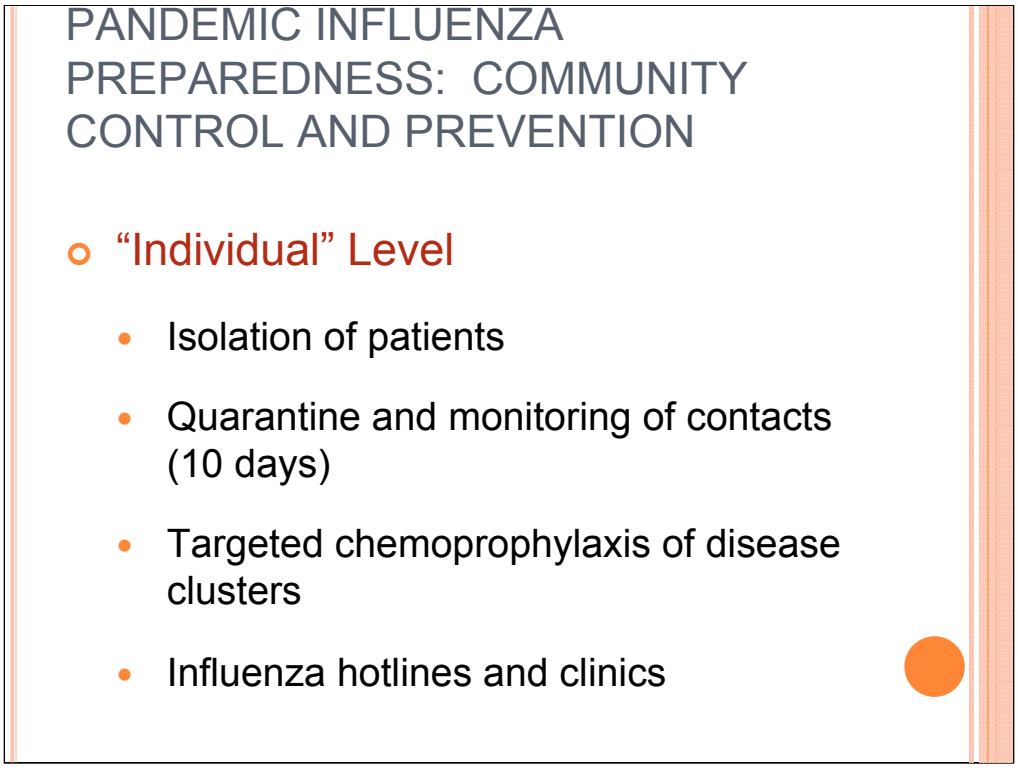
St. John, et al.
Emerging Inf Dis 2005;11:6-10.

Perhaps even of greater concern, when these investigators reviewed the situation for people who travelled through the airport and who turned out subsequently to have SARS, and may have been incubating it during the time they were being screened, in fact, screening detected none of these individuals.

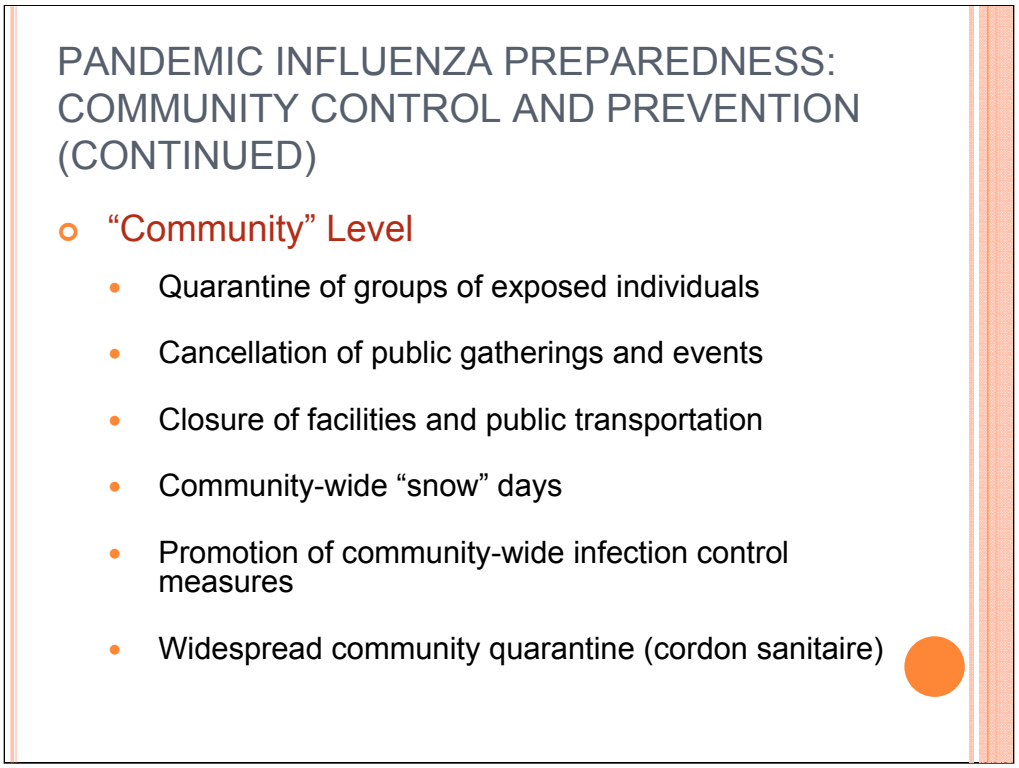
So, there is reason to be skeptical that this type of screening in airports is a very effective mechanism. I think it's inevitable that countries may choose to use this, but it's certainly not, based on experience, likely to be a very useful process.

And there are reasons to think that for influenza this process might be even less useful than for SARS, because people with SARS tend to be infectious much later in the course of their illness, as opposed to people with influenza, who as I have already said, are infectious pretty much on the very first day of their illness – and possibly even the day before they develop symptoms at least some of them are shedding the virus.

So, I think there is reason to be concerned that this approach may not work, and the evidence just in today's paper (21 May, 2009) that Japan's very careful attempt to try to keep people out to prevent the H1N1 virus from entering Japan have proved not to work. There is now a quite substantial distribution of the H1N1 virus in Japan.



When we talk about individual-level prevention and control, again we might be talking about isolation of patients, quarantine and monitoring of contacts, chemoprophylaxis of disease clusters, and things of that type at the individual level.

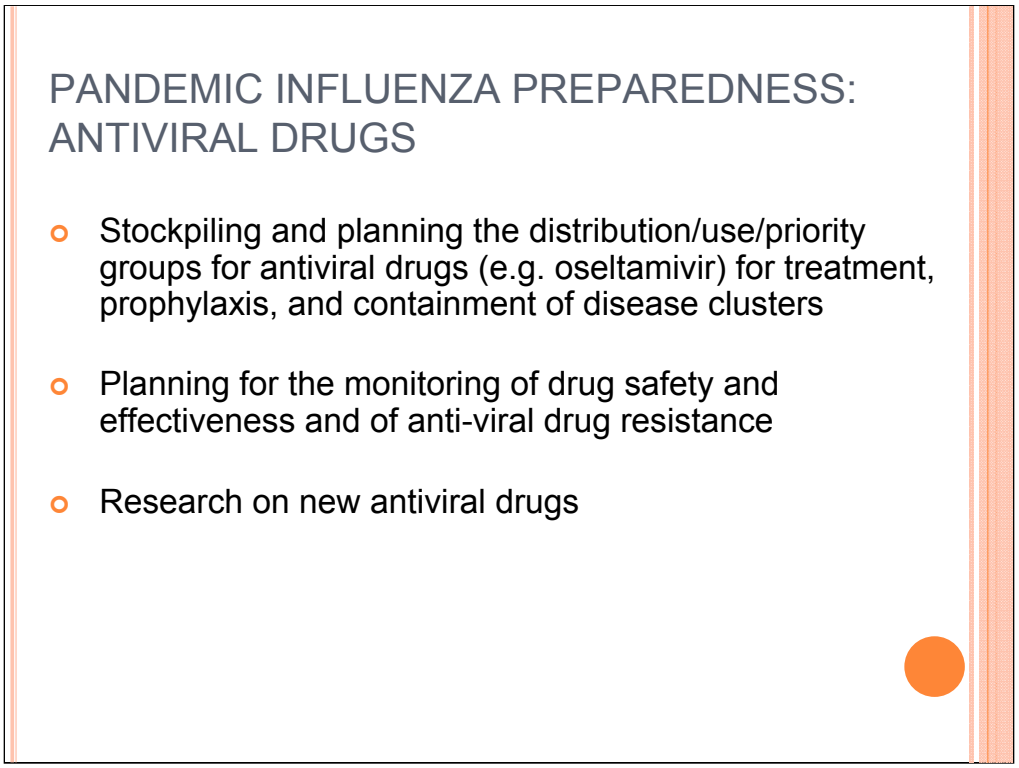


When we move up to the community level, as we have seen recently in New York City, for example, there are attempts sometimes to quarantine groups of exposed individuals, rather than individuals, to cancel public gatherings and events, to close facilities, even public transportation. Community-wide "snow" days refers to asking everyone to stay home.

Other approaches include promoting of community-wide infection control measures, closing of schools, things of that type. And, again, there is no doubt that these things are being done in the context of the H1N1 problem and that they will continue to be done. There are a lot of reasons why they may be reassuring to the public and the political leaders, but it's not clear how effective they can be.

I know that mathematical models suggest that they can have some impact on the transmission of influenza, but many of those models presume, I think, that, for example, if you close schools the children who are not in school will, in fact, be at home. At least the experience in the United States is that many of them go to the shopping mall or other places, where they are certainly still capable of transmitting respiratory viruses.

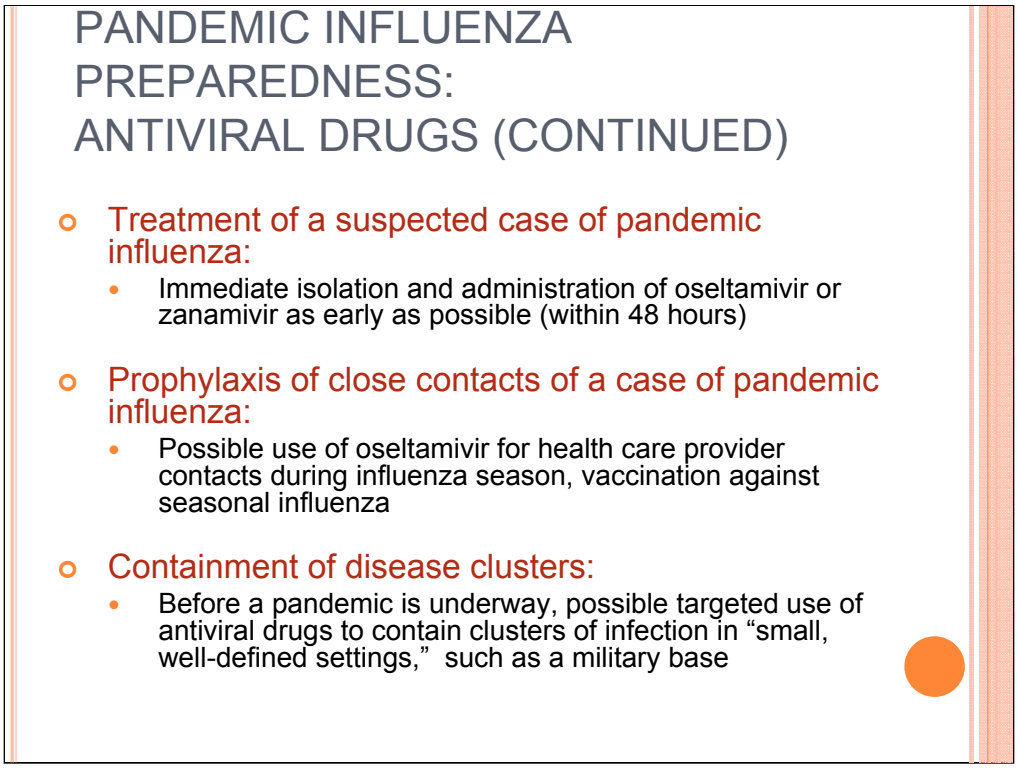
So, exactly how effective these types of community-level interventions can be really remains unclear, but I personally am doubtful that they will do anything other than perhaps delay somewhat the spread of influenza virus in a community.



Another issue related to preparedness, as I've already said, is stockpiling and planning for the distribution for antiviral drugs, such as Tamiflu, both for treating people early in the course of their influenza, in some contexts for use as prophylaxis, and perhaps for containment of disease clusters.

There have been some instances where there have been concerns about the safety and possible side effects, particularly in children, in the use of these drugs, and, as I'll come to in a moment, of course, the influenza virus can develop resistance to these drugs fairly quickly.

So there is also a need for research on newer antiviral drugs as well.



We can use these antivirals to treat suspected cases.

We can use these antivirals for prophylaxis of close contacts of cases, and again we can use them in the context of trying to contain disease clusters.

NEWSFOCUS

A 'Wimpy' Flu Strain Mysteriously Turns Scary

Researchers are trying to figure out why resistance to the most widely used flu drug has skyrocketed—and what that means for pandemic preparedness

Everything is constantly changing in the world of influenza, but the latest development has taken even veteran researchers by surprise. A strain of flu resistant to the most widely used antiviral drug—oseltamivir, more commonly known as Tamiflu—has raced from country to country and has now become established around the globe. As winter took hold in Europe at the end of 2007, it began to rise to prominence, especially in Norway; it then jumped to the Southern Hemisphere, only to come back and conquer Asia and the United States this winter.

That wasn't supposed to happen. Based on lab studies and clinical experience, oseltamivir resistance had seemed a minor, manageable problem. Researchers are well-acquainted with the resistance-conferring mutation, called H274Y, that has now circled the planet; they have studied it for more than a decade. And almost everything they learned indicated that the mutation also made the virus less viable, or "wimpy," as one researcher puts it. The extraordinary spread of the drug-resistant strain has turned that wisdom upside down.

From a public health point of view, the spectacular rise of the strain is not as threatening as it sounds. In most countries, oseltamivir is used for only the sickest of patients or not at all; Japan and the United States are the drug's main users. Besides, the mutation affects only the influenza A virus H1N1, one of three human flu subtypes that circulate annually, and one that happens to be relatively mild. The other two, H3N2 and influenza B, are still susceptible. And other drugs, such as oseltamivir's lookalike zanamivir, still work against H1N1. That's why this year's flu season in the United States could even end up killing fewer people than last year's, when the more aggressive H3N2 was the most active subtype.

Scientifically, however, the spread of the strain with the H274Y mutation is "extremely interesting," says Keiji Fukuda, an influenza specialist at the World Health Organization (WHO) in Geneva, Switzerland. Researchers don't understand why a mutation that seemed to cripple the virus in lab studies now seems to have no effect at all on its viability in the real world. "A natural experiment comes along and gives you a very different answer," says John Skehel, an influenza scientist at the MRC National Institute for Medical Research in London.

Online
sciencemag.org
Podcast interview with author Martin Enserink.

The findings have also renewed the debate on how countries should prepare for an influenza pandemic. After the influenza subtype H5N1 started its romp through Asia, Africa, and Europe in 2004, infecting millions of birds and some 400 people so far, pandemic worries led many countries to buy massive amounts of oseltamivir. The specter that this particular mutation or another could take those precious supplies out of commission in a matter of months is troubling, says Angus Nicoll of the European Centre for Disease Prevention and Control (ECDC) in Stockholm. "This has changed the landscape," he says. "One now has to now imagine that you could have a pandemic strain that is drug-resistant."

Unfortunate accident

Oseltamivir, which hit the market a decade ago, blocks the action of neuraminidase, an enzyme on the viral surface that cleaves a molecular structure called sialic acid sitting on the infected host cell membrane—the first step in the release of thousands of new virus particles from the cell. It's not the first flu drug to run into resistance problems. Over the past 4 decades, researchers have occasionally seen resistance against two older flu drugs, the adamantanes, pop up. Between 2002 and 2005, resistance to these drugs exploded in H3N2, a development some researchers have blamed on their excessive use in some countries (*Science*, 23 September 2005, p. 1976).

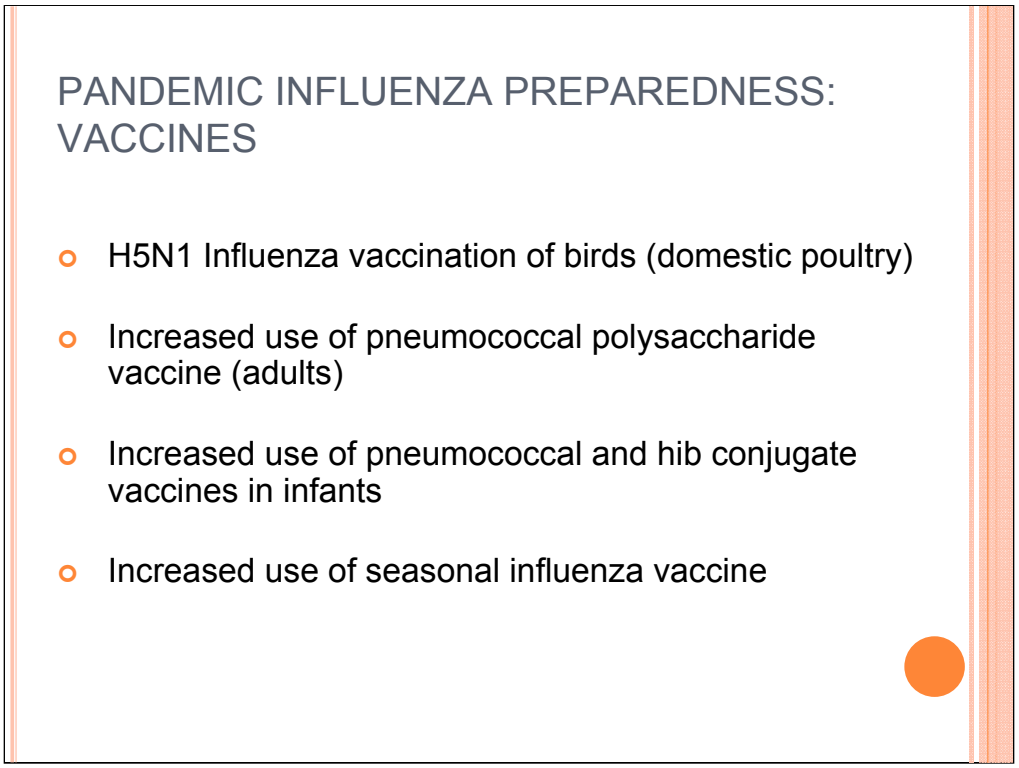
Flu scientists knew resistance could arise in oseltamivir as well. Studies had identified at least four mutations that seemed to lead to resistance, and H274Y, the one causing problems now, had been studied intensely because it occurred so frequently. Most scientists found the results quite reassuring.

In H274Y, one of neuraminidase's histidine amino acids is replaced by a tyrosine—the number 274 indicates the exact position of the amino acid in the protein. A study published in *Nature* last year showed that the replacement

But, as illustrated in this slide, in fact the influenza virus is capable of developing resistance to Tamiflu and to these antivirals fairly quickly.

If we are talking about the H1N1 that is causing the current problem, that virus is currently susceptible to Tamiflu, and that's very good news, but this article refers to the influenza virus that was circulating in the United States a few months ago and causing much of our annual influenza epidemic, this year that very, very quickly developed widespread resistance to Tamiflu.

So we can't be certain that the H1N1 that's currently circulating will remain susceptible to antivirals such as Tamiflu.

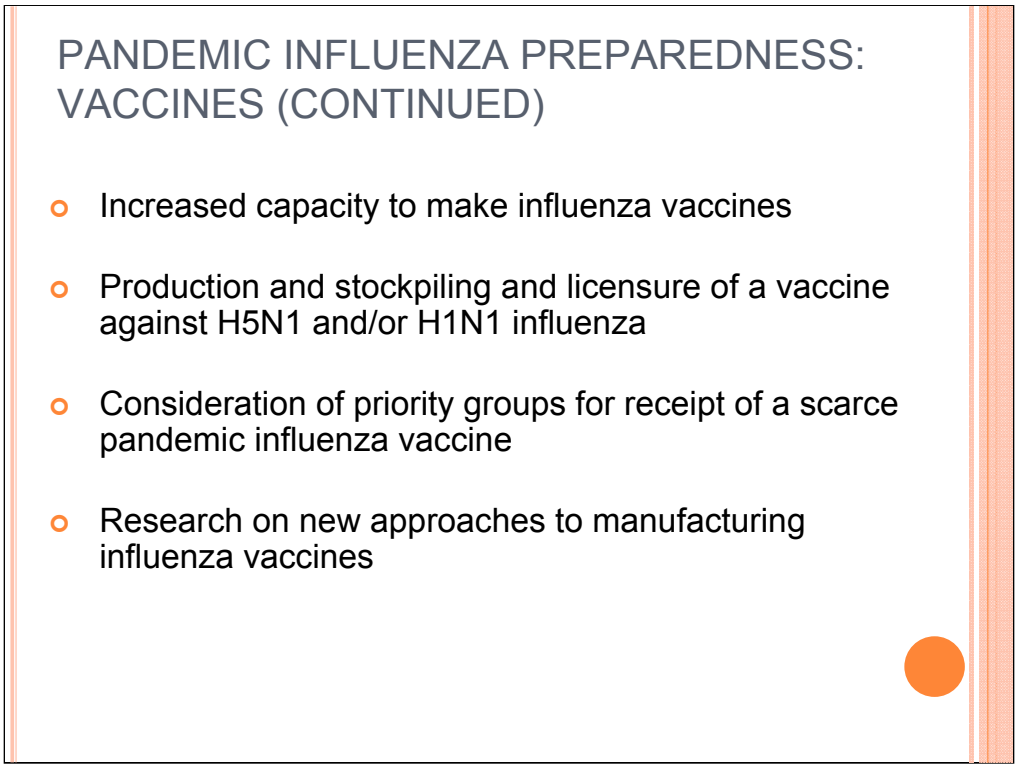


That brings me to the use of vaccines, and how they might be useful in terms of preparedness.

When we think about the H5N1 bird flu virus, one possible use of vaccine might be to vaccinate domestic poultry. I suspect that many of you are familiar with the controversy over the use of vaccine in that regard. One of the problems is that if you vaccinate the domestic poultry, which is not necessarily easy in countries in Southeast Asia, where the chickens are in people's backyards in very small numbers scattered over large areas, the vaccine protects the birds from disease, and reduces the economic catastrophe of having your birds dying of H5N1, but it also allows the virus to continue to circulate among these birds, but to do so in a silent fashion. So there is controversy about the use of H5N1 influenza vaccine in birds. But that is certainly one possible use of a vaccine strategy for trying to be better prepared for influenza pandemics or reduce the possibility of having one.

As I'm going to come back to, use of vaccines against the bacteria that are likely to cause secondary bacterial infections is another important thing to consider. This might include the pneumococcal polysaccharide vaccine, the 23-valent purified polysaccharide vaccine which we give to adults. It also might include pneumococcal and *Haemophilus influenzae B* conjugate vaccines, which we give to infants. And then last, of course--not last, but next--we might also want to increase the use of seasonal influenza vaccine, and there are a variety of reasons why that might be helpful in pandemic influenza preparedness.

One of them is by having a greater capacity on an annual basis to make seasonal influenza vaccine, we have a greater existing capacity to switch over and make a pandemic vaccine in larger amounts more quickly. So that's one of the reasons that we'd like to increase the use of seasonal influenza vaccine.



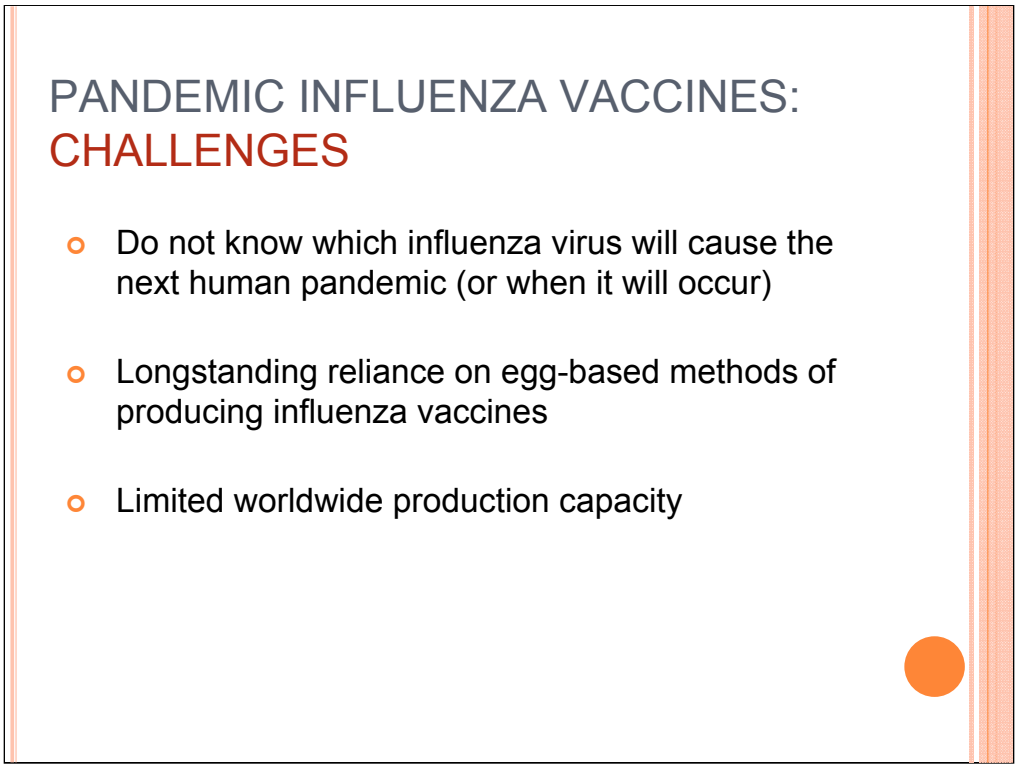
As I've said, that feeds into other ways in which we might increase capacity to make flu vaccines, particularly moving from egg-based methods that we've relied on for 50 years to cell-based methods, which might eventually allow us to make much larger quantities of influenza vaccine more quickly.

Other strategies involve producing and stockpiling and licensing vaccines against possible pandemic strains. That has been done, as I'll come back to for the H5N1 avian virus, and there is obviously very, very intense discussion going on at the moment about doing that with the H1N1 swine flu virus. I think it's safe to say that that process will be going forward for that virus as well.

It's also important ahead of time to develop plans for the use of a pandemic influenza vaccine, because we know for certain that if we need one of these vaccines, we will have relatively inadequate numbers of doses for the size of the globe's population for some period of time, and it's going to be necessary to decide which priority groups should receive a scarce pandemic influenza vaccine.

And of course there is also a need, an ongoing need, for further research on newer approaches to manufacturing safe and effective influenza vaccines in very large quantities in as short a period of time as possible.

So these are some of the research needs that you undoubtedly are familiar with.

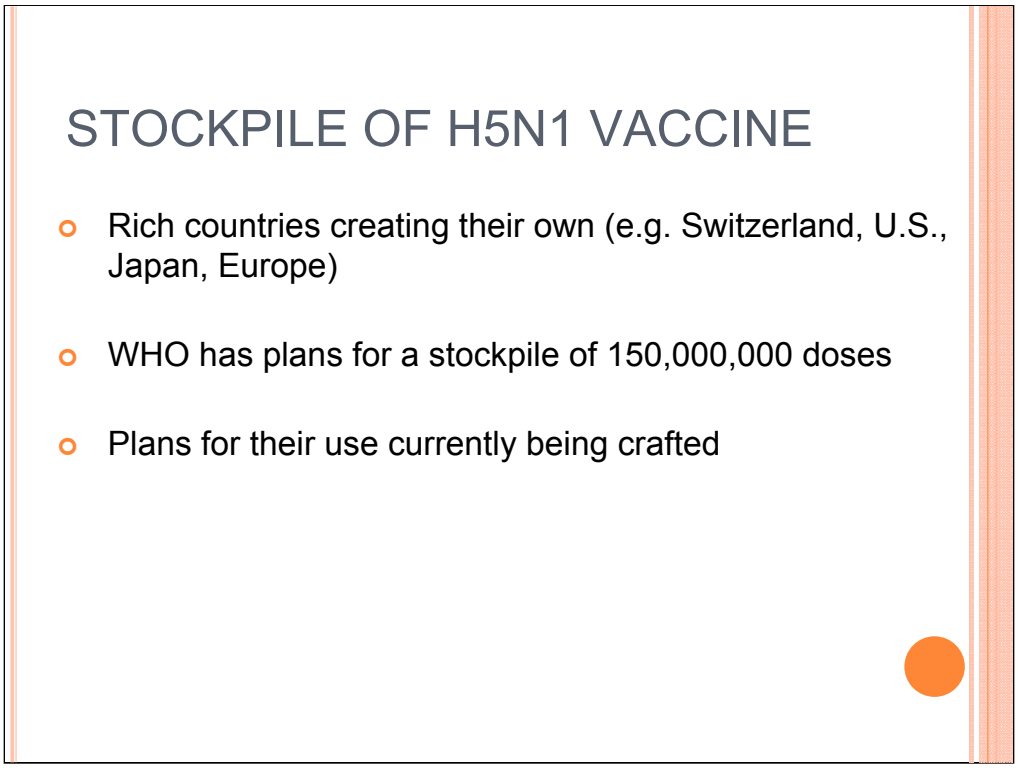


So, what are some of the challenges to having and using pandemic influenza vaccines?

Well, of course, the first one is we don't know which influenza virus will cause the next human pandemic or when it will occur. It certainly appears at the moment that the new H1N1 virus is the most likely candidate to cause the next human pandemic, since it is spread widely around the world at this point, but it was only two months ago that people thought the most likely influenza virus to cause a pandemic was the H5N1 bird flu virus. So one has to acknowledge that we really can't be certain at the time we have to make these decisions which virus is going to cause the next pandemic.

Secondly, we have, as I've referred to, this longstanding reliance on egg-based methods of making flu vaccines, and there are many, many problems associated with using eggs to produce flu vaccines, and so that is a challenge. There is limited worldwide production capacity for making flu vaccines to use in people and if there are approximately 6 billion people in the world at the moment and if a pandemic is caused by a virus to which no one has immunity and therefore it's likely that each person would need two doses of the vaccine to be protected, that's 12 billion doses. At current worldwide production capacity, it would take probably in the range of at least 4 years to produce that much influenza vaccine for human use.

So, clearly, there is not the production capacity globally to rapidly produce vaccine for everyone alive on the planet at the moment.



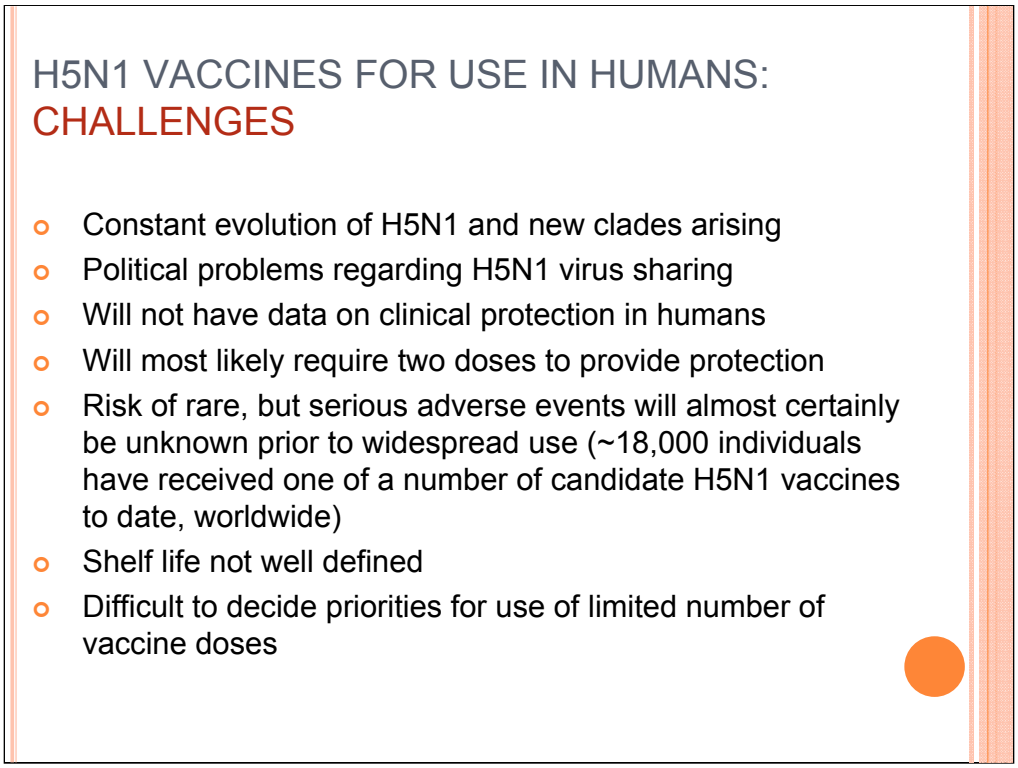
There are rich countries that have already created their own stockpiles of H5N1 vaccines.

Switzerland has a stockpile that would cover its entire population, Japan has a stockpile of 20 million doses, the U.S. and various European countries and Canada have developed stockpiles.

In addition to that, the World Health Organization has plans for a stockpile of H5N1 vaccine that would total 150 million doses that would be available for use in countries that don't have their own stockpile.

Plans for use of these stockpiles are basically still in the process of being finalized, and there are many, many complexities about those plans that I don't have time to get into.

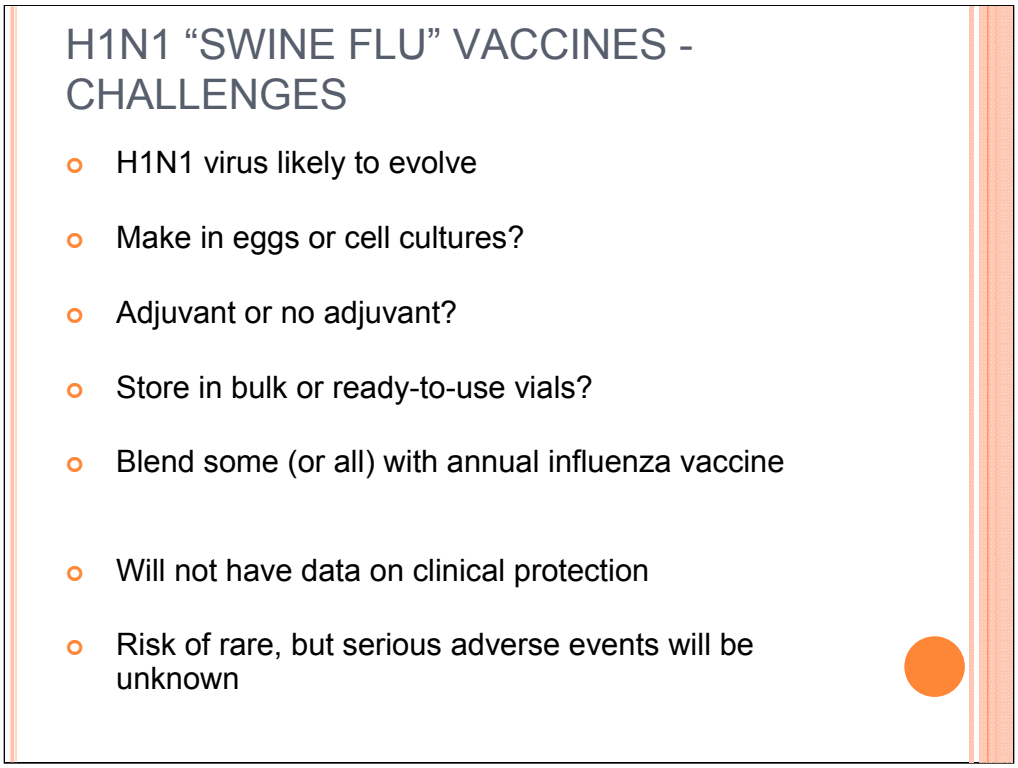
Of course, if the next pandemic is caused by H1N1 instead of H5N1, these stockpiles may not turn out to be terribly relevant.



So, what are some of the challenges to using, if we needed to, an H5N1 bird flu vaccine in people? Well, one problem with this virus and quite possibly with the H1N1 virus is that these viruses are constantly evolving. New clades of the virus are arising and to the extent that those clades depart antigenically from the virus that was used to make the vaccine, it's important that whatever vaccine we have gives cross-protection against whatever clade might actually cause the pandemic.

There have been political problems regarding the sharing of H5N1 viruses. I won't get into those, but they have certainly slowed down the process of sharing viruses for possible vaccine production. We have to acknowledge that with an H5N1 vaccine or with a new H1N1 vaccine, we won't have data on clinical protection in humans. We may have data on clinical protection in an animal model, such as a ferret. We will have good immunogenicity data, mostly from healthy adults, but we won't really know directly about clinical protection, vaccine efficacy, if you will. It's very likely that most people will need two doses of vaccine, given at least several weeks apart in order to provide protection, rather than being able to protect people soon after a single dose

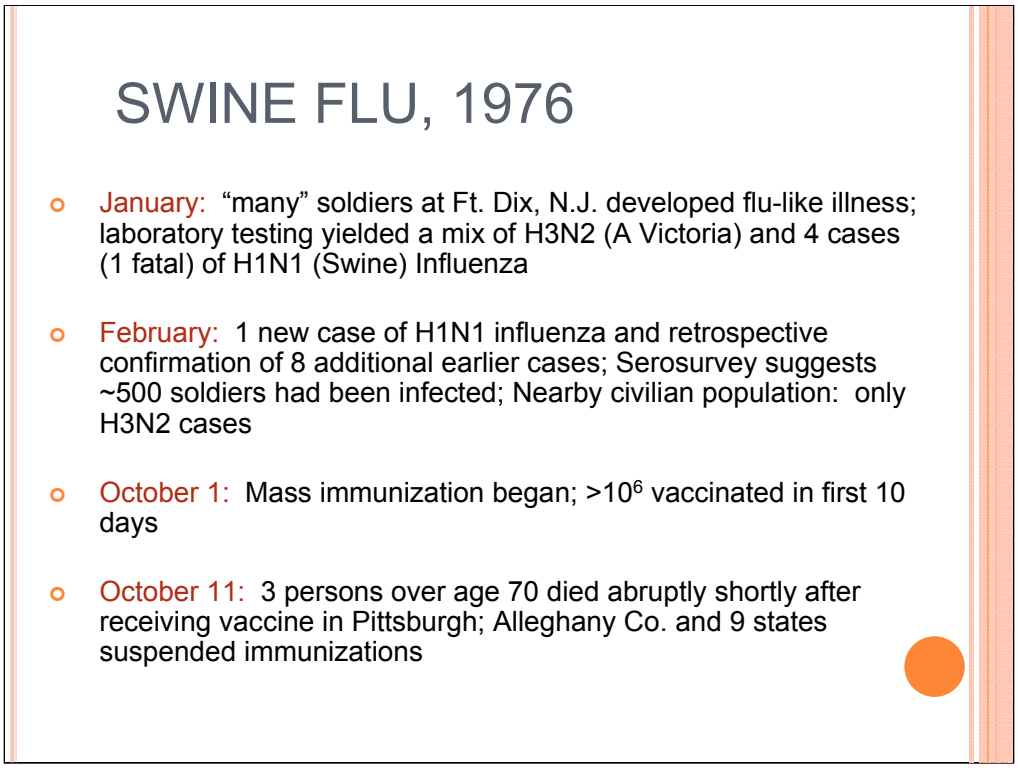
Another challenge is the risk of rare but severe adverse events that might occur as a result of vaccination. At the moment, for example, with the H5N1 vaccine, that vaccine, has been given worldwide to something in the range of 18,000 people, it appears quite safe with minor mild side effects in those 18,000 people, but as anyone with a little statistical training will know, testing something in 18,000 people does not assure that there might not be an adverse effect that occurs, for example, one in 100,000 times. So the risk of rare but serious adverse events will really not be known prior to the widespread use of a new pandemic influenza vaccine. Another problem is the shelf life is not well defined--it depends in part on whether the vaccine is stored in bulk, whether there is an adjuvant present, and things of that type. And of course there are challenges to deciding the priorities for the use of a limited number of vaccine doses.



Pretty much the same challenges await us in terms of development of an H1N1 swine flu vaccine.

Again, this virus is probably going to evolve in humans. We don't know that for a fact, and we don't know how much it will evolve, but the virus we use to make a vaccine in the next few months might not necessarily be the virus that causes a large problem in the next year or the year after. Again, questions about: Will this all have to be made in eggs or can some of it be made in cell cultures? Are we ready with cell culture technology to make this vaccine? Will there be an adjuvant or not? The use of adjuvants can reduce the amount of antigen we need to protect someone, so antigen-sparing is the advantage of using an adjuvant. But use of an adjuvant raises the safety concern of perhaps unknown possible side effects with using adjuvants. There are questions about whether it should be stored in bulk or in ready-to-use vials, and the very compelling question about whether an H1N1 vaccine should be blended together with the annual influenza vaccine we normally would be giving, or whether it would be kept separate and given as a separate injection or set of injections, and there are problems with each of those approaches.

Again, we not will have direct data on clinical protection of an H1N1 vaccine, and again the risk of rare but serious adverse events will be unknown.

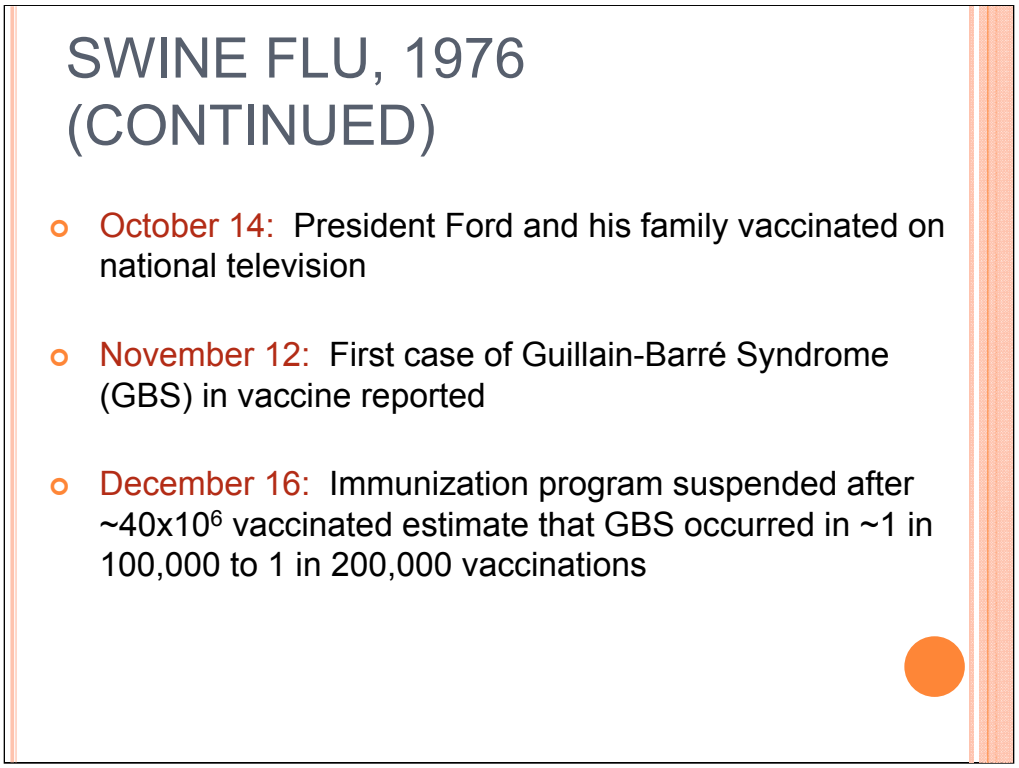


This just, for those of you not familiar with the history, points out what took place in 1976, in the United States, when we had a very small, limited swine flu cluster in Fort Dix, New Jersey.

In January of that year, there was one confirmed death caused by a swine flu virus and a number of other confirmed cases. It turns out in retrospect they were limited to the military base; swine flu did not spread to the nearby civilian population.

A decision was made to prepare a vaccine and to give the vaccine, once it was ready, so you can see in October of 1976 a mass immunization began.

About a million people were vaccinated in the first ten days, and then several elderly people died abruptly after receiving the vaccine.



These deaths were on the news, and, not surprisingly, it generated a lot of concern in the general public about the safety of the vaccine, and vaccination was suspended in many states.

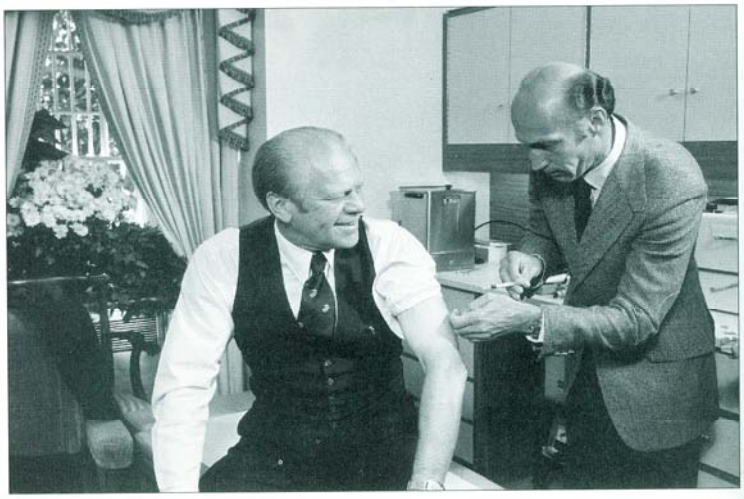
As a result, then-President Gerald Ford and his family went on television and had themselves vaccinated on TV to re-instill confidence in this vaccine.

And then unfortunately, a month later we began to have cases of a very serious neurological condition called Guillain-Barre Syndrome in vaccinated individuals, and in the middle of December after about 40 million people had received the vaccine, the program was suspended.

In retrospect, there was never a pandemic, or even an epidemic of swine flu in the United States, but pretty good evidence that the swine flu vaccine given in 1976 produced Guillain-Barre Syndrome in about 1 in 100,000 to 1 in 200,000 vaccinations.

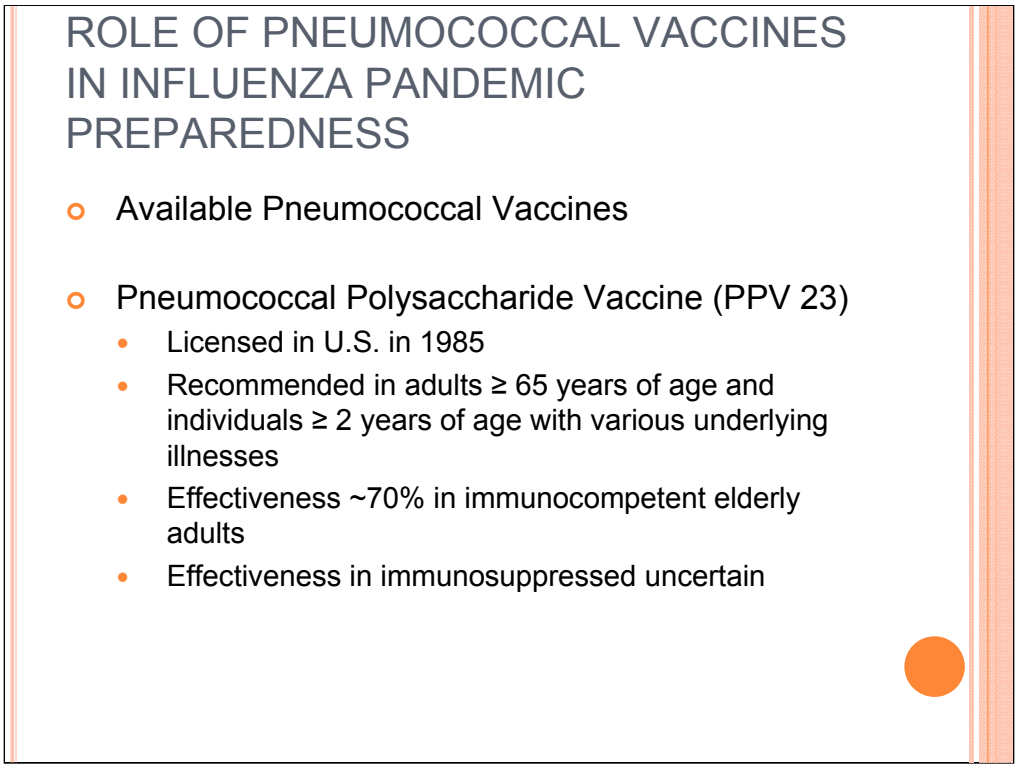
So, this raises the concern, if you will, about what we will or won't know about the safety of another swine flu vaccine, how certain we can be that it will be safe, and whether the public will accept it or not, because of this prior history.

Clearly, this will be an interesting set of issues to address if it turns out that we need to use a new H1N1 vaccine – and the past experience illustrated above emphasize the importance of having in operation an effective system of public health surveillance and response.



In 1976, afraid that the 1918 virus had reappeared in the form of swine flu, the Federal government instituted a national immunization campaign. When some who had been vaccinated died, President Gerald Ford was immunized in an effort to assuage public fears. Here he receives his flu shot from Dr. William Lukash (*Courtesy of the Gerald R. Ford Library*)

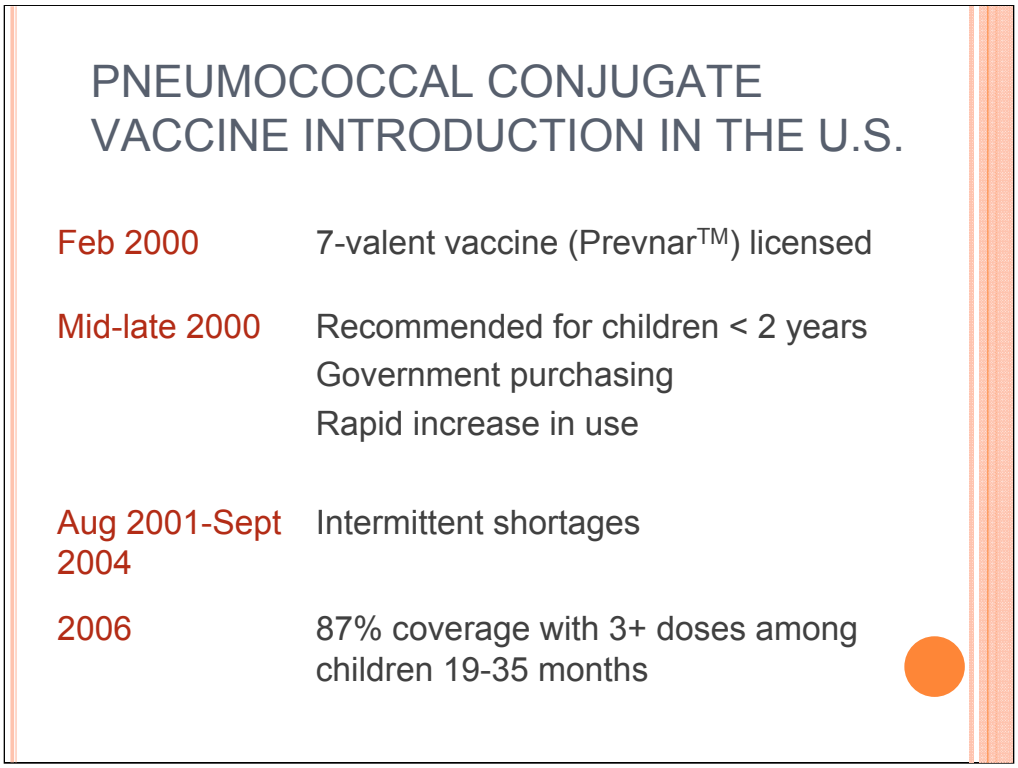
This is just a picture of President Ford getting his swine flu shot back in 1976.



Now, I'd like to come back to the question of whether we can use bacterial vaccines to enhance our preparedness, to reduce morbidity and mortality in the context of an influenza pandemic.

We basically have two pneumococcal vaccines available in addition to the *Haemophilus influenzae B* conjugate vaccine given to infants. The Hib conjugate vaccine is a very safe, very effective vaccine. And to the extent that secondary bacterial infections in children might be caused by *Haemophilus influenzae B*, achieving high levels of coverage with the Hib conjugate vaccine in young children would be very likely to prevent those cases. I've already shown you data that pneumococcal infections are a very, very important part of the pneumonias, the severe pneumonias, the hospitalizations, and the deaths that occurred in terms of the context of an influenza pandemic. We have two new pneumococcal vaccines:

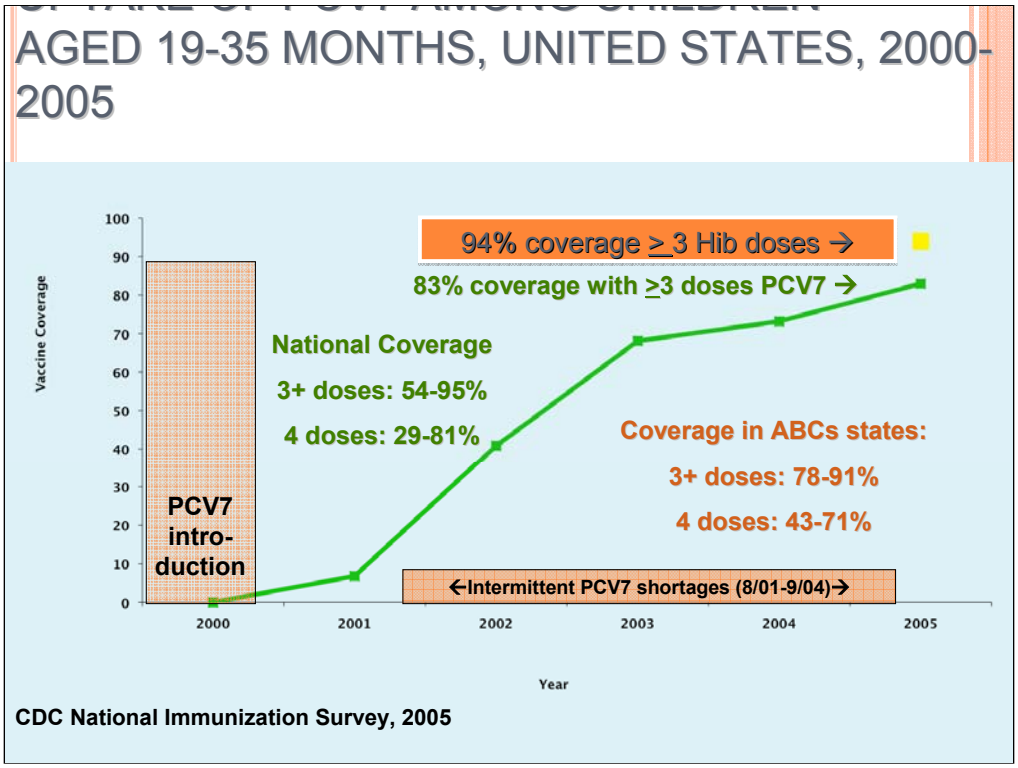
The purified polysaccharide vaccine with 23 serotypes was licensed in the United States in 1985. I suspect many of you are aware of this vaccine. In many wealthy countries, including the United States, it's recommended in all adults over the age of 65; in some countries, even all adults over the age of 60, even 55, and it's also recommended for use in individuals over the age of 2 with various underlying illnesses. Now, there is, I would say, some controversy about the effectiveness of the pneumococcal polysaccharide vaccine, but in immunocompetent elderly adults, in people with only age as a risk factor, or underlying illnesses that don't suppress the immune system, like heart disease, the effectiveness is probably in the range of 70%. In individuals who are immuno-suppressed, such as those with advanced HIV infection, leukemia, diseases of that kind, in all likelihood this vaccine is not protective at all.



The good news, if you will, in terms of pneumococcal vaccines came about in the year 2000, when Prevnar or the 7-valent pneumococcal conjugate vaccine was licensed for use in the United States, following the example of *Haemophilus influenzae B* conjugate vaccine, where that purified polysaccharide of the pneumococcus is conjugated, or chemically linked to a protein.

This was done for the seven serotypes responsible collectively for about 80% of pneumococcal infections in children in the United States and was shown in a randomized controlled trial to be highly effective in preventing invasive pneumococcal infections and pneumonia.

As a result, the vaccine was licensed in February of 2000, recommended later in the year 2000, and we achieved high levels of coverage with this vaccine in young children quite quickly.



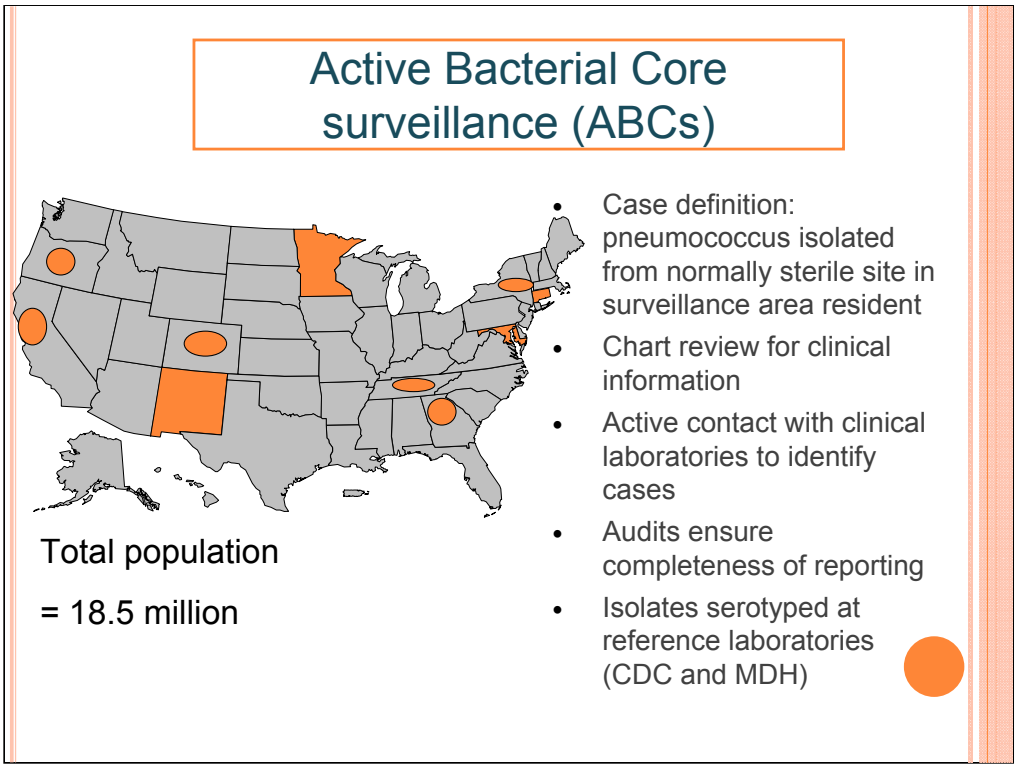
This slide shows the impact of introducing the 7-valent pneumococcal conjugate vaccine (PCV-7) in children 19 to 35 months of age.

Here you can see the green line showing the coverage, with either 3 or 4 doses, increased very rapidly, up to almost 90% within a few years.

In order to monitor and evaluate the impact of high levels of coverage with Prevnar, we use a very, very good, active, population-based, laboratory-based system for finding pneumococcal infections, which we refer to as ABCs. I am fortunate enough to direct the ABC site in California, but here you can see in the United States, our ABCs Active Surveillance Program (ASP) covers quite a large population, and in all of these sites, we have very, very good resources for doing surveillance.

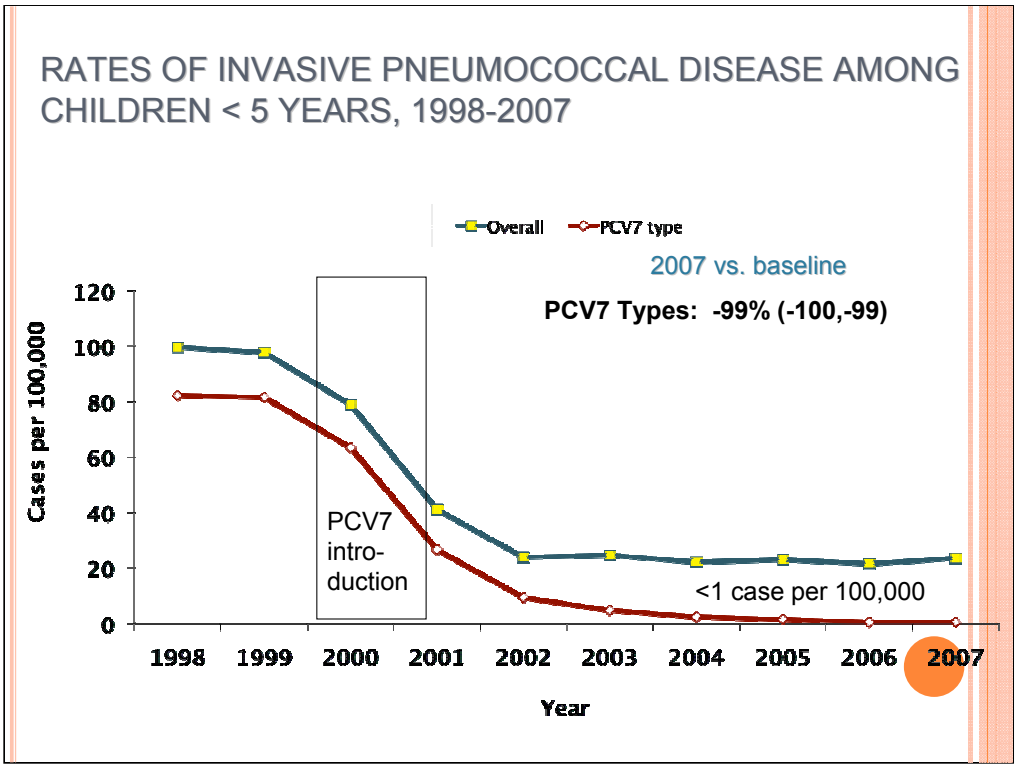
We go into every clinical microbiology laboratory and we find every single case, not only of *Streptococcus pneumoniae* infection in a normally sterile site, but many, many other infections as well, including *Haemophilus* and *Neisseria meningitidis*, and many, many others. And we are, therefore, able to look at changes in the rates of disease, antibiotic resistance, serotype distribution, risk factors, and a host of other things.

Using that system, we have been able to document what's happened as a result of introducing the pneumococcal conjugate vaccine.



And here you can see that for the seven pneumococcal types that are in the pneumococcal conjugate vaccine given to children, we've seen a 99% reduction in invasive pneumococcal infection in children under the age of five, following the introduction and high coverage achieved with this vaccine.

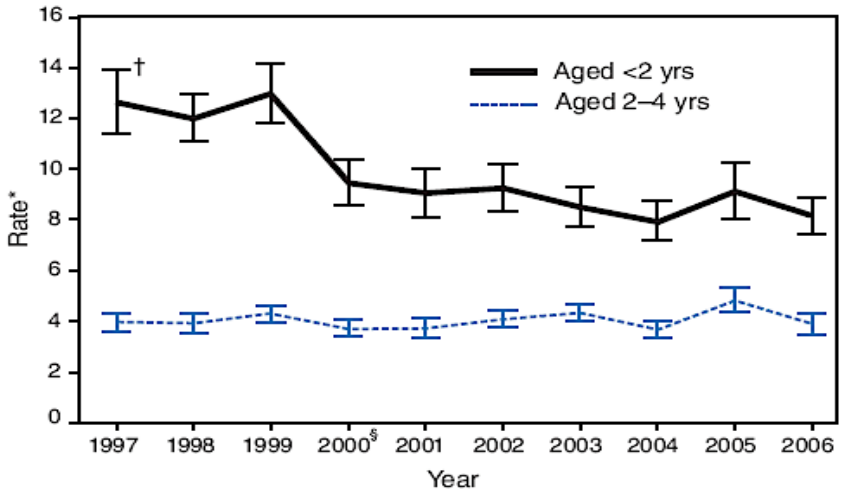
The use of the ABC Active Surveillance Program has enabled us to document what has been a remarkable public health success story, one which has now been replicated in many European countries and in Australia and in Canada and in a variety of other places.



This just shows further evidence of the impact of introducing PCV7, which has been a reduction in all-cause pneumonia hospitalizations among children.

These are obviously pneumonias caused by many etiologic agents, but these data show an impact on all-cause hospitalization rates for pneumonia.

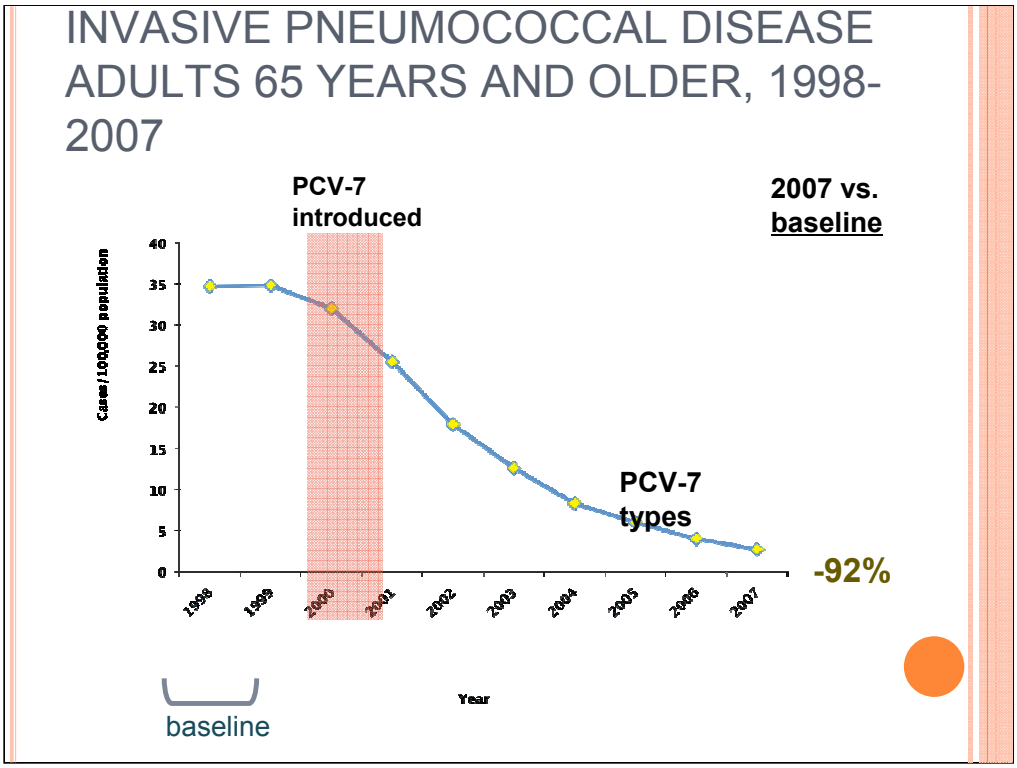
FIGURE. Annual all-cause pneumonia hospitalizations rates* among children aged <2 years and 2–4 years — Nationwide Inpatient Sample, United States, 1997–2006



* Per 1,000 population.
† 95% confidence interval.
§ 7-valent pneumococcal conjugate vaccine licensed in February 2000.

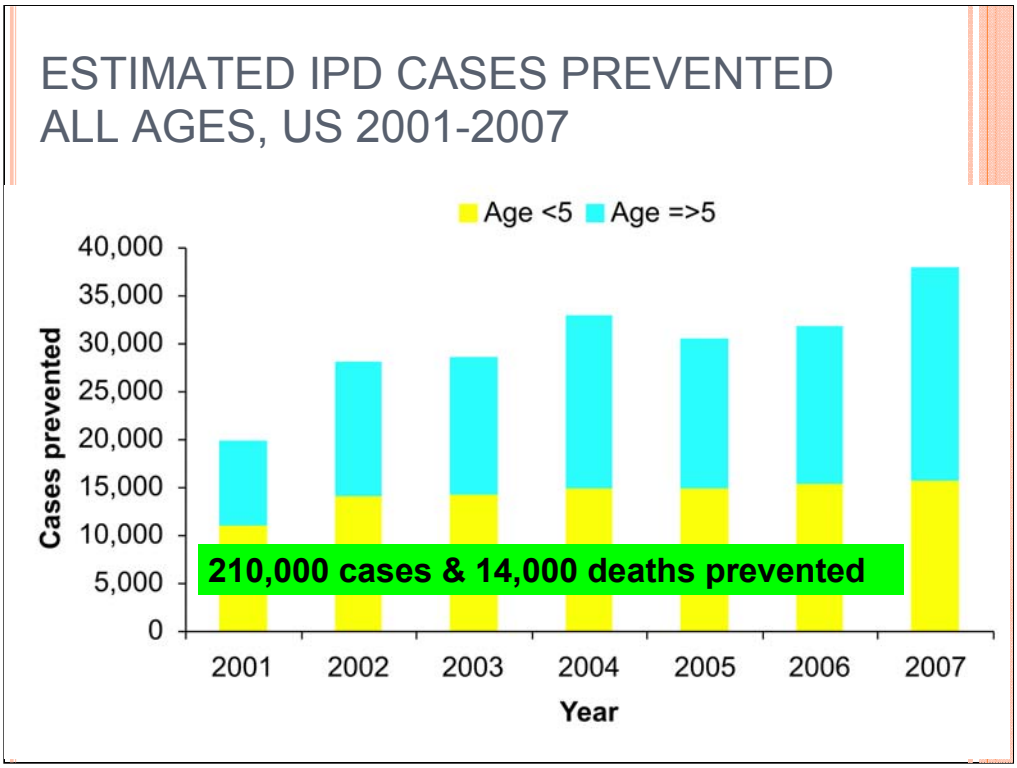
And perhaps even more astonishing, unexpected by even the experts, is that the vaccination of young children has had a dramatic effect also in pneumococcal infections in the younger siblings of those vaccinated, the older siblings of those vaccinated and the parents and grandparents of those vaccinated.

This is very, very dramatic evidence of “herd immunity”. This is not surprising, because the pneumococcus is spread through the respiratory route, and young children are the primary source of infection for other children and adults.



In this slide, you can see what's happened in adults 65 years of age and older, for the seven pneumococcal types that are in the conjugate vaccine.

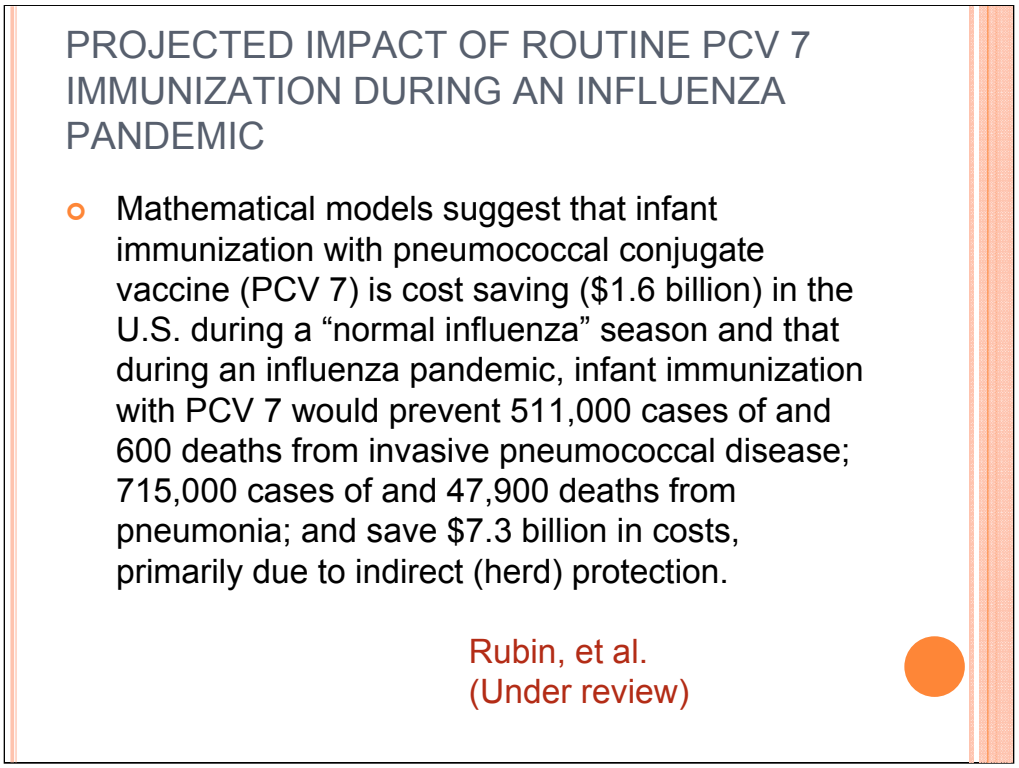
You again see this dramatic decline, this 90% decline in disease, not in those receiving the vaccine, but in the elderly in the same community, so, in fact a huge impact due to indirect or “herd” immunity.



And, in fact, what this slide shows, in the yellow bars, are the cases of invasive pneumococcal disease prevented in children under the age of 5, those targeted for vaccination, and the blue part of each bar is the number of cases prevented in those over the age of 5, in essence, the cases prevented through indirect “herd” immunity.

In fact, the number of illnesses and deaths prevented through the use of this vaccine in infants is even larger through its indirect effects than it is through the direct effect in the vaccinated population.

So, we have come to understand that this vaccine is having an extremely potent effect in the population, and I would be very optimistic that this widespread use of PCV-7 will serve us well whenever we have the next influenza pandemic.

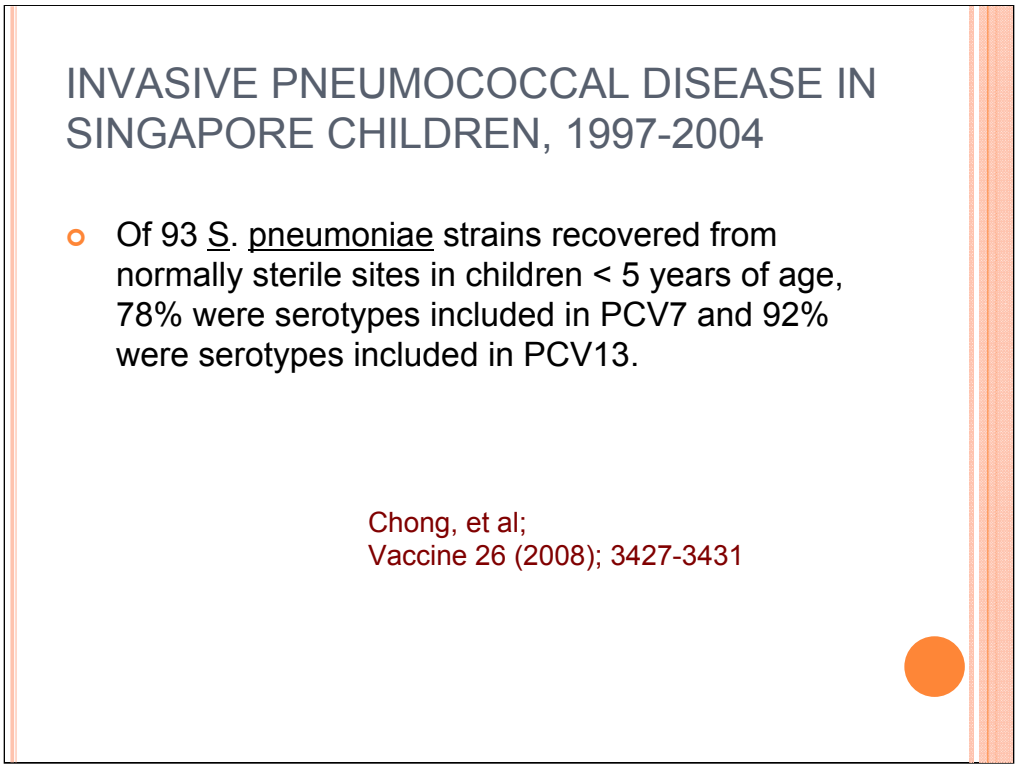


The research described here is from an article by investigators at Emory University and Harvard University – the article is under peer review and not yet published.

The use of mathematical simulation models suggest that high levels of coverage with this pneumococcal conjugate vaccine in children in the United States is cost-saving during a "normal influenza" season, saving about $1.6 billion in health care costs. During an influenza pandemic, the high levels of coverage of infants with PCV-7 in the U.S. National Immunization Program would prevent about 500,000 cases and 600 deaths from pneumococcal disease and 700,000 cases and almost 50,000 deaths from pneumonia at a savings of about $7 billion in costs.

Most of these public health and economic benefits, again, would be due to the indirect “herd” protection in adults.

So very, very good evidence that routine use of this vaccine in the community is going to turn out to be very, very beneficial in the context of influenza pandemics or even influenza epidemics.

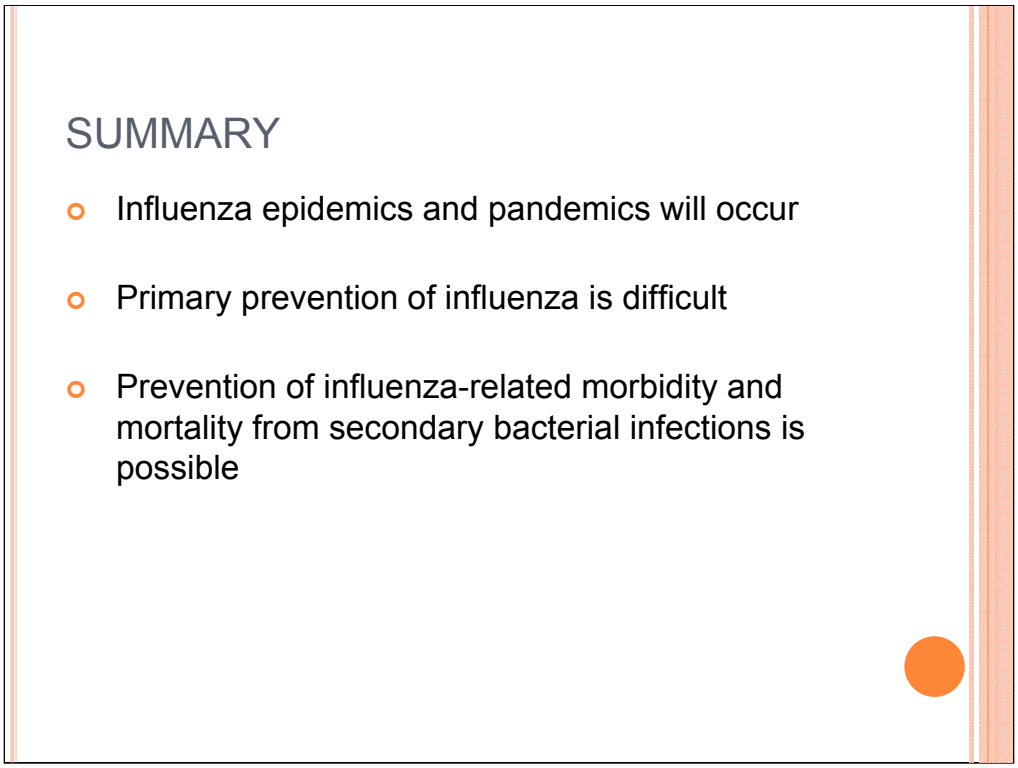


Now I just want to close by pointing out that I managed to dig up a little bit of information about pneumococcal infection in Singapore.

This slide just shows one study published last year by Chong and colleagues that, in essence, indicates that the serotypes causing pneumococcal infection in Singapore, turn out not to be very different from the ones that cause disease in the United States.

In this one study, almost 80% of the pneumococcal isolates from normally sterile sites in kids under the age of five in Singapore are of serotypes included in the current 7-valent conjugate vaccine (Prevenar) and 92% of the isolates would be preventable in a planned 13-serotype vaccine.

So, for those of you who are more focused on the situation in Singapore, these data suggest that the routine use of this conjugated pneumococcal vaccine may also be very, very helpful in Singapore, especially in the context of epidemic or pandemic Influenza .



So, to sum up and to close, I think it's very clear that influenza epidemics and pandemics are going to continue to occur. The most recent example is the one we're living with right now, the H1N1 situation. For a variety of reasons that I've alluded to during this talk, primary prevention of influenza is very difficult. Attempts to limit travel, to exclude ill individuals, to close facilities, are all things that, as I have said, there is enormous public pressure to do. But, there is very little evidence that they are going to do anything more than, at most, slow the spread of the influenza virus. So, primary prevention of influenza is difficult, absent a substantial amount of an appropriate influenza vaccine. I've pointed out why there can be substantial delays in having a vaccine in large quantities against a new influenza virus.

I would like to leave you with the good news that one approach, at least, to preventing morbidity and mortality is to prevent some of the secondary bacterial infections that frequently are responsible for a lot of that morbidity and mortality, those infections either caused by *Haemophilus influenzae B* or by the pneumococcus.

There are those of us in the United States and in other parts of the world who believe that achieving high levels of coverage in our populations with these bacterial vaccines is one element in being better prepared for the next influenza pandemic. A number of countries are certainly considering this as they think about the introduction of these bacterial vaccines, if they haven't already introduced them.

So, I'm going to close there. I may have exceeded my time a little bit. I know that there will be an opportunity for me to have an interaction with you through the internet, to answer your questions, to engage in conversation, and I look forward to that. So, again, I'm very sorry I could not join you in Singapore; I was very much looking forward to the visit, but I do hope that this has been informative, and I look forward to answering your questions and interacting with you through the electronic media (**reingold@berkeley.edu**). So thank you very much.