Mitigating the Impact of Pandemic Influenza through Vaccine Innovation

The Council of Economic Advisers

September 2019

Executive Summary

September 2019

This report estimates the potentially large health and economic losses in the United States associated with influenza pandemics and discusses why the most commonly used vaccine production technologies are unlikely to mitigate these losses. We estimate the value of new vaccine technologies that would make vaccines available more quickly and likely improve their effectiveness in moderating the risks of pandemics. We discuss why private market incentives may be insufficient to develop new vaccine technologies or promote the uptake of existing, faster but more expensive technologies, despite their large expected value to society. And we argue that increased utilization of, and investment in, these new technologies—along with public-private partnerships, to spur innovation—may be valuable to decrease the impact of both pandemic and seasonal influenza.

Every year, millions of Americans suffer from seasonal influenza, commonly known as "the flu," which is caused by influenza viruses.[1] A new vaccine is formulated annually to decrease infections resulting from the small genetic changes that continually occur in the most prevalent viruses and make them less recognizable to the human immune system. There is, however, a 4 percent annual probability of pandemic influenza resulting from large and unpredictable genetic changes leading to an easily transmissible influenza virus for which much of the population would lack the residual immunity that results from prior virus exposures and vaccinations. The Council of Economic Advisors (CEA) finds that in a pandemic year, depending on the transmission efficiency and virulence of the particular pandemic virus, the economic damage would range from $413 billion to $3.79 trillion. Fatalities in the most serious scenario would exceed half a million people in the United States. Millions more would be sick, with between approximately 670,000 to 4.3 million requiring hospitalization. In a severe pandemic, healthy people might avoid work and normal social interactions in an attempt to avert illness by limiting contact with sick persons. By incapacitating a large fraction of the population, including individuals who work in critical infrastructure and defense sectors, pandemic influenza could threaten U.S. national security.

Large-scale, immediate immunization is the most effective way to control the spread of influenza, but the predominant, currently licensed, vaccine manufacturing technology would not provide sufficient doses rapidly enough to mitigate a pandemic. Current influenza vaccine production focuses on providing vaccines for the seasonal flu and primarily relies on growing viruses in chicken eggs. Egg-based production can take six months or more to deliver

[1] In this report, we use the terms "influenza" and "flu" interchangeably.

substantial amounts of vaccines after a pathogenic, influenza virus is identified—too slowly to stave off the rapid spread of infections if an unexpected and highly contagious pandemic virus emerges.

Egg-based production can also diminish vaccines' efficacy in protecting against influenza infection in both seasonal and pandemic years. Influenza viruses must be adapted to grow in chicken eggs, which can lead to modifications in their surface proteins (antigens) so that the vaccine prepared from them may not match the circulating influenza viruses well. In addition, the length of time needed for egg-based production may impair vaccine efficacy in two ways: the virus selected for vaccine manufacture may no longer be the predominant circulating virus six months later; or, even if the selected virus remains the predominant circulating virus, it may mutate between the time it is identified and the time the vaccine is available six months later, making the vaccine less effective. During the severe 2017–18 influenza season, the overall effectiveness of the vaccine against the circulating viruses was 38 percent. The vaccine created for the last pandemic, which occurred in 2009–10, was 62 percent effective in protecting people under age 65 years and 43 percent effective for those age 65 and older—the age group at highest risk of medical complications and death from influenza. And in 2014–15, when there was a mismatch between the virus used for the vaccine and the predominant circulating virus, the vaccine was only 19 percent effective.[2]

Improving the speed of vaccine production and vaccine efficacy are both important goals to mitigate pandemic risks and may also decrease the costs of seasonal influenza. Our analysis shows that innovation to increase the speed of vaccine production is key. Improving vaccine efficacy alone will be of little value in a pandemic if, as is the case with current egg-based production, the vaccine only becomes available after a large number of infections have occurred. Improving efficacy only yields value after greater speed has been achieved.

The CEA finds that technologies that could deliver sufficient doses of vaccine at the outset of an influenza pandemic could produce about a $730 billion benefit for Americans over the course of an average pandemic, primarily due to the prevention of loss of life and health. Combining this increase in production speed with a 30 percent increase over the vaccine effectiveness seen in the last pandemic (2009–10) would generate a larger benefit of about $953 billion— about one half the cost of an average pandemic. The benefits dissipate quickly, however, with each week of delay in the vaccine's availability, as the number of unexposed people to protect diminishes. The cost of a 1-week delay at the baseline vaccine effectiveness from the last pandemic is $41 billion per week, on average, for the first 12 weeks; falls to $20 billion per week for the next 12 weeks; and disappears entirely if the vaccine's availability is

[2] We use "efficacy" as a general term to describe how well a vaccine prevents infection and "effectiveness" to describe how well the vaccine performed in historical studies of previous influenza epidemics.

delayed by more than 39 weeks, because the outbreak would be over before the vaccine prevented new infections. Adding a 30 percent improvement to the vaccine effectiveness seen in the last pandemic makes the per-week cost of delay $53 billion over the first 12 weeks, on average, falling to $26 billion over the next 12 weeks.

The expected value of having a vaccine available at the outset of a pandemic—that is, the savings discounted by the 4 percent annual probability of having a pandemic—is $29 billion, or $89.63 per American. Adding a 30 percent increase to the baseline pandemic vaccine's effectiveness to the faster production increases the expected value to $38 billion, or $117.07 per American. The expected per capita value from increasing the production speed for pandemic vaccines is over four times the current per-dose cost for egg-based vaccines.

Newer technologies, like cell-based or recombinant vaccines, have the potential to cut production times and improve efficacy compared with egg-based vaccines and are currently priced below the expected per capita value of improved production speeds for pandemic vaccines. But these existing technologies have not yet been adopted on a large scale. Besides improving pandemic preparedness, new vaccine technologies may have an additional benefit of potentially improving vaccine efficacy for seasonal influenza. We estimate the economic benefits that these new technologies could generate for each seasonal influenza vaccine recipient, and find that the benefits are particularly compelling for older adults (65+) who are at high risk of influenza complications and death.

We discuss why the private market has not embraced these newer vaccine production technologies and the lack of private incentives to develop and utilize improved vaccine production technologies that could better mitigate pandemic risk. First, there is a key misalignment between the social and private returns from medical research and development (R&D) and capital investment in pandemic vaccines. R&D and investment costs are only recouped by sales when the pandemic risk occurs. Part of the value of vaccines that can mitigate future pandemic risks, however, is their *insurance value* today that provides protection against possible damage. This insurance value accrues even if the pandemic does not occur in the future, and it implies that the social value of faster production and better vaccines is much larger than its private return to developers. This divergence leads to an underprovision in vaccine innovation because it does not get rewarded for its insurance value. Second, pandemics represent a risk with a small probability of occurring but with large and highly correlated losses across the population. The rarity of influenza pandemics and the fact that the last serious one in this country occurred a hundred years ago may lead consumers and insurers to underestimate the probability and potential impact of a future influenza pandemic. Moreover, the risk cannot be effectively pooled because everyone is at risk concurrently.

Although vaccine innovation is not currently rewarded for its insurance value, public-private partnerships created under a 2006 statute have been key in the development of the newer vaccine production technologies that offer the prospect of improved seasonal influenza vaccines and the accelerated timelines needed for improved pandemic preparedness. Push incentives like public-private partnerships combined with pull incentives—such as the government's preferential purchase of vaccines produced domestically with newer, faster technologies—that may create more efficacious seasonal vaccines, especially for older people, can promote additional cost-effective innovation and lessen the impact of future pandemics.

Introduction

One hundred years ago (1918–19), an influenza pandemic sickened 500 million people worldwide (about a third of the world's population), killing an estimated 50 million, including 675,000 Americans (Taubenberger and Morens 2006). In that year, the average U.S. life expectancy fell by 12 years (CDC 2018h). Although our ability to combat influenza viruses has greatly improved since then—thanks to the availability of flu vaccines, better public health measures, and antiviral and antibiotic medications—current technology would still be inadequate to combat another severe influenza pandemic.

Influenza is a familiar disease in the United States, with an annual epidemic known as the seasonal flu usually peaking between December and February. Small mutations in seasonal influenza viruses from year to year change the viruses' surface proteins (antigens) that the human immune system recognizes. As a result of these changes, along with natural decreases in peoples' antibody levels over time, the residual population immunity due to prior infection or vaccination is incomplete. Seasonal influenza remains a serious public health problem, causing widespread illness and even death, and exacting substantial economic losses. To lessen the impact, large-scale immunization campaigns are undertaken yearly in the U.S. At the end of February of each year, government health authorities analyze global data sets and identify the influenza viruses that are expected to prevail the following flu season. Private vaccine manufacturers start production with the goal of delivering vaccines against the three or four most likely circulating viruses to healthcare practitioners by early fall.

In contrast, pandemic influenza is more sporadic. Over the past 100 years, there have been only four pandemics, with the most recent instance in 2009, suggesting a 4 percent chance of one occurring in any given year (Uyeki, Fowler, and Fischer 2018). Pandemic viruses have had larger antigenic changes than seasonal influenza viruses. As a result, the population largely lacks residual immunity. Easily transmissible viruses will spread rapidly from person to person, infecting a large fraction of the population in a short period with what can be a more severe form of influenza. Tens of millions of people could become ill, with many requiring hospitalization; and a significant number—especially among the vulnerable elderly population—could die. Aside from the high costs associated with the high rates of illness, missed work, hospitalizations, and deaths, a severe pandemic influenza could disrupt the government's vital defense and security functions by incapacitating large numbers of people with nonfatal and fatal illness and changing the daily behaviors of healthy people who seek to avoid exposure to infection. Because the infection will spread rapidly during the early weeks of a pandemic, when there is a large pool of unexposed people, it is imperative to find ways to mitigate the impact of a pandemic influenza through an early and effective immunization campaign.

Unfortunately, the United States is unprepared to deliver a sufficient number of vaccine doses quickly enough to stop the rapid initial spread of a pandemic virus. Current vaccine production primarily utilizes viral replication in chicken eggs, which can take six months or more to produce substantial doses of vaccine. Egg-based production may also diminish vaccine efficacy in preventing the spread of infection and illness in both pandemic and seasonal influenza. Viruses must be adapted to grow in chicken eggs, so the vaccine prepared from them may not match the original viruses selected for vaccine production. In addition, the lengthy production process can decrease efficacy because of a possible vaccine virus mismatch—the candidate viruses selected for seasonal vaccine manufacture in February may no longer be the predominant circulating viruses in the fall season. Moreover, even if the candidate virus is correctly identified, a circulating virus can change between the time it is first identified and the time the vaccine becomes available six months later.

This report estimates the large potential losses to the United States associated with this slow production of vaccines in case of an influenza pandemic. We estimate the value of faster vaccine production technologies and improved vaccine efficacy to mitigate pandemic risks and argue that public-private partnerships along with preferential government purchases of vaccines prepared with newer, faster production technologies may be valuable to overcome the misalignment between private and social returns in the development of adequate risk mitigation for pandemics.

To estimate the value of faster production capability, we used infection propagation scenarios, historical estimates of vaccine effectiveness, and the existing capacity for administering vaccines based on published papers and inputs from the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Office of the Biomedical Advanced Research and Development Authority (BARDA). Our main finding is that improving vaccine production speed is the key to mitigating the effects of a pandemic, because under most pandemic scenarios, the predominant egg-based production only delivers vaccines after the peak in influenza infections. Improving the efficacy of vaccines interacts with speed by adding more value the more quickly the vaccines can be produced.

Technologies that could deliver sufficient doses of vaccine at the outset of a pandemic when there are only a small number of infected people could produce about $730 billion in benefits at the level of vaccine effectiveness seen in the last (2009) pandemic in an average pandemic year. Combining this increase in production speed with a 30 percent improvement in the vaccine effectiveness seen in the last pandemic would increase the benefits to about $953 billion. But these savings decline each week that vaccine availability is delayed beyond the onset of the pandemic. The average savings forgone per week of delay during the first 12 weeks with no improvement in efficacy is $41 billion, declining to $20 billion per week during the following 12 weeks. Adding a 30 percent improvement in the effectiveness seen in the last

pandemic brings the average savings forgone per week of delay during the first 12 weeks is $53 billion, declining to $26 billion during the following 12 weeks. Savings disappear after week 39, as the pandemic would run its course without vaccine intervention.

The large losses associated with delays in vaccine availability during an influenza pandemic suggest that developing and utilizing faster vaccine production technologies would have great value. Factoring in the 4 percent annual probability of a pandemic occurring in a given year generates an expected savings of $29 billion from faster production that makes vaccines available at the outset of a pandemic and $38 billion from faster production, plus a 30 percent improvement over baseline effectiveness. On a per capita basis, this translates into $89.63 and $117.07 in value, respectively. The current price per dose to adults for standard egg-based vaccines ranges from $17.84 to $19.77, and the price of vaccines made with newer, existing technologies that could increase production speed ranges from $22.79 to $53.37. Hence, utilizing existing, faster vaccine production technologies and developing additional faster production technologies, even if they were a bit more expensive than current vaccines, would make economic sense.

Nevertheless, the development of, and demand for, faster vaccine production technologies have lagged. Newer, existing technologies, like cell-cultured or recombinant vaccines, have the potential to cut production times compared with egg-based vaccines, but they currently only account for 10 to 15 percent and 1 to 2 percent of the market, respectively. In addition to improving pandemic preparedness, new vaccine technologies may have an additional benefit of improving vaccine effectiveness for seasonal flu.

In the face of this slow development, we discuss the lack of appropriate market incentives for developing faster vaccine production technologies to decrease pandemic risk. Part of the value of vaccines that can mitigate future pandemic risks is through their insurance value today. Just as life insurance benefits the vast majority of buyers who survive their policy, being insured against pandemic risk through the development of faster vaccine production and more effective vaccines would still be beneficial in the years when pandemics did not emerge. This insurance value implies that the social return from faster and more effective vaccines is larger than their private return to developers. Because private vaccine innovation currently does not get rewarded for this insurance value, we argue that public-private R&D partnerships and increased government purchase of vaccines produced with faster technologies that may also be more efficacious, will enhance welfare. This combination of what many term push and pull

incentives can promote cost-effective innovation and the availability of better vaccines for both seasonal and pandemic influenza.[3]

The rest of the report is organized as follows. The first section describes in more detail the differences between seasonal and pandemic influenza and estimates the losses associated with each, given current vaccine technology. The second section describes the barriers to improving influenza vaccine effectiveness created by the currently prevalent, egg-based vaccine production, and in particular describes why its lengthy production process makes it inadequate for combating pandemic influenza. The next section describes how outcomes can be improved through innovation that speeds up vaccine production and improves vaccine effectiveness over previous years, and by increases in the percentage of people vaccinated. We calculate the potential cost savings in a given pandemic year and the expected savings over time for improved production technologies. The fourth section describes new vaccine technologies that may address the problem of pandemic influenza by shortening production times and produce more effective vaccines than egg-based production for both pandemic and seasonal influenza. We provide our estimates of the value of switching vaccine production to the newer technologies in seasonal influenza years in the subsequent section. The following section discusses the difference in private versus social returns to explain why private markets may fail to provide the innovation needed to improve pandemic influenza preparedness. The final section describes how public-private partnerships have led to the development of the newer, faster vaccine and production techniques and how these partnerships and other government actions can be helpful in promoting innovation and the widespread adoption of new vaccine production technologies.

Estimating the Costs of Seasonal and Pandemic Influenza with Current Vaccine Technologies

This section describes the differences between seasonal and pandemic influenza. It then estimates the annual cost of each given the current, predominant vaccine production technology.

[3] "'Push incentives' that lower the cost of drug research and development are widely used by governments to support new antibacterial discovery. 'Pull incentives,' which provide a known return on investment and reward successful development, are increasingly viewed as viable mechanisms to engage industry to develop new antibacterial drugs" (CDC 2017b). Also: "Incentives used to engage the participation of commercial parties are generally thought of as either 'push' or 'pull' incentives, with push funding inputs, and pull funding or rewarding outputs" (Institute of Medicine 2010).

The Nature of Seasonal and Pandemic Influenza

Influenza, or "the flu," is caused by an infection with a virus that is endemic—that is, one permanently present in some form (but with some variation) in humans and animals. The annual "seasonal flu" typically circulates in the United States from October to May, peaking between December and February (CDC 2018d). Only some of the people who come in contact with the viruses that are circulating that season will contract influenza, and most of those who do will fully recover. However, influenza can cause serious illness, leading to hospitalization and even death, especially among vulnerable populations like senior citizens, young children, pregnant women, and people with certain chronic medical conditions (Grohskopf et al. 2018).

An influenza pandemic is the worldwide spread of a new influenza virus that is different than recent, commonly circulating seasonal influenza viruses. Rates of illness, serious complications, and mortality are higher than for the usual seasonal influenza. In the last 100 years, there have been four major influenza pandemics leading to substantial deaths worldwide: the 1918 pandemic, popularly (but misleadingly) known as the "Spanish Flu," with more than 50 million dead; the 1957 "Asian Influenza," with more than 1 million dead; the 1968 "Hong Kong Influenza," with 1 million dead; and the 2009 "Swine Flu," with 151,700 to 575,400 dead (CDC 2018i).

The difference between the seasonal influenza that we experience every year and a pandemic influenza that we experience infrequently results from the degree of change in the genetic composition of the influenza virus. Every year, mutations in the influenza virus's genetic material, or ribonucleic acid (RNA), change the protein (antigens) on the surface of the virus, which enables the virus to partly evade the immunologic protections people have developed from previous flu vaccinations or virus exposures. Usually, these changes are small, and are described as "antigenic drift." Antigenic drift usually causes enough change in seasonal influenza viruses so that seasonal flu vaccines are updated annually. Large, abrupt changes in the influenza virus's genetic makeup that cause larger changes in the virus's surface proteins are called "antigenic shift." Antigenic shift produces a virus to which most people have limited immune memory, and therefore have little or no immune protection from infection. As a result, the virus has the potential to infect people easily and spread from person to person in an efficient and sustained way. Though only certain groups (e.g., infants, the elderly, and people with underlying medical conditions) are at high risk of serious disease during seasons when the virus has undergone antigenic drift, antigenically shifted viruses put all ages and previously healthy people at risk of serious complications (CDC 2018f). When a virus has undergone an antigenic shift, spreads easily from person to person, and causes serious illness in a broad range of persons, it produces a pandemic (CDC 2017a; NIH 2017).

There are four types of influenza viruses: A, B, C, and D. Only influenza A and B are common causes of disease in humans, and only type A viruses have the potential to cause a pandemic because type B viruses do not undergo antigenic shift (CDC 2017a). Influenza A viruses are divided into subtypes based on the proteins (hemagglutinin, H; and neuraminidase, N) on the surface of the virus. There are 18 known H subtypes and 11 known N subtypes. Each subtype is further divided into clades. Aquatic birds and other animals are hosts to influenza A viruses that do not normally infect people. Random mutations lead to antigenic drift in the viruses' H and N proteins. However, larger genetic changes lead to antigenic shift, for example, when nonhuman viruses exchange genes with one another and with human viruses to gain the ability to infect humans.

The Annual Cost of Seasonal Influenza

In this subsection, we derive the cost estimates from published papers that were based on surveys and medical spending data. These estimates of the cost of medical care, lost productivity, and fatalities for the seasonal flu will allow us to make cost estimates for pandemic flu later in this report and to quantify to what extent market incentives could help move vaccine production toward improved production technologies. For the purposes of this estimation, whenever applicable, we adjust the cost estimates from previously published papers for inflation to express them in 2018 dollars. Finally, whenever the age brackets presented in a paper do not fully correspond to the age brackets used in this report, we use data for the adjacent/overlapping age brackets and use population-based weights to adjust the numbers for the age brackets presented in this report. The distribution of the U.S. population by age is from the Census Bureau's estimates for 2016.

Our main cost estimates come from Molinari and others (2007), who estimated the cost of seasonal influenza to the United States economy and obtained their risk and cost estimates from the meta analysis of papers published in academic journals and other public sources. Their paper estimated the costs for the following age groups: 0–4, 5–17, 18–49, 50–64, and 65 and older. We also use these age groups in this part of our analysis.

The probability of getting the flu in a given year is called the clinical "attack rate," which is a measure of contagiousness and population immunity.[4] Because young children experience more physical contact with other people and have less acquired immunity from past influenza, they face the highest risk of flu infection and illness. The elderly may also have a mild increase in infection risk due to the erosion of their immune response.

[4] "Attack rate" is also sometimes used to designate the probability of being infected by the influenza virus, and would include those who become sick and show symptoms (clinical attack rate) plus those who remain asymptomatic.

A person who becomes ill with the flu can have several possible outcomes. The person may or may not decide to seek medical help, such as an outpatient visit. A subset of ill people require hospitalization, and some of these people die. As shown in table 1, these adverse scenarios are unevenly distributed across age groups, with the youngest and the oldest age groups generally being at highest risk. Additionally, each age group has a proportion of "high-risk" individuals who have other medical conditions that make the flu illness more serious and more likely to result in complications, resulting in higher medical costs. The percentage of people at high-risk generally rises with age.

Table 1. Seasonal Influenza: Associated Risks

Measure	Age group					
	0–4	5–17	18–49	50–64	65+	Population-weighted average
Proportion of U.S. population (%)	6.2	16.6	42.4	19.6	15.2	100.0
Attack rate (%)	20.3	10.2	6.6	6.6	9.0	8.4
Proportion (high-risk) (%)	5.2	10.6	14.9	33.0	51.2	22.7
Probability (outpatient visit)						
Low-risk individuals (%)	45.5	31.8	31.3	31.3	62.0	36.9
High-risk individuals (%)	91.0	63.5	62.5	62.5	82.0	67.4
Probability of hospitalizations (%)	1.4	0.1	0.4	1.9	4.2	1.3
Probability of death (%)	0.004	0.001	0.01	0.1	1.2	0.2

Sources: Molinari et al. (2007); CEA calculations.

When estimating the costs incurred due to illness, we again use data from Molinari and others (2007) and inflate the costs to 2018 dollars. For the value of lost productivity, we multiply the number of workdays missed by the value of a productive day ($151.88 per day).[5] Medical costs include the cost of medicine and the cost of a doctor's visit or hospital stay. They are summed for each person, and cases are grouped by the highest level of care used (e.g., each hospital case includes inpatient, outpatient, and pharmaceutical costs for that person). Table 2 presents cost estimates associated with various flu illness outcomes across all age groups. It presents the fact that both people who recover from the flu (the first three categories) and people who go on to die (the fourth category) incur medical costs and productivity costs from missing work while ill.

[5] This is an update to 2018 of the value used by Molinari et al. (2007). Lost productivity attributed to children and the elderly captured lost days of work of their caretakers, who are typically parents and family members.

Table 2. Costs Associated with Various Flu Illness Outcomes, 2018 Dollars

Outcome	Age group					Population-weighted average
	0–4	5–17	18–49	50–64	65+	
Case not medically attended						
Medical cost (all risk)*	5.08	5.08	5.08	5.08	5.08	5.08
Lost productivity (all risk)	151.88	75.94	75.94	75.94	151.88	92.20
Outpatient visit						
Low-risk medical costs	282.62	160.77	211.54	253.85	409.54	245.95
Low-risk lost productivity	151.88	151.88	151.88	303.77	455.65	227.93
High-risk medical costs	971.39	1,098.31	1,226.92	1,240.46	805.54	1,128.22
High-risk lost productivity	911.31	607.54	303.77	607.54	1,063.19	566.98
Hospitalization						
Low-risk medical costs	18,412.33	25,408.34	32,174.19	37,745.28	19,378.64	29,342.16
Low-risk lost productivity	1,215.07	1,366.96	1,822.61	1,974.50	1,974.50	1,762.30
High-risk medical costs	138,085.70	70,938.24	80,760.40	69,907.62	28,346.19	72,548.85
High-risk lost productivity	4,708.41	3,493.34	3,189.57	3,645.22	2,733.92	3,353.56
Fatalities						
Low-risk medical costs	48,768.98	48,768.98	129,184.15	200,665.62	70,989.01	115,991.85
Low-risk lost productivity**	1,215.07	1,366.96	1,822.61	1,974.50	1,974.50	1,762.30
High-risk medical costs	453,461.15	453,461.15	128,429.38	201,117.47	55,864.84	205,686.86
High-risk lost productivity**	4,708.41	3,493.34	3,189.57	3,645.22	2,733.92	3,353.56
VSL (millions)***	5.76	5.76	12.34	7.75	5.29	8.87

Sources: Molinari et al. (2007); Aldy and Viscusi (2008); CEA calculations.
Note: Cost estimates shown are per person per influenza incident, assuming the individual is symptomatic.
*Costs for those who did not seek medical attention assumes average over-the-counter medication costs per case.
**Molinari did not calculate the lost productivity (work days missed) while ill of the eventual fatalities. We used the lost productivity costs incurred by the hospitalization group as a lower-bound value.
***Value of Statistical Life (VSL)

In addition, we must account for the value of the lives lost. For influenza fatalities, we assign a monetary value based on calculations of the value of a statistical life (VSL) for different age groups derived by Aldy and Viscusi (2008).[6] Using the probabilities given in table 1 and the

[6] The CEA (2017) applied a similar approach to valuing fatalities adjusted for age brackets in evaluating the opioid epidemic. The VSL summarizes willingness to pay for small changes in the risks of premature death (OMB 2003). This measure is widely used by government agencies to evaluate policies. We use the VSL to place a monetary value on the extra risks of death due to the influenza virus. Throughout this report we refer to the monetary value of the fatality risks as a component of the "costs" of influenza and to the monetary value of reductions in fatality risks as "cost savings" or "benefits."

direct costs of various outcomes given in table 2, and adding in the cost of fatalities using age-based VSL valuations, we calculate the cost of seasonal influenza. Given the 2017 U.S. population of 325.7 million, the probability distributions presented in table 1 suggest that a typical seasonal flu would cause illness in 27 million; of these, 368,000 will need to be hospitalized but will survive and 59,000 will die. The vast majority of the fatalities, about 89 percent, will be among the population over 65 years of age. We estimate the total cost of seasonal influenza to be $361 billion per year, in 2018 dollars, due largely to the value of lives lost.[7] Of this total cost, $30 billion is incurred as the immediate cash cost, which equals the sum of medical expenditures and lost productivity due to work missed while sick.[8]

Cost Estimates of Pandemic Influenza

If pandemic influenza were to hit the United States, the assumptions from table 1 would need to be revised because pandemic influenza would result in a higher attack rate and a greater risk of adverse outcomes compared with seasonal influenza. Relying on Biggerstaff and others (2015) and Meltzer and others (2015), who estimated hypothetical pandemic influenza scenarios informed by past pandemic flu outcomes, we consider four pandemic flu scenarios: those having a high or low attack rate (which we refer to as high/low contagiousness scenarios) and those having a high or low risk of medical complications, including death (high/low severity rate).

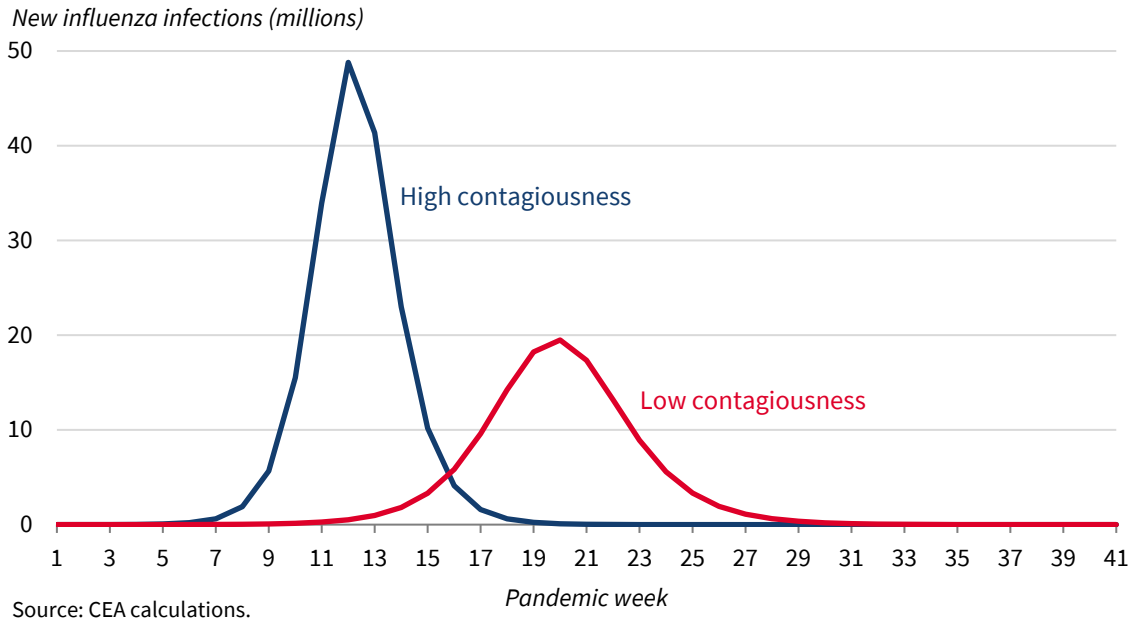
For the high and low contagiousness scenarios, we assume population-weighted average attack rates of 30 percent and 20 percent (Biggerstaff et al. 2015). Rates vary by age group (Meltzer et al. 2015). Though overall attack rates are increased compared with seasonal influenza, the attack rate for pandemic flu is lower among older people relative to other age groups because the elderly may have already experienced a similar flu strain in the past and have residual immunity. In the high-contagiousness scenario, the rates range from a high of 39 percent in the 11–20 age group down to a low of 20 percent among people over 60. In the low-contagiousness scenario, rates range from a high of 29 percent in age 11–20 group down to a low of 12 percent for people over 60. In the high-contagiousness scenario, each infected person infects another 1.65 previously unexposed people, and in the low-contagiousness scenario, each infected person infects another 1.3 previously unexposed people, on average.

[7] Molinari et al. (2007) estimated this cost to be significantly lower, largely because they used lower VSL assumptions and their estimate was 2003 dollars.

[8] There is also the possibility of lost productivity during epidemics resulting from healthy people avoiding work out of fear they will be infected by coworkers. Molinari did not include this cost. This sort of absenteeism may be especially common among healthcare providers (Qureshi et al. 2005) and would be most pronounced in a severe pandemic. Because reliable estimates of how big this effect is during seasonal and pandemic influenza epidemics are not available, we do not add this effect to the estimates we derived from Molinari.

Figure 1 plots the so-called pandemic curve, which is the evolution of new infections over weeks that follow, for both scenarios. Following Biggerstaff and others (2015), we assume that in week 0, at the start of the flu pandemic in the United States, the first 100 people are infected.

Figure 1. New Infections per Pandemic Week without Vaccination



Source: CEA calculations.

In the figure, both plots have a bell shape. At the outset, infected people come into contact with a large number of previously unexposed people who lack immunity to the virus, some of whom become infected. As the pandemic progresses, a higher fraction of the population would have been exposed and developed immunity, and there are fewer new people to become infected. For this reason, the number of new infections initially increases, peaks, and then declines with time.

In the high-contagiousness scenario, the number of newly infected people peaks in week 12 and then gradually declines to zero by week 27. The total number of infected people equals 187,959,100 in the United States. In the low-contagiousness scenario, the number of new infections peaks later, in week 20, and gradually declines to zero by week 42. The total number of infected people is also lower than for the high- contagiousness scenario and equals 127,346,700.

Following Biggerstaff and others (2015), we break the higher risks of adverse outcomes (hospitalizations and fatalities) in pandemic influenza into low- and high-severity scenarios. Biggerstaff and colleagues calculated the risk of hospitalization and death by age group based

on historic pandemics.[9] These age groups were different than the groups utilized by Molinari and others (2015) for the seasonal flu. In addition, Biggerstaff and colleagues assumed that half of all infections would be asymptomatic and therefore, only applied the risk of adverse outcomes to the half of infected people who were sick (symptomatic) with the flu. The probabilities for low- and high-severity scenarios are presented in table 3.

Table 3. Probability of Hospitalizations and Fatalities Conditional on Pandemic Influenza Infection

Severity		Age group			Population-weighted average
		0–19	20–59	60+	
Low	Probability of hospitalization (%)	0.08	0.23	3.48	0.88
	Probability of death (%)	0.01	0.02	0.28	0.07
High	Probability of hospitalization (%)	0.30	0.90	14.00	3.53
	Probability of death (%)	0.04	0.11	1.75	0.44

Sources: Biggerstaff et al. (2015); CEA calculations.

Note: Biggerstaff's probabilities of adverse events conditional on becoming symptomatic are halved since the infected population is approximately twice the symptomatic population.

Utilizing age-weighted averages of the costs of adverse events derived from Molinari and others (2007) (table 2, supra), we estimate the total costs (fatality costs utilizing VSL, plus immediate cash costs) for the four pandemic scenarios that we have described and an average of the four. These costs, as well as the number of illnesses and fatalities, for each of the four scenarios are presented in table 4.

Nearly 54,000 to over half a million people could die in the United States. Hospitalizations, which disrupt peoples' ability to participate in the workforce, would range from 669,889 to 4,304,752. Total pandemic costs would be between $413 billion in the low-contagiousness/low-severity scenario and $3.79 trillion in the high-contagiousness/high-severity scenario, with an average total cost of $1.81 trillion. These cost numbers are substantially higher than the $361 billion total cost of seasonal flu that we estimated above. The bulk of these costs is due to the VSL values attributed to fatalities. The immediate cash costs of the pandemic (ignoring VSL) range from almost $55 billion for the low-contagiousness/low-severity scenario to $250 billion for the high-contagiousness/high-severity scenario. It is possible that absenteeism by healthy people who, fearing infection, avoid contact with sick fellow workers, could be substantial in a pandemic with high attack

[9] Biggerstaff et al. (2012) estimate the probability that a person with a flu-like illness would seek medical care using data from a large-scale telephone survey conducted by the Centers for Disease Control and Prevention (CDC) during the 2009 pandemic influenza season.

rates and illness severity, resulting in higher immediate costs. The costs imposed by disease avoidance behaviors rise with the prevalence of infectious diseases (Philipson 2000). We do not calculate these costs because there are few reliable estimates of how big this effect might be.[10]

Table 4. Cost Outcomes for the Four Pandemic Flu Scenarios

Scenario	Low contagiousness	High contagiousness
Low severity		
Number of hospitalizations	669,889	1,071,650
Number of fatalities	53,674	85,868
Total costs (billions of dollars)	412.61	649.68
Total immediate cash cost (billions of dollars)	54.76	85.14
High severity		
Number of hospitalizations	2,690,569	4,304,752
Number of fatalities	336,321	538,094
Total costs (billions of dollars)	2,399.61	3,786.14
Total immediate cash cost (billions of dollars)	158.58	250.33
Average total costs (billions of dollars)	1,812.01	
Average immediate cash cost (billions of dollars)	137.20	
Average total costs per capita (dollars)	5,563.43	
Average immediate cash cost per capita (dollars)	421.26	

Sources: Molinari et al. (2007); CEA calculations.

Current Barriers to Vaccination Programs' Effectiveness

Vaccination programs can mitigate the costs of influenza pandemics. But the impact of vaccines is limited by four factors: the speed with which vaccines can be manufactured for emergent viruses; the effectiveness of the vaccine in preventing infection; the number of doses that can be manufactured, distributed, and administered in a given period; and the percentage of the population that is vaccinated. Current methods of influenza vaccine manufacturing constrain the first three of these four factors and limit the effectiveness of vaccination programs as a response to pandemics. The low percentage of people vaccinated is another obvious problem.

Limitations of the Vaccine Manufacturing Timeline

The main method of producing flu vaccines currently in use relies on production in chicken eggs and takes six months or more to produce adequate doses of vaccine. Every year, influenza

[10] See note 8 supra.

centers in more than 100 countries conduct influenza surveillance. They select and send representative viruses to five Collaborating Centers for Reference and Research on Influenza around the world that are sponsored by the World Health Organization (WHO). After reviewing the results of the surveillance, laboratory, and clinical studies, WHO recommends which viruses to include in the vaccine for the upcoming seasonal virus season. This occurs in February for the Northern Hemisphere. In the United States, the FDA makes the final decision about which viruses to use in the vaccine (CDC 2018l).

These candidate vaccine viruses (CVVs) are altered (adapted) so that they can be grown efficiently in chicken eggs, isolated, and then provided to private vaccine manufacturers. The manufacturers replicate the CVVs in large numbers of eggs, harvest and inactivate the viruses, and then purify the viral surface proteins (antigens) for the vaccine. The FDA tests and approves vaccines before release and shipment (CDC 2018e).

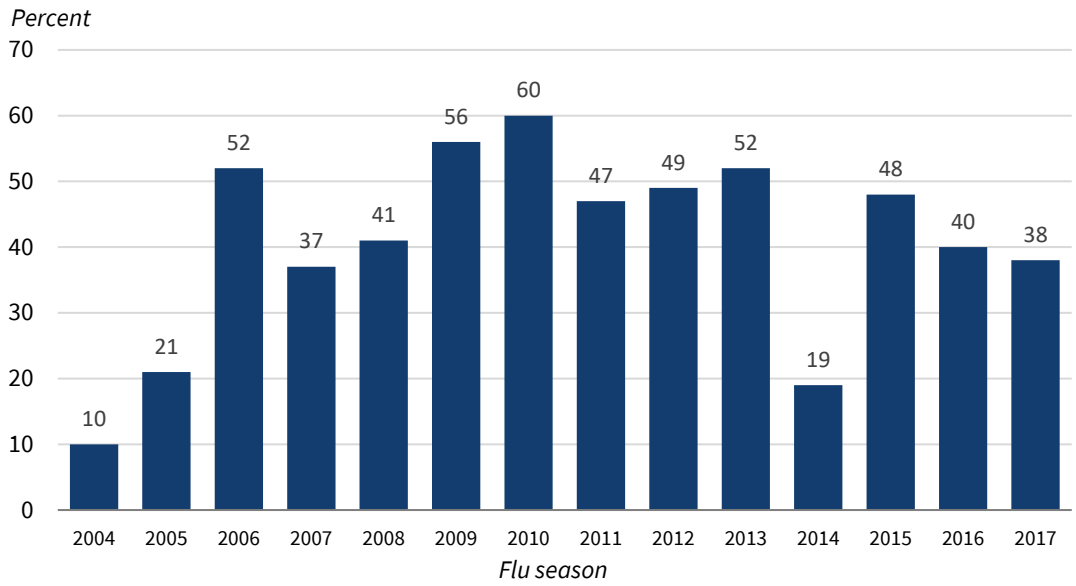
Essentially, the same 6-month, egg-based process is used to make vaccines in the case of pandemics (WHO 2009). The pandemic curves in figure 1 suggest that the vaccine would arrive too late to avert a meaningful number of infections and deaths. The experience with the 2009 A(H1N1)pdm09 pandemic is illustrative. The first human infections by the virus were noted in April 2009. Within a week, the CDC began to identify candidate viruses for vaccine manufacture. Increased disease surveillance, stockpiling of antiviral medications, and procurement of respiratory protective equipment were undertaken. In June 2009, WHO officially declared a global pandemic, and cases were reported in all 50 States and Puerto Rico. Despite efforts by the FDA and CDC to speed approval, a new monovalent vaccine for the H1N1 pandemic virus was not approved until September 15. The national vaccination program did not start until October 2009, the same month that influenza activity peaked. During the first six weeks of the program, vaccine supplies were limited, and use was targeted to high-risk populations. Widespread vaccination for anyone who wanted it only became available in December, months after the pandemic peaked (CDC 2010).

Low Vaccine Effectiveness

There is considerable variation from year to year in how much the flu vaccine reduces the risk of contracting the seasonal flu and flu-related illnesses. Figure 2 shows that over the past 14 years, influenza vaccine effectiveness has ranged between 10 and 60 percent. Much of the variability depends on which viruses predominate in a given year. For reasons that are discussed below, egg-based production is least effective against A(H3N2) viruses. Hence, during this past 2017–18 season, which was an A(H3N2)-dominated season, the egg-based vaccine was 38 percent effective overall but just 22 percent effective against the circulating A(H3N2) (Rolfes et al. 2019). The vaccine did even worse among persons 65 or older, with,

respectively, 18 percent and 17 percent effectiveness against any influenza strain and A(H3N2) viruses (Flannery et al. 2018).

Figure 2. Seasonal Influenza Vaccine Effectiveness



Source: CDC 2019.
Note: Each flu season is from October of the year indicated to May of the following year.

Although the rarity of pandemics makes it hard to determine vaccine effectiveness during pandemics, the monovalent A(H1N1) vaccine prepared during the most recent pandemic in 2009 was 62 percent effective for people less than age 65 and 43 percent effective for people age 65 and older (Borse et al. 2013).

Efficacy Problems Stemming from Egg-Based Vaccine Production

Egg-based production creates two types of problems with creating effective vaccines that match the circulating virus. First, human viruses must be adapted to grow efficiently in chicken eggs. This process may alter the CVVs' antigens so that they differ from the circulating viruses' antigens, thereby reducing the vaccine's effect. This occurs in all influenza virus types but is most evident in A(H3N2) viruses—the virus type that predominated during 22 of the last 40 flu seasons (CDC 2018n). Mutations in the genes that code for H3 are especially likely to be induced by adaptation to grow in chicken eggs, resulting in decreased vaccine effectiveness (Skowronski et al. 2014). In addition, the A(H3N2) virus grows poorly in eggs, making it difficult to obtain candidate vaccine viruses. Despite WHO's and governmental efforts to select optimal candidate vaccine viruses, "the evolution of A(H3N2) subtype viruses in recent years has resulted in viruses that limit the availability of optimal egg-based vaccine strains" (Barr et al. 2018).

Second, the length of time needed for egg-based production could reduce vaccine efficacy. There can be antigenic drift in the circulating virus between the time it is isolated and prepared for vaccine manufacture in February and the flu season the next fall. The A(H3N2) viruses are more likely to change in ways that have an impact on vaccine effectiveness than are A(H1N1) or B viruses (CDC 2018n). Another problem with long lead times is that the wrong virus could be selected for vaccine production. A pathogenic virus may not appear until later in the season, making it difficult to prepare a candidate vaccine virus in time for vaccine production. In 2014–15, mismatched H3 viruses were first detected in March, a month after the February candidate virus selection. But it did not become clear that they would be the predominant H3 virus until later in the season, and it was not clear that H3 viruses would be the predominant virus for the 2014–15 flu season until it started (CIDRAP 2014). The result was a major mismatch between the seasonal vaccine and the predominant circulating virus—and the vaccine was only 19 percent effective (see figure 2 above).

Although a mismatch between the vaccine and the so-called wild virus circulating during a flu season reduces efficacy, current vaccines still provide some protection against flu illness (CDC 2018m) and decrease the severity of the illness (CDC 2018n), due to immunologic similarity between the viruses. In addition, seasonal vaccines are designed to protect against the three (trivalent vaccine) or four (quadrivalent vaccine) viruses that are predicted to be most prevalent during the upcoming flu season. The trivalent vaccine includes two type A viruses, an A(H1N1) and an A(H3N2), and one type B virus. The quadrivalent vaccine adds a second type B. When there is a less-than-ideal match against one virus, the vaccine may protect well against the other viruses.

Mismatches and lengthy vaccine production times can become severe issues during a pandemic, when the seasonal flu vaccine that is routinely prepared will be ineffective against the newly emerged, and substantially different, pandemic virus. The 2009 A(H1N1)pdm09 pandemic virus was first detected in April—months after the seasonal vaccine viruses, including a different, seasonal A(H1N1) virus, had been selected. The bulk of the monovalent vaccine against the pandemic virus was unavailable for the first few months of the pandemic—after the peak of infections (Weir and Gruber 2016).

Low Vaccination Rates

Low vaccination rates limit a vaccine's ability to protect the public, no matter how effective the vaccine is. In the 2009 pandemic, the percentage of people vaccinated with the monovalent vaccine varied by age group from 16 to 43 percent but was only 27 percent overall (Borse et al. 2013). Over the past eight seasonal flu seasons, the percentage vaccinated for children (6 months to 17 years) averaged 58 percent, and for adults (18 and above) averaged 41 percent (CDC 2018b, 2018c). Overall, the average population-wide vaccination rate for the seasonal flu

was only 45 percent, but was higher for the most vulnerable groups, young children and older adults. Average vaccination rates for each age group over the past 8 influenza seasons (2010–11 to 2017–18) are reported in table 5. A recent survey found two categories of major reasons that people cite for not getting the seasonal flu vaccine: concerns about vaccine safety (36 percent worried about vaccine side effects and 31 percent believed the vaccine could give them the flu); and doubts about the need for and effectiveness of vaccines (31 percent say vaccines do not work well, 30 percent say they never get the flu, and 27 percent do not believe you can get very sick from the flu) (NORC 2018). These misconceptions about vaccine safety—vaccines do not cause the flu and vaccine side effects are rare, usually mild (unless there is a serious allergic reaction), and generally limited to one or two days (CDC 2018g)—and the potential seriousness of influenza infection persist despite major public education campaigns.

Table 5. Average Vaccination Rates Over the Past Eight Seasonal Influenza Years

	Age group						Population-weighted average
	0.5–4	5–12	13–17	18–49	50–64	65+	
Vaccination rate (%)	68.7	58.9	43.3	31.2	44.1	64.7	44.7

Sources: CDC 2018b, 2018c.
Note: Simple average is shown for vaccination rates by age group.

Improving Pandemic Outcomes by Improving the Speed of Production, Vaccine Efficacy, and the Number of People Vaccinated

We now revisit the pandemic flu scenarios described earlier in this report and analyze what would happen if the speed of vaccine production increased, effectiveness improved over prior years, and the percentage of the population vaccinated increased.[11] We start with the 2009 pandemic as a baseline. Vaccine production took about 24 weeks. The age group from 6 months to 9 years old received 2 vaccine doses, 4 weeks apart. Vaccine effectiveness was 0 percent after the first dose and 62 percent after the second. Every other age group received a single dose. Effectiveness was 62 percent, except for people 65 or older, for whom it declined to 43 percent. Overall, only 27 percent of the population was vaccinated (Borse et al. 2013). As noted above, this is substantially below the 45 percent average vaccination rate for the seasonal flu. Like Biggerstaff and others (2015), we assume in our calculations that during a pandemic, "demand for vaccine would be such that 80 percent of the U.S. population" would

[11] Pandemics often have multiple waves. For simplicity, we look only at the impact on the first wave. Improved vaccine availability should have maximum impact on the first wave because once it is being produced, it would be available for any subsequent waves.

be vaccinated.[12] Though 80 percent is a high figure compared with historical norms, we believe it is reasonable in the setting of a severe pandemic with high infection and illness rates. The large number of people who cite doubts that they will get the seasonal flu or that it will cause serious illness as a reason to avoid the seasonal flu vaccine (NORC 2018) would be more inclined to be vaccinated in a pandemic with high attack rates and high rates of complication. Moreover, multiple studies have demonstrated that there is high prevalence-elasticity of demand for vaccines for infectious diseases, meaning that as the prevalence of influenza rises in a pandemic, the demand for vaccine will also rise (Philipson 2000). We also allow for a 2-week delay in protection against the virus after administration of the vaccine to account for the time it takes people to mount an immunologic reaction to the vaccine. Finally, we adopt the assumption by Biggerstaff and others (2015) that 30 million vaccine doses can be administered per week.[13]

There is a well-developed, worldwide system of surveillance to uncover threatening viruses. This allows vaccine manufacture to begin before the outbreak of a pandemic, during what is officially called "the recognition interval . . . when increasing numbers of human cases or clusters of novel influenza A infection are identified anywhere in the world, and the virus characteristics indicate an increased potential for ongoing human-to-human transmission" (CDC 2014). During the 2009 pandemic, the process started within a week of the first two infections reported in the U.S.—8 weeks before the pandemic was officially declared. We use this timeline as our early virus discovery scenario. There is, however, a possibility, for natural or nefarious reasons, that a pandemic virus would not be apparent until later, when a larger number of infections are noted. Therefore, we also consider an alternate scenario—late virus discovery—where vaccine production would not begin until the onset of a pandemic, which is defined in our model as the first 100 confirmed infections (Biggerstaff et al. 2015).[14]

[12] The objectives of vaccination coverage proposed in the United States—80 percent in healthy persons and 90 percent in high-risk persons—are sufficient to establish herd immunity, while those proposed in Europe—only 75 percent in elderly and high-risk persons—are not sufficient. Current levels of annual vaccination coverage in the U.S. and Europe are not sufficient to establish herd immunity (Plans-Rubió 2012).

[13] Biggerstaff et al. (2015) studied two different scenarios: that the vaccination program could administer either 10 million doses per week, the maximum doses administered per week during seasonal flu programs; or 30 million doses per week, "an untested assumption." We utilize the higher figure on the assumption that in the event of a pandemic, resources to produce and administer vaccines will be mobilized far in excess of what is utilized for the seasonal flu. Moreover, new developments like an oral flu vaccine now in development, which are discussed below, could significantly increase the number vaccinated by making the administration easier and by appealing to patients who resist taking shots.

[14] This is officially called "the initiation interval, . . . when human cases of a pandemic influenza virus infection are confirmed anywhere in the world with demonstrated efficient and sustained human-to-human transmission." The 2005 WHO global pandemic plan describes six phases or intervals for defining a pandemic—the investigation,

In the early virus discovery scenario, innovations that increase the speed of vaccine production from the current egg-based baseline of 24 weeks down to 8 weeks would move vaccine availability from pandemic week 16 to the outset of the pandemic (pandemic week 0). Faster production in the late virus discovery scenario would move vaccine availability from pandemic week 24 to pandemic week 8.

We also consider the impact of innovation that results in a 30 percent improvement over the baseline 2009 vaccine effectiveness while keeping production speed constant or improving it.[15] A total of 30 percent is a reasonable lower bound improvement because, as we discuss below, early studies of existing recombinant vaccine production have demonstrated this improvement. In addition, it approximates the high-efficacy vaccine (80 percent) that Biggerstaff and others (2015) posit would be available in a future pandemic.[16]

Figure 3 plots the number of new infections per week with no vaccine; a vaccine using baseline egg-based production technology; vaccines using innovations that improve production speed; and vaccines where improved production speed is combined with improved vaccine effectiveness, in four different scenarios under the alternative contagiousness possibilities of a 20 percent attack rate and a 30 percent attack rate and the alternative scenarios for early and late virus discovery.[17] The area between the curves represents the number of infections averted by the current egg-based vaccine and by vaccines improved by innovations. The aggregate number of infections for the four different scenarios with early and late virus discovery and low and high contagiousness are presented in table 6.

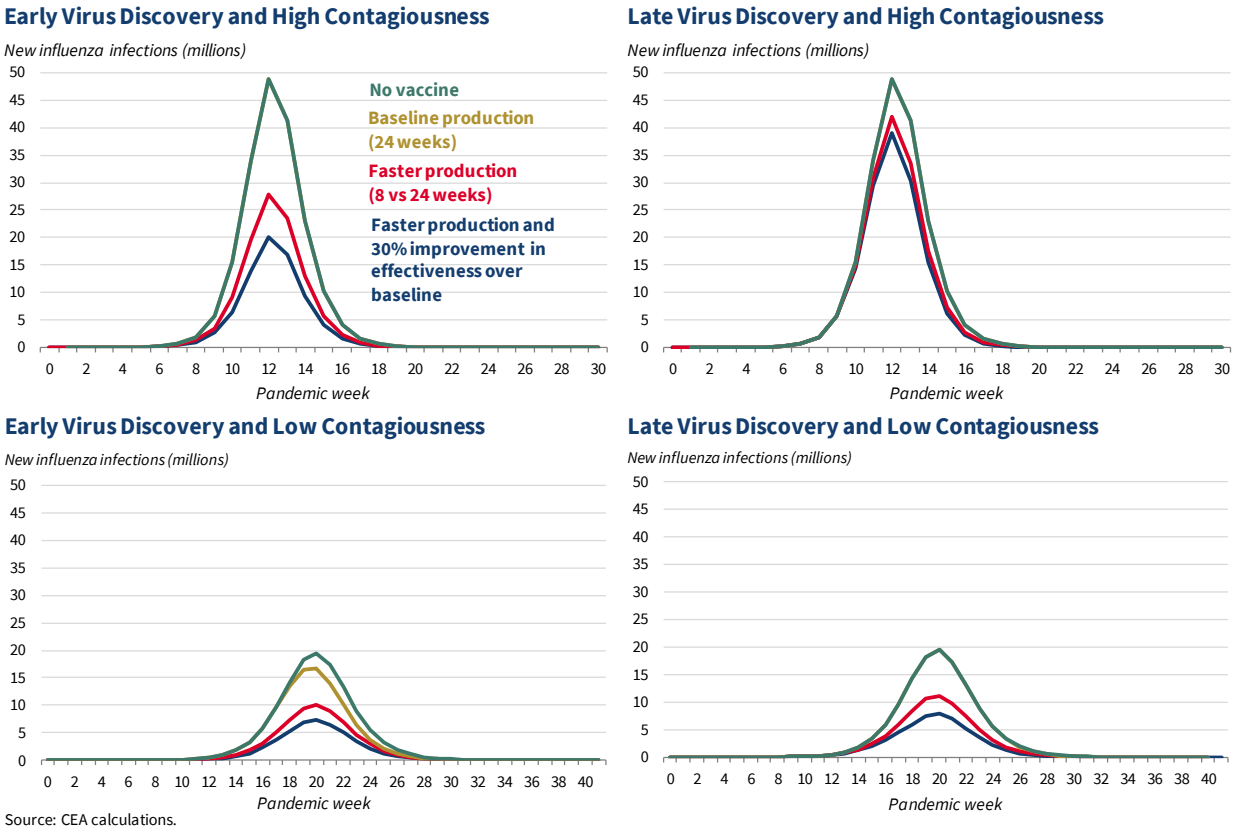
recognition, initiation, acceleration, deceleration, and preparation for subsequent pandemic wave intervals (CDC 2014).

[15] Because baseline effectiveness was zero percent for children receiving a first dose, we assume an increase of 40 percentage points in efficacy for the first dose (as assumed by Biggerstaff et al. 2015) and move from 62 to 81 percent (a 30 percent increase) for the second dose.

[16] Biggerstaff et al. (2015) studied two vaccine efficacy scenarios, the first of which had lower efficacy (62 percent) based on the vaccine effectiveness of standard, unadjuvanted, vaccine in the 2009 pandemic. Our 30 percent increase in over that effectiveness approximates his alternate high vaccine efficacy value of 80 percent, which assumed the use of high-antigen concentrations or the addition of adjuvant to vaccine that are likely to be used in a pandemic setting.

[17] A separate line for improving vaccine effectiveness at current production speeds was omitted for the sake of visual clarity. It did not differ significantly from the yellow curve representing baseline production speed and effectiveness.

Figure 3. New Infections per Pandemic Week with and without Vaccination Under Different Scenarios



Source: CEA calculations.

It is apparent that improving the speed of vaccine production is more important for decreasing the number of infections than improving vaccine efficacy. The long production time of the current egg-based vaccine limits its impact on pandemics because the vaccine only becomes available after infections peak in every scenario except the early discovery, low-contagiousness scenario where it becomes available shortly before the infections peak. Figure 3 and table 6 demonstrate that improving effectiveness at current production speeds only makes a difference in the most favorable, early discovery, low-contagiousness scenario. At current production speeds moving from no vaccine (essentially zero percent effectiveness) to our baseline effectiveness of 62 percent for people below 65 and 43 percent for those 65 and older only averts a substantial number of infections—18.97 million—in the most favorable, early discovery, low-contagiousness scenario and makes little difference in the other three scenarios. This is illustrated in figure 3, where the yellow curves for the current vaccine are not easily visualized because they are virtually superimposable on the green, no vaccine curves. The yellow vaccine curve is only visible in the bottom left panel of figure 3, the early discovery, low-contagiousness scenario. The numbers in table 6 confirm this and also demonstrate that a 30 percent increase over the baseline effectiveness alone, with no change in production

speed, makes little or no difference in the same three scenarios and only averts a substantial number of infections—about 8 million— in the early discovery, low-contagiousness scenario.

Table 6. Infections in Four Pandemic Scenarios with Adjustments for Faster Production and Improved Effectiveness

(thousands of infections)

Virus discovery	Low contagiousness	High contagiousness
Early virus discovery (vaccine available pandemic week 16 baseline)		
No vaccine	127,347	187,959
Baseline production	108,377	187,885
Improvement over baseline effectiveness	100,641	187,856
Faster production	66,792	107,657
Faster production and improved effectiveness	48,302	77,810
Late virus discovery (vaccine available pandemic week 24 baseline)		
No vaccine	127,347	187,959
Baseline production	126,873	187,959
Improvement over baseline effectiveness	126,792	187,959
Faster production	74,511	158,820
Faster production and improved effectiveness	54,912	146,908

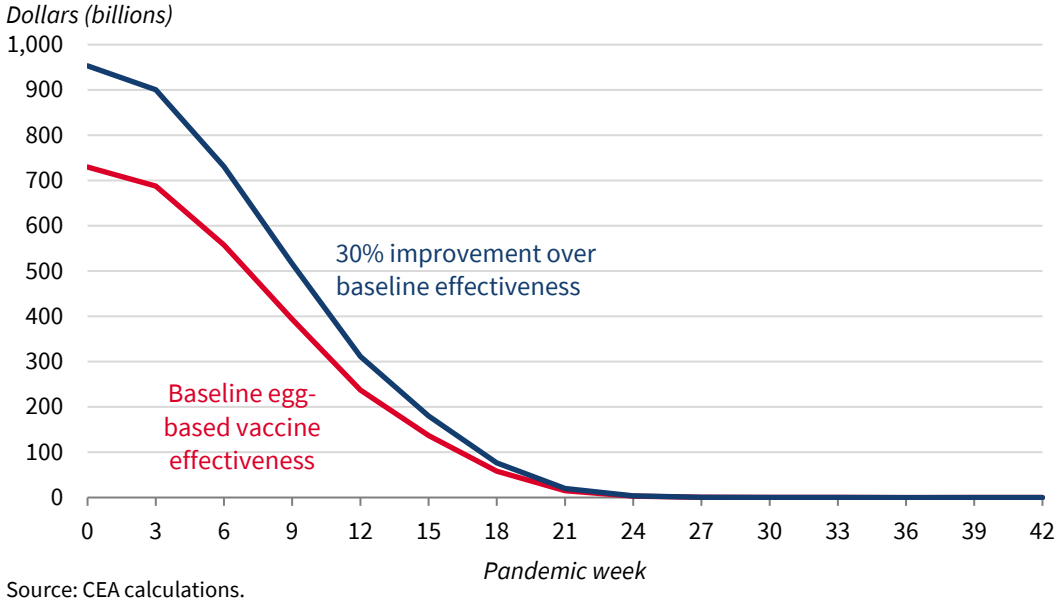
Source: CEA calculations.
Note: Faster production indicates decreasing production time from 24 weeks to 8 weeks. We assume an improved effectiveness by 30 percent.

Improving the speed of production from the baseline 24 weeks to 8 weeks with no improvement over baseline effectiveness averts substantial numbers of infections in all four scenarios. Once faster production is in place, improving vaccine effectiveness substantially reduces the number of infections in all four scenarios, as evidenced by the blue curves in figure 3 and the numbers in table 6.

Next, we calculate the benefits (cost savings) that could be achieved by week of vaccine availability starting at pandemic week 0. We assume that each of the four pandemic flu scenarios (high/low contagiousness and high/low severity) occurs with an equal probability, to generate an average number of infections, complications, and resulting costs. Figure 4 plots the benefits monetized in dollars per year, conditional on a pandemic occurring, as a function of the week in which the first 30 million vaccine doses become available. Starting with the benefits if a vaccine was available at the outset of the pandemic (week 0), we demonstrate the benefits forgone (cost) by each week of delay in vaccine availability. We plot benefits with the baseline 2009 pandemic vaccine effectiveness described above and with a 30 percent improvement over baseline effectiveness.

Figure 4 shows that with no improvement over the 2009 baseline pandemic vaccine effectiveness, making vaccines available at the outset of the pandemic could generate $730 billion in benefits. A 30 percent improvement over baseline effectiveness raises the benefits to $953 billion—or about one half of the total cost of an average pandemic shown in table 4. But these cost savings decline quickly as a function of the delay in vaccine availability relative to the start of the pandemic. They decline to $0 after week 39 because the vaccine would be too late to prevent new infections.[18] The benefits forgone per each week of delay during the first 12 weeks with baseline effectiveness is $41 billion, declining to $20 billion during the following 12 weeks. When a 30 percent effectiveness improvement is added in, the benefits forgone per each week of delay during the first 12 weeks is $53 billion, declining to $26 billion during the following 12 weeks.

Figure 4. Annual Benefits by Week of Vaccine Availability in a Pandemic



Source: CEA calculations.

To determine the value of an improvement in the speed of pandemic vaccine production, we calculate the expected cost savings resulting from making a vaccine available at the outset of a pandemic. Given the 4 percent annual probability of a pandemic occurring in a given year, we multiply the savings at pandemic week 0, illustrated in figure 4 above, by the likelihood of a pandemic. This generates an expected cost savings of $29 billion from faster production that makes vaccines available at the outset of a pandemic and $38 billion from faster production, plus a 30 percent increase over baseline effectiveness (table 7). On a per capita basis, this translates into $89.63 and $117.07 in value per American, respectively. We also calculate

[18] Because the last infections would occur in pandemic week 41, vaccines would not have any impact after pandemic week 39 due to the two weeks needed after vaccination to elicit immunity.

$112.04 and $146.34, respectively, in value per vaccinated person, assuming, as we did above, that 80 percent of the population would be vaccinated during a pandemic. These values are well above the current price per dose for standard egg-based vaccines, which range from $17.84 to $19.77 (CMS 2018), and suggest that society should be willing to pay a premium over four times more than current vaccine prices for improved influenza vaccines. As is discussed below, newer, potentially faster and more effective vaccine production technologies already exist that cost less than the expected values of improved pandemic vaccines. But these technologies have not yet been widely utilized.

Table 7. Expected Benefits from Improved Vaccines in a Pandemic

Measure of benefit	Improved speed, 30% effectiveness improvement	Improved speed, baseline vaccine effectiveness
Total cost savings (billions of dollars)	953.27	729.81
per capita (dollars)	2,926.82	2,240.75
per vaccinated person (dollars)	3,658.53	2,800.94
Total expected savings (billions of dollars)	38.13	29.19
per capita (dollars)	117.07	89.63
per vaccinated person (dollars)	146.34	112.04

Source: CEA calculations.

Newer Technologies to Produce More Effective Vaccines More Quickly

Currently, about 85 percent of influenza vaccines are produced with egg-based manufacturing, which has been in use for more than 70 years. Two newer methods to produce vaccines are available: cell-cultured vaccines, which account for 10 to 15 percent of the market; and recombinant vaccines, which account for 1 to 2 percent. These new production methods may offer better antigen matching because they avoid egg adaptation issues, and faster production allows later selection of CVVs closer to the flu season, thereby minimizing the problem of genetic drift in circulating viruses or viruses arising unexpectedly after the CVVs are selected (Barr et al. 2018). Although vaccines produced with these new methods are more expensive than egg-based vaccines, costs should come down with process optimization and economies of scale.

In 2012, the FDA approved a cell-cultured, influenza vaccine, Flucelvax, in which egg-isolated CVVs were grown in cultured mammalian cells instead of chicken eggs. Four years later, the FDA approved an update to Flucelvax using cell-grown CVVs in cell-cultured vaccine production. Hence, the entire process, from virus isolation to virus growth and vaccine preparation, now occurs in mammalian cells. This eliminates the egg adaptations needed to grow influenza viruses in chicken eggs and may produce more effective vaccines that contain virus antigens closer to the wild types that are circulating (CDC 2018a). This new vaccine, which contained a virus derived from a purely mammalian cell culture, was used for the first time this past 2017–18 season. A CDC/FDA study of Medicare beneficiaries who are older than 65 shows that the cell-based vaccine was 10.4 percent more effective than the most commonly used quadrivalent egg-based vaccine during the 2017–18 flu season in which an A(H3N2) virus predominated (Lu 2018). But another study, by Kaiser Permanente Northern California of its members age 4–64 during the same 2017–18 season, found no significant difference in the effectiveness of cell-culture vaccine compared with standard egg-based vaccine (Klein et al. 2018).

Cell-culture manufacture is also potentially faster and more flexible than egg-based manufacturing. Manufacturing can start later than the current February egg-based date to account for viruses that are identified later on and antigenic drift in the original CVVs. In addition, cell-based production provides the potential for a faster start-up in the event of a pandemic. Unlike eggs, cells for Flucelvax production can be frozen to ensure that a supply of cells is available for vaccine production if there is an unexpected need like a pandemic virus (Klein et al. 2018; FDA 2013).

The second new method of producing influenza vaccines using recombinant technology was approved in 2013. It does not require the growth of influenza virus in mammalian cells or eggs. Instead, the vaccine, Flublok, is produced by taking the genes that code for the hemagglutinin (H) proteins from wild-type viruses, inserting them into viruses that infect insects' cells, and utilizing the insect cells to rapidly produce the influenza vaccine H protein (antigen), which is then harvested from the insect cells and purified. Like the cell-based technology, the recombinant method does not use eggs at all, and thus its effectiveness will not be limited by the selection of viruses that adapt for growth in eggs. Dunkle and others (2017) estimated that the recombinant vaccine was substantially more effective than the quadrivalent egg-based vaccine during the 2014–15 season—an A(H3N2) predominant year—among adults who were 50 years of age or older, reducing the probability of illness by 30 percent. They cautioned that the recombinant vaccine contains higher antigen concentrations per dose (45 micrograms/dose) than standard dose egg-based vaccines (15 micrograms/dose) and that "it is uncertain whether a higher antigen content or genetic fidelity to the recommended strain was responsible for the better relative vaccine efficacy" in the trial (Dunkle 2017, p. 2435). This

question is particularly important considering the finding in the FDA/CDC study of cell-cultured vaccines discussed above that just as cell-cultured vaccine is more effective (10.4 percent), high dose, egg-based trivalent vaccine was also 8.4 percent more effective than the standard egg-based vaccine, and there was no significant difference between the cell-cultured and the high dose, egg-based vaccines' effectiveness (Lu 2018). Regardless, it does highlight another advantage of both non-egg-based vaccine production techniques, especially recombinant vaccines, that they are more efficient at producing viral antigens than is the egg-based process. Dunkle and others (2017) advised repeating trials of recombinant vaccine in other flu seasons to see if the results will be replicated when there are different predominant circulating viruses.

Perhaps the biggest advantage of the recombinant vaccine manufacturing is speed, because it can produce vaccines within six to eight weeks once a pathogenic virus is identified and isolated, matching the speed gain in our simulation above, as opposed to six months with the egg-based process (Dunkle et al. 2017). This will be useful in creating vaccines for unexpected, pandemic viruses. It should also be faster than cell-cultured vaccines, given that it does not need to await the development of cell-based CVVs (Weir and Gruber 2016). Its major limitation is that its 9-month shelf life is shorter than those of other flu vaccines (CDC 2018k).

Medicare currently pays $22.79 and $53.37, respectively, for cell-cultured and recombinant vaccines (CMS 2018). These are both well below the expected values of improved pandemic vaccines calculated above. It seems clear that investment to expand manufacturing capacity for recombinant vaccine is warranted. The same will be true for cell-cultured vaccine manufacture if it proves to be appreciably faster than egg-based production.

Another production process, self-amplifying mRNA (SAM) vaccine manufacturing, which is patented but does not yet have an FDA-approved product, could shorten the vaccine manufacturing timeline even further. The SAM vaccine has been shown to be effective in mice (Hekele et al. 2013). Per interviews with government experts on influenza vaccines, both recombinant and SAM vaccines hold great promise for substantially shortening the vaccine manufacturing timeline and may provide the flexibility to engineer what would be a significant advance in the fight against influenza—a "universal" influenza vaccine.

Seasonal vaccines target a part of the influenza H surface antigen—the head—that varies from year to year. But there is another part of the antigen that is consistent across influenza strains and does not change—the stem. Although more research will be required, recent advances suggest that a successful vaccine against this part is possible. The potential benefits are clear. Unlike current vaccines that are strain-specific, a universal vaccine would not need to be reformulated on an annual basis and could be available to provide rapid protection in an emerging influenza pandemic. If it provides a durable immune response, seasonal vaccines

would not need to be administered each year. This is an area of active research by both the NIH's National Institute of Allergy and Infectious Diseases and private companies (NIH 2018).

The Value of Switching to New Vaccine Technologies for Seasonal Influenza

Switching to existing cell-cultured or recombinant vaccines and investing in production capacity may also be justified by savings that could be achieved in seasonal influenza years.

Avoiding the Loss of Efficacy Due to Egg Adaptations

Assuming that the results from the most optimistic early studies hold up, a cell-cultured vaccine could improve vaccine effectiveness by about 10.4 percent, and a recombinant vaccine could improve effectiveness by 30 percent over egg-based vaccine in years when A(H3N2) is the predominant virus by avoiding egg adaptations. We assume no change in effectiveness in non-A(H3N2) years, but, because effectiveness could improve for years when other viruses also predominate, our estimate should be considered a lower bound. To estimate the probability of a future prevalence of the A(H3N2) virus, we can consider the past outcomes. A(H3N2) viruses predominated during 12 out of the past 20 flu seasons and 22 out of the last 40 flu seasons.[19] Taking the longer-term view, the probability of the A(H3N2) virus dominating in any of the future years is 55 percent.[20] We then estimate the cost savings from the new-technology vaccines based on the 10.4 and 30 percent reductions in the number of illnesses that would occur in an A(H3N2) season among people who are vaccinated (as estimated from table 5).

Table 8 presents expected savings in each age group for the entire U.S. population and per vaccine given our improved vaccine effectiveness assumptions from avoiding egg-adaptation in A(H3N2) seasonal flu years. The table shows that the cost savings are the highest for the oldest age group due to the high rate of adverse outcomes from influenza. The expected savings from a switch to new-technology vaccines is about $3.1 billion per year for cell-based vaccines and $8.9 billion for recombinant vaccines. On a per-vaccinated-person basis, the value of the new seasonal vaccines, pricing in the improvement over historical vaccine effectiveness, could be $15.69 higher per dose for cell-based vaccines and $45.25 per recombinant dose. The value of these new vaccines is greatest for the 65+ age group—$82.58 per cell-based dose, and $238.22 per recombinant dose.

[19] We thank the CDC for providing this information to us.
[20] 22/40 = 55 percent.

Table 8. Expected Benefit Due to Improved Effectiveness from Avoiding Egg Adaptations in Seasonal Influenza Years

Measure of benefit	Age group					Total savings (millions of dollars)
	0–4	5–17	18–49	50–64	65+	
Cell-based vaccines						
Savings (millions of dollars)	38.2	13.9	63.8	319.2	2652.1	3087.1
Savings per vaccinated person (dollars)	2.77	0.48	1.48	11.34	82.58	15.69
Recombinant vaccines						
Savings (millions of dollars)	110.2	40.0	184.0	920.8	7650.2	8905.2
Savings per vaccinated person (dollars)	7.99	1.40	4.27	32.72	238.22	45.25

Source: CEA calculations.

Note: Data are from seasonal influenza.

Medicare currently pays up to $53.37 per dose of recombinant quadrivalent vaccine (Flublok), $22.79 per dose for cell-cultured quadrivalent vaccine (Flucelvax) and between $17.84 and $19.77 for standard-dose, egg-based vaccines (CMS 2018).[21] Medicare pays $53.37 for the high-dose, egg-based vaccine (Fluzone), the same as recombinant vaccine but substantially more than cell-based vaccine. Both high-dose egg and cell-based vaccines showed significantly improved effectiveness over standard egg-based vaccines this past season, but the improvement was not statistically different between them (Lu 2018).

The Value of Faster Vaccine Production for Seasonal Flu

The calculations above only account for improvement in efficacy due to the absence of antigen mismatch that results from egg adaptation. Cell-cultured and recombinant vaccines have so far been prepared with the same candidate viruses (minus the adaptation changes) selected for egg-based production in February of each year by the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). But recombinant and possibly cell-culture manufacturers do not need the six months required for egg-based production. Modifying the official calendar so that additional recommendations for the influenza-strain come closer to the actual flu season could enable vaccine manufacturers with short lead times to make more effective vaccines by avoiding antigenic drift that occurs between February and the flu season or inaccurate initial candidate virus selection.

[21] Medicare payment allowances for seasonal influenza vaccines are 95 percent of the average wholesale price, except where the vaccine is furnished to a hospital outpatient, when it is based on a reasonable cost (CMS 2018).

The framework for later candidate virus selection is already in place. Worldwide surveillance is continuous throughout the year, and the results are published in the CDC's *Weekly Influenza Surveillance Report*. A placeholder in the VRBPAC's calendar for a May–June update already exists, although it seems to have been implemented only once, for the H1N1 Swine Flu pandemic strain in 2009 (Weir 2017).

Updates after the initial February CVV selection would allow manufacturers with short lead times to differentiate their products in the market while enhancing surge capacity to deal with pandemics. A strain selection update does not mean that the FDA should decertify the previously certified CVVs. Rather, it would enhance vaccine consumers' (doctors, hospitals, drugstores, and clinics) choices. Consumers can already choose between authorized egg-based trivalent, quadrivalent, high-dose and adjuvanted vaccines, as well as cell-cultured and recombinant vaccines, all based on the February viruses. A late-entry vaccine would present one more authorized choice. If their speed and flexibility allowed them to produce superior vaccines—something that would need to be validated over time by reporting vaccine effectiveness—the financial rewards for the rapid-production techniques would support the building of additional surge capacity to confront a pandemic.

Only limited data are available on the frequency of substantial drift between February and the start of the flu season and on the degree of mismatch between the vaccine viruses and the viruses circulating during flu season. Using CDC data that are available about the past 13 seasonal flu years, however, we conduct the following thought experiment to illustrate the possible market advantage from starting vaccine production later in the season and therefore being better able to match the vaccine to the prevailing strain. In the past 13 seasonal flu years,[22] there were three years with a substantial mismatch between the predominant circulating virus and the virus in the vaccine.[23] Using this 23 percent probability, we can determine what savings would be expected from improving the vaccine effectiveness observed in mismatch years (10, 19, and 21 percent) up to the effectiveness that would be seen in a year with a good match. The average effectiveness observed in the 10 match years over the past 13 flu seasons was 47 percent. This is consistent with CDC estimates that seasonal vaccine effectiveness ranges between 40 and 60 percent in years when the circulating virus is well matched to the vaccine (CDC 2018n).

[22] One of the past 14 years, 2009, was a pandemic year, in which the CDC reported that there was not a significant amount of the seasonal vaccine virus circulating during flu season—the predominant circulating virus was the pandemic A(H1N1) virus (CDC 2010). Although this represents a complete mismatch, we dropped 2009 because it was not a typical seasonal flu year, leaving 13 seasonal flu seasons in the past 14 years.

[23] In two years when there were no direct data on the degree of mismatch but vaccine efficacy was high, we assumed there was little mismatch.

The total savings and savings per vaccinated person expected from faster vaccine production, enabling vaccine production to be closer to the actual season and better vaccine matches to the circulating viruses, are presented in table 9.

Table 9. Expected Benefits from Improved Vaccine Effectiveness in Years with the Wrong Strain Forecast

Measure of benefit	Age group					Total
	0–4	5–17	18–49	50–64	65+	
Expected savings (millions of dollars)	184.5	67.0	308.1	1,541.9	12,811.0	14,912.5
Expected savings per vaccinated person (dollars)	13.37	2.34	7.15	54.80	398.91	75.77

Source: Molinari et al. (2007); CEA calculations.

Note: The total expected savings per vaccinated person is the population-weighted average.

According to this calculation, the decreased mismatches result in an expected $75.77 savings per vaccinated person. The most impressive benefits are for the 65+ age group—$398.91 per elderly vaccinated person.

If this suggested adjustment to the FDA's calendar led to a documented improvement in seasonal vaccine efficacy, faster production technologies would likely increase their market share, which would have the additional benefit of contributing, at little cost, to the Nation's ability to rapidly respond to a pandemic. There are many similarities between a surprise emergence of a seasonal influenza virus and the emergence of pandemic virus (although pandemics, by definition, have higher mortality and/or higher transmission rates). Both cause a surge in morbidity and mortality that can be mitigated by shorter vaccine production timelines.

It is likely that vaccine efficacy improvements from less antigen mismatch due to egg adaptation and antigenic drift during prolonged production periods will both result from innovative vaccine technologies. We cannot say they would be perfectly additive, because the egg adaptations and antigenic drift will vary from year to year depending on the predominant viruses and are likely independent of each other.

Why the Private Market Might Not Sell Pandemic Insurance

We have shown that new technologies that speed vaccine production and avoid the need for egg adaption could have substantial benefit in the event of an influenza pandemic and may, if preliminary studies can be replicated, have value for seasonal flu. However, adoption of existing new manufacturing techniques and the development of other innovative technologies

has been slow. Here, we discuss the lack of a market for innovative technologies to better mitigate pandemic risk.

Mitigating the losses from pandemic flu is dependent on medical innovation that speeds up vaccine production or increases vaccine effectiveness. The problem with such innovation is that medical R&D into vaccines that better mitigates the risk of a pandemic is only recouped by sales when the pandemic risk occurs. However, part of the value of vaccines that mitigate future pandemic risks is their *insurance value* today. This value accrues even if the pandemic does not occur in the future. To illustrate, most life insurance buyers do not die in a given year but still get value from holding the policy as it mitigates risk in case of death. Similarly, faster vaccine technologies and more effective vaccines would be valuable even when the pandemic did not occur because they mitigate the risks of illness and losing one's life to a possible pandemic. The new vaccine technology would provide insurance against pandemic risk both in terms of monetary losses and losses in one's health.

This insurance value of vaccine technologies implies that the social value of faster vaccine production is larger than its private return to developers, which is based on sales when the pandemic occurs once every 25 years or so.[24] This divergence leads to an underprovision in vaccine innovation because it does not get rewarded for its insurance value. As a result, manufacturers have little incentive to move from the current dependence on egg-based production, which is unable to ramp up production quickly enough, or to target the vaccines closely enough, to mitigate a pandemic. This divergence might become less important if and when the value of newer, existing technologies (cell-based, recombinant) or as-yet-undeveloped vaccine technologies can be conclusively demonstrated for seasonal flu vaccines.

A second barrier to a private market solution is that pandemics represent a risk with large and highly correlated losses across the population, against which it is inherently difficult to get the market to provide private insurance. Insurance works by pooling risk between a few affected people and a large number of people who are not affected by the risk insured against. Unlike the usual insurance scenario, where one person's risk of a car accident has little or no influence on the risk of an accident of other insured motorists with whom she pools the risk, a pandemic (similar to a hurricane) is an instance where a large number of people are simultaneously affected. The risk cannot be pooled because everyone is at risk concurrently. Whenever risks are correlated, private insurance has less value. To illustrate, consider a risk such as a pandemic that either does not affect anyone or affects nearly everyone. If the insurance

[24] We realize that positive externalities of vaccination (vaccination protects me plus those around me from contracting disease) could also be counted in social value; but for the purposes of this report, we do not separately estimate these effects.

company is to stay solvent and pay out claims when the pandemic occurs, its premiums must be close to the actual loss on a per capita level. This makes the premiums so expensive that the insurance is not valuable; why pay a dollar to receive a dollar if the risk occurs? The basic issue is that insurers must meet self-imposed and regulatory solvency requirements for the policies that they issue so that they have sufficient capital to compensate for a given level of losses. Kousky and Cooke (2012) demonstrate that the requisite premiums to cover disastrous events can become so high that consumers are not willing to pay large homeowners' premiums. The central issue is that there is little or no pooling of risk when risks are highly correlated. Because pandemic vaccine demand would be hard to insure, it would limit the demand for the superior vaccine technology developed.

A third barrier may be that insurance decisions are often based on past experiences and emotions (Kunreuther, Pauly, and McMorrow 2013). Though people frequently overestimate the likelihood of uncommon events, they sometimes underestimate the likelihood of tail events—rare, high-impact events—based on the "availability heuristic," which leads people to estimate the probability of an event by how easy it is to recall episodes of the event (Barberis 2013). In the case of pandemic flu, there have only been four episodes over the past 100 years, and only one of them, the 1918 flu, resulted in widespread illness and death in the United States. In addition, people may conflate the high expected costs of pandemic flu with the far-more-common, lower-cost, seasonal flu. It is not surprising that people might underappreciate the economic and health risks posed by pandemic flu and not invest in ways to reduce these risks.

Finally, insurers may also undervalue the economic and health risks of pandemics. "Pandemic exposure can present significant tail risk to insurers. The life and health insurance industries will be most severely impacted. However, the property/casualty (P/C) industry could see substantial losses from secondary impacts" (NAIC 2018). Nevertheless, there is inadequate private demand for developing and investing in vaccine technologies to deal with the pandemic flu threat. Insurers undervalue the risk to economic stability and growth and do not value the positive impact investment and research into pandemic flu prevention could have in other medical areas (Sands, Mundaca-Shah, and Dzau 2016).

Given the underprovision of pandemic risk mitigation by the private sector, the public sector has a role in stimulating the development of, and demand for, newer vaccine technologies that are better able to provide pandemic preparedness. Public-private partnerships that stimulate such innovation may enhance welfare.

The Role of the Public–Private Partnerships in Moving Toward Faster, More Flexible, and More Effective New Vaccine Production Technologies

All influenza vaccines in the United States are privately manufactured by a handful of firms. Most resources are invested in egg-based production, which has been the predominant method of vaccine production for 70 years. Moving to different production methods requires large capital expenditures in a market with low profit margins earned by vaccine producers.

Public measures have been key in advancing vaccine innovation. The Pandemic and All-Hazards Preparedness Act, enacted in 2006, established the Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services to facilitate research and development of countermeasures for chemical, biological, radiological, and nuclear threats, including the development of vaccines for the risks posed by pandemic influenza (HHS 2018).[25] The statute supported public-private partnerships to achieve pandemic preparedness. Public-private partnerships were key in the development of cell-cultured and recombinant protein-based vaccines. Seasonal and pandemic flu preparedness are closely linked, given that vaccine production for seasonal flu viruses is the foundation for vaccines production for pandemic flu.

About half of flu vaccines administered in the United States are to people covered by government health insurance. Hence, the government has a strong interest in purchasing the most cost-effective seasonal flu vaccines. Public-private partnerships can continue to push cell-cultured and recombinant protein vaccine technologies or other, as-yet-unknown innovations, to offer greater flexibility and perhaps improved effectiveness than egg-based vaccines while supporting accelerated timelines for vaccine composition updates to cope with changes in seasonal flu viruses and to respond to the inevitable, future pandemic viruses. One promising approach being developed by a private company, supported by a contract with BARDA, is a recombinant, oral flu vaccine. Preliminary results suggest that it is at least as effective as standard vaccines (Hackett 2018). An oral vaccine would be easier to administer because it does not require specialized personnel and could increase vaccination rates among people who resist getting injections—the NORC (2018) survey reported that among people not planning on getting a flu vaccine, 13 percent cited fear of needles and shots as a major reason and 15 percent as a minor reason. This creates the possibility that more than the 30 million doses a week that we used in our model above could be administered and higher vaccination rates achieved, resulting in improved health benefits and decreased economic costs.

[25] Public Law 109-417, 109th Congress: Pandemic and All-Hazards Preparedness Act, Washington.

Another promising area of public-private collaboration is the development of a universal influenza vaccine, which was described above when discussing new vaccine technologies. The National Institute of Allergy and Infectious Diseases has stated that developing a universal vaccine "will require a global collaborative effort among government agencies, industry, philanthropic organizations, and academia that incorporates interdisciplinary approaches and new technological tools" (NIH 2018).

If the improvements of cell-culture and recombinant technologies over the effectiveness of egg-based vaccine production can be replicated over several influenza seasons with documented cost savings, or other innovative technologies come to the fore, government purchases will likely switch to the more cost-effective products. This increased demand should pull private, domestic production toward better vaccine manufacturing technologies, decreasing the impact of both seasonal and pandemic influenza.

Conclusion

Pandemic influenza is a low-probability but high-cost problem that should not be ignored. The current influenza vaccine manufacturing infrastructure in the U.S. is dependent on egg-based production that is too slow to produce adequate doses of vaccines for unexpected pandemic outbreaks and may impair vaccine efficacy. This could lead to tremendous, avoidable costs. This report has outlined the importance of innovation in reducing these costs. Improving the speed of vaccine production is key. Once shorter production timelines are achieved, improving vaccine efficacy can also have an important impact. Faster vaccine production that would make sufficient doses of vaccine available at the outset of a pandemic could generate $730 billion in benefits. If combined with improvements in vaccine effectiveness, the benefits would rise to $953 billion. The expected value of improving pandemic vaccine production speed is many times the cost of existing influenza vaccines, suggesting that investment in and adoption of faster, more effective production technologies is worthwhile. New, non-egg-based vaccine production methods able to deliver sufficient doses of vaccine faster in the case of a pandemic, saving millions of lives and billions of dollars, already exist and could be improved upon with additional innovation. These new vaccine technologies may also result in improvements to the past effectiveness of seasonal flu vaccines, ultimately lowering the costs of the annual flu season. The Federal government has played a role through public-private partnerships in the development of these new vaccine technologies. The government should continue to partner with the private sector to develop and adopt new vaccine technologies that mitigate the risks of pandemic influenza and improve outcomes for the seasonal flu. When the value of these new technologies is confirmed, government can move to purchase the most cost-effective vaccines available.

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September 2019