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"The Cost of Being Sick: H1N1 and Paid Sick Days"
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Introduction

Mr. Chairman and members of the Committee, I wish to thank you for the invitation to appear before you today to address issues related to our preparedness for H1N1 flu. While this influenza is, so far, proving less virulent than once feared, it is still a very dangerous virus.[1] This is especially true for vulnerable populations such as pregnant woman[2], young children, and those with compromised immune systems or lung disease[3] [4]. H1N1 infections are expected to decline in November and December of 2009 but then peak again with higher mortality from March to May 2010. In this way, some experts believe H1N1 may emulate the 1957 pandemic – decreasing late this year only to pick up again in the spring.[5]

This flu has taken a substantial toll on Americans, affecting their health but also their financial security -- as we are here today to discuss -- whether its through lost wages, missed workdays, or increased job insecurity during a deep recession. But legislation regarding employment policy for this particular flu doesn't appear to be the right focus for our resources or response. It would be hard to administer. There also doesn't seem to be a compelling public policy case for singling out this particular flu from others – many of which have actually hit the older and working-age population much harder in the past.

[1] A Kumar, R Zarychanski, R Pinto, DJ Cook, et al, for the Canadian Critical Care Trials Group H1N1 Collaborative. Critically Ill Patients With 2009 Influenza A(H1N1) Infection in Canada. Journal of the American Medical Association 2009;302(17):1872-1879. Published online October 12, 2009 (doi:10.1001/jama.2009.1496)

[2] Pregnant women are among the groups of people who have been hit particularly hard by the swine flu, and officials recommend they be vaccinated. Since the H1N1 virus was first discovered in April, more than 100 pregnant women have been hospitalized and 28 have died, according to the most recent government figures.

[3] JK Louie, M Acosta, K Winter, C Jean, et al. for the California Pandemic (H1N1) Working Group. Factors Associated With Death or Hospitalization Due to Pandemic 2009 Influenza A(H1N1) Infection in California. Journal of the American Medical Association 2009;302(17):1896-1902

[4] In contrast to seasonal influenza, elderly persons have proven less likely to contract the virus; nevertheless, many elderly persons who do contract the virus have had serious complications.

[5] Dr Paul Auwaerter, clinical director of the division of infectious diseases at Johns Hopkins University, noted that most or all of the H1N1 vaccine doses will be delivered by early December. He added that H1N1 infections will likely decline in November and December of 2009 but then peak again with higher mortality between March to May 2010. Redd added that the infections may decrease by late this year and pick up again in the spring, similar to the 1957 pandemic.

Instead, I believe our focus should be on ways we can mitigate these risks in the future, if more Americans were able to benefit from vaccination earlier in the course of a pandemic.

The good news is that we were much better prepared to deal with this flu than we would have been as recently as five years ago. This owes to steps taken by the current administration to contract for development of an H1N1 vaccine early last spring, when the virus first emerged. Collaborative steps to speed vaccine production were undertaken immediately, even before it was clear a vaccine would be needed, including work between U.S. government agencies, international partners, and drug firms to provide viral reference strains and reagents needed for vaccine production. These tasks were accomplished in record time despite technical challenges. In addition, extensive pandemic planning undertaken by the Bush Administration[6] left us with much better capacities to deal with this crisis. But there are still significant gaps in our preparedness, and nagging vulnerabilities.

Too many of the policy choices we were confronted with in this crisis forced us to sacrifice on the speed and reliability of vaccine production in order to assuage concerns about vaccine safety. Vaccine supplies are increasing, but we still do not have the quantities we expected, in the time frame that we needed.[7] Among other things, we chose to forgo the use of vaccine additives that could[8] boost effectiveness and might have helped us stretch our limited supply of vaccine raw material over more shots. We are compelled to rely on old, unpredictable manufacturing technology because we haven't developed the necessary capacities with more modern tools. We also lack domestic vaccine manufacturing facilities, which in at least two cases put us behind other countries in getting vaccine orders filled.

The bottom line is we have relied for too long on outdated capacity for our flu vaccines, in part because of our cultural reluctance to embrace new methods. This is not simply a regulatory issue, but reflects the public mood when it comes to vaccine products.

There are good reasons why the regulation of vaccines is unique. Vaccines are given to millions of otherwise healthy people, and administered over a compressed time period. This is especially true for flu vaccines. That rapid and widespread administration limits the ability to uncover latent risks after products are approved and marketed. It means, by the time we intervene to prevent exposure to an emerging side effect, millions of people might have already received a seasonal product. This is a unique risk. For these reasons, a strong pre-market regulatory process is imperative. And new vaccine technology, like any innovation, invariably brings some new uncertainties – heightening regulatory caution.

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[6] Under the HHS Pandemic Influenza Plan (November 2005), the Department's key goals for vaccine preparedness were: Stockpile enough pre-pandemic influenza vaccines to cover 20 million persons in the critical workforce; Develop sufficient domestic manufacturing capacity to produce pandemic vaccine for the entire U.S. population of 300 million persons within six months of pandemic onset.

[7] J Norman. H1N1 Flu Vaccine Supply Expected to Increase Soon. Congressional Quarterly Healthbeat, November 6, 2009

[8] It is not clear from past or current data, including with H1N1, whether clinical effectiveness of vaccine will be increased by adjuvants, although it is clear out supply could have been stretched by incorporating these additives, making a smaller quantity of vaccine as effective as a larger dose. The human immunogenicity data for the H1N1 vaccine do not show a difference so far in the antibody response to the vaccine for the majority of the populations studied. Inclusion of an adjuvant may be most substantive in truly immunologically naïve situations, for example with H5N1, or in young children, where there is no preexisting immunologic memory. This is still a potentially important contribution.

For all of these reasons and many others, we are slow to embrace change to flu vaccine production. But with the right tools and investments, we should be able to mitigate any reasonable risk. We can have more effective vaccines, and more predictable and timely supply, while maintaining our high degree of safety. This should be our focus.

Right now, our decisions to stick with safe and familiar methods also obligate us to embrace too much uncertainty about product supply. In the setting of a pandemic, these tradeoffs are simply not acceptable. While manufacturing problems at the drug firms contributed to delays in vaccine availability this year, the bottom line is that the policy choices we made also played a role. The drug makers are easy targets in our political culture and have been received criticism from some public officials in recent weeks. But fault for today's shortages don't rest with them alone, any more than it rests with the public health officials overseeing our pandemic response. These are problems of biology and technology. Still, I worry that too much time spent finger pointing obscures the mission we should be focused on. Fixing blame will not improve our readiness. It will not increase our vaccine supply.

These issues are matters of national security. The fact is that European countries share our regulatory standards and our focus on vaccine safety. But they are far ahead of us in using new and more reliable technology into their production of new flu vaccines. It's true we remain farther ahead with other vaccine products, such as our adoption of conjugate vaccines or live attenuated approaches (FluMist, for example, is not approved in Europe). But when it comes to pandemic planning, and response to flu, there is more we need to be doing. Understanding the tradeoffs made by our policy choices and gaps in the technology we use -- and taking steps to improve future readiness -- should be our focus.

Use of Vaccine Additives to Improve Yield and Effectiveness

One step to improving our readiness for the future is to better integrate the use of vaccine additives called adjuvants into our pandemic planning.

An adjuvant is a substance incorporated into a vaccine that enhances or directs the immune response of the vaccinated patient. Adjuvants are designed to bring the vaccine's antigen into contact with the immune system and, therefore, enhance the magnitude of immunity produced as well as the duration of the immune response.

Novartis[9] and GSK, among other drug firms, have done innovative work incorporating new generations of adjuvants into vaccines marketed in Europe this fall for H1N1. A lot of the recent activity in Europe to deploy adjuvants was based on "mock up" preparations of pandemic vaccines that those nations had been pre-approved and stockpiled.

In the U.S., our decision to forgo use of adjuvants, that can work to increase the protective effects of a given quantity of vaccine, limited our ability to stretch our already limited stock

[9] John Carroll, "Novartis Readies Key Adjuvant for Swine Flu Use," Reuters, April 30, 2009.

of H1N1 vaccine raw material (the vaccine antigen).[10] It is worth noting that no country has had earlier large supplies of vaccine, including in Europe. The three countries first out with substantial vaccine (the U.S., Australia and China) all used non-adjuvanted egg based vaccines. So the capacity issues, and challenges are a global problem. But to improve for the future, we need to be better prepared to embrace these new methods.

In 2008, GSK became the first company to obtain a European license for an adjuvanted prepandemic vaccine, Prepandrix. This vaccine is designed to raise immune protection against several strains of the H5N1 (Avian) flu virus.[11] GSK also recently became the first drug manufacturer to get U.S. Food and Drug Administration (FDA) approval for a modern adjuvant that is used in conjunction with a vaccine distributed domestically. That vaccine, Cervarix is administered to prevent cervical cancer and precancerous lesions caused by human papillomavirus (HPV) types 16 and 18. Cervarix contains the adjuvant ASO4, which is a combination of aluminum hydroxide[12] and monophosphoryl lipid A (MPL).[13] It is the first vaccine licensed by the FDA that includes MPL as an adjuvant. ASO4 is a close cousin of the adjuvants that are already in wide use in Europe, and shares some similarities[14] to adjuvants included in some of the versions of H1N1 vaccine being used around the world.

There is no adjuvant approved for use in a flu preparation in the U.S. and no adjuvanted H1N1 vaccine available in this country. Integrating an adjuvant into the U.S. H1N1 vaccine would not have been as easy as borrowing the data used by Europe.

For one thing, the European approvals for pandemic vaccines, and most of the clinical data that were reviewed by the European Medicines Agency (EMEA) to support them, are not with the identical vaccine antigens or from same facilities from which the U.S. H5N1 vaccines are manufactured. There are differences that potentially can occur when different antigens are mixed with different adjuvants. So it's not a sure bet that the antigen available for the U.S. vaccine could be effectively used in conjunction with the same adjuvants being used in the European vaccines. The safety profile of vaccines can also be affected by minor changes in how a protein is presented. Nonetheless, there is good reason to believe that for most patients, these adjuvants (one is already used in a U.S. stockpiled vaccine that targets pandemic avian flu[15]) could boost our present supply of a H1N1 vaccine as much as fourfold,[16] or even more when an adjuvant is used in a vaccine for children.[17] [18]

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[10] The antigens are basically components of the virus that have lost their property to infect people but remain similar to wild-type virus. When injected as part of a vaccine, they stimulate our immune systems to develop antibodies that will target the natural, "wild-type" virus.

[11] I. Leroux-Roels et al., "Antigen Sparing and Cross-Reactive Immunity with an Adjuvanted rH5N1 Prototype Pandemic Influenza Vaccine: A Randomised Controlled Trial," The Lancet 370, no. 9,587 (August 18, 2007): 580-89.

[12] Gupta RK. Aluminum compounds as vaccine adjuvants. Adv Drug Deliv Rev. 1998 Jul 6;32(3):155-172

[13] FDA News Release. FDA Approves New Vaccine for Prevention of Cervical Cancer, October 16, 2009. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm187048.htm

[14] MPL works differently than oil in water, another adjuvant, although the two do have in common novelty

[15] Steve Usdin and Erin McCallister, "Opportunity in Crisis."

[16] For example, an adjuvanted H1N1 vaccine being used in Europe contains 3.75 micrograms of vaccine stock. The same vaccine in the U.S., without the adjuvant, requires 15 micrograms of vaccine for equal potency.

[17] Data shows the adjuvanted vaccine produced by GlaxoSmithKline can produce close to 100% protection in children with 1.9 microgram of vaccine antigen whereas 15 micrograms are required for the U.S. licensed vaccine that doesn't contain adjuvant.

U.S. public health authorities laid some groundwork toward the use of adjuvants in the event that the H1N1 vaccine proved to be ineffective in the absence of these components. It was with the strong urging of the FDA that studies by vaccine manufacturers and National Institutes of Health (NIH) included both adjuvanted and non-adjuvanted formulations of H1N1 vaccine. The Department of Health and Human Services (HHS) also purchased and filled and finished a large stockpile of adjuvant in case it was needed.

In addition, U.S. public health authorities asked for data that could inform the effects of adjuvants and whether they would be beneficial and needed for H1N1 vaccine. The studies that regulators around the world relied on to evaluate the immunogenicity of both non-adjuvanted and adjuvanted vaccines are largely the result of requests for this data by FDA. The U.S. worked to keep an adjuvant option "on the table" was it to be needed.

Despite the foundational work done by FDA and others, the U.S. might not have been prepared to license an adjuvanted H1N1 vaccine through our customary regulatory process should it have been necessary. In all likelihood, if we had to incorporate adjuvant this fall, we would have been forced to make an adjuvanted H1N1 vaccine available under an Emergency Use Authorization (EUA),[19] which is an authority that authorizes use of a product for treatment or prevention of well-defined, public health emergencies when the relevant product has not already been approved for this specific use by the FDA.[20] A vaccine supplied through such an expedited authorization would have surely raised public concerns about its safety, perhaps reducing vaccination rates and offsetting any public health gains achieved by the use of the adjuvant. As a result, while the option of using an adjuvant was kept on the table, it was set on the very edge of the table.

Ultimately, the U.S. decision to not employ adjuvants was based on clinical data that showed an excellent response to standard doses of the licensed vaccines in the absence of any adjuvants. But that meant that the H1N1 vaccine required much higher quantities of vaccine

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[18] We may see a pattern where the effects of adjuvants may not be as profound when there is some background immunologic memory in the population. But data are either not readily available or are pending, many of the studies do not examine lower levels of non-adjuvanted vaccines. In some, lower levels of non-adjuvanted may also turn out to be immunogenic in some select populations

[19] The Project BioShield Act of 2004 (Public Law 108–276), among other provisions, established the comprehensive EUA program. EUA permits the FDA to approve the emergency use of drugs, devices, and medical products (including diagnostics) that were not previously approved, cleared, or licensed by FDA or the off-label use of approved products in certain well-defined emergency situations. Issuance of an EUA is predicated on a Declaration of Emergency that justifies the authorization of the EUA by the secretary of HHS. Following the HHS secretary's Declaration, the FDA commissioner may issue an EUA if he or she concludes that 1) the agent listed in the emergency declaration can cause a serious or life-threatening disease or condition; 2) on the basis of the totality of scientific evidence available, it's reasonable to believe that the medical product may be effective in diagnosing, treating or preventing this disease or condition or a serious or life-threatening disease or condition caused by another EUA-authorized product or an otherwise approved or licensed product; 3) the known and potential benefits of the medical product outweigh the risks, both known and potential; and 4) no adequate, approved, alternative medical product is available.

[20] SL Nightingale, JM Prasher, and S Simonson. Policy Review: Emergency Use Authorization (EUA) to Enable Use of Needed Products in Civilian and Military Emergencies, United States, Emergency Infectious Diseases. Volume 13, Number 7. July 2007

raw material (antigen) than would have been required if adjuvants had been incorporated.[21] [22] While the amount of antigen in the U.S. H1N1 vaccine is equivalent to the quantity used in the seasonal flu vaccine distributed around the world each year, in this case, we had very limited quantities of H1N1 antigen. Stretching supply was imperative. In the U.S., we were compelled to spread a limited supply of vaccine antigen across fewer shots than Europeans.

In a future pandemic, we may not have this same opportunity. Even today, the decision to forgo the use of adjuvant has to be considered as one of the tradeoffs contributing to our current H1N1 vaccine shortage. This kind of tradeoff doesn't need to exist in the future.[23]

What measures can be taken to improve our process for evaluating vaccine adjuvants? First, FDA should consider creating formal guidance on the development and use of adjuvants to help guide product developers. The EMEA developed formal guidance on adjuvants three years ago. The document is available on that agency's website.[24] FDA doesn't have a similar guidance document, and while it hasn't indicated it plans to write one, the FDA held a meeting on the topic in December 2008. It workshop could serve as a prelude to the development of formal guidance-writing process.

The U.S. should also consider stockpiling pre-approved vaccine preparations that could be used in a public health emergency. There is now ample experience in Europe on which we can draw.[25] Adjuvants are not approved as stand alone substances because they do not always perform the same with different vaccines or types of vaccines or, at times, even with different versions of the same antigen.[26] Nonetheless, the European strategy of having pandemic vaccines pre-approved, as mock-ups, was a prudent step.

Upgrading our Manufacturing Technology

Seasonal flu vaccines and the H1N1 vaccine are still made by the same process that has been used for fifty years: they are grown inside chicken eggs.[27] This process is unpredictable, slow,

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[21] FC Zhu, H Wang, HH Fang, JG Yang, et al. A Novel Influenza A (H1N1) Vaccine in Various Age Groups. Published at www.nejm.org October 21, 2009 (10.1056/NEJMoa0908535). Available at http://content.nejm.org/cgi/content/abstract/NEJMoa0908535v1

[22] ME Greenberg, MH Lai, GF Hartel, CH Wichems, et al. Response after One Dose of a Monovalent Influenza A (H1N1) 2009 Vaccine — Preliminary Report. Published at www.nejm.org September 10, 2009 (10.1056/NEJMoa0907413). Available at: http://content.nejm.org/cgi/content/full/NEJMoa0907413

[23] It's important to note that it isn't clear how much of the U.S. reluctance to embrace adjuvants is a function of our caution, and how much is a function of sponsors. More likely, it's an element of both. One reason Novartis' older adjuvanted vaccine hasn't been approved in the U.S. is that they acquired it from Chiron, which wasn't able to implement a formal U.S. regulatory or commercial strategy. The adjuvanted vaccine was approved in Italy in 1997, although only for the elderly and using antigen from a specific EU facility. Apportioning blame between FDA and the drug firms would be clearer if Novartis or GSK had filed an application to license an adjuvanted vaccine in the U.S. and FDA had rejected it, but they haven't. It's hard to know if this is because FDA has discouraged it or for other reasons. But none of these facts change the steps we should be focused on.

[24] Available at www.emea.europa.eu/pdfs/human/vwp/13471604en.pdf

[25] See European Medicines Agency, "Guideline on Adjuvants in Vaccines for Human Use," EMEA/CHMP/VEG/

[26] As one example, aluminum compounds – which are the only adjuvants used widely with routine human vaccines and are the most common adjuvants in veterinary vaccines – do not work with influenza vaccine.

[27] C Gerdil, "The Annual Production Cycle for Influenza Vaccine," Vaccine 21, no. 16 (May 1, 2003): 1,776-79.

and difficult to scale. It is also expensive, costing more than $300 million to build a new plant and requiring more than five years to bring an egg-based production facility online.

Here is how the egg-based process works: Flu, as with any virus, will grow only in living cells. In the case of flu vaccine, production of the vaccine components has used the cells of embryonated (fertilized) hens' eggs. The success of this system is primarily dependent upon the availability of adequate flocks of chickens. These flocks must be hatched about six months in advance to achieve maturity at the time that the eggs are needed. A bipartisan investment that helped improve our readiness was support of year round flocks. Nonetheless this egg-based process requires long lead times and has other risks.

The flocks, for example, are susceptible to their own diseases.[28] Another challenge of the egg-based process is virus yield. This refers to the number of viral particles that come out of an egg that could be used to make the vaccine. As a rule of thumb, one to three eggs are needed to produce each individual shot of the seasonal flu vaccine. Eggs are typically low-yield factories for the production of vaccine components.

This was certainly true this year. The H1N1 virus that was adapted by the Centers for Disease Control (CDC) for growing inside the chicken eggs, and sent to the manufacturers as the "seed" stock[29] (for jumpstarting manufacturing lines) was slow in being shipped to the drug firms owing to the difficulty in developing this template strain. Once it arrived, it was not well suited to the production lines, and turned out to yield low quantities of vaccine antigen.[30] Manufacturers spent several weeks before they realized this seed stock was yielding low vaccine quantities. It took still more weeks for the drug firms to re-engineer the seed stock to come up with a more effective template for growing vaccine antigen in the chicken eggs.[31] [32] This experience underscores the unpredictable qualities of our present flu vaccine manufacturing process, and how vulnerable we are as a result of our dependence on it.

Because of the uncertainties and delays inherent to this production process -- and because the emergence of pandemic strains of influenza virus may occur outside the normal time frame for vaccine production (when chicken flocks are not at peak availability) we need alternative production systems for flu vaccine. The principal alternative to the egg-based process is tissue culture cell lines that can be used as incubators for viral replication.[33]

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[28] DJ Alexander, "A Review of Avian Influenza in Different Bird Species," Veterinary Microbiology 74, nos. 1-2 (May 22, 2000): 3-13.

[29] N. Bardiya and J. H. Bae, "Influenza Vaccines: Recent Advances in Production Technologies," Applied Microbiology and Biotechnology 67, no. 3 (May 2005): 299-305.

[30] Virus yield is increased substantially by using strains of the virus that are specially tweaked to make them produce more viral particles and survive better in the eggs. That is because the "wild-type" viruses that are isolated from patients do not grow well in the eggs that are used for their manufacture. Therefore, the wild-type viruses need to be altered or reassorted to grow well in eggs while still retaining the ability to make the viral antigens that are needed for an effective vaccine. But this process of making reassortant strains takes time. At present, there are not many labs that are capable of working on developing these reassortants.

[31] B McKay, C Simpson and J Whalen. Obama Targets Swine-Flu Response. The Wall Street Journal, October 26, 2009. A1

[32] J Burns. Health Officials Frustrated by H1N1 Vaccine Shortage. The Wall Street Journal, November 4, 2009. B1

[33] M. G. Pau et al., "The Human Cell Line PER.C6 Provides a New Manufacturing System for the Production of Influenza Vaccines," Vaccine 19, nos. 17-19 (March 21, 2001): 2,716-21.

Using cell cultures instead of chicken eggs cuts three to four weeks from the time required to mass-produce a vaccine. But the biggest advantage of cell-based manufacturing is its more rapid scale-up and is potentially better predictability. These attributes are typically more variable using older egg-based processes. Moreover, the use of hundreds of thousands of eggs can be a more dirty process, making it prone to production glitches.[34]

There are many approved cell culture vaccines made in the US – this includes most of our viral vaccines such as Measles, Mumps and Rubella (MMR) as well as vaccines for polio and Zoster, among others. An issue for flu vaccines has been getting good yield and a good clinical response using cell cultures. Only in recent years has there been real progress on these steps. As a result, the U.S. has recently begun to scale up work on cell-based manufacturing for influenza vaccines. More needs to be done. Our current vulnerabilities are too significant to be satisfied with merely incremental progress.

The Biomedical Advanced Research and Development Authority (BARDA) awarded one federal contract for $487 million last spring to Novartis for the construction of the first U.S. facility to manufacture cell-based flu vaccine.[35] That facility is scheduled to open this year, but it won't be producing licensed vaccine until 2014.[36] [37] GSK and Sanofi-Aventis are also working on cell-based production of influenza vaccine.[38] Baxter recently became the first company to gain marketing authorization by the European Commission for a cell-based vaccine.[39] That cell-based vaccine product is not available in the U.S.[40]

Cell based vaccine production is not without its own obstacles, and risks. In addition to issues around getting adequate yields from cell-based production processes, there are also challenges with immunogenicity[41] and reactogenicity[42]. All of these problems have come up in past attempts to scale cell based production processes. There is also a remote and theoretical safety concern around the ability of genetic material to jump from the cell lines, into the vaccine, and then integrate into human tissues. FDA has issued a guidance to provide a pathway for safe use of novel cell substrates that tries to address the proper testing that flu vaccine manufacturers should undertake in order to rule out these risks.

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[34] Steve Usdin and Erin McCallister, "Opportunity in Crisis," BioCentury, May 4, 2009.
[35] Dr Bruce Gellin, director of the HHS National Vaccine Program, recently noted publicly that other federal collaborations with private companies for expedited development of new vaccine technologies are also underway, although he has not cited the names of other companies.
[36] U.S. Department of Health and Human Services, "HHS Awards $487 Million Contract to Build First U.S. Manufacturing Facility for Cell-Based Influenza Vaccine," news release, January 15, 2009, available at www.hhs.gov/news/press/2009pres/01/20090115d.html (accessed May 6, 2009).
[37] It's also worth noting that the North Carolina Novartis plant will also produce an adjuvant, MF59
[38] 21. Bruce Japsen, "Flu Vaccines No Easy Remedy: Low Sales Mean Lack of Incentive for Drugmakers," Chicago Tribune, April 29, 2009.
[39] Baxter's Celvapan H1N1 pandemic vaccine using Baxter's Vero cell technology. Celvapan H1N1 is the first cell culture-based and non-adjuvanted pandemic influenza vaccine to receive marketing authorization
[40] Baxter Receives European Commission Approval for CELVAPAN H1N1 Pandemic Influenza Vaccine, October 07, 2009. http://www.baxter.com/about_baxter/press_room/press_releases/2009/10_07_09-celvapan.html. Press Release
[41] Immunogenicity is the ability of a particular substance, such as an antigen or epitope, to provoke an immune response.
[42] Refers to the ability of some biologics to cause unwanted immunological reactions.

Given the strategic advantages of the cell-based process, we need to invest in developing this capacity more quickly. BARDA should support development of similar facilities to the one being constructed in North Carolina. A typical cell-based facility costs as much as $600 million and would only be able to produce about 40 million doses of seasonal "trivalent" flu vaccine a year. The Novartis facility will be able to produce around 150 million doses of "monovalent" vaccine--containing just one viral strain, as opposed to the seasonal flu vaccine, which contains three different viral strains--in the event of a pandemic.

All of this illustrates the more challenging economics of vaccine production, for which significant upfront expenditures are required to build facilities capable of producing largely fixed capacities of vaccine. So long as seasonal flu vaccines remain commoditized products, with slim margins and little product differentiation (public health agencies want vaccines coming from different manufacturers to be largely interchangeable) then there will not be large enough private profits to support substantial new investments in manufacturing infrastructure. Getting additional facilities on-line will require federal investment. This capacity, however, is a matter of national strategic security and should be a U.S. priority.[43] [44]

Ensuring Domestic Production Capabilities

We also need to make sure that an adequate proportion of the worldwide influenza vaccine production capacity is domiciled in the U.S. – enough to adequately supply a reasonable portion of the U.S. market in the event of a pandemic.

It is hard to envision other nations allowing limited supply of vaccine raw material to be shipped outside their borders in the event of a full-blown pandemic with a very dangerous flu. More likely, nations would take steps to nationalize their domestic production capacity.

The drawback to relying on foreign plants was made clear recently when foreign countries claimed priority for the H1N1 vaccine produced in their own countries. That was the case in Australia, where the government pressured vaccine manufacturer CSL to keep its vaccine at home instead of fulfilling its contract for 36 million doses of swine flu vaccine for the United States.[45] [46] [47] In Canada, where GSK maintains one of its two flu vaccine production facilities, the company had to assure the Canadian government that the Canadian population

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[43] The margins made on flu vaccines are also narrow by drug-industry comparisons. Flu vaccine doses cost about $3 each to manufacture, according to industry insiders. This does not include the depreciated costs of the capital needed to invest in manufacturing facilities. Each vaccine ultimately sells for $10-12 for each dose. The fixed costs related to quality assurance, administration, and depreciation are estimated to account for 60 percent of total production costs

[44] "After Decades of Malaise, the Vaccine Industry Is Getting an Injection," Knowledge@Wharton, November 2, 2005, available at http://knowledge.wharton.upenn.edu/article.cfm?articleid=1306 (accessed Nov 4, 2009).

[45] J Norman. H1N1 Vaccine Delayed for Priority Groups Until January. CQ Healthbeat. November 4, 2009

[46] One CSL Biotherapies' vaccine manufacturing facility (which it shares with CSL Behring) is located in King of Prussia, PA. It has been supplying vaccine in the U.S. since the 2007-2008 flu season. Its parent company, CSL Limited, is located in Melbourne, Australia. On August 18, 2009 FDA licensed CSL's new vaccine filling and packaging facility, located in Kankakee, Ill. CSL Biotherapies may use it to fill and package H1N1 vaccine if requested to do so by HHS. CSL Biotherapies' contract for bulk antigen with HHS is $180 million.

[47] DG McNeil. Nation Is Facing Vaccine Shortage for Seasonal Flu. New York Times, November 4, 2009. A1

would be served first from that facility before any other countries that rely on that manufacturing site – including the U.S. – received fulfillment of their H1N1 vaccine orders.[48]

This risk is compounded by the fact that all but one of the vaccine production facilities we depend on is located outside the United States.[49] There are five companies licensed to sell seasonal flu vaccine in the U.S. But only one, Sanofi-Pasteur, has a domestically located plant. The others — GlaxoSmithKline, Novartis, CSL Ltd. and MedImmune — use plants in England, Germany and Australia.

MedImmune's main vaccine facility is in Gaithersburg, MD but after it was acquired by AstraZeneca, additional production capacity was located in Cambridge, UK in 2008. Novartis, based in Switzerland, operates a cell-culture vaccine production facility in Marburg, Germany. The cell culture facility maintained by Baxter for production of flu vaccine is located in the Czech Republic. There also appears to be significant limitations in global fill and finishing capacities for flu vaccine, which is also limiting supply.

Ideally, we need more of the companies that produce flu vaccines to locate new manufacturing, filling, and finishing facilities in the U.S.

There are business impediments to building new facilities – these production sites require substantial investments and the financial return on flu vaccine, in particular, is small. Flu vaccines generate modest margins relative to other vaccines and drug products.

One of the additional business impediments companies face to making investments in multiple, differently situated vaccine production facilities stems from how these facilities are regulated. The vaccine produced from each facility needs to be separately licensed by both the FDA and the EMEA. That means that if the same company produces flu vaccine at two different facilities (even in cases where it uses the same processes at each facility) the company often has to conduct separate clinical trials for each vaccine. While FDA has approved vaccines where little or no U.S.-specific data was available, there remain many situations where redundant trials were required or European data was not fully leveraged.

This drives developers to expand existing facilities rather than create new ones. Since the clinical trials require substantial investments of time and money, it is far more economical to maintain a few very large vaccine production facilities. After all, each facility's vaccine will be treated as a completely new product with its own expensive clinical trials. There are good scientific reasons why biologicals coming from distinct facilities are treated independently by drug regulators. But there may be better ways to enable more cooperation between requirements set forth by different regulators or make use of studies that could bridge between products from a single manufacturer's different manufacturing lines.

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[48] GSK maintains two flu vaccine production sites, on in Germany and the other in Canada. The German facility is licensed to supply vaccine to Europe while the Canadian facility supplies other countries, including the United States.

[49] That domestic facility, operated by Sanofi, was supported by grants from HHS/BARDA that significantly increased its capacity. FDA licensed an additional production line this May at that facility. See http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149577.html

The ability to conduct these kinds of bridging studies, if they could streamline the requirements for entirely separate clinical trials, could save time and money. It would also reduce the economic impediments firms face to creating redundant manufacturing capacity.

Other measures that would help create more domestic capacity include guaranteed markets for seasonal flu vaccines. This would create additional incentives for building U.S. manufacturing capacity, especially if the tender process favored domestic manufacturers.

Other Areas for Improvement

We also need to develop new types of vaccines. BARDA has made grants available to fund research into completely new platforms for vaccinating against flu. Just this past June, BARDA awarded a research and development contract for work on a recombinant flu vaccine. We are making incremental but meaningful progress. We should be undertaking a more robust process to put substantial resources behind these scientific efforts.

The complexity of developing a vaccine against pandemic flu is similar to the problems posed by development of the seasonal flu shots. The vaccine needs to be adapted to match each specific strain of the flu virus. In the case of the seasonal flu, we have to develop a new vaccine each year to guard against that season's circulating strains of influenza.

It also means that we depend on just-in-time delivery when it comes to flu vaccine. This owes to the fact that the vaccine targets proteins on the surface of the flu virus that itself undergo easy mutation. Since these proteins change easily, a new vaccine must be developed to target the unique proteins found on each particular strain of influenza.

Better technologies can enable development of vaccines that require much shorter development timelines, or that protect against a broader range of flu strains.

On the first point, for example, Virus Like Particles (VLPs) have been suggested as a promising platform for new viral vaccines. In the light of a pandemic threat, VLPs have been recently developed as a new generation of non-egg based cell culture-derived vaccine candidates against influenza infection.[50]

Influenza VLPs are formed by a self-assembly process incorporating structural proteins of the flu virus.[51] These particles resemble the virus from which they were derived but lack viral nucleic acid, meaning that they are not infectious. VLPs used as vaccines are often very effective at eliciting both T cell and B cell immune responses. The human papillomavirus and Hepatitis B vaccines are the first VLP-based vaccines approved by the FDA.

[50] SM Kang, JM Song, FS Quan, RW Compans RW. Influenza vaccines based on virus-like particles. Virus Res. 2009 Aug;143(2):140-6. Electronic publication 2009 Apr 15.

[51] They are assembled into budding particles composed of the hemagglutinin (HA), neuraminidase (NA) and M1 proteins, and may include additional influenza proteins such as M2.

Research suggests that VLP vaccines could provide stronger and longer-lasting protection against flu viruses than conventional vaccines.[52] Production may begin as soon as the genetic sequence of the virus is published online, without an actual sample of the agent, and it may take as little as 12 weeks, compared to 9 months for traditional vaccines.[53] The VLP may be grown in either plants or insect cells. As it contains no genetic material, some ingredients of traditional vaccines such as formalin and detergent treatments, are not needed.[54] In some recent clinical trials, VLP vaccines appeared to provide complete protection against both the H5N1 avian influenza virus and the 1918 Spanish influenza virus.

There is also opportunity to create a vaccine that protects against a broader variety of influenza strains, reducing the need to tailor a new vaccine to each individual strain of circulating flu. A universal vaccine would target more "conserved" regions of the flu virus's structural proteins--parts of the flu virus architecture that do not undergo much mutation and, therefore, are unlikely to change, regardless of the particular strain of flu.

Right now, our vaccines target proteins that are on the outer surface of the flu virus. Since our immune systems attack these proteins, the proteins themselves undergo adaptation, mutation, and change in order to evade our immune response. But structural proteins that are core components of the architecture of all flu viruses would be less likely to undergo mutation, regardless of the pressure from nature to change in order to survive.

Theoretically, to target these core proteins, a universal vaccine would need to recruit our T cells to attack the flu virus, as opposed to today's vaccines, which recruit an antibody response. For that reason, some suggest that such a "universal" vaccine would more likely be a therapeutic tool, as opposed to a protective vaccine. There is some literature to suggest that a T cell response alone may not be sufficient to protect us fully from flu, but work continues, and a universal vaccine is at least possible.

Drug firms sometimes complain that there is a disconnect between the advice and goals of different government agencies, especially between those charged with trying to develop new technologies (BARDA) and those charged with ensuring their safety (FDA).

It remains important for FDA to preserve its distinct mission to assure product safety and effectiveness and for the agency to remain independent. But when it comes to areas of critical public health need, where the government is engaged in a substantial effort to fund development of new technology, there's more we can do. FDA meets early with academic and industry developers of novel technologies especially for critical public health needs like flu and terrorism. But there may be more opportunities to create clearer pathways to market by also engaging FDA more closely in the government procurement process.

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[52] TP Luo, Z Yang, M Gao, Z Pan. Virus-like particle vaccine comprised of the HA, NA, and M1 proteins of an avian isolated H5N1 influenza virus induces protective immunity against homologous and heterologous strains in mice. Viral Immunology 2009 July;22(4):273-81.
[53] New Vaccine Strategy Might Offer Protection Against Pandemic Influenza Strains. American Society for Microbiology. 5-18-2009. http://gm.asm.org/index.php?option=com_content&task=view&id=217&Itemid=1
[54] Dobbs, David (October 22, 2009). "Delivering a Virus Imposter Quicker". Technology Review. http://www.technologyreview.com/biomedicine/23782/

One opportunity is to couple BARDA funding of new technology with regulatory programs that provide additional, early feedback to sponsors development those new methods. Multiple studies have shown that early and frequent FDA feedback helps sponsors avoid mistakes and results in timelier access to safe and effective products. This kind of regulatory effort is time and labor intensive, however, and would need to be funded inside FDA.

Finally, we also need to spend time examining how limited vaccine has been distributed during this pandemic, and take steps to put in place a better process for the future. My own view is that we should have relied more on the clinical community as a way to target the vaccine to high risk Americans. Doctors who treat high-risk patient populations – for example obstetricians that see pregnant women or pulmonologists who treat people with lung disease – in many cases had no access to the vaccine in many states. To target these populations of patients, we need to work through, and target, the doctors that care for them.

Conclusion

The Obama team deserves credit for ordering vaccines early last spring when H1N1 first emerged and for acting quickly to support their development. It wasn't clear, at that moment, whether H1N1 would emerge as a pandemic or fade into the summer and fail to re-emerge in the fall. The Administration's decision to undertake a crash effort to field vaccine saved lives.[55] Moreover, many of the shortcomings in our current preparedness are not the product of policy choices, but are challenges that relate to biology and the inherent complexity of targeting viruses that change rapidly and frequently. The fact that the U.S. has quickly fielded a program with high quality licensed vaccines despite the old technology and processes we relied on is a substantial public health accomplishment.

This shouldn't, however, obscure the fact that at many points we made deliberate decisions to rely on those old methods rather than adapt new ones because of our concerns about safety and our comfort with the tried and true approaches. Some of our policy choices did have consequences, and contributed to the limited availability of vaccine. These tradeoffs can be reduced in the future if we make a concerted effort today to increase our capacity for timely development of safe, effective and innovative vaccines.

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[55] S Gottlieb. Why You Can't Get the Swine Flu Vaccine. The Wall Street Journal, October 28, 2009. A22.