



Seasonal Influenza Vaccine

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Every year the medical effort to vaccinate the public begins anew. This vaccine is unique amongst those most people are familiar with because vaccination in prior years has little application in the current year, and therefore needs to be repeated annually. Though the best technology today has this limitation, efforts to change the flu vaccine to address this issue are ongoing and may one day in the future make the annual effort to vaccinate more than three hundred million Americans a part of vaccination history.

Many people choose not to vaccinate themselves or their family to protect against seasonal influenza. The most common rationales I've heard over the years are: "The last time I got a flu vaccine I got the flu from the vaccine!" This can be buttressed by the next most common rationale: "I've never gotten a flu vaccine and I've never had the flu!" Or how about this one: "I got the flu vaccine and I got the flu anyway!"

The first of these comments is pure urban myth. Like any good urban myth it is first and foremost a myth—a widely held, but false belief or idea. There is not now and never has been an instance of influenza caused by the vaccine. The manufacturing process produces a killed viral or attenuated viral antigen that is incapable of causing influenza. I can see some circumstances where a causal relationship could be believed to exist, so let's examine these circumstances. So for the sake of discussion, patient A gets a flu vaccine and a week later several office employees miss work due to illness. Two days later patient A has cough, congestion, sore throat and fever. It's only been nine days since the vaccine and not knowing why the other employees are absent, a conclusion is drawn that the flu vaccine is responsible for this case of the "flu". There is a second flaw in this rationale beyond the obvious; the assumption that the vaccine has caused another case of the flu. The inaccurate use of the term "the flu" is rampant. In winter for many, any cough, congestion and fever could be labeled the "flu". The overlap in symptom interpretation in the lay population who've not recently had medically documented influenza makes this area a source of considerable inaccuracy. Influenza is a specific illness and not all "cold" symptoms rise to a level deserving of the "influenza" label.



So let's move on to the next common rationale: "I've never had a flu vaccine and I've never gotten the flu!" This statement can be true or nearly so. In an average year, no more than twenty percent of the population contracts influenza. So, if you are fortunate, you can go a good number of years never having had influenza. Add a dose of forgetfulness and you can see how the "never" belief came to be. The last of those rationales: "... I got the flu anyway" can, even if you take away all the medical inaccuracies of this assumed diagnosis, be true. That is far from the whole story. Patients do get influenza in spite of being vaccinated. Even if strain changes in circulating influenza did not occur and the match between vaccine strain and circulating influenza strains was perfect, the vaccine will not provide universal protection. Some of this has to do with the individual immune system each of us has. The immune system is a dynamic system, changing over time as the individual ages. In the very young and the elderly, the efficiency of the immune system is lacking relative to the rest of the population. This is well known enough that a different and much stronger version of the influenza vaccine exists for those sixty-five years of age and beyond. We also don't give the vaccine before six months of age because response by the very youngest immune systems is lacking enough that the administration is not warranted. Put all that aside and there is one significant take home message. Those people who've been vaccinated who then contract influenza will almost always have lessened (attenuated) symptoms. They'll typically have fewer days of symptoms and less fever over all. Ask a physician experienced in the diagnosis of influenza and you'll learn how obvious the diagnosis can be in a patient who has not been vaccinated. What you'll also learn is how mild the illness can appear to be in the vaccinated patient with attenuated symptoms because of the protection afforded by the vaccine. From the doctor's perspective, this "breakthrough" infection is **not** a vaccine failure. This is part of the spectrum of protection from the vaccine. That patient will be less ill and return to function far sooner than the unvaccinated patient. Perhaps more importantly, that patient is much less likely to become critically ill or die as nearly 20,000 annually do in the United States. Of those who die, one hundred or so will be children, the overwhelming majority of whom will be ordinary healthy children. Certainly, children with preexisting cardiac and pulmonary conditions are at heightened risk. The overwhelming numbers of healthy children compared to the special risk categories mean that at the end of the day, most child death will fall on the shoulders of healthy children. So for different and yet similar reasons, both special risk and healthy children and adults deserve to be vaccinated year after year until the science of population control of influenza advances beyond its current state. Don't diminish the considerable progress and protection current



medical science can provide you. By the same token, look forward to advances in influenza science and be hopeful that the progress will derail the possibility of a new pandemic influenza outbreak.

The next pandemic flu, an influenza strain that is novel to the world population living at the time of the outbreak, will undoubtedly come from the natural reservoirs of influenza in nature. Those reservoirs are mostly avian (birds) and to a lesser extent swine (pigs). Denoting its point of origin, this is why when a novel strain of influenza is discovered it is invariably referred to as swine or bird flu.

If you've had enough science, this would be a good time to stop reading and make appointments to get your family vaccinated. If you're still interested, read on, as the jargon of science, specifically influenza science is going to grow more intense.

These natural reservoirs deserve further comment and if you've noticed, until now, all the conversation has been about influenza A. This is because the influenza B viruses circulate widely only among humans. As such, there is far less probability of significant viral genetic re-assortment (antigenic shift) occurring and resulting in a novel pandemic influenza B. Couple that with the knowledge that influenza B produces less severe influenza disease and you can see why the juggernaut of influenza remains influenza A (H1 variants) in our experience thus far.

Influenza A is divided into subtypes based on two surface antigens: the hemagglutinin (H) and the neuraminidase (N). There are 18 hemagglutinin subtypes and 11 neuraminidase subtypes. Wild birds are the primary natural reservoir for influenza A and are believed to be the reservoir for influenza A viruses in all other animals. All subtypes have been found among birds except H17N10 and H18N11, which have been found only in bats. The range of disease among birds is quite variable. Most avian disease causes asymptomatic or only mild disease. Some variants, mostly H5 and H7 are capable of producing severe disease with widespread death in birds, especially domestic chicken and turkey. Those strains producing severe disease represent special risk to humankind in the event of antigenic shift. Swine are a unique problem in influenza A pandemic risk because they can be infected with avian, human and swine strains of influenza A. If infection occurs with two strains simultaneously, as the viruses replicate (multiply), the potential for exchange of one or more of the influenza genes can occur. If enough genetic material were exchanged in this process, the resulting new virus would be the creative product of "antigenic shift" and could be novel enough to represent pandemic risk.



Depending on the source for the bulk of the newly incorporated genes, the new influenza A virus would be deemed avian or swine.

So in 2009 when the current H1N1 variant of influenza was discovered in Southern California in humans, genetic evaluation of the virus demonstrated genetic similarity to United States and Eurasian swine influenza lineages. Hence the novel H1N1 influenza was initially referred to as a swine (point of origin) pandemic (potential for devastating widespread disease) influenza. Eventually the cloned virus used to make the vaccine for the 2009 novel influenza by CDC (centers for disease control) would be designated as A / California / 07 / 2009 H1N1. Likely a technical point, this novel strain is not regarded by experts as being of swine origin despite the genetic similarity to other swine influenza lineages. This is largely due to the inability to demonstrate widespread carriage of this strain in U.S. swine herds and the lack of historical contact between the early human cases of this novel H1N1 strain and pigs. This strain of H1N1 influenza remains one of the dominant influenza A strains and will be represented in the current (2014-2015) vaccine by an A / California / 07 / (H1N1) pdm09-like virus with minimal change to account for antigenic drift in five plus years since its original appearance as a novel strain.

The current problems with H7N9 (an avian / bird strain of influenza) in China remains confined to birds and those who work closely with large numbers of birds. This particular strain is a troublesome concern for humankind for a variety of reasons. Infected birds spread the virus within the species, but do not get sick and die. So, killing sick individual birds or infected flocks is not a viable prevention strategy. The early experience with this virus has demonstrated that the virus is still lacking the two genetic changes that allow a swine or avian flu to become a viable candidate as a novel pandemic virus. First, the virus must "cold adapt" and become able to replicate effectively at the cooler core temperatures of humans versus swine and birds. Second, the virus must acquire the ability to spread by an airborne / droplet route so that person to person spread will be easier. This is good news because early and very limited experience with this novel H7N9 virus suggested the case fatality rate may be as high as forty to fifty percent of humans infected. WHO and CDC laboratories have this novel vaccine, but as these adaptations have not taken place as the WHO continues to monitor the situation, vaccine development has not progressed beyond the earliest stages.

The most recent experience with devastating widespread pandemic novel influenza was the H1N1 influenza outbreak of 1918-1920. The case fatality rate was estimated to be between ten and twenty



percent of infected individuals. In our modern experience with influenza, H1 types of influenza A viruses inflict the most serious disease, as was the case in 1918. So if we study potential future pandemics, including the potential that the H7N9 variant in China from a population basis, some things are obvious. The case fatality rate is an uncertain projection. Early experience in China with too few cases to be a great predictor suggests that of those patients ill enough to seek medical care and have the illness identified as H7N9, up to forty percent will die. What is uncertain is whether or not the known cases represent all or nearly all of the cases. If there are a larger number of cases not ill enough to be identified and counted, then the case fatality rate could be less than these early calculations. This is a bit of a leap of faith, but forty percent fatality rates would put H7N9 in the same area as Ebola hemorrhagic fever or our own Hanta virus experience in the four corners region of the United States. Retrospective analysis of the 1918 pandemic showed a case fatality rate far less (5--10%) than this. It seems with modern medicine at our disposal that the case fatality rate could be far less than century ago, but at least two things should be considered in this assumption. First, look at history and you'll see how and who in the population bore the brunt of the critical and fatal outcomes. You be surprised to learn that "cytokine storm" in young healthy adults put most of the death in the laps of healthy adults. The part of the population with the most vibrant immune systems and their "cytokine storm" was their undoing. So what is this "cytokine storm"? Simply put, this is inflammatory response to lower respiratory (lungs) and systemic (vital organs) infection. The overactive response compromises lung function and oxygenation, blood pressure and oxygen delivery to the tissues. I could go on, but you can see how grisly this sounds already. So modern medical support for sick patients will be often primarily directed at diverting "cytokine storm" and supporting vital functions that are already adversely affected by this storm. This is inpatient and often times ICU or near ICU levels of medical care. This will create an unprecedented demand for critical care services in this country will little time to prepare for this need. Assume the pandemic scenario is less virulent than that of 1918 or the early data from China and H7N9 in the present day and a case fatality rate is only two percent over a two-year period. There are in excess of 300,000,000 Americans living today. That case fatality rate translates to six million deaths and a much larger number of critically ill who will need care to survive. Think about caring for this influx of patients and remember that other illnesses won't go away while this influx takes place. Doing the math for just the numbers of patients who will die is a staggering exercise. Assume that care will be delivered in the largest one hundred-fifty urban centers in the country. That would mean each center would care for 40,000



critically ill or dying patients in a two-year period. Urban centers in round numbers would receive fifty new and likely critically ill patients each day, day after day for two years if the assumptions in this scenario are accurate.

Being more optimistic, let's assume the scenario assumes a case fatality rate that is ten times too high and the actual rate is two per thousand (0.2%) not two per hundred (2%). So now the number of critically ill patients presenting to each urban center is "only" five per day, day after day for a two-year period. These are not one-day illnesses and in very little time ICU hospital beds and the personnel needed to staff them will be stretched to the bursting point. Further, remember that "cytokine storm" will be targeting the healthy adult, many of whom are health care workers in the front line of exposure and the roster of personnel capable of staffing those hospital beds will be just that much smaller.

This was a part of the concern when the new variant evolved in California before becoming a worldwide outbreak. It was a pleasant surprise and a windfall to worldwide health when the virulence of this novel H1 influenza A virus was less than it could easily have been. If you can remember the anxiety and urgency of that one to two year period when uncertainty was palpable, imagine what the country could have been like had the doomsday scenario played out to its fullest extent.

People have a short attention span and a cavalier disregard for what they don't understand very well. In any given year with seasonal influenza vaccine, immunization rates at the end of the vaccination season in adults approach thirty percent of the population. With children we do a little better and can push that to thirty-five percent of the population. The "basic reproductive number" (R_0 naught) is a figure used in public health to define how many new cases a single case of any disease will spawn through exposure before the patient recovers or dies and no longer is an infectious risk. In pandemic influenza, that number is two to three. That information allows calculations about what percentage of a population needs to be protected through immunization to have herd immunity halt the spread of disease through a population. In influenza, the hope of herd immunity based on these calculations would require sixty percent of the population to be immunized. In the absence of a novel and virulent pandemic influenza outbreak and case fatality rates high enough to provoke terror, it is doubtful the population would be motivated enough to be vaccinated well enough to have herd immunity provide a protective envelop. Even if we achieve that sort of motivation,



developing a vaccine to combat a novel pandemic influenza A virus would take months. In April 2009, the novel H1N1 Influenza A / California was identified as a threat and with the best efforts applied, the new H1N1 vaccine was not available in large quantities until eight months later.

Consider the costs in human terms or any other terms you'd rather consider if we have a truly lethal novel influenza virus to confront.

In the face of a new pandemic, we cannot rely on the existing antiviral medications. Four of these exist today. Two of the four are ineffective and the other two are not too effective. At best, they make modest alterations in the severity of the disease. Reports of resistance to the remaining two are becoming more common. In time, it's suspected they will be of limited use as well. Our best hope as with the group of other lethal illnesses we've limited or conquered with modern public health techniques, lies with immunization. The vaccine needs improvement though, so that the annual vaccine effort can be replaced with a vaccine that can be given once or twice and afford the patient long-term protection as do the other vaccines in widespread use today. A new generation of influenza vaccine that does this will need to target other surface proteins that do not change through the genetic re-assortment techniques of antigenic drift and shift. If this can be done successfully, then we have a reasonable hope of getting more than sixty percent of the population vaccinated and limiting influenza through herd immunity.

In the meantime, we need a population that is more motivated to help one another through widespread immunization efforts. People need to quit hiding behind the three urban myths (I'm sure there are others) detailed at the beginning of this. The segment of the population that relies on herd immunity in the protection against other vaccine preventable diseases they and their children enjoy while they selfishly do not themselves vaccinate, need to understand that in influenza we do not achieve the critical mass necessary to attain herd immunity. Influenza, that many regard as trivial remains the number one annual killer among the vaccine preventable diseases. Unless the annual deaths gobble up a loved one, it's doubtful the pervasive lassitude regarding influenza vaccinations will change. We don't seem to have the political will to force change, so change with current techniques will have to come through volunteerism and personal responsibility.