



Vaccine Readiness in a Time of Pandemic: Policy Promises Realized and the Challenges That Remain

By Scott Gottlieb, M.D.

The recent outbreak of swine flu, originating in Mexico but now identified in hundreds of cases worldwide—and probably a factor in thousands of other milder illnesses—has brought flu vaccination to the center of public discussion. The outdated egg-based method for making flu vaccines takes too long to make enough vaccines both to prevent seasonal flu and to inoculate large populations rapidly to a newly emerging pandemic strain. The vaccine industry has been pioneering new approaches to manufacturing vaccines, such as cell cultures, as well as new techniques to stretch supplies and make existing vaccines more effective. But much work remains to be done, and vaccine readiness will require additional investments in production capacity and science and a favorable regulatory environment from the Food and Drug Administration (FDA).

As the H1N1 swine flu continues to spread, the focus has turned to the prospects for quickly developing a vaccine that can protect Americans. So far, most infections in the United States have been mild, but even if this flu strain turns out to be no more potent than the seasonal flu, there is reason to believe that more people will be stricken—and with more serious illnesses.¹

This summer—not the season in which flu traditionally spreads—may provide a backstop that limits the spread of the virus. But even under

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Key points in this *Outlook*:

- Flu vaccines are still made by the same process that has been used for fifty years, and that process is risky, expensive, and slow.
- We have made considerable progress in the past five years in preparing for a pandemic, and a revitalized vaccine market has reemerged. Today, there are three times as many manufacturers for seasonal flu vaccine as four years ago.
- The FDA has helped with practical regulatory changes that have reduced development risks, but the agency can take additional steps to encourage innovation and open pathways to new products, such as a universal vaccine.
- We need alternate production systems for a flu vaccine, including cell-based vaccine technology and facilities—and preferably more domestic capacity.
- Reducing patent life on biologics like vaccines favors generics and lowers drug costs, but it reduces incentives to invest in these technologies. Intellectual property protections have fostered investment in vaccines and led to innovations that give us new opportunities.

optimal circumstances, we could still see slow but continued transmission of H1N1 through the spring and summer, followed by a spike in cases this fall, when flu season returns.² Regular flu is associated with 250,000–500,000 deaths worldwide every year, including those of 30,000–50,000 Americans.³ So far, swine flu appears relatively mild outside of Mexico. For reasons we cannot yet explain, the virus is infecting more young people than elderly and more women than men.⁴ Even a mild virus could still cause widespread illness and harm, since our population is naïve to this new strain—we probably harbor no innate immunity. Moreover, the current strain of H1N1 could still undergo changes that would make it a more dangerous infection. Thus, as of this writing, the decision to make a vaccine has not been formally made. But it seems highly likely that the Centers for Disease Control and Prevention (CDC) will proceed with developing one once they have the virus fully isolated in a few weeks. The only question is how quickly they can make a vaccine.

The good news is that today we are much better prepared to deal with this challenge—and to develop a new influenza vaccine rapidly—than at any time before. This owes in large measure to specific actions that we have taken in the last five years to prepare for pandemic flu and other emerging biological threats, including infections that would be used deliberately as terrorist weapons. As of this week, the CDC was planning to request that vaccine manufacturers expedite their production of seasonal influenza vaccine and then prepare to produce H1N1 vaccine.⁵

The H1N1 flu, which is an assembly of genes from swine, avian, and human viruses, poses the biggest threat of a large-scale pandemic since the appearance of the H5N1 avian flu strain in 2003 that killed millions of birds and hundreds of people.⁶ That disease proved lethal to more than half of the people who contracted it, though the virus largely did not spread from person to person and only infected 421 people.⁷ (In many cases, the qualities that can make a virus highly contagious—spreading from person to person—also make it less deadly. The World Health Organization is distressed that H5N1, which kills 63 percent of its victims, is becoming less deadly, which could mean that the virus is evolving toward a less lethal but more contagious form with enough lethality to cause significant morbidity and mortality.⁸) While we are better equipped today for confronting a pandemic because of the efforts we undertook to ready ourselves against avian flu, there are still some additional steps we need to take to improve our national preparedness.⁹

Some of these steps require longer-term policy-making, but others we must take very quickly to respond to the present threats. Production of an H1N1 vaccine could require some difficult trade-offs, especially a decision to reduce the amount of seasonal flu vaccine we can ultimately produce for the fall. It appears that with proper policy steps, we can address this trade-off when it comes to a vaccine for H1N1. But if we make the right investments today, in the future, we could avoid these difficult trade-offs altogether when another pandemic inevitably arises.

The vaccine industry has undergone a renaissance in recent years.

Working in our favor is the fact that the vaccine industry has undergone a renaissance in recent years. This is a result of three developments in this product category. First, government incentives and grants helped subsidize the creation of demand for new vaccines, especially those targeting pandemic flu strains. These grant programs also helped to create more domestic vaccine production capacity, an important strategic asset. Second, improvements in how vaccines are regulated by the FDA mitigated some of the cost and risk in making new products. Third and finally, new scientific advances in the production, delivery, and effectiveness of vaccines demonstrated that intellectual property created in this field could be rewarded through higher margins and increased consumer demand. This is also true when it comes to vaccines that target pandemic flu, for which advances in science underpinned improvements that have created a market for these products. These policy developments and their impact on the vaccine industry have improved our medical footing. It is important that we build on these efforts, even as we deal with swine flu.

A Renaissance for Vaccine Production

Vaccines were long seen as commodities, marked by little new investment. This is especially true when it came to vaccines for flu. The sector made products that reflected little innovation and sold them cheaply, mostly to government agencies that valued low prices that enabled wider use over advances in how vaccines worked or were manufactured. The end result was a declining industry, with few reliable suppliers. As recently as five years ago, only two manufacturers produced most of our flu vaccine,

and just one of these was a domestic company. Even today, seasonal flu vaccines are still made by the same process that has been used for fifty years: growing inside chicken eggs.¹⁰

This chicken egg process is dirty, slow, and expensive, costing more than \$300 million to build a new plant and requiring more than five years to bring it on line. Here is how it works: The influenza virus, as with any virus, will grow only in living cells. In the case of seasonal 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 approximately six months in advance to achieve maturity at the time that the eggs are needed for production of flu vaccine. This process is not without risk. The flocks, for example, are susceptible to their own diseases.¹¹

The egg process, therefore, requires a long production cycle. Since vaccine strains are usually selected between the end of January and the end of March for the upcoming winter flu season, we are finishing now our production of seasonal flu vaccine. That means we can largely wrap up production of seasonal flu vaccine before we need to shift to production of a vaccine against H1N1. But vaccine manufacturers will have to restart the six-month egg process to produce a full run of swine flu vaccine. Moreover, we may not catch this break next time a pandemic inevitably arises. A pandemic strain could emerge at the beginning of the production cycle for the seasonal vaccine. This would force a hard decision whether to shift some of the production capacity for a seasonal vaccine into efforts to manufacture a vaccine against pandemic virus. These vulnerabilities and our present efforts to make a vaccine to H1N1 illustrate the shortcomings and risks of the egg-based process.

Another challenge of the egg-based process is virus yield—in other words, the number of viral particles that come out of an egg that could be used to make the vaccine. Eggs are typically low-yield factories for the production of vaccine components. This limits how much vaccine can be produced in a limited time. As a rule of thumb, three eggs are needed to produce each individual shot of the seasonal flu vaccine. 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.¹²

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. 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. But this process of making reassortant strains takes time.¹³ It is this process that CDC refers to when it says it is working on the “seed” of the swine virus to give to vaccine manufacturers.¹⁴ At present, there are not many labs that work on developing these reassortants.

Thus, the egg-based process is slow and involved. When it comes to H1N1, based on current knowledge about the virus, “it would take at least two to three weeks for vaccine strain preparation, seed virus preparation would take another three or four weeks, putting the start of bulk production at the end of June,” according to a timetable provided by Novartis. “Standardizing reagents would not be available for another eight weeks, and quality control would tack on an additional one to two weeks. . . . That would bring us to a time frame of early September when we could start distributing the vaccine.”¹⁵ The CDC estimates that it will have the seed prepared in two weeks.

Advancements That Improve Our Preparedness

Because of the uncertainties and delays inherent to our current vaccine production process—and because the emergence of pandemic strains of influenza virus may occur outside the normal time frame for vaccine production—we need alternative production systems for flu vaccine. This includes the use of tissue culture cell lines as incubators for vaccine production instead of eggs.¹⁶ We must invest in other approaches that can help improve the effectiveness of a flu vaccine. These include the use of recombinant DNA proteins; the development of a universal flu vaccine that protects against a range of flu strains; and the use of vaccine additives called adjuvants, which boost the efficiency of vaccines while enabling producers to stretch limited vaccine stock.

In the past five years, the vaccine market has reemerged as a key industry and growing business for the large drug firms, which have invested heavily in better ways of making these products. These investments are the result of rising profit margins for these products and the success of several new consumer vaccines against

important infectious targets, such as herpes zoster (the cause of shingles) and human papillomavirus (a major cause of cervical cancer). Other new vaccines target global public health challenges. For example, Merck's RotaTeq helps prevent infection with rotavirus, a gastrointestinal illness that is a major cause of morbidity and mortality among young children, especially in developing countries. As a result of the commercial successes of new products, between 2004 and 2007, vaccines generated a compound annual growth rate of 32 percent for the drug industry.¹⁷ This encouraged additional investment in new vaccines and underpinned a number of key innovations in how vaccines are developed and manufactured.

The renewed interest in vaccines is also a consequence of legislation that created new incentives for manufacturers to develop these products and practical regulatory changes at the FDA that lowered development risks for sponsors by applying better scientific tools to evaluating vaccines. This is especially true when it comes to flu vaccine, which is a product segment that has functioned much differently from the rest of the vaccine sector. The market for flu vaccine was marked by underinvestment. This was largely a result of low-bid government contracts for vaccine that was distributed largely through public health agencies. These contracts valued low price in order to spread fixed government budgets widely. But they did not provide a margin to support new investments or to promote innovations in how vaccines worked or were made. In recent years, this has changed as a result of policies specifically aimed at promoting investment in flu vaccines.

These policies include a series of key guidance documents issued by the FDA's biologics center, mapping out a streamlined development process for the approval of flu vaccines.¹⁸ It relied on more rapid measures of benefit from tests against biological markers that gauge immune system response to the vaccine. These measures reduced development costs and created more predictability for new vaccine developers. The FDA also put in place an express inspection process for certifying new vaccine manufacturing facilities.¹⁹ The agency also worked collaboratively with manufacturers to help them develop the new cell-based vaccine technology. While this technology is still under development, it could become especially important for making vaccines against a potentially virulent form of pandemic flu that might not be efficient or even possible to manufacture using the egg-based production method. Another factor that helped increase the incentives for additional production

of flu vaccine was a significant increase in Medicare payments for flu vaccine and administration. Taken together, these regulatory steps gave rise to new vaccine products that give today's policymakers many more options in responding to the H1N1 outbreak.

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The Department of Health and Human Services also established a government grant-making and contracting process for vaccines under its BioShield program for medical products that could protect against biological weapons and other threats. One contract for \$487 million was awarded three months ago to Novartis for the construction of the first U.S. facility to manufacture cell-based flu vaccine.²⁰ That facility should be on line by 2014. Baxter, GlaxoSmithKline, and Sanofi-Aventis (among others) are also working on cell-based vaccine production.²¹ According to *BioCentury*, cell culture cuts three to four weeks from the time required to mass-produce a vaccine with the egg-based method. But the biggest advantage of cell culture manufacturing is rapid scale-up, which is impossible using older processes because hundreds of thousands of eggs cannot be produced on short notice.²²

A typical cell-based facility, however, 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 "mavalent" 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. 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. 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.²³

Near- and Long-Term Options for Ramping Up Vaccine Supply

If we need to deploy a vaccine against a pandemic flu, the cell-based process could be used in a pinch. But few of these worldwide facilities are operational, and so far, none are approved by the FDA. The FDA would probably have to invoke its Emergency Use Authorization²⁴—which allows unapproved medical products to be made available in a public health emergency—to make a cell-based vaccine available. The agency needs to prioritize the development and certification of more of these cell-based facilities. But in the meantime, in all likelihood, we are going to have to rely on the egg-based process for the near future.

The good news is that today there are three times as many manufacturers licensed to make flu vaccine using the egg process as there were just four years ago. Since there are more manufacturers making seasonal flu vaccine, and since each has some extra “surge” capacity to make more, we have the ability to make limited quantities of a pandemic vaccine using the egg process, even if its production had to overlap with the usual production cycle for seasonal vaccine. But if the need for large-scale production of a vaccine against a virulent pandemic flu collided with the same timetable for the manufacture of a seasonal vaccine, we would be hard pressed to produce sufficient quantities of both vaccines. We would need to make some difficult trade-offs.

Avoiding these trade-offs requires more scalable production capacity. The cell-based process is ideally suited to this challenge. Another option is to extend the supply of vaccine using an adjuvant. Adjuvants work to bring the antigen into contact with the immune system and, therefore, influence the type of immunity produced as well as the magnitude and duration of the immune response. Right now, there are two different adjuvants that are approved as safe and effective in Europe that experts believe could be used in a swine flu vaccine. Novartis²⁵ and GlaxoSmithKline have both done innovative work incorporating new adjuvants into vaccine products. In 2008, GlaxoSmithKline 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 virus.²⁶ But none of these adjuvant products is approved for use in the United States. There is good reason to believe that these adjuvants (one of which is already used in a U.S. stockpiled vaccine that targets pandemic avian flu²⁷) could boost the supply of a swine flu vaccine as much as fivefold. The FDA needs to assess these adjuvants rapidly and decide if it will permit their use in this case. The FDA has taken a cautious view on these vaccine additives, but there is now ample experience in Europe on which the agency can draw.²⁸ The FDA should develop clear guidance on the approval process for adjuvanted products.

Intellectual property creation has been a key component of driving more investment into vaccines—not only for vaccines targeting new infectious diseases, but also for flu vaccines.

The potential benefits offered by technology such as adjuvants and cell-based manufacturing underscore why we must continue to invest in the capacity to develop vaccines, creating incentives for the development of better products and more and better manufacturing facilities. So long as the market for new vaccines continues to remain robust, there is every reason to expect that more manufacturers will continue to enter this field. But our improved preparedness is not a sure thing, nor are continued advances in vaccines that can reduce risks and improve our preparedness.

One significant reason is diminishing incentives for investment in research and development of vaccines and new industrial capacity to manufacture them. Intellectual property creation has been a key component of driving more investment into vaccines—not only for vaccines targeting new infectious diseases, but also for flu vaccines. In particular, the need to develop vaccines against new pandemic flu strains has required companies to invest in new processes for developing and delivering these products. These innovations have had more generalized benefits, spilling into improvements being recognized in other kinds of vaccines, including seasonal flu vaccines.

For example, one technique for developing pandemic vaccines, pioneered by the biotechnology firm MedImmune, has created significant new capabilities against pandemics and generated an attractive royalty stream for the company. The technique is called reverse genetics, and it can be used to engineer the specific seed strain rapidly. With the reverse genetics method, scientists can splice the desired genes into small circular pieces of DNA called plasmids. The plasmids are then put into animal cells, and the vaccine seed virus grows. The seed stock can then be grown in mass quantity for vaccine production either in the traditional chicken egg or in cell culture.²⁹ Using reverse genetics is a potentially more predictable process for developing these seed strains. Reverse genetics can also be used to improve the process for making seasonal flu vaccine, shaving time and uncertainty off that process. It seems only a matter of time before manufacturers move away from using the customary process for developing seed strains for the seasonal flu vaccines and adopt reverse genetics as a universal tool.

Reverse genetics is the process currently being used by the CDC in the development of a seed strain for a vaccine targeting H1N1. The development of this technique is an instructive example of how the creation of new intellectual property rewards investment while significantly improving our pandemic preparedness. But the patent protections that secure these investments are in doubt. The average patent life on big new drugs has been reduced to as little as ten years from more than twelve just nine years ago, in part by legislative endeavors favoring generics and lower drug costs.³⁰ These measures improve access to medicines but reduce incentives to invest in new plants and technology.

Now, proposed legislation sponsored by Representative Henry Waxman (D-Calif.) would reduce the effective patent life on biologics like vaccines still further—to as little as five years under some measures. This legislation is intended to address the approval of follow-on biologics (FOBs) or so-called generic biologics. But it contains no carve-out for vaccines, even though the vaccine industry has narrower margins than those for traditional biologics. The intellectual property protections afforded under any potential legislation on FOBs is likely to reflect a compromise that affords these drugs substantially more protection than Waxman's proposed five years. Nonetheless, the unusual economics of the vaccine industry means that it should be treated separately, not lumped in with traditional biologics as part of a new legislative scheme.

At a time when we are trying to create new incentives for manufacturers to invest in this product category, we should be considering longer, not shorter, patent terms for products that embody genuine innovations and advances in intellectual property, especially products that target low-probability but potentially high-impact threats like a global flu pandemic. Newly created intellectual property has been an important factor in coaxing more investment in the development of many new vaccines. Ultimately, it is through new innovations like these that we will be able to thwart the risk from pandemic flu.

Preparing for future threats requires a broad armamentarium and the residual capacity to create new things quickly.

To these ends, the holy grail would be a universal flu vaccine that protects against all varieties of influenza, including pandemic strains like H1N1. The complexity of flu vaccine owes to the fact that we have to develop a brand new vaccine each year to guard against that year's circulating strains of influenza. This stands in marked contrast to vaccines against other infectious diseases, which do not vary over time, enabling the vaccines to be mass-produced and stockpiled. With flu vaccine, just-in-time delivery is required. The idea of a universal vaccine is not far-fetched, however. A universal flu vaccine that would cross-react against a broader range of influenza viruses is more than theoretically possible. Several biotech companies are working on such a product.

In the case of H1N1, a possible complication to a new vaccine is that the product will be made using the strain available now; whether that will work if the virus mutates is uncertain. A universal vaccine, by contrast, 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 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.

Steps the FDA Must Take to Improve Vaccine Readiness

Preparing for future threats requires a broad armamentarium and the residual capacity to create new things quickly. Even as we respond to the present threat, policymakers must be looking downfield at the longer-term steps we need to take to improve our readiness. Perhaps most important are those efforts undertaken by the FDA to open up pathways to products that will continue to improve capacity. A few of the steps that the FDA can take to continue to improve our preparedness deserve a high degree of attention from policymakers. First, the agency should develop guidance on the regulatory review pathway for other emerging technologies, such as DNA-based vaccines, the use of adjuvants, cell-based methods, and a universal vaccine that triggers T cell responses. Regulatory uncertainties and delays have in the past been obstacles to realizing benefits from new vaccine technologies. Additional FDA guidance may require some new investments in the FDA's scientific capacity. The FDA needs to develop the capacity to play a more proactive role in providing advice on the development and testing of these important technologies.

Once vaccine is available, it is the FDA's responsibility to make sure that the products are potent and free from potential contaminants. Impurities in the egg-based manufacturing process create health risks and have triggered some recent vaccine shortages. Rapid assays are necessary to control manufacturing quality and accelerate the process for releasing lots of vaccines after they are manufactured. The FDA needs to work with manufacturers to develop standardized assays for the rapid assessment of vaccine potency, quality, safety, and potential contamination. Many current assays are outmoded and difficult to perform. Since the FDA sets the standards for testing and certifying new vaccine lots, the agency needs to play a key role in directing the science to develop better tools for

assuring that new lots of vaccine are safe and effective. This also includes tools for establishing the standards for vaccines produced using new techniques.

More broadly, we need to invest—through federal grants if necessary—in additional facilities for manufacturing flu vaccine, in particular cell-based facilities. These plants could be scaled quickly to enable rapid production of a pandemic vaccine. A certain amount of this production capacity needs to be maintained domestically. In a full-blown pandemic, with a very deadly strain of flu causing mass casualties, it is hard to envision that foreign nations would allow limited supplies of potentially life-saving vaccines to be shipped outside their borders. The reaction to H1N1, an infection that is turning out to be milder than first feared, demonstrates how quickly international panic can set in, prompting governments to take extraordinary and sometimes severe measures, such as China's decision to place Mexican visitors under extended, involuntary quarantines.³¹ In a full-blown pandemic, we can expect vaccine-manufacturing facilities to be nationalized. Much of the flu vaccine production capacity exists outside the United States. The creation of more domestic capacity for rapid vaccine production should be viewed as a strategic asset.

Finally, the development of countermeasures will require an embrace of new technology. One of the most significant impediments to these investments remains an antitechnology and anti-drug industry bias that permeates many policy decisions, thwarting innovation and targeting new therapeutics. One of the external ringleaders of this anti-industry bias is Public Citizen chief Sidney Wolfe, who in 1999 said of Relenza, the antiviral drug that is being deployed as a potential backstop against swine flu, "This drug should never have been approved. The benefits are close to zero."³² That type of unfortunate miscalculation—and lack of foresight—too often holds prominence in policy considerations. Preparing for future threats will require vision and accommodation in our embrace of new technologies and their uncertainties.

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