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INFLUENZA

**Progress Made in
Responding to Seasonal and
Pandemic Outbreaks**

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Highlights of [GAO-13-374T](#), a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

Why GAO Did This Study

Influenza—in both its seasonal and pandemic forms—is an ongoing public health concern. In the United States, seasonal influenza has been associated with thousands of deaths each year, according to CDC. In a pandemic, such as the 2009 H1N1 influenza pandemic, the disease causes a global disease outbreak with the potential for many more deaths. HHS has responsibility for coordinating the nation's response to public health emergencies, including an influenza pandemic. Within HHS, CDC makes recommendations on vaccination, tracks the disease, and disseminates public health messages on influenza. This testimony discusses (1) lessons learned from federal responses to prior influenza outbreaks and (2) federal investments to strengthen the U.S. vaccine supply and production capacity.

This testimony is based on prior GAO work on issues related to influenza vaccine supply and distribution; federal investments in domestic vaccine production capacity and production technologies; and the federal response to the 2009 H1N1 pandemic. This prior work includes analyses of information and interviews with officials within HHS, CDC, and FDA, as well as officials from vaccine manufacturers, medical supply distributors, state and local governments, provider groups, and other stakeholders. GAO also obtained updated information from HHS on the severity of the past three seasons, the numbers of vaccine doses distributed, and the status of advanced vaccine technology projects funded by HHS. HHS reviewed updated information and provided technical comments, which are incorporated as appropriate.

View [GAO-13-374T](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

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What GAO Found

GAO's prior work has identified a number of lessons from federal responses to seasonal influenza vaccine shortages and the 2009 H1N1 pandemic that carry implications for future influenza seasons or another influenza pandemic. These lessons include the value of planning that involves the Department of Health and Human Services (HHS); the importance of effective communication among all levels of government and with the public; and the difficulty of matching vaccine supply with the public's demand for it. First, planning is critical to an effective response, and it particularly helped in responding to the H1N1 pandemic. Planning activities, such as exercises and interagency meetings, built relationships that positioned the government to respond effectively. Second, clear and consistent communication, especially regarding the availability of vaccine, is key. The failure to effectively manage public expectations of vaccine availability can undermine government credibility and contribute to individuals' failure to seek or receive an influenza vaccination. Recognizing the importance of sharing updated information, HHS's influenza website includes a vaccine finder for individuals, and the Centers for Disease Control and Prevention's (CDC) website helps providers find vaccine available for purchase. Third, predicting all of the influenza virus strains that will be circulating in a given season and their likely severity is difficult. Finally, matching influenza vaccine supply to demand is challenging, as the supply of and demand for vaccine can vary throughout seasons and across multiple seasons. HHS has taken a number of steps to address these lessons learned; however, the department continues to face challenges, particularly in communicating messages in changing circumstances and in facilitating the matching of available vaccine supply with public demand.

HHS has taken steps to strengthen the U.S. influenza vaccine supply by making investments in the development of vaccine production technologies and by enhancing domestic production capacity. Influenza vaccine has generally been produced in a complex egg-based process that poses limitations in timeliness and the susceptibility of the egg supply to certain influenza viruses. Prompted by these disadvantages, HHS has made investments in alternative vaccine production technologies, including cell-based and recombinant technologies. Since fiscal year 2005, HHS has awarded over \$1 billion in contracts to manufacturers to develop cell-based technology. One of these manufacturers recently received approval from HHS's Food and Drug Administration (FDA) for its cell-based seasonal influenza vaccine, which it intends to produce for the 2013–2014 influenza season. In addition, in fiscal year 2009, HHS entered into a contract worth approximately \$81 million with one manufacturer for the continued development of recombinant technology; that manufacturer's seasonal influenza vaccine made using this technology is expected to be available for the 2013–2014 influenza season. HHS has complemented its investments in vaccine production technologies with its investments in domestic manufacturers' production capacity. Since fiscal year 2005, these investments have contributed to the doubling of the number of domestic influenza vaccine manufacturers and a general increase in the number of influenza vaccine doses produced and distributed.



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United States Government Accountability Office
Washington, DC 20548

Chairman Murphy, Ranking Member DeGette, and Members of the Subcommittee:

I am pleased to be here today as you reflect on the current influenza season and examine issues related to influenza preparedness. Influenza, in both its seasonal and pandemic forms, is an ongoing public health concern. In the northern hemisphere, seasonal influenza may begin as early as August and generally diminishes by April. It has been associated with 3,000 to nearly 50,000 deaths each year in the United States in recent decades, according to the Department of Health and Human Services's (HHS) Centers for Disease Control and Prevention (CDC).¹ In a pandemic, such as the recent 2009 H1N1 influenza pandemic, influenza causes a global disease outbreak with the potential for many more deaths than in a typical influenza season.²

My remarks today focus on (1) lessons learned from federal responses to prior influenza outbreaks and (2) federal investments to strengthen the U.S. vaccine supply and production capacity. My testimony is based on multiple GAO reports and testimonies in relation to seasonal and pandemic influenza.³ Specifically, this body of work includes issues related to influenza vaccine supply, distribution, and shortages; federal investments in the U.S. vaccine supply and alternative technologies for influenza vaccine production; and the federal response to the 2009 H1N1 pandemic. This prior work includes analyses of information and interviews with officials within HHS, such as those from CDC and the Food and Drug Administration (FDA); as well as officials from influenza vaccine manufacturers, medical supply distributors, state and local governments, provider groups, and national associations such as the Association of State and Territorial Health Officials. In preparation for this testimony, we obtained updated information from HHS, including on the numbers of

¹CDC, "Estimates of Deaths Associated with Seasonal Influenza—United States, 1976–2007," *Morbidity and Mortality Weekly Report*, vol. 59, no. 33 (2010): 1057-1062.

²Pandemics occurring in the past 100 years include the "Spanish flu" of 1918, which killed an estimated 675,000 people in the United States; the "Asian flu" of 1957, responsible for approximately 70,000 deaths in the United States; the "Hong Kong flu" of 1968, which caused an estimated 34,000 deaths in the United States; and the 2009 H1N1 pandemic, which caused from 8,870 to 18,300 deaths in the United States. Influenza pandemics can have successive "waves" of disease and last for up to 3 years.

³See a list of related GAO products at the end of this statement.

vaccine doses produced and distributed, the severity of the past three seasons, and the status of advanced technology projects funded by HHS. We conducted our work in accordance with generally accepted government auditing standards.⁴ Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings based on our audit objectives. We provided HHS with a copy of updated facts in this statement for its review. HHS provided technical comments, which we incorporated as appropriate.

Background

Influenza is characterized by cough, fever, headache, and other symptoms and is more severe than some viral respiratory infections, such as the common cold. Most people who contract seasonal influenza recover completely in 1 to 2 weeks, but some develop serious and potentially life-threatening medical complications, such as pneumonia. Groups at higher risk of developing serious influenza-related complications include those aged 65 years and older; those with chronic medical conditions; young children, particularly those under 2 years of age; and pregnant women. During an influenza pandemic, different groups may be affected. For example, some past influenza pandemics have affected healthy young adults who are not typically at high risk for severe influenza-related complications.

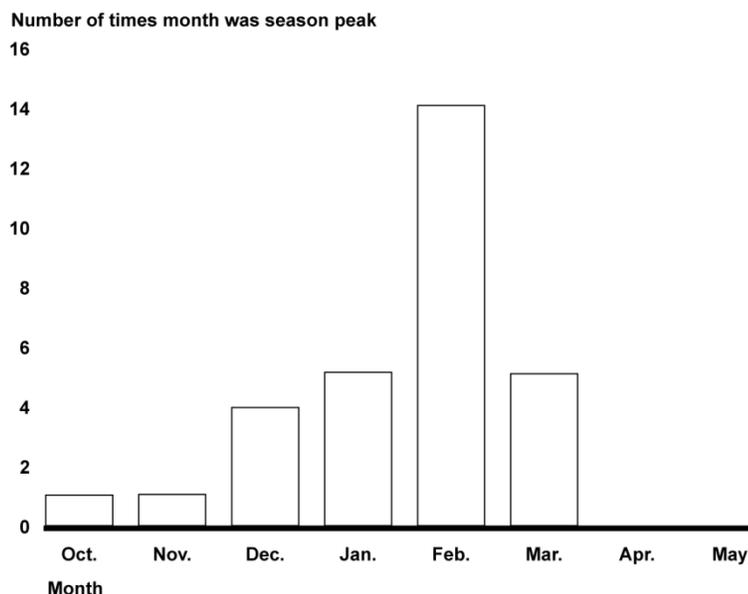
Annual vaccination is the main method for preventing seasonal influenza. Since 2010, CDC and its Advisory Committee on Immunization Practices have recommended annual influenza vaccinations for everyone aged 6 months or older.⁵ After vaccination, the body takes about 2 weeks to produce the antibodies that protect against infection. Vaccination in the fall, before the U.S. influenza season begins, is preferable; however, because influenza in the United States typically begins to increase in late December or early January and peaks in February most seasons,

⁴We conducted our work from November 2000 to June 2011, and February 2013. See the list of related products at the end of this statement for more information on our work.

⁵Some people should not get a flu vaccination without first consulting a physician, including people who have had a severe reaction to an influenza vaccination and people who have a severe allergy to chicken eggs. See <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6132a3.htm> for ACIP's recommendations for the 2012–2013 influenza season (accessed Feb. 7, 2013).

vaccination in December or later can still be beneficial. The influenza season peaked in February in nearly half (14) of the influenza seasons over the past three decades (see fig. 1).

Figure 1: Month of Peak Influenza Activity, 1982–1983 through 2011–2012 Seasons



Source: CDC.

Note: This figure shows peak influenza activity for the United States, by month, for the 1982–1983 through 2011–2012 seasons.

Within the federal government, HHS has primary responsibility for coordinating the nation’s response to public health emergencies, such as an influenza pandemic. Additionally, as the principal department for protecting the nation’s public health, HHS is the primary department funding the research and development of influenza vaccines. Within HHS, CDC makes recommendations on who should be vaccinated, tracks the spread of influenza and vaccination rates, and disseminates public health messages encouraging vaccination and other protective measures, such

as hand washing. FDA is responsible for selecting the influenza strains to include in the annual influenza vaccines and for licensing vaccines.⁶

In a typical season in the United States, influenza vaccine production and distribution are largely the purview of private manufacturers and distributors. Manufacturers sell seasonal influenza vaccine directly to providers who administer vaccination, including physicians, hospitals, pharmacies, federal agencies, state and local health departments, and mass immunizers. In addition, manufacturers sell vaccine to medical supply distributors, who in turn sell it to providers and other customers. Providers administer vaccinations in a variety of locations, including physician's offices, public health clinics, nursing homes, and nonmedical locations such as workplaces and retail stores. Millions of individuals receive influenza vaccinations through mass immunization campaigns in these nonmedical locations, where organizations such as visiting nurse agencies under contract administer the vaccine. The reliance on this private-sector system affects when and how vaccine is distributed—that is, when a provider receives vaccine can depend on which manufacturer that provider ordered from and the distribution route the vaccine takes from the manufacturer to the provider. Because the influenza vaccine production process typically takes 6 or more months to complete, manufacturers must estimate the potential demand for vaccine and what their production levels will be well before the start of the season.⁷ At the end of the influenza season, any unused vaccine doses expire and therefore cannot be used in subsequent years. Accordingly, manufacturers seek to match their vaccine production to expected demand for the vaccine so that no doses remain unsold at the end of the influenza season. Manufacturers may decide to limit or stop production if they do not believe there is sufficient demand to sell all of the vaccine

⁶Each year, public health experts, including those from FDA, the World Health Organization, and CDC, study influenza virus samples and global disease patterns to identify virus strains likely to cause the most illness during the upcoming season. Based on that information and the recommendations of FDA's Vaccines and Related Biological Products Advisory Committee, FDA selects the strains for inclusion in the annual influenza vaccine for the United States. FDA has traditionally selected three strains of influenza virus—two strains of influenza type A and one strain of influenza type B—to include in the annual influenza vaccine.

⁷Influenza vaccine has generally been produced in a complex process that involves growing viruses in millions of fertilized chicken eggs. This egg-based process has been used to make vaccine in past influenza seasons, the current season, and the 2009 H1N1 pandemic.

doses they have the capacity to produce—thereby limiting the quantity produced for that season and how late in the season the vaccine is available.

Although the production and distribution of seasonal influenza vaccine is largely a private-sector endeavor, federal, state, and local governments may become more involved, particularly when there is a vaccine shortage or in the event of a pandemic. For example, during a period of vaccine shortage in the 2004–2005 season, the federal government worked with a major manufacturer and with state and local health officials to help prioritize how to distribute available vaccine to provide better access for those at high risk for influenza related complications.⁸ In the event of a pandemic, the federal government may assert more control over vaccine production and distribution than in a nonpandemic influenza season. For example, in response to the 2009 H1N1 pandemic the federal government purchased vaccine directly from manufacturers and worked with state and local governments to determine the distribution of that vaccine. In a pandemic situation when the federal government purchases all of the vaccine, the federal government can guarantee manufacturers that they will sell a certain number of doses.

⁸Of the three manufacturers of seasonal influenza vaccine for the 2004–2005 influenza season, two produced and distributed vaccine and one ceased production and did not distribute any vaccine for the U.S. market after its license was suspended by the United Kingdom in October 2004. As a result, close to half of the 100 million doses estimated for the 2004–2005 season—approximately 47 million doses—were not produced. Instead only 61 million doses were produced, of which 57 million were distributed.

Lessons Learned on Influenza Response Include the Importance of Planning, Effective Communication, and the Difficulty of Matching Vaccine Supply with Public Demand

Our prior work has identified a number of lessons from the federal response to seasonal influenza vaccine shortages and the 2009 H1N1 pandemic that carry implications for future influenza seasons or another influenza pandemic. The primary lessons can be grouped into four broad, interrelated categories: the value of planning, the importance of effective communication, the difficulties in predicting all of the influenza virus strains that will be circulating in a given season, and the challenge in facilitating the matching of available influenza vaccine supply with public demand.

First, our work found that planning is critical to an effective response.

- A lesson learned from the 2004–2005 season, when there was an abrupt and unexpected loss of nearly half of the nation’s expected vaccine supply, was that planning is critical to ensure timely delivery of vaccine to those who need it when demand for vaccine exceeds the available supply. That season, CDC’s lack of a contingency plan contributed to delays and uncertainty about how to ensure that high-risk individuals had access to vaccine.
- We also found that planning paid off in the response to the 2009 H1N1 pandemic. For example, planning activities—including planning exercises, and interagency meetings prior to the H1N1 pandemic—built relationships that were valuable and positioned the government to respond effectively.

HHS has taken action in planning for future seasons or pandemics. For example, following the shortage of the prior season, CDC published ordering and distribution strategies for the 2005–2006 season, when there was uncertainty in vaccine production, encouraging the distribution of vaccine in multiple shipments as vaccine became available so providers could have some vaccine for their high-risk patients when vaccine was initially distributed.⁹ CDC continues to encourage this type of multiphased distribution strategy. Additionally, following the 2009 H1N1 pandemic, HHS reported that it would incorporate lessons learned from the pandemic response into its plans for responding to such incidents in

⁹See CDC, “Influenza Vaccine Prebooking and Distribution Strategies for the 2005–06 Influenza Season,” *Morbidity and Mortality Weekly Report*, vol. 54, no. 12 (2005): 307–308.

the future. These included lessons that we identified, as well as other lessons HHS identified in its after-action report.

Second, our work found that clear and consistent communication—between all levels of government and with providers and the public—is key. Because the failure to effectively manage public expectations can undermine government credibility, it is essential that vaccine production efforts be paired with effective communication strategies by the federal government regarding the availability of the vaccine. The effect of communication is illustrated by past seasons:

- During the 2004–2005 season, in some instances, uncoordinated communication from federal to state and local jurisdictions, and to providers and the general public, contributed to confusion, frustration, and individuals’ failure to seek or receive an influenza vaccination.
- During the summer of 2009, HHS conveyed to state and local jurisdictions, and to the public, that a robust H1N1 vaccine supply, about 120–160 million doses, was expected to be available in October 2009. Ultimately, however, fewer than 17 million doses were shipped out that month, which did not meet the expectations of state and local governments or the public. Consequently, the public had an unfavorable view of the federal government’s ability to provide the country with the H1N1 vaccine. A Gallup survey of U.S. adults from early November 2009 found that 54 percent of adults said the federal government was doing a poor (41 percent) or very poor (13 percent) job of providing the country with adequate supplies of the vaccine.
- In our work on past influenza seasons and the 2009 H1N1 pandemic, state and local health officials emphasized the value of communication, including updating information when responding to changing circumstances, using diverse media to reach diverse audiences, and educating the public about nonpharmaceutical interventions, such as hand washing and covering coughs.

Recognizing the importance of sharing updated information, in response to problems in the past, HHS has taken steps to work with stakeholders to communicate on vaccine availability. For example, HHS’s influenza website, www.flu.gov, includes an influenza vaccine finder for individuals

seeking to find providers offering vaccination in their area.¹⁰ In addition, CDC's website has links to help health care providers find available vaccine to purchase.¹¹

While these efforts, along with regular communication and sharing of information between CDC and other stakeholders—including public health officials, providers, manufacturers, and distributors—have improved influenza-related communication, effective and consistent communication is a challenge. For example, as we reported in October 2007, one CDC official involved in communicating messages about influenza told us that it is difficult to maintain a consistent message during or between influenza seasons, because messages need to adapt to the dynamic and complex situations that constitute influenza seasons. For example, messages need to be modified to account for changes in the Advisory Committee on Immunization Practices' recommendations, which could result in the public hearing different messages before and after these revisions are made.

Third, our work found that ensuring that the annual influenza vaccine protects against the influenza virus strains that will cause serious illness for a given influenza season is difficult, because it is not possible to predict with certainty which influenza viruses will predominate that season. Traditionally, the influenza vaccines licensed by FDA for use in the United States contain three different influenza virus strains. FDA must pick which viruses to include in the vaccine many months in advance in order for vaccine to be produced and delivered on time, so there is always a possibility of a less than optimal match between circulating viruses and the virus strains in the vaccine. In recent years, the match between the viruses in the vaccine and those identified during the season has been good; however, in some seasons, this has not been the case. For example, for the 2007–2008 season's vaccine, FDA did not select the

¹⁰CDC initially created a version of the Flu Vaccine Finder to help state and local officials direct available vaccine to certain high-risk groups; this system provided state and local officials with information on where vaccine had been shipped and also allowed them to order available vaccine.

¹¹During influenza seasons when vaccine supply is challenged, the Influenza Vaccine Availability Tracking System (IVATS) becomes operational. IVATS, which is on the website of the National Influenza Vaccine Summit (www.preventinfluenza.org), enables health care providers to view at a glance which distributors have vaccine available to sell. IVATS was initiated in 2006.

influenza A virus strain that became the predominant virus in the United States that season for the vaccine, and the vaccine was not well-matched with the strains circulating in the United States that season. During a typical influenza season, including the current season, there may be two different influenza B strains circulating, or the B strain selected for inclusion in the vaccine may not be the influenza B strain that eventually circulates and causes illness. To increase the likelihood of adequate protection against circulating influenza strains, FDA approved two new vaccines that can protect against a total of four influenza strains—one more strain than traditional seasonal influenza vaccines. These new vaccines—called quadrivalent vaccines—are expected to be available for the 2013–2014 season.¹²

Finally, another lesson learned is that matching influenza vaccine supply with the public's demand is challenging, particularly as the supply of and demand for vaccine can vary throughout the season and across multiple seasons. For instance:

- While the roughly 78 million doses eventually produced for the 2000–2001 season were about the same amount produced in the previous year, a delay resulted in a shortage of vaccine during October and November when people normally receive their vaccination. During the shortage, many providers who wanted to purchase vaccine faced rapidly escalating prices from distributors with an available supply.
- For the 2003–2004 season, shortages of vaccine occurred when there was an earlier and more severe influenza season and higher than normal demand, likely resulting from media coverage of pediatric deaths associated with influenza. Manufacturers that season had produced about the same number of doses used in the previous season—about 87 million doses total—which was not adequate to meet the increased demand, according to CDC officials.
- Even in seasons when there were few licensed manufacturers or periods when demand exceeded the available supply, more doses of

¹²FDA approved MedImmune's FluMist Quadrivalent in February 2012 and GlaxoSmithKline's Fluarix Quadrivalent vaccine in December 2012 for the prevention of seasonal influenza for their intended populations. According to FDA, the approval of these quadrivalent influenza vaccines was not for a specific influenza season and the timing of the marketing launch of a new vaccine to make it available to the public is a decision made by each manufacturer.

seasonal vaccine have generally been produced than distributed, according to data from CDC, FDA, and the American Medical Association. Similarly, overall supply exceeded demand even in the 2009 H1N1 pandemic; HHS has acknowledged that the doses of H1N1 vaccine arrived too late in the response, and local health department officials told us that once the H1N1 vaccine became available, parents were not interested in vaccinating their children because H1N1 influenza vaccine activity had already peaked in their area.

The challenges in matching vaccine supply with demand in a given season are illustrated in the past two seasons. For the 2011–2012 season, manufacturers produced about 162 million doses, slightly more than the 158 million doses distributed in the prior season. However, the 2011–2012 season began late, peaked in March, and was mild compared to most previous seasons, and manufacturers were left with about 30 million doses that were produced but not distributed at the end of the season. For the current 2012–2013 season, manufacturers are expected to produce about 145 million doses. Unlike last season, CDC has reported that this season has been characterized by early and intense influenza activity throughout much of the country, and there are reports of spot shortages. Figure 2 shows the percentage of outpatient visits for influenza-like illness by month for influenza seasons in 2010–2011, 2011–2012, and 2012–2013.

Figure 2: Percentage of Outpatient Visits for Influenza-Like Illness by Month, 2010–2011, 2011–2012, and 2012–2013

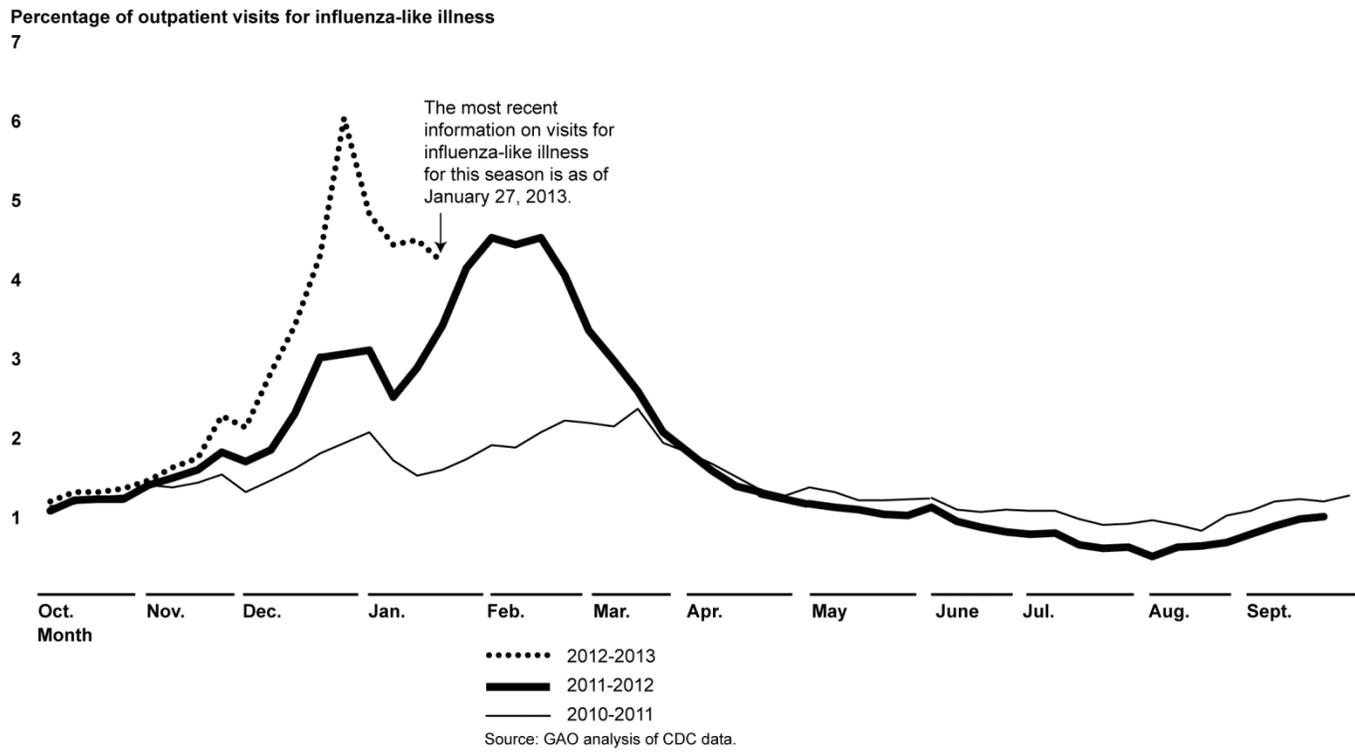
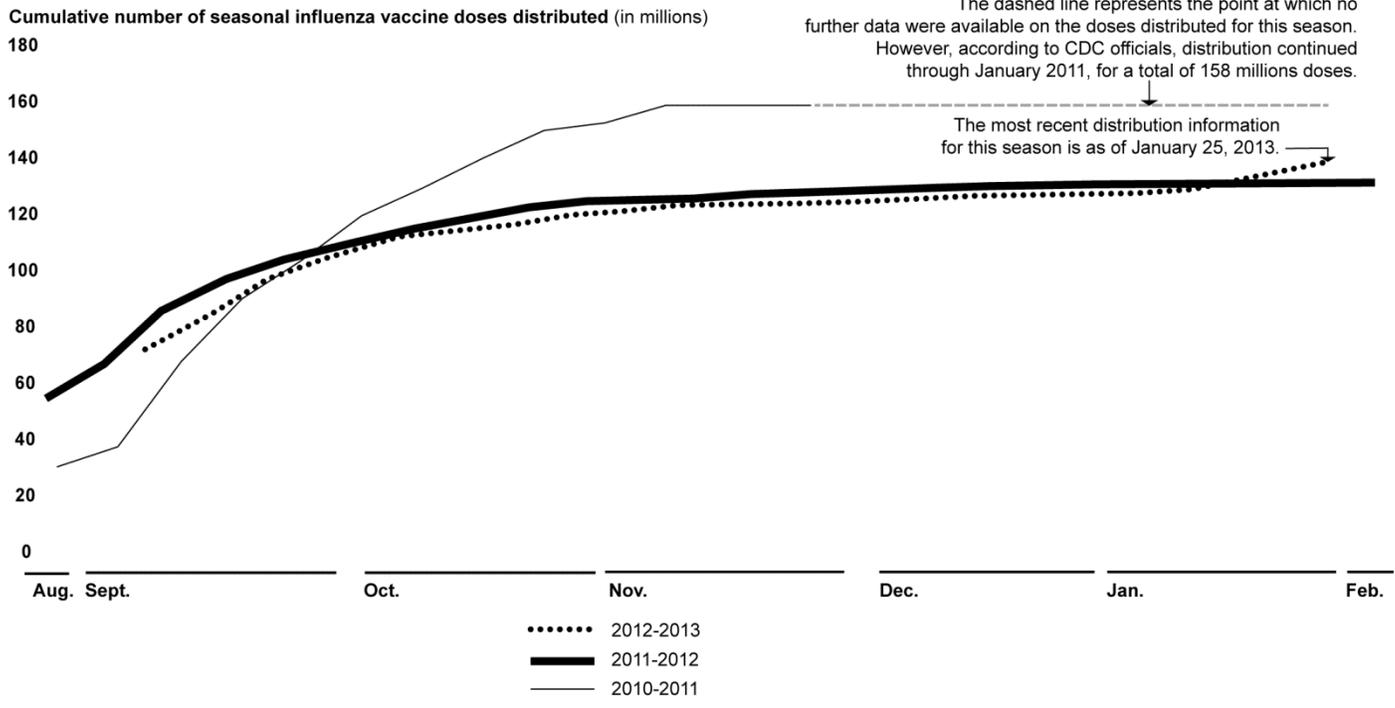


Figure 3 show the cumulative number of doses of influenza vaccine distributed by month for the same seasons.

Figure 3: Cumulative Number of Seasonal Influenza Vaccine Doses Distributed by Month, 2010–2011, 2011–2012, and 2012–2013



Recognizing the potential for a mismatch in vaccine supply and demand for vaccinations, beginning with the 2004–2005 season, CDC began purchasing a late-season influenza vaccine stockpile to provide a limited quantity of vaccine for children using federal Vaccines for Children (VFC) program funds. The purpose of this stockpile is to ensure that some vaccine would be available in the event of a late-season outbreak of influenza and related demand for vaccine.¹³ For the current season, CDC shipped about 400,000 pediatric doses of vaccines during the week of January 21, 2013, to federal depots so that 32 immunization awardees

¹³Under CDC’s VFC program, vaccines are provided free of charge for certain children 18 years of age or younger, including those who are Medicaid-eligible, uninsured, or those without insurance coverage for vaccinations.

could place additional orders to protect children.¹⁴ Despite these efforts, many challenges remain. Predictions of the severity and timing of a coming seasonal outbreak, and the circulating strains, are imprecise. The vaccine production process relies on an annual manufacturing cycle that has a history of disruption. Given this production cycle, decisions must be made months in advance of a seasonal outbreak and vaccine supply orders are often placed before providers know what patient demand will be. Manufacturers may be reluctant to produce and providers may be reluctant to order vaccine that exceeds their projected demand because the product must be destroyed at the end of the season if it is not used.

HHS Has Made Investments to Strengthen the U.S. Vaccine Supply

HHS has taken steps to strengthen the U.S. influenza vaccine supply by making investments in alternative technologies—including cell-based and recombinant technologies—and enhancing domestic production capacity.¹⁵ (See app. I for additional information on these technologies). Potential threats to the egg supply such as from the H5N1 virus, in part, prompted HHS to make investments in alternative technologies for producing influenza vaccine.¹⁶ Specifically, since fiscal year 2005, HHS awarded over \$1 billion in contracts to manufacturers to develop cell-based technology.¹⁷ These contracts involved six manufacturers, and, according to HHS, established goals for manufacturers to develop cell-

¹⁴CDC reported purchasing 517,280 doses for its pediatric influenza vaccine stockpile for the 2012-2013 season. CDC reached out to immunization awardees to determine if they had the need for any additional VFC vaccine to serve VFC-eligible children in their jurisdictions. Based on this request, CDC made available approximately 400,000 doses of this stockpiled VFC vaccines to 32 immunization awardees. These doses were shipped to the federal depots serving these awardees during the week of January 21, 2013, so that the awardees could place orders.

¹⁵HHS refers to this technology as recombinant/molecular technology. According to HHS, this technology is also used for researching and developing a universal influenza vaccine. HHS's National Institutes of Health is conducting research on a universal vaccine, which it defines as a vaccine that would theoretically provide protection against any strain of influenza without needing to be updated or administered every year to protect against newly emerging annual or pandemic strains. HHS has also made other investments to enhance the U.S. vaccine supply, such as in antigen-sparing technology using adjuvants.

¹⁶In addition to human infections, strains of the H5N1 virus have infected chicken flocks and other poultry, resulting in the culling of these flocks, raising concern that the egg supply for influenza vaccine could be at risk.

¹⁷Cell-based technology has the potential to increase the overall amount of vaccine available at the end of the production process, but it does not speed up the production process itself.

based technology for influenza vaccine and obtain FDA licensure for such a vaccine.¹⁸ One of those manufacturers—Novartis Vaccines and Diagnostics, Inc. (Novartis Vaccines)—received FDA approval for its cell-based seasonal influenza vaccine, called Flucelvax, in November 2012. According to HHS, Novartis Vaccines plans to produce and distribute this vaccine for the 2013–2014 influenza season.¹⁹ (See app. II for more information on these contracts.)

In addition to investments in cell-based technology, HHS has also awarded contracts to manufacturers for the research and development of recombinant technology.²⁰ Specifically, in fiscal year 2009, HHS entered into a contract worth approximately \$81 million with Protein Sciences Corporation (Protein Sciences) for the continued development of recombinant technology for use in producing an influenza vaccine.²¹ In January 2013, FDA approved Protein Sciences’s seasonal influenza vaccine made using recombinant technology, FluBlok, which will be available for the 2013–2014 influenza season.²²

HHS’s investments in alternative vaccine technologies have been complemented by its investments in domestic manufacturers’ production capacity. As we noted in prior work, the lack of U.S. production capacity was cause for concern among experts, in part because it is possible that countries without domestic production capacity will not have access to influenza vaccine in the event of a pandemic if countries where vaccine is produced prohibit the export of the pandemic vaccine until their own

¹⁸According to HHS, it awarded multiple contracts because it expected some attrition by manufacturers as the development of new influenza vaccines progressed.

¹⁹According to HHS, Novartis Vaccines has produced 230,000 doses of its cell-based influenza vaccine; however, none of these doses have been distributed as of February 2013.

²⁰Recombinant technology has the potential to increase the overall amount of vaccine available at the end of the production process and speed up the production process itself, in part, because unlike egg-based and cell-based technologies, it does not depend on the replication of the influenza virus for production.

²¹HHS has also made investments in the research and development of pandemic influenza vaccines using recombinant technology. See table 3 in app. II for more information on these investments.

²²According to HHS, Protein Sciences has produced 100,000 doses of its recombinant influenza vaccine; however, none of these doses have been distributed as of February 2013.

needs are met.²³ Since fiscal year 2005, HHS has made investments in enhancing domestic production capacity using egg-based technology by, for example, supporting a program to ensure a year-round, secure, domestic egg supply. Prior to this funding, manufacturers maintained a 9-month supply of eggs—enough for production only during the regular influenza season without any additional capacity for emergencies, such as an influenza pandemic. Additionally, in fiscal year 2007, HHS entered into contracts with two manufacturers for the retrofitting of existing domestic egg-based production facilities. According to HHS, the retrofitting has doubled the production capacity for one of these manufacturers and tripled the production capacity for the other. This additional capacity was used during the 2009 H1N1 pandemic to produce pandemic vaccine. Also, as a condition of receiving funding to develop cell-based technology, HHS required manufacturers to have a domestic facility where cell-based influenza vaccine can be produced. In fiscal year 2009, HHS entered into a \$486.6 million contract with Novartis Vaccines for the construction of a cell-based influenza vaccine production facility in the United States to enhance domestic production capacity. This facility was completed in November 2009 and is the facility where Novartis's Flucelvax is expected to be produced for the 2013–2014 influenza season.²⁴ These investments by HHS have contributed to the doubling of the number of domestic influenza vaccine manufacturers and a general increase in the number of influenza vaccine doses produced and distributed. (See table 1.)

²³See GAO, *Influenza Pandemic: Efforts Under Way to Address Constraints on Using Antivirals and Vaccines to Forestall a Pandemic*, [GAO-08-92](#) (Washington, D.C.: Dec. 21, 2007). This situation occurred during the 2009 H1N1 pandemic when CSL Biotherapies in Australia and GlaxoSmithKline, plc, in Canada were required to fulfill their domestic orders for the pandemic vaccine prior to releasing vaccine to the United States.

²⁴According to HHS, Novavax Vaccines is currently producing this vaccine at its facility in Marburg, Germany.

Table 1: Number of U.S.-Licensed Manufacturers of Seasonal Influenza Vaccine and Number of Doses Produced and Distributed for the 2000–2001 through 2012–2013 Influenza Seasons

Influenza season	Number of licensed manufacturers	Total number of doses produced (in millions)	Total number of doses distributed (in millions)
2000–2001	3	78	70
2001–2002	3	88	78
2002–2003	3	95	83
2003–2004	3	87	83
2004–2005	3 ^a	61	57
2005–2006	4	92	82
2006–2007	5	121	104
2007–2008	6	141	113
2008–2009	6	143-146	111
2009–2010	6	114	114
2009 H1N1 pandemic ^b	5	186 ^c	173 ^d
2010–2011	6	168	158
2011–2012	6	162	132
2012–2013	6 ^e	145 ^f	134 ^g

Source: GAO analysis of CDC, FDA, and American Medical Association data.

Notes: Table includes the number of doses produced by manufacturers and distributed to customers, such as medical supply distributors, physicians, or other types of providers.

^aOf the three manufacturers of seasonal influenza vaccine for the 2004–05 influenza season, two produced and distributed vaccine and one ceased production and did not distribute any vaccine for the U.S. market after its license was suspended by the United Kingdom in October 2004. In addition to these three manufacturers, two foreign manufacturers' vaccines were purchased by the Department of Health and Human Services (HHS) for potential use in the United States under an investigational new drug protocol; however, none of these doses were distributed.

^bFor the 2009 H1N1 pandemic, vaccine was purchased exclusively by the federal government for distribution to state-designated locations.

^cAccording to HHS, 240 million doses of bulk pandemic vaccine was produced, of which 186 million doses were filled.

^dThis number includes doses distributed for the U.S. public, the Department of Defense, and for international response efforts.

^eThis number does not reflect FDA's most recent approvals for seasonal influenza vaccines using cell-based and recombinant technologies.

^fThis amount includes the 230,000 doses of cell-based influenza vaccine produced by Novartis Vaccines and the 100,000 doses of recombinant influenza vaccine produced by Protein Sciences. These doses of vaccine produced using alternative technologies were not distributed, according to HHS.

^gThis number is as of January 25, 2013.

Concluding Observations

Over the last decade, progress has been made in the federal government's preparation for and response to seasonal and pandemic influenza events. Planning activities have helped with response efforts, communication with the public regarding where and when to get vaccine has been clearer and more effective, and manufacturers have been encouraged to enhance domestic production capacity and develop alternative production technologies. Yet, the fact remains that when facing a typical influenza season, manufacturers must make decisions about how much vaccine to produce, providers must determine how much vaccine to order, and individuals—who may be influenced by a particular season's perceived severity and media reports—make their own decisions about whether, when, and where to seek vaccination. These disparate factors, along with challenges inherent in the vaccine production process and influenza seasons that are unpredictable in terms of duration and severity, can present barriers to successfully making desired quantities of influenza vaccine available when and where it is needed.

Chairman Murphy, Ranking Member DeGette, and Members of the Subcommittee, this completes my prepared statement. I would be pleased to respond to any questions that you may have at this time.

GAO Contact and Staff Acknowledgments

If you or your staff have any questions about this testimony, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this statement. Kim Yamane, Assistant Director; Tom Conahan; Kaitlin Coffey; Cathy Hamann; and Gay Hee Lee were key contributors to this statement

Appendix I: Influenza Vaccine Production Technologies

Traditionally, influenza vaccine—both seasonal and pandemic—has been produced using egg-based technology. However, the Food and Drug Administration (FDA) recently approved two new seasonal influenza vaccines produced using alternative technologies—one using cell-based technology and a second using recombinant technology.¹

Egg-Based Technology

Egg-based technology has been used to produce influenza vaccine—both seasonal and pandemic—for several decades. Department of Health and Human Services (HHS) officials we spoke with described it as a “tried and true” production technology with which regulators and manufacturers are familiar. This technology is used to make seasonal and pandemic influenza vaccine. This technology utilizes fertilized eggs as the medium for producing the vaccine.² Additionally, several decades of safety and efficacy data on the influenza vaccine produced using egg-based technology are available. However, the timeliness of vaccine production is hindered, in part, by egg-based technology’s reliance on seed strain development and growth. Another factor affecting the production timeline is the amount of antigen produced per egg.³ For example, during the 2009 H1N1 pandemic, vaccine delivery was delayed, in part, because of poorer yields of antigen per egg than expected. Also, the amount of influenza vaccine that can be produced depends on the manufacturer’s egg supply. It generally takes 12 to 18 months to establish an egg supply large enough to meet the demands of either seasonal or pandemic influenza.⁴

¹The Department of Health and Human Services (HHS) refers to this technology as recombinant/molecular technology. According to HHS, this technology is also used for researching and developing a universal influenza vaccine. The National Institutes of Health, which is conducting research on a universal vaccine, defines it as a vaccine that would theoretically provide protection against any strain of influenza without needing to be updated or administered every year to protect against newly emerging annual or pandemic strains.

²Producing these fertilized eggs is more difficult than producing eggs for human consumption. The fertilized eggs are typically 9 to 12 days old, and FDA requires that these eggs meet particular sanitation and other requirements.

³Antigen is the active substance in a vaccine that provides immunity by causing the body to produce protective antibodies to fight off a particular influenza strain.

⁴Since fiscal year 2005, HHS has made investments in enhancing domestic production capacity using egg-based technology by, for example, supporting a program to ensure a year-round, secure, domestic egg supply.

Cell-based Technology

The key potential benefit to cell-based technology is the ability to increase the overall amount of vaccine available at the end of the production process. This technology for influenza vaccines typically relies on the use of well-established cell lines, such as those originally derived from the kidney cells of monkeys or canines. These cells can exponentially increase in number, allowing for the rapid expansion of the medium used for influenza vaccine production. Additionally, cells can be stored in freezers and prepared for use within days or weeks for large-scale production demands. Vaccines using cell-based technology are licensed for use in the United States for use against other infectious diseases, such as polio. Despite the potential benefits of cell-based technology, there are challenges associated with its use. Similar to egg-based technology, cell-based technology relies on seed strain development and growth to obtain the influenza vaccine's antigen.

Recombinant Technology

Recombinant technology potentially increases the overall amount of vaccine available at the end of the production process and speeds up the production process itself. First, this technology can also utilize specialized cells—from mammals or from other sources, such as from bacteria, yeast, insects, or plants—that can exponentially increase in number as the medium for influenza vaccine production, allowing for the rapid expansion of the medium used for influenza vaccine production. Recombinant technology also has the potential to speed up the production process because it does not rely on the development and growth of a seed strain to obtain the influenza vaccine's antigen. Instead, antigen is derived from the protein(s) on the surface of the influenza virus or from the virus's genes. Recombinant technology is currently used in U.S.-marketed vaccines against other diseases, such as hepatitis B and the human papillomavirus, so FDA has experience reviewing licensing applications for vaccines produced using this technology.

Appendix II: HHS's Contracts for the Research and Development of Cell-Based and Recombinant Influenza Vaccines

Table 2: HHS Contracts Awarded for Research and Development of Cell-Based Influenza Vaccine

Manufacturer	Fiscal year of award	Total obligations (dollars in millions) ^a	Development status as of February 2013			
			Vaccine approved	Application pending	Vaccine in development	Contract no longer active
sanofi pasteur ^b	2005	\$77.0 ^c				X ^d
GlaxoSmithKline	2006	274.8			X	
Novartis Vaccines	2006	220.5	X ^e			
DynPort/Baxter ^f	2006	242.3 ^g		X ^h		
MedImmune, LLC	2006	169.5				X ⁱ
Solvay Pharmaceuticals ^j	2006	48.6 ^k				X ⁱ
Total		\$1032.7				

Source: GAO analysis of HHS and manufacturer data.

Notes: HHS data are as of February 2013, while manufacturer data are as of June 2011.

^aObligations are definite commitments that establish the legal liability of a federal agency to make payments for goods or services ordered or received, immediately or in the future. Because payments are typically made as goods or services are received, the funds listed may not have been expended. Upon termination of a contract, unexpended funds may be deobligated and, depending on the terms of their appropriation, may remain available to the agency.

^bThe policy of sanofi pasteur is to spell its name without capital letters.

^cThis amount reflects a \$20 million deobligation in fiscal year 2009. A deobligation refers to the cancellation or downward adjustment of previously incurred obligations.

^dThe manufacturer concluded that cell-based technology was not more advantageous than egg-based technology and lacked a clear path for further development, and thus the manufacturer chose to forgo pursuit of cell-based technology. According to HHS, the department terminated this contract for the development of a cell-based influenza vaccine in fiscal year 2009.

^eThis vaccine, Flucelvax, was approved by FDA in November 2012 and is expected to be available during the 2013–14 influenza season.

^fHHS contracted with DynPort Vaccine Company LLC (DynPort), which collaborated with Baxter International Inc., (Baxter) to develop a seasonal and a pandemic influenza vaccine using cell-based technology. Baxter oversaw the development of the vaccine, including supporting licensure efforts for the seasonal vaccine. Baxter also oversaw the completion of clinical trials for the pandemic vaccine. DynPort managed the overall project as well as clinical trials. For the purposes of this statement, we refer to this contract as DynPort/Baxter because of the collaboration between the two manufacturers.

^gThis amount includes a modification of \$201.3 million made in fiscal year 2007 to the existing contract. The original contract was awarded for \$41 million.

^hAccording to HHS, Dynport/Baxter anticipates submitting a licensing application to FDA in 2013.

ⁱAccording to HHS, a stop-work order was issued in fiscal year 2010 and discussions related to the termination of this contract are ongoing, as of February 2013.

^jAbbott Laboratories purchased Solvay Pharmaceuticals in February 2010.

^kThis amount reflects a \$250 million deobligation in fiscal year 2009.

^lThe manufacturer discontinued plans for the construction of a cell-based influenza vaccine production facility in the United States because of lack of commercial viability. HHS terminated this contract for the development of a cell-based influenza vaccine in June 2009.

Appendix II: HHS's Contracts for the Research and Development of Cell-Based and Recombinant Influenza Vaccines

Table 3: HHS Contracts Awarded for Research and Development of Recombinant Influenza Vaccine

Manufacturer	Fiscal year of award	Total obligations (dollars in millions) ^a	Development status as of February 2013			
			Vaccine approved	Application pending	Vaccine in development	Contract no longer active
Protein Sciences ^b	2009	\$81.3	X ^c			
Novavax ^d	2011	97.3			X	
VaxInnate ^d	2011	117.9			X	
Total		\$296.5				

Source: GAO analysis of HHS data.

^aObligations are definite commitments that establish the legal liability of a federal agency to make payments for goods or services ordered or received, immediately or in the future. Because payments are typically made as goods or services are received, the funds listed may not have been expended. Upon termination of a contract, unexpended funds may be deobligated and, depending on the terms of their appropriation, may remain available to the agency.

^bAccording to HHS, this contract requires Protein Sciences to establish enough domestic manufacturing capacity to provide finished vaccine within 12 weeks of the beginning of a pandemic and to produce at least 50 million doses of pandemic vaccine within 6 months of the beginning of a pandemic.

^cThis vaccine, FluBlok, was approved by FDA in January 2013 and is expected to be available during the 2013–2014 influenza season.

^dAccording to HHS, this manufacturer is currently conducting clinical trials for its recombinant pandemic influenza vaccine.

Related GAO Products

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