



Transitioning Away From the Egg-Based Flu Vaccine

John Hennessy

American Institute of Chemical Engineers
Bucknell University

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Executive Summary

Seasonal flu causes an average of 36,000 deaths and 200,000 hospitalizations each year in the United States. The direct medical costs associated with these visits averages \$10.4 billion each year. With additional considerations taken into account, such as missed days of work, it is estimated that seasonal flu costs \$87.1 billion in lost GDP. The threat of pandemic influenza is imminent and the consequences can be much worse. The Congressional Budget Office has estimated that a severe pandemic could infect 90 million Americans and kill 2 million. The GDP is expected to drop 4.25% if a severe pandemic were to occur.

The best way to stop the spread of influenza, thereby curtailing the economic and medical effects, is through the use of vaccines. Unlike most vaccines, a new flu vaccine must be made and administered each year because the virus changes just enough from year to year to make previous vaccinations ineffective. Each year a seasonal vaccine is created containing three of the most prevalent strains of the virus. For the most part, seasonal flu is not considered much of a security concern, and with rare exceptions, everything runs smoothly.

America is not prepared for a pandemic. In the *National Strategy for Pandemic Influenza: Implementation Plan* there are two goals concerning the production of pandemic flu vaccine. The first, which has been achieved, is to have 20 million pre-pandemic vaccines of any strain considered to be a threat. The second is to have the domestic capacity to produce enough pandemic vaccine for everyone in the country within 6 months. This goal is far from being achieved. The current capacity is well below the goal and the current egg-based method cannot mass produce vaccines in 6 months.

All vaccines currently produced in the United States are made using the egg-based method. The live virus is grown inside a chicken egg, inactivated, and then used in the vaccine. Because the egg-based method takes too long and because of the method's susceptibility to an avian flu outbreak at multiple points, increasing capacity through the egg-based method is not acceptable. New technologies must be used to address the capacity issue.

The government supports the building of new facilities using the mammalian cell-based method. This method only slightly decreases the time need for production. With other factors included, it is a better method, but not so much better that it justifies an infrastructure overhaul. Newer methods are currently in late stages of development that address the issues of safety, effectiveness, public acceptance, timeliness, and pandemic reliability more effectively than either egg or cell-based methods.

Instead of investing in cell-based facilities, the government should invest in facilities that make vaccines that use virus-like particles and recombinant hemagglutinin. These methods can mass produce the vaccine in as little as 3 months and provide a broader immune response. In addition the government should assist in developing a universal flu vaccine which has currently undergone successful Phase I trials.

Table of Contents

Executive Summary.....	2
Medical and Economic Effects of Influenza	4
Influenza.....	6
Ecology	6
The Relationship between Seasonal and Pandemic Influenza	7
Current Policy.....	9
Seasonal Flu Policy	9
Selecting the Strains for the Vaccine	10
FDA Approval Process	12
Pandemic Flu Policy	13
Egg-based Method	15
Why hasn't there been a Change?.....	18
Policy Alternatives.....	20
Criteria for Measurement	20
Mammalian Cells.....	21
Virus-like Particles.....	24
Recombinant Hemagglutinin	27
"Universal" Influenza Vaccine.....	29
Recommendations	32
Bibliography	34

Medical and Economic Effects of Influenza

Every winter the United States goes through flu season. To those who are young and healthy, this is often brushed off as a mere nuisance, nothing to be worried about. For those who are elderly, already dealing with another ailment, or taking care of others, the flu is a much more serious problem. In any given year, 5 to 20% of the American population will catch some strain of the seasonal flu. Seasonal flu typically runs from October to May. Each year around 36,000 deaths and 200,000 hospitalizations can be attributed to the flu and complications in the United States. The chances of either death or hospitalization increase dramatically as someone gets older.¹

The annual economic damage from the flu significantly outweighs the amount of money that is put into it. Of those who get those who get sick from the flu, 31.4 million require outpatient visits. The 200,000 people who are hospitalized spend a total of 3.1 million days in the hospital. The annual direct medical cost associated with seasonal influenza is \$10.4 billion, \$4.2 billion of which results from patients over 65. The total economic burden of the flu has been estimated at \$87.1 billion annually.²

If a new strain of the flu virus starts to infect humans, it can lead to a pandemic. The consequences of a pandemic are much more severe than those of a seasonal outbreak. Past pandemics and have had devastating effects on both the population and economy of the world. Pandemic strains put people in all age groups at increased risk for hospitalization and death. It has been estimated that

¹ "2008-09 Flu Facts for Policy Makers." *CDC influenza E-brief*, September 2008, http://www.cdc.gov/washington/pdf/flu_newsletter.pdf

² Bridges, Carolyn B. et al, "The annual impact of seasonal influenza in the US: Measuring disease burden and costs." *Vaccine* 25 (2007): 5086-5096.

675,000 Americans died during the Spanish Flu pandemic of 1918. Across the world, more people died from influenza in that year alone than the entire four year span of the Black Death Bubonic Plague.³

In 1918, a flu vaccine did not exist. Had one existed, the effect of the Spanish Flu pandemic would not have been as severe. But even with the technological capability to produce vaccines for pandemic flu, it still remains an imminent threat. The World Health Organization (WHO) has stated that the question is not if there will be another severe flu pandemic, but when. According to the Congressional Budget Office (CBO), a severe pandemic has the potential to infect 90 million Americans and kill 2 million of them. It is also estimated that the GDP would drop about 4.25%, an economic downturn comparable to a typical business cycle recession.⁴

Even with a long established vaccine, influenza remains a problem. Part of the problem is the timeliness and reliability of the current flu vaccine production method. The current method uses chicken eggs to grow strains of the flu virus, which are then inactivated and used in the vaccine. While the egg-based method has done a decent job handling seasonal flu in the past, there is a growing concern about whether it could handle a severe pandemic and the growing demand for seasonal vaccination.

New methods exist that could address some of the issues left unanswered by the egg-based process. In order to secure the well-being of the country, these new methods must be adopted by industry. The reliance on a single method that has so many drawbacks is not sufficient.

³ Billings, Molly, "The Influenza Pandemic of 1918," June 1997. <http://virus.stanford.edu/uda/>

⁴ Congressional Budget Office, "A Potential Influenza Pandemic: Possible Macroeconomic Effects and Policy Issues," 27 July 2006. <http://www.cbo.gov/ftpdocs/69xx/doc6946/12-08-BirdFlu.pdf>

Influenza

Ecology

Influenza is a viral respiratory infection more commonly known as the flu. It can be spread from person to person through casual contact. An individual will become infectious about one to three days after his original contact. After this, he is capable of spreading the virus for the next three to six days. The disease and symptoms typically last between two to seven days. Death is a possible outcome but it is rarely caused by flu alone. Instead, it will more often weaken the immune system of the person, making it more likely for him to acquire a second disease. A combination of diseases is what becomes overwhelming and most often leads to death.⁵

It is believed that once one recovers from a particular strain of the flu, they are immune to it for life. Evidence for this was shown by an accidental reintroduction of a captured strain of the flu. The strain released in the laboratory accident was identical, both antigenically and genetically, to one that had been captured 20 years before. The virus only spread to and caused illness to those under 20. Those over 20 had previously been introduced to the virus and therefore possessed the necessary antibodies to fight the strain.⁶

The flu virus is unique due to its ability to change at a rapid pace. Every year, the virus manages to change just enough to potentially infect those that were exposed to it the year before, a process known

⁵ Dushoff, Jonathan, David J.D. Earn, and Simon A. Levin, "Ecology and evolution of the flu," *Trends in Ecology & Evolution* 17, no. 7 (July 2002): 334-340.

⁶ Oxford, J.S., "Influenza A pandemics of the 20th century with special reference to 1918: virology, pathology and epidemiology," *Reviews in Medical Virology* 10, (2000): 119-133.

as drift. The slight change is enough to make the existing antibodies less effective. Major antigenic shifts can cause pandemics, and are held responsible for the pandemics of 1918, 1957, and 1968.

Influenza exists in three forms: A, B, and C. A is the most rapidly mutating and is the greatest threat to people both seasonally and pandemically. Strains of influenza A are primarily characterized by two proteins that exist on the virus's surface, hemagglutinin (HA) and neuraminidase (NA). In total, there have been 16 HA variations and 9 NA variations. The naming system used to categorize influenza A relies on which variations of HA and NA are present in the strain. When swine flu is called H1N1, it is being described as containing the first HA and first NA proteins to be discovered.

The Relationship between Seasonal and Pandemic Influenza

While seasonal flu may be easily brushed off by those who are neither elderly nor considered at high risk, the idea of pandemic flu strikes fear in everyone. Flu pandemics occur in one of two ways. If a virus that has been developing only in animals manages to evolve in a way that allows it to infect and spread among humans, a pandemic can occur due to the novelty of the strain. This occurred in 2009 with the H1N1 swine flu. An existing H1N1 virus had already been in circulation, but because the new virus evolved outside of humans, people did not have the necessary immunity to fight it off.

A pandemic can also occur if either of the HA or NA proteins in a strain of seasonal flu changes drastically. This has led to the worst pandemics, including the 1918 "Spanish flu," which killed between 20 and 40 million people worldwide when the seasonal H1N1 changed

into H2N2. Again, it becomes a pandemic because people have a significantly lower immunity to the new variation than to the old one.

After the first year that a pandemic virus is introduced into the population, it fades from pandemic status to seasonal status. Each year that the pandemic strain remains in circulation, it will have less and less of a dramatic effect on the population. While the 2009 pandemic H1N1 virus required its own vaccine at the time, the strain will be incorporated into the traditional vaccine in 2010 and should be no more problematic than seasonal flu strains from previous years.

When it comes to research, development, and production of a new vaccine, what is good for seasonal flu is good for pandemic flu. From start to finish of vaccine production, the method used each year for the seasonal vaccine is the same as that which would be used to produce a pandemic vaccine. Therefore, any money put into developing the capacity to make more pandemic vaccines increases the total number of seasonal vaccines that can be made as well. Any new technology invented to accelerate the production of either flu vaccine will have the same effect on production for the other.

Current Policy

Seasonal Flu Policy

The manner in which the flu vaccine is produced greatly effects how long it will take to produce. Under the current system, it takes roughly 8 months for to go from when the components of the flu vaccine are determined to when the vaccine is available to the public. The first batches of the vaccine are only available when the flu vaccine is in highest demand. This leads to seasonal shortages of the vaccine.⁷

Six companies are approved to sell their own version on the flu vaccine in the US. There is a very strong relationship between flu vaccine manufacturing companies and the government. It is the role of the government and international bodies to determine which three strains of the virus will be put into the vaccine. Vaccine manufacturers may not participate in the selection of the vaccine strains, despite the fact that they are so heavily invested into the process. Mandated strains can be advantageous for flu vaccine manufacturers because it alleviates the costs associated with searching for the most ideal combination of strains for their product. The requirement that everyone must use the same three strains in their vaccine also reduces competitiveness between the manufacturers, reducing the need to differentiate the products. If WHO or the FDA makes a poorly advised recommendation, it is the manufacturers who will hold the burden financially. Successive unsuccessful recommendations could lead to public belief that the flu vaccine is ineffective and not worth getting. This would lead to the downfall of flu vaccine manufacturers, not to the FDA, unless something was done to change the system.

⁷ Dushoff, Jonathan, "Ecology and evolution of the flu," 334-340.

The government has taken it upon themselves to help financially support the flu vaccine market. Money that is used to fund flu research, development, production, and distribution primarily goes through the Department of Health and Human Services. The government is highly involved in incentivizing the flu vaccine manufacturers to continue to produce the vaccine instead of focusing resources on other more profitable fields.⁸

The CDC first became involved with influenza prevention in 1956. Its main role at the time was national and international influenza surveillance. It now cooperates with similar agencies throughout the world to increase surveillance, research, diagnostics, prevention, outbreak response, and vaccine development. They make recommendations on who should receive the flu vaccine, which now includes everyone over the age of 6 months.⁹ It contributes to the recommendations made by WHO and the FDA for what viruses should be placed into the seasonal vaccine. In the 2007-2008 season, it examined over 225,000 people with flu-like symptoms and tested 4100 viruses. The CDC is also responsible for building the Strategic National Stockpile (SNS). As of April 3, 2009, the SNS contained about 105.8 million N95 respirators, 51.7 million surgical masks, and antiviral drugs for 50 million people along with other materials needed in case a severe pandemic outbreak occurred.¹⁰

Selecting the Strains for the Vaccine

The task of determining what goes into the seasonal flu vaccine is headed by the World Health Organization (WHO). Twice a year consultations are held to decide which strains of influenza will be put

⁸ Congressional Budget Office, "U.S. Policy Regarding Pandemic-Influenza Vaccines," September 2006.

⁹ "Seasonal Influenza (Flu)," CDC, <http://www.cdc.gov/flu/index.htm>

¹⁰ Center for Disease Control and Prevention, "Justification of Estimates for Appropriations Committee, Fiscal Year 2010," Department of Health and Human Services, 2009.
http://www.cdc.gov/fmo/topic/Budget%20Information/appropriations_budget_form_pdf/FY2010_CDC_CJ_Final.pdf

into the vaccine, one for both the northern and southern hemisphere. The one for the northern hemisphere, and therefore the one that is of more concern to the United States, occurs each year in late February. At this meeting, WHO finalizes the information collected by the Global Influenza Surveillance Network (GISN), a collection of national laboratories that focus on influenza strains currently in the population. The gathered information is then discussed by representatives from various influenza based laboratories and academia. Flu vaccine companies are not eligible to participate or even observe. After discussion, it is up to the WHO Collaborating Centres on Influenza and the Essential Regulatory Laboratories to collectively make the final recommendations for which three viruses will go into this year's vaccine.¹¹

WHO traditionally makes three recommendations for what strains should be put into the vaccine. For the 2009-2010 season, the selected strains were: an A/Brisbane/59/2007 (H1N1)-like virus, an A/Brisbane/10/2007 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus. The selected strains are chosen because they are believed to be the best combination to handle the most likely outbreaks.¹²

Four days after the WHO's conference the Food and Drug Administration debated, discussed, and released its recommendations. The group put in charge of this task is the FDA's Vaccine and Related Products Advisory Committee. The committee decided on each of the following strains: an A/Brisbane/59/2007 (H1N1)-like virus, an A/Brisbane/10/2007 (H3N2)-like virus, and a

¹¹ "How recommendations are made on the composition of influenza vaccine." *World Health Organization*, 11 February 2010, http://www.who.int/csr/disease/influenza/ganda_vaccinerechow.pdf

¹² World Health Organization. "Recommended composition of influenza vaccines for use in 2009-2010 northern hemisphere influenza season," http://www.who.int/csr/disease/influenza/recommendations2009_10north/en/index.html

B/Brisbane/60/2008-like virus. These selections were made unanimously and were identical to the ones recommended by WHO.¹³

FDA Approval Process

Before the final vaccine may be put on the market it must be approved by the FDA. The specific branch of the FDA put in charge approving vaccines is the Center for Biologics Evaluation and Research (CBER). Unlike most vaccines, which only need to get approval when they first enter the market, the annual updates made to the flu vaccine require annual approval. In order for any vaccine to be licensed, the manufacturers must show that the final product is “safe, pure, and potent.” To demonstrate that the vaccine is potent, or effective as its meaning has been interpreted to be, an “adequate and well controlled” clinical study must be done. The study should consist of a population that is not at increased risk of flu related complications. People determined to be at risk is defined by the Advisory Committee on Immunization Practices. The effectiveness of the vaccine for those not included in the study is tested by evaluating the immune response instead of the chances of acquiring the disease. Finally, the manufacturers must prove that the vaccine is safe. The exact size and detail of the trials is dependent on the age range the vaccine is intended for, the amount of experience of the particular manufacturer, and safety concerns that arise during preclinical studies.¹⁴

¹³ Center for Biologics Evaluation and Research. “Summary Minutes: Vaccines and Related Biological Products Advisory Committee Meeting 116.” 19 February 2009.
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM167154.pdf>

¹⁴ Center for Biologics Evaluation and Research, “Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccine.” May 2007.
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091990.pdf>

Under certain circumstances, the CBER allows for an accelerated approval process. Instead of having to prove that the vaccine effectively stops the flu, the manufacturers only need to show that the vaccine causes people to produce higher levels of the antibody that will fight the flu in order for it to go onto the market. It is only once the vaccine is already on the market that the manufacturer must do studies to show that the product does bring the desired benefit. If this cannot be shown or is not done diligently and accurately, the FDA is able to withdraw its approval. Like the traditional process, the manufacturers must show that the vaccine is both effective and safe. The effectiveness focuses on antibody production. For safety, the manufacturer must show that serious adverse effects occur less than 1 in 300. For this to be achieved with 95% certainty there must be no adverse effects in a group of 1150 or more. If an adverse effect occurs in one of these people, more tests are required.¹⁵

Pandemic Flu Policy

The *National Strategy for Pandemic Influenza: Implementation Plan*¹⁶ is the primary guideline document used to minimize the damaging effects of a pandemic outbreak. It was written in May of 2006 by the Department of Homeland Security by the request of George W. Bush. The *Strategy* has remained in effect under the Obama Administration and was accepted by the Department of Health and Human Services.

The *Strategy* covers the entire spectrum of a pandemic flu outbreak. The majority of the *Strategy* addresses what should be when a pandemic is occurring and has already occurred. It addresses

¹⁵ Center for Biologics Evaluation and Research, "Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccine." May 2007. <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091990.pdf>

¹⁶ Homeland Security Council, *The Strategy for Pandemic Influenza: Implementation Plan*, Department of Homeland Security, May 2006. <http://hosted.ap.org/specials/interactives/wdc/documents/pandemicinfluenza.pdf>

not just the medical concerns that will arise but also the social and economic concerns. There are chapters in the *Strategy* that focus on human health, animal health, law enforcement and public safety, international cooperation, and transportation.

The part of the *Strategy* that concerns flu vaccine production is the chapter titled, “US Government Planning for a Pandemic.” This chapter explains why the country should have a pandemic flu plan and how the government can prepare itself for a coming flu pandemic. Most of the things addressed here are about increasing communication, working with other countries, working with organizations inside the United States, and treating the pandemic as a threat to national security.

Two primary vaccine related goals are stated in the *Strategy*. First, enough pre-pandemic flu vaccines are to be on hand to immunize 20 million people for any strain that is deemed to be a pandemic threat. As of right now, only the avian strain H5N1 is considered to be at this level. Second, the domestic capacity to produce flu vaccines must be enough to vaccinate the entire domestic population. The first goal has been achieved. The stockpile of pre-pandemic H5N1 vaccine must constantly be updated as some of the vaccines expire. Since the pre-pandemic vaccine can be made during the “off season” of seasonal influenza, this isn’t much of a concern.

Goal two has not yet been achieved. The domestic capacity of pandemic flu vaccines is closer to 12.5 million. The capacity to produce a pandemic vaccine is only one quarter of the maximum capacity to produce seasonal vaccine.¹⁷ Because of the production method currently used to make all of these vaccines, it is questionable whether the vaccines could be made within 6 months. In addition the current method is highly susceptible to H5N1 related complications at multiple points in the process.

¹⁷ Congressional Budget Office, “U.S. Policy Regarding Pandemic-Influenza Vaccines,”

In order to achieve this goal, we must increase the domestic capacity for flu vaccine production. This could be achieved using the current method, but because of its questionable reliability for emerging pandemic strains, it may be better to increase capacity by using new methods of vaccine production.

In the *Strategy*, there are additional concerns identified about coming up with the exact production capacity. Because the pandemic strain would be completely novel to humans, multiple doses or higher concentrations of HA will be needed to induce an acceptable immune response. If a pandemic were to occur, any vaccines produced outside of the United States could not be counted on. The countries in which these vaccines are produced are expected to secure these vaccines for their own populations.

Egg-based Method

The process currently used by all companies in the United States involves growing the virus in chicken eggs. The FDA distributes live strains of the selected flu virus to vaccine manufacturers. The manufacturers take the strains and put them in separate eggs. The virus spreads within the egg for about the next 5 months. Once the virus has fully grown within the egg, the virus filled fluid is removed from the egg to undergo further treatment. After the virus is removed from the egg, it is purified, inactivated and then fragmented. For seasonal vaccines, the three strains are then combined into a single vaccine. The final product is tested for safety and effectiveness.¹⁸

The resulting vaccine is known as an inactivated influenza vaccine. The inactivation process is a chemical process that stops the virus from being able to infect the vaccine recipient. The inactivation

¹⁸ Berndt, Ernst R., Rena N. Denoncourt, and Anjali C. Warner, "U.S. Markets for Vaccines: Characteristics, Case Studies, and Controversies," AEI Press, May 2009.

process makes the vaccine much safer than when in its original state. Inactivation is used in all but one of the FDA-approved vaccines currently on the market. Inactivation can lead to alterations in primary proteins used to induce an immune response, which can lead to a less effective vaccine.

There are many draw backs to the current egg-based production method. The amount of time the entire process must be completed in is about 8 to 10 months. The egg-based method takes up almost all of this, leaving no room for error. Errors in any batch by any of the companies that manufacture the flu vaccine could lead to an early seasonal or pandemic shortage. The egg in itself can also contribute to variability and instability to virus production. Differences within individual eggs lead to differences in the quality of the viral product.

Once manufacturers are made aware of and receive some of the selected strains, there is a limited time where scientist can make modifications to the virus to increase the rate at which is grows within the egg. Because they are limited in time, how effectively this can be done for each strain is different. The exact repercussions of this modification cannot be seen until after the virus has been removed from the egg. It is the growth rate of the slowest growing strain that limits the entire vaccine. All three strains must be present for the seasonal vaccine to be approved by the FDA. If there is a shortage of any single virus, there is a shortage of the entire vaccine.

The biggest drawback to the length of time required by the egg-based method is the inability of the manufacturers to adjust to demand. The production goals for each manufacturer must be set before the virus strains start to grow in the eggs. This must take place months before there is any actual demand for the product. The demand for seasonal flu vaccine is very instable from year to year, therefore making it extremely difficult for manufacturers to accurately predict what the demand will be. While individuals often have the ability to make a decision about getting a flu shot on very short notice,

the manufacturers do not have the ability to produce it as rapidly. If there is a sudden increase in demand as time goes on because flu season is expected to be severe, vaccine manufacturers cannot do anything to react to it.

In order to produce the egg-based vaccine, a large supply of eggs is required. The United States government currently pays the company Sanofi-Aventis to maintain a year round supply of chicken eggs solely for vaccine production. Concerns arise from this though because this process is highly vulnerable to an avian flu outbreak.¹⁹ Avian flu has only infected 499 people worldwide since 2003, but 295 of them have died.²⁰ If the virus ever managed to mutate itself in a way that made it more contagious among humans, the outcome would be devastating. It has been estimated by the Congressional Budget Office that a severe pandemic would lead to nearly 90 million infections and 2 million deaths.²¹ Birds, who are already very susceptible to avian flu, would also suffer increased fatalities if the virus could be carried by humans. This could lead to a shortage of eggs, therefore a shortage of vaccine when it is needed the most. Even if there were plenty of eggs available, any form of avian flu could kill the chicken embryo inside the egg, decreasing the total number of pandemic vaccines that can be made.²²

The current system of producing the flu vaccine has too many holes. It is an outdated method that cannot handle the current demand. It takes too long and will not be helpful if an avian flu pandemic occurs. It must be replaced with a method that is quicker, can more readily respond to changes in demand, and that could adequately handle a pandemic.

¹⁹ Palache, Bram, "New vaccine approaches for seasonal and pandemic influenza." *Vaccine* 26, (2008): 6232-6236.

²⁰ "Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO." World Health Organization, 8 June 2010.

²¹ Congressional Budget Office, "A Potential Influenza Pandemic: Possible Macroeconomic Effects and Policy Issues,"

²² Kang, Sang-Moo, et al, "Influenza vaccines based on virus-like particles." *Virus Research* 143, (2009): 140-146.

Why hasn't there been a Change?

Why then, when all of these concerns are shared and agreed upon, has the method not been updated or replaced? There is no disagreement over the idea that the current method has substantial faults that need to be addressed. Nor has there been a technological snag that has kept the flu vaccine industry from updating their methods.

The first main reason why the egg-based method continues to be the only method used to produce the flu vaccine is because it works. There are many concerns, but in all, the final vaccine product is safe, effective, and cheap. As long as everyone is doing their job and completing things on schedule, the process runs smoothly. The egg-based method has been used for many years and is long past the development stage. It has been perfected.

This came into question though in 2004 when one of the companies failed to produce the number of vaccines that it originally intended. This led to a shortage that required rationing. The shortage brought the process of flu vaccine production into the spotlight, where it was reexamined and the search for a more reliable method began.

The second reason why industry is not making the necessary adjustment by itself is because there is very little financial incentive. One of the major problems with flu vaccine development is that the current vaccine is too cheap for companies to justify exploring other options. The total annual market for flu vaccines is only \$3 billion. Just to develop a new drug ranges from \$800 million to \$2 billion.²³

²³ Masia, Neal, "The Cost of Developing a New Drug," America.gov, 23 April 2008.
<http://www.america.gov/st/econ-english/2008/April/20080429230904myleen0.5233981.html>

The financial incentive to develop a pandemic vaccine is even worse. Why would a company invest large amounts of money into an infrastructure that may never be used? Unless a pandemic occurs, there is no demand for a pandemic vaccine. If a pandemic is declared, it is too late to build the facilities to reach the surge capacity. Since companies can really only count on seasonal flu, it should only be expected that they have the facilities to handle seasonal flu demands, not pandemic surge demands.

Therefore, the main concern is not if we should move away from the egg-based method, but how are we going to convince companies to do so. With such a small annual market, there is very little incentive for a company to take the necessary steps in order to upgrade from the current system. In the past, the main manner in which companies have completed research or increased flu vaccine production capacity has been through large government grants. If the government would like to continue to see development in these two areas, they will have to continue to provide money to companies in exchange for the companies' promise to be able to produce a specified number of vaccines within 6 months of a pandemic declaration.

If it is taken as a given that money will be needed to help make the transformation away from egg-based vaccine, then the government's main concern should be deciding which technologies that they should invest in. It would be a mistake for the government to invest in technologies that only partially cover the goals stated in the *Strategy*, or to invest in a technology that is not as good as other available options.

The current egg based method has reached an economic and developmental plateau. In order for there to be a drastic increase in supply, there must be a drastic increase in the amount of money put into production. There is little room for innovation left in the process.

Policy Alternatives

Criteria for Evaluation

Any choices that HHS makes in funding new technologies and facilities should be made based on the following criteria:

- Safety

The new flu vaccine technology must be at least as safe as the current egg-based vaccine. The ideal solution would not cause adverse effects in any vaccine recipient. The new technology must also be able to cover as wide of a group as possible while still being safely administered. The current method is unsafe for those who have egg allergies.

- Effectiveness

The vaccine must effectively prevent the flu. It should be effective across the entire population. It should particularly be effective in preventing disease amongst those who are most likely to have flu related complications, the elderly and high risk.

- Public acceptance

If there is any aspect of the vaccine that seems unsafe or ineffective about the vaccine, whether or not it actually is, people will not accept it. If people are not willing to receive the vaccine, then any new facilities would be a waste. The goal is not necessarily to get everyone to accept the vaccine, but to make sure everyone who already takes it or is on the fence about it to be comfortable with it.

- Timeliness of production

In the case of a pandemic, a vaccine must be produced as quickly as possible. For seasonal flu, the virus strain selections must be made in a timely manner based on how long the process takes. If the strain selection can be made later in the year, the vaccine will be more effective.

- Pandemic Reliability

When a pandemic occurs, the vaccine supply should not be in question. Any concerns about the methods reliability during a pandemic must be taken into account. The country's vaccine capacity should not be dependent on the reliability of the method used.

- Phase of Development

The further along the vaccine method is, the better of a choice it will be. Vaccines that are further along in development will require less money from the government to bring to completion. There is also a great chance of success with any given technology if it has already proven itself through previous trials.

Mammalian Cells

A new manner to produce the vaccine uses mammalian cells instead of chicken eggs. An experiment done by Liu tested how the flu virus would grow in cells. Of the five different cell types they experimented with, one stood out as an acceptable alternative. The Madin Darby Canine Kidney (MDCK) cells were found to produce a sufficient amount of live attenuated viruses for vaccine production. The MDCK cells were shown to produce high levels of virus for all 13 strains tested. The

strain variations represented all three of the types most commonly recommended by WHO and put into the vaccine: A/H1N1, A/H3N2, and B.²⁴

The production time is expected to be quicker than the egg-based method. This should help in reaching the goals of having enough vaccine for everyone within 6 months. Compared to other methods, the time required for production is only slightly less than the egg-based method and there is debate whether or not it is enough to bring any significant advantage.²⁵ The exact time the whole process will take will not be known until a facility is in full production

The finished product will be very similar to that which is currently available. It too will be an inactivated vaccine with a similar safety and effectiveness as the egg-based vaccine. Because it is not made inside of an egg, this vaccine will not contain the egg protein. It will be safe for people with egg allergies to use.²⁶

While the cell based method does take care of many of the issues that are currently being faced, it does have some problems of its own. The product yield is dependent on the specific strain of virus and is highly variable. Each step in the manufacturing process requires high levels of biosafety to insure that there is no contamination. The intensive biosafety requirements lead to more difficult quality

²⁴ Liu, Jonathan, et al, "Use of MDCK cells for production of live attenuated influenza vaccine." *Vaccine* 27, (2009): 6460-6463.

²⁵ Congressional Budget Office, "U.S. Policy Regarding Pandemic-Influenza Vaccines,"

²⁶ Liu, Jonathan, et al, "Use of MDCK cells for production of live attenuated influenza vaccine." *Vaccine* 27, (2009): 6460-6463.

control. The total cost to produce mammalian cell based vaccines should be about the same or slightly more than the current method.²⁷

The government has already invested a significant amount of money into this possible new solution. In 2005 and 2006, the Department of Health and Human Services gave a total of over \$1.1 billion to six different companies to research and develop cell-based flu vaccines. The money came from the \$3.3 billion that Congress appropriated for pandemic preparedness in December of 2004.²⁸ It is the only alternative mentioned in the *National Strategy for Pandemic Influenza: Implementation Plan*.

One company is currently seeking FDA approval for the cell-based method. Novartis, makers of the cell-based flu vaccine Optaflu, has already received regulatory approval from the European Union. With the expressed plans of the Novartis to expand into the United States, boasting the capability to produce 50 million doses each year, the U.S. Department of Health and Human Services has given them \$487 million to produce both seasonal and pandemic flu vaccines.²⁹

Four of the companies are still developing the technology, and need either additional funding or approval to continue the process. One company, Sanofi Pasteur, has decided to stop pursuing advances in cell-based technology. This is significant because Sanofi Pasteur is the leading producer of flu vaccine and has been for some time. In addition, it was the first company to receive funding to develop the cell-based flu technology. They have chosen to stop because they felt that the advantages of the cell-based

²⁷ Krammer, Florian, and Reingard Grabherr, "Alternative influenza vaccines made by insect cells," *Trends in Modern Medicine* 16, (2010): 313-320.

²⁸ Congressional Budget Office, "U.S. Policy Regarding Pandemic-Influenza Vaccines,"

²⁹ Novartis, "US Department of Health and Human Services awards Novartis USD 486 million contract to build manufacturing facility for pandemic flu vaccine," 15 January 2009. <http://www.novartis.com/newsroom/media-releases/en/2009/1282432.shtml>

method did not outweigh the costs associated with implementing it and moving away from the time tested egg-based method.³⁰

Sanofi-Aventis, the company tasked with producing a year round supply of eggs specifically to be used for flu vaccine production, is the parent company of Sanofi Pasteur. If the cell-based method were to be fully adopted and utilized there would no longer be a need for a constant supply of chicken eggs provided by Sanofi-Aventis. Therefore, it would not be advantageous for Sanofi Pasteur to continue to develop the cell-based flu vaccine as it would hurt the company overall.

Despite the fact that Sanofi Pasteur may have no financial motive to continue researching cell-based flu vaccines, its doubt about the technology may be genuine. Of the six companies given funding, only Novartis is taking steps to mass produce a mammalian cell-based vaccine. When Novartis received funding, they were already developing the cell-based method in Europe. They had a head start, and plan on using the vaccines novelty and uniqueness to gain their share of the US market. The other four companies have yet to commit to the cell-based method, indicating that they too see problems with it and do not yet feel it has been fully developed. In addition, the development of cell-based vaccines is primarily funded by the government, not industry. If industry felt confident about the technology, they would spend more money on it.

Virus-like Particles

Over the past 5 years, many studies have focused on the use of virus-like particles (VLP) for an alternative for the current flu vaccine. VLPs are already used in the hepatitis B and human

³⁰ Roos, Robert, "Novartis unveils US cell-based flu vaccine plant," 24 November 2009.

papillomavirus vaccines that are on the market. The flu vaccine has not yet reached this level primarily because it has a more complex virus structure.³¹

VLPs resemble the actual virus in a manner that causes an immunological response without having the capability to infect and spread within the person. VLPs are made up of multiple proteins that mimic the virus when they are assembled. For Influenza VLPs, the surface is the same as with a live virus, but it lacks the genetic makeup on the inside that gives the virus its ability to infect. The immune system cannot distinguish the difference between the surface of the VLP and the surface of an actual virus, so produces antigens to fight it. The surface proteins, the parts that the immune system recognizes, are added to the VLP in a natural manner that does not disturb the protein's natural state. Keeping the native conformation intact gives this method an advantage over the traditional egg and cell based methods, which must go through a chemical inactivation step that can modify the arrangement of the protein.³²

VLP vaccines tend to induce a stronger and broader immune response than any other form of flu vaccine. By producing a broader immune response, the strain selection made by the FDA is not as critical in the efficiency of the vaccine. If the FDA happens to choose a virus that is not a good match, or chooses one that undergoes a relatively significant change between the time of the recommendation and when the vaccine becomes available, there is a greater chance that recipients of VLP vaccine will be immune compared to those who receive the traditional vaccine.³³

³¹ Kang, Sang-Moo, et al, "Influenza vaccines based on virus-like particles." *Virus Research* 143, (2009): 140-146.

³² Krammer, Florian, and Reingard Grabherr, "Alternative influenza vaccines made by insect cells," *Trends in Modern Medicine* 16, (2010): 313-320.

³³ Kang, Sang-Moo, Jae-Min Song, Fu-Shi Quan, and Richard W. Compans, "Influenza vaccines based on virus-like particles." *Virus Research* 143, (2009): 140-146.

VLP vaccine could be counted on if a pandemic were to occur. Because the VLPs are created inside of an insect cell, there is no concern about host cell becoming infected with the pandemic virus. The distant relationship between human and insect cells makes it very unlikely that any disease would develop the ability to cross infect. The flu virus is never introduced to the insect cell, greatly lowering the safety requirements needed to insure nothing goes wrong.

Novavax has developed a VLP flu vaccine that has passed through Phase II trials. The vaccine showed acceptable levels of HA immune response comparable to the traditional vaccine. In addition, it induced an NA immune response well above the traditional vaccine.³⁴ A Phase II trial has also been done specifically focusing on people over 60 and similar successful results were obtained. The vaccine showed no adverse effects in any of the subjects. As of now, there is no indication that the VLP vaccine would be unsafe.³⁵

The expected time it will for the vaccine to be produced is 3 months.³⁶ This is significantly shorter than the egg-based method. Even if complications were to occur, manufacturers using VLPs should easily be able to produce the desired number of vaccines within 6 months as long as they have the capacity to do so.

In a survey done by the Consumer Reports National Research Center found that 41 percent of people who chose not to get the seasonal flu vaccine did so because they or someone they knew got

³⁴ Richardson, Tricia T., "NOVAVAX Releases Final Results from its Trivalent Seasonal Influenza Vaccine Phase II Clinical Study in healthy Adults," 29 March 2010. <http://www.novavax.com/download/releases/SeroFO.pdf>

³⁵ Driscoll, Fred, "Novavax's Seasonal Influenza VLP Vaccine Candidate Shows Positive Results in Phase II Clinical Trial in Older Adults," 29 April 2010. http://www.novavax.com/download/releases/4-29-10_PhaseIIa202study_rs.pdf

³⁶ Krammer, Florian, and Reingard Grabherr, "Alternative influenza vaccines made by insect cells," *Trends in Modern Medicine* 16, (2010): 313-320.

sick from the flu shot.³⁷ While it is impossible to get sick from most of the vaccines, and there is only a slight chance from the vaccine that uses a live weakened version of the virus, the public perception that the vaccine can make you sick is still there. People may not be aware that it takes about two weeks for the vaccine to provide maximum immunity, so if they develop symptoms soon after being given the vaccine, they will likely incorrectly blame it on the vaccine.

VLPs, like inactivated viruses, do not run the risk of infecting the recipient. But because of the nature of VLPs, they can rebrand the flu vaccine in a more consumer friendly manner. It is be difficult to convince someone that they will be protected from a virus by injecting the exact same virus into them. With VLPs, the flu vaccine can now be marketed as a product that protects one from the flu without ever introducing the flu virus into the person. While neither may have the capacity to actually infect the recipient, the second scenario seems much safer to someone who has not researched further.

Recombinant Hemagglutinin

Hemagglutinin (HA) is a surface protein on flu viruses that causes it to attach to living cells. It is also one of the parts that is constantly changing and requires the vaccine to be updated annually. In addition, it is one of the main proteins responsible for inducing an immune response. Unlike VLPs which are three different proteins assembled together to mimic the virus, a recombinant hemagglutinin (rHA) vaccine would only contain HA.³⁸

³⁷ Consumer Reports National Research Center, "Top 12 excuses for skipping the flu shot are exposed," Consumer Reports Health.org, November 2008. <http://www.consumerreports.org/health/healthy-living/health-safety/getting-the-flu-shot-this-year/12-top-excuses-exposed/getting-the-flu-shot-this-year-no-excuses-for-skipping-the-flu-shot.htm>

³⁸ Krammer, Florian, and Reingard Grabherr, "Alternative influenza vaccines made by insect cells," *Trends in Modern Medicine* 16, (2010): 313-320.

In order to make rHA, the virus gene for HA is inserted into an insect cell. This tricks the insect cell in to producing the protein. The HA is removed from the cell and purified. The resulting product is rHA. Unlike with the actual virus or VLPs, rHA is not connected to any other proteins.³⁹

In most cases rHA vaccines had results comparable to traditional flu vaccines. It has been shown to produce the same amount of antibodies as the egg-based method when only one or two strains of HA were applied in a single vaccine. When three different types of HA were mixed into a single vaccine, it outperformed the tradition vaccine. Since this is the current standard, it is also the one that is most important when comparing the results. The total HA content in an rHA vaccine that could safely be administered was nine times greater than the HA content that could safely be administered through traditional inactive vaccines. The higher amounts of HA can lead to a more sustained and broader immune response or they can be used to allow for more doses to be produced in a short period of time.⁴⁰

One company, Protein Sciences Corporation is currently producing an rHA flu vaccine, FluBlok. FluBlok has three times the amount of HA as traditional flu vaccines do. Unlike mammalian cell-based production, rHA vaccines do not require as high biosafety, which makes the process less expensive and quicker. From the time the virus is received by the company from the CDC, it takes about two months

³⁹ Krammer, Florian, and Reingard Grabherr, "Alternative influenza vaccines made by insect cells," *Trends in Modern Medicine* 16, (2010): 313-320.

⁴⁰ Cox, Manon M.J. and Jason R. Hollister, "FluBlok, a next generation vaccine manufactured in insect cells," *Biologicals* 37, (2009): 182-189.

for the company to manufacture FluBlok and one more before it can be on the market, significantly less time than the six months to grow the virus in eggs for traditional vaccines.⁴¹

Because rHA does not rely on the HA from once living flu viruses, rHA does not go through the inactivation process that traditional vaccines do. The inactivation process has the tendency to denature the HA, making it less effective at causing an immune response. As a result, the HA of a living flu virus is closer to the final product HA made by the insect cells than to the HA of flu viruses that have been inactivated. The closer resemblance makes the rHA a more effective vaccine than the traditional vaccine.⁴²

Just like with VLPs, the lack of virus going into the vaccine, whether it is inactivated or live, will improve the public's perception of the vaccine. Even more so than VLPs, rHA is even further removed from the idea of injecting the disease to avoid the disease. With rHA, the only thing being put into the person is the protein that gives the virus the ability to latch onto cells, not the parts that cause infection, release the virus from the host cells, or give the virus its general shape.

“Universal” Influenza Vaccine

Influenza is a tricky virus. It changes just enough each year that a new vaccine must be made every year to account for these changes. Flu vaccines, both the ones being made currently and those that are likely to appear on the market the next couple of years, work by targeting the parts of the virus that change. But some parts of the virus never change. If a vaccine could be developed that causes an immune response that targets these parts of the virus instead of the parts that continually change, it

⁴¹ Cox, Manon M.J. and Jason R. Hollister, “FluBlok, a next generation vaccine manufactured in insect cells,” *Biologicals* 37, (2009): 182-189.

⁴² Krammer, Florian, and Reingard Grabherr, “Alternative influenza vaccines made by insect cells,” *Trends in Modern Medicine* 16, (2010): 313-320.

could potentially be a universal vaccine. Like with all other non-flu vaccines, this vaccine would only need to be administered a limited number of times for a person to have complete immunity.

One part of the flu virus that remains relatively constant across all flu subtypes and over time is the matrix 2 (M2) protein. M2 is proton channel found on the surface of the virus. It has remained relatively the same across subtypes and time for two reasons. By itself, it does not induce much of an immune response. Because it does not induce an immune response, there is no evolutionary selection pressure to change. In addition, part of the genetic coding of M2 overlaps the genetic coding for the matrix 1 (M1) protein. M1 has long been considered the most stable, unchanging protein in the flu virus. M1 does not change because it is vital in many different ways, being part of the structure, formation, and assembly of the virus. Because M1 and M2 share some of the same genetic coding, if one were to change the other one would likely need to change also. Since it is rare for either of them to change individually, it is even rarer for either of them to change when they share part of the genetic sequence. The M2 protein appears to be a very good candidate for the basis of a universal vaccine.⁴³

The current vaccine and the other methods mentioned are all strain specific. They must be redeveloped each year and only provide protection from the selected strains. While many of the other technologies improve upon the current concerns of the egg-based method, a universal vaccine would take many of these concerns off of the table.

One benefit of using something other than the egg-based method would be quicker production time. If a universal vaccine were to become available, it would not matter how quickly the vaccine could be produced because there would be no start time or deadline that manufacturers would need to fit the process into. The vaccine could be made year round regardless of the specific prevalent strain. With a

⁴³ Du, Lanying, Yusen Zhou, and Shibo Jiang, "Research and development of universal influenza vaccines," *Microbes and Infection* 12, (2010): 280-286.

universal vaccine, a pandemic would not be needed to be declared before vaccine manufacturers could begin production. Since a universal vaccine would render immunity to all flu viruses, seasonal and pandemic, the time that it would take to produce the vaccine is insignificant as long as they could be produced at the rate that people were born at.

While other methods may increase the annual capacity of vaccine production, a universal vaccine would significantly reduce the required annual production capacity. Instead of the current goal of a vaccine for everyone within six months, a universal vaccine would only be need at the same rate that people are born at. Instead of 300 million vaccines, the new goal would be around 2.5 million over the same amount of time.⁴⁴

Most importantly, a universal vaccine would move flu into the same category as all other vaccines. Of the diseases that the CDC recommends that people get vaccinated for, influenza sticks out as being the only one where people are ignoring the recommendation.⁴⁵ If the flu vaccine only had to be administered once or twice in a person's lifetime, people would much more readily get the vaccination.

While a universal vaccine addresses all the major concerns of egg-based method and more, it is the least developed of all the mentioned technologies. Sanofi Pasteur, the leading supplier of egg-based flu vaccine in America, has recently gone through Phase I trials for an M2 based universal vaccine, ACAM-FLU-A. So far, the trials have shown that ACAM-FLU-A is both safe and effective. Further trials for this universal vaccine are planned to take place.⁴⁶

⁴⁴ Glaister, Dan, "Number of babies born in the US reaches record levels," *Guardian.co.uk*, 18 March 2009.

⁴⁵ Center for Disease Control and Prevention, "Justification of Estimates for Appropriations Committee, Fiscal Year 2010," Department of Health and Human Services, 2009.

⁴⁶ Fiers, Walter, et al, "M2e-based universal influenza A vaccine," *Vaccine* 27, (2009):6280-6283.

Recommendations

- Invest in research the works toward developing a universal flu vaccine

The ultimate goal for flu vaccine production would be to develop a single universal vaccine instead of strain specific vaccine. Concerns regarding seasonal and pandemic flu would not exist. If one could be developed, influenza will become a thing of the past.

- Assist companies in the process of getting approval for either VLP or rHA flu vaccines and to help them build the necessary facilities to produce the vaccine

Both VLP and rHA vaccines are in the final stages of approval. Both effectively address the concerns of the egg-based method and do it better than the cell-based method. While the ultimate goal is to develop a universal vaccine, VLP and rHA will be critical in pandemic preparedness until a universal vaccine is fully developed. Even after a universal vaccine has been developed, the steady state demand will be significantly lower compared to the initial demand. For the first few years, there will be shortages of the universal vaccine, a gap that will be needed to be filled by VLP and rHA vaccines. By assisting companies in building the facilities necessary to produce VLP and rHA vaccines, the capacity goal will be met. These are also the most reliable and quickest methods that are currently available.

- Stop funding mammalian cell-based technology

Production of mammalian cell-based vaccines should be handled in a similar fashion as the egg-based method. While there are some advantages to the cell-based method not exhibited in the egg-based method, they are trumped by the quickly developing VLP and rHA vaccines. Any money spent on mammalian cell-based production facilities could be better spent on VLP and rHA vaccines.

- Continue to subsidize the production of egg-based flu vaccines

The biggest mistake that can be made in the quest for a universal vaccine is to lose sight of what is being used to protect us now. Government money should not be spent on new facilities using egg or mammalian cell-based methods, but it should continue to support the production of the vaccine by current methods. Until America has the capacity to produce enough vaccines for everyone within 6 months, it should not differentiate on how these vaccines are made. Once this goal is surpassed, only then should the companies using older technologies see a decrease in subsidies.

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