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# Influenza Vaccine Economics

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This issue brief is one of five produced for the Assistant Secretary for Planning and Evaluation (ASPE) by RTI International. The contents of these briefs is based on research involving a review of literature including peer-reviewed journals, media reports, and other nonreferenced sources (including those identified using the Worldwide Web search engine Google) as well as confidential interviews with 30 key informants representing influenza vaccine manufacturers, wholesalers, community immunizers, state and local public health officials, and other experts. The other briefs in the series are

- § *Influenza Vaccine: Who Buys It and Who Sells It*
- § *Influenza Vaccine Demand: The Chicken and the Egg*
- § *Influenza Vaccine Manufacturing*
- § *Influenza Vaccine Overview: Summary and Assessment.*

This issue brief was written by Amanda Honeycutt, PhD, Tara Robinson, BA, and Christine Layton, PhD, MPH.

# INFLUENZA VACCINE ECONOMICS

## ISSUE BRIEF

### 1. Introduction

In the fall of 2004, the United States experienced a severe shortage of influenza vaccine when Chiron, a manufacturer that had pledged to provide 46 to 48 million doses of the vaccine to the U.S. market, was forced by U.S. and U.K. regulators to suspend production due to possible bacterial contamination in its Liverpool, England, plant. The loss of Chiron's 46 million doses reduced the number of influenza vaccines available in the United States to approximately half the amount anticipated. Sanofi Pasteur<sup>1</sup> had been expected to supply approximately 54 million doses, and MedImmune intended to provide about 1.1 million doses of its FluMist vaccine, which is licensed for use in healthy persons 5 to 49 years of age (Centers for Disease Control and Prevention [CDC], 2004). Following the announcement of Chiron's lost vaccine production, Sanofi Pasteur and MedImmune increased production, ultimately producing approximately 58 million and 3 million doses, respectively (U.S. Influenza Supply, 2005).

This issue brief summarizes factors affecting the supply of influenza vaccine to the U.S. market and possible strategies to reduce or eliminate future vaccine shortages. In the next section, we provide some context for our discussion by describing recent changes in the influenza vaccine industry and in regulatory requirements for vaccine production. Section 3 contains a description of the influenza vaccine industry and factors affecting the profitability of vaccine production compared to production of other biologic products or pharmaceuticals. In Section 4, we consider factors affecting the decisions of individual suppliers about the amount of influenza vaccine to produce in a given year. In Section 5, we discuss possible strategies to prevent future shortages of influenza vaccine.

Shortages or delays in the supply of influenza vaccine to the United States have occurred in three of the past four influenza seasons (Coleman, Sangruee, Zhou, & Chu, 2005). The shortages mean that many people who want a "flu shot" at the going price are unable to get one. Even more disturbing, these shortages suggest that U.S. systems for manufacturing and distributing influenza vaccine are ill prepared to stem the spread and impact of a pandemic influenza viral strain.

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<sup>1</sup>In 2004, Sanofi merged with Aventis Pasteur to create the Sanofi Aventis Group. The vaccine division of the Sanofi Aventis Group changed its name to Sanofi Pasteur.

Academic, government, industry, and media researchers have offered several possible explanations for the recent shortages and shortfalls of influenza vaccine. One possible explanation is that excessive regulation of vaccines and their production processes for the U.S. market drove several manufacturers out of the vaccine market and creates barriers to entry for firms new to the industry (Calfee & Gottlieb, 2004). Another is that the relatively low profitability of producing vaccines compared to pharmaceuticals discourages new manufacturers from entering the industry (Kremer & Snyder, 2003). Further, because demand for the influenza vaccine is uncertain, and any excess supply of vaccine has essentially no value past January, manufacturers tend to err on the side of producing too little rather than too much vaccine. Frank Sloan is an academic economist who has written extensively about vaccine financing and supply issues. He has likened annual decisions about how much influenza vaccine to produce to the decision of how many turkeys to stock in grocery stores the week before Thanksgiving: “Some stores must throw away turkeys on Friday, but they make enough on turkeys they sell, and don’t want to run out” (Manning, 2004). However, unlike turkeys for Thanksgiving, influenza vaccine prices may not be sufficiently high to cover manufacturers’ losses when vaccines go unused and must be thrown out.

## **2. Background**

In the 1990s, four companies supplied the United States with influenza vaccine. However, in 1999 the U.S. Food and Drug Administration (FDA) adopted new laws regulating the production of vaccines, which ultimately led to the exit of two suppliers from the influenza vaccine industry (Grady, 2004).<sup>2</sup> Parkedale was ordered to cease operations in 2000 after FDA identified compliance problems, and Wyeth left the market in 2002 after being fined more than \$30 million for manufacturing practice violations (Danzon, Pereira, & Tejwani, 2005). The exit of Parkedale and Wyeth left only two firms supplying trivalent inactivated influenza vaccines (TIVs) to the U.S. market: Sanofi Pasteur and Chiron. In 2003, Chiron expanded production capabilities by purchasing a Powderject influenza vaccine plant in Liverpool, England, and rapidly increased influenza vaccine production from 25.6 million doses in 2002 to 35.6 million in 2003 (Danzon et al., 2005). Chiron pledged to supply 46 to 48 million doses to the U.S. market in 2004 (Danzon et al., 2005). Although MedImmune produces FluMist as a viable alternative to TIV, FluMist is not a perfect substitute because it is a live, attenuated influenza vaccine (LAIV) that is currently licensed for use only in healthy individuals between 5 and 49 years of age. Therefore, this brief focuses primarily on production shortages of TIVs, which are licensed for use in all age groups and for people with chronic medical conditions.

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<sup>2</sup>The companion brief *Influenza Vaccine Manufacturing* identifies the companies that have produced influenza vaccine over the past several years and indicates the names of the vaccine products manufactured and sold.

The decline in the number of vaccine manufacturers is not unique to the influenza vaccine market. The number of major U.S. vaccine manufacturers fell from 17 in 1980 to 5 in 2004 (Offit, 2005). Only four manufacturers currently produce children’s vaccines for the U.S. market, and some of those vaccines have only one manufacturer (Coleman et al., 2005).

The small number of manufacturers providing influenza and other vaccines to the U.S. market is a major contributor to shortages or disruptions in supply. If a vaccine has only one manufacturer, a production problem “immediately disrupts supply” (Coleman et al., 2005). But even when there are two or three manufacturers, as in the influenza vaccine market, the loss or delay of one manufacturer’s output generally cannot be made up quickly by other suppliers. In the next section, we examine the influenza vaccine industry and attempt to understand the features of the industry that may be related to recent shortages of influenza vaccine. Our discussion specifically addresses why there are so few suppliers of the influenza vaccine to the U.S. market, despite recent increases in the number of people in groups targeted for the vaccine (Harper, Fukuda, Uyeki, Cox, & Bridges, 2005), and why influenza vaccine manufacturers tend to produce such limited quantities of the vaccine.

### **3. The Influenza Vaccine Industry**

Although influenza vaccination may be associated with significant benefits for society, such as reduced influenza-related medical care costs and increased productivity among working adults, the vaccine is manufactured by private, for-profit pharmaceutical companies that may not take the broad societal benefits into account when deciding whether and how much vaccine to produce. These companies make decisions about whether to produce for the U.S. influenza vaccine market and how many doses to produce based primarily on profit considerations—whether they can sell influenza vaccine for more than it costs to make it. As one industry informant described, “We are a for-profit, publicly traded company. What I like to tell people is that neither Santa Claus nor UNICEF is listed on the NYSE.” In this section, we first consider the relationship between the number of producers in a vaccine market and vaccine shortages. We then discuss several factors that may affect manufacturers’ decisions about whether to participate in the influenza vaccine market.

The production of influenza vaccine typically requires 6 to 8 months from start to finish. Although newer technologies are under development to produce vaccines using cell-based technologies (the current process requires growth of influenza virus in chicken eggs), cell-based methods are expected to minimally reduce production times, to about 5 months (Rosenwald, 2004). Because of the long time required to produce influenza vaccines, the loss of one



manufacturer's production can rarely be made up by other manufacturers during the same influenza season. Moreover, when only two manufacturers provide the full supply of TIV, as in the U.S. market in 2004–2005, the loss or delay of one producer's output is likely to create a significant vaccine shortage. The loss of Chiron's vaccine output in 2004–2005 essentially cut in half the amount of influenza vaccine available for U.S. consumers. In this section, we consider several possible explanations for the small number of influenza vaccine suppliers to the U.S. market: barriers to entering the industry, low profits for vaccine manufacturers, and low demand for the influenza vaccine.

### **3.1 *Barriers to Entry***

The term “barriers to entry” refers to production costs that must be borne by a new manufacturer upon entry to an industry but are not borne by incumbents. Common examples of barriers to entry are ownership of exclusive rights to a resource (e.g., oil) or a license to produce (e.g., a patent) and large sunk costs, such as large investments in production facilities. In the case of the influenza vaccine market, FDA licensing and regulatory requirements for vaccine manufacturers may serve as significant barriers to entry for potential new producers.

FDA requires evaluation of the safety and efficacy of all new vaccines through clinical trials in the target population. The cost of conducting these trials may account for as much as half of the overall costs of developing and producing a new vaccine. According to one industry informant, vaccine clinical trials cost several thousand dollars per enrollee, and approximately 30,000 to 70,000 individuals must be enrolled to clearly demonstrate safety. In addition to the cost of conducting a clinical trial for a vaccine, the firm must bear the cost of building a small-scale production facility to make the vaccine used in a clinical trial.

FDA will accept clinical trials conducted outside of the United States only if they meet FDA requirements. Currently, there are 17 World Health Organization (WHO)–approved global manufacturers of influenza vaccine (WHO, 2005). They produce a total of 25 influenza vaccine products, 3 of which are sold in the United States (Fluzone, Fluvirin, and FluMist). If vaccine clinical trial data from other countries were approved for use in the United States, it is likely that some of the other 14 global manufacturers of influenza vaccine would decide to produce vaccine for the U.S. market. To help protect against future shortages of influenza vaccine in the United States, FDA has reported a willingness to “consider approaches to licensing such as accelerated approval based on likely surrogate markers (e.g., the degree of antibody response to the vaccine), followed by postlicensure clinical effectiveness evaluation” (Goodman, 2005).

Another barrier to entering the influenza vaccine market is the requirement that firms demonstrate the capacity to produce vaccine before FDA will grant a production license. Production facilities take 5 to 7 years to build (Brown, 2004b), and because they are highly specialized, cannot easily be converted for use in producing alternative vaccines or biologic products. Consequently, firms that decide to enter the influenza vaccine market must bear the risk of losing about \$100 million to \$150 million in production facility investments if FDA decides not to grant a production license (although FDA has never yet failed to grant such a license).

A related challenge is that each vaccine production facility must be in compliance with current Good Manufacturing Practices (cGMPs) (Orenstein, Douglas, Rodewald, & Hinman, 2005), which demonstrate the safety of the production process, equipment, and overall plant. To demonstrate compliance with cGMPs, firms must engage in a process of continuous evaluation and plant upgrades, which can be expensive, especially for new entrants to the market. Incumbents may have a cost advantage over new manufacturers if they have already developed and implemented strategies for complying with cGMP regulations that allow them to produce the vaccine at a lower cost per dose.

### **3.2 Vaccine Profits**

Most vaccines are now manufactured by large pharmaceutical companies that produce drugs and a broad range of biologics, including vaccines. It has been argued that the relatively low profitability of vaccines, compared to drug profits, is driving pharmaceutical companies to abandon vaccine production in favor of drug production. A number of pharmaceutical companies have pointed to low profits as their reason for exiting the vaccine industry. Although global vaccine sales in 2001 were approximately \$5 billion, sales of therapeutic drugs exceeded \$300 billion (Thomas, 2002).

When asked why vaccines are still being manufactured by private, for-profit companies, some industry informants indicated that pharmaceutical companies are developing and producing vaccines primarily to obtain positive recognition and press about these activities rather than for the profit motive. To provide a clearer picture of why pharmaceutical companies might rationally choose to abandon vaccine production in favor of making drugs, Kremer and Snyder (2003) modeled the decision about whether to produce vaccines or drugs and demonstrated that drugs are more profitable than vaccines under a number of plausible assumptions.

However, for the influenza vaccine, it may not be low profits that are driving firms out of the industry or keeping potential new entrants out. Firm profits are equal to revenue minus

production costs, where revenue is calculated as the price of the vaccine multiplied by the number of doses sold. If the profits associated with the production of influenza vaccine are, in fact, lower than the profits from producing drugs, then either the production costs for influenza vaccine are much higher than for drugs, prices are lower, the market for the vaccine is smaller (i.e., the number of influenza vaccine doses that can be sold is lower than for drugs), or some combination of all three. In this section, we focus on whether low anticipated influenza vaccine profits limit the number of producers for the U.S. market. In Section 4, we address the impact of profit considerations (i.e., pricing, costs, market size, and competitors' behavior) on individual firms' decisions about how much influenza vaccine to produce in a given year.

### *3.2.1 Influenza Vaccine Prices*

Although production costs for influenza vaccine may have increased over the past few years due to the need to comply with expanded cGMPs, prices have also been rising. Influenza vaccine prices have risen fourfold since the late 1990s (Pollack, 2004). Although the federal government purchases a large fraction of recommended children's vaccines and could potentially exert significant control over the pricing of those vaccines, only a small fraction of the total output of influenza vaccine is purchased directly by the federal government. The notion that federal government purchases of vaccine effectively establish the "going price" at the government price per dose is probably not relevant for the influenza vaccine market. In 2004–2005, the government price for the influenza vaccine was \$6.80 per dose, whereas the wholesale price for private purchasers was \$8.50 (Manning, 2004).

### *3.2.2 Market Size for the Influenza Vaccine*

The size of the market for influenza vaccine is difficult to predict from year to year because demand for the vaccine depends to some extent on unpredictable features of the influenza season, such as the timing and severity of outbreaks. Demand uncertainty will be discussed in some detail in Section 4 and also in the companion brief *Influenza Vaccine Demand: The Chicken and the Egg*. Despite fluctuations from year to year, the overall demand for influenza vaccine has grown since the early 1990s. Demand is likely rising because of (1) demographic changes in the United States, creating growth in the size of the target population; (2) expansion of the target population for the vaccine (Harper et al., 2005); and (3) increases in the number of healthy individuals who obtain the vaccine to protect family members and minimize work loss and suffering due to influenza illness. Additionally, because the influenza vaccine is administered annually, the market is much larger than for vaccines that require only a few doses over the lifetime.

Merrill Lynch, an investment firm, expects continued growth in the worldwide demand for influenza vaccine and reports that the influenza vaccine is “one of the few vaccine products that has drug-like sales growth” (Merrill Lynch, 2003). In the United States, the number of people in priority target groups for the vaccine in 2004–2005 was 88 million, and the number in additional target groups (e.g., health care workers) was 95 million. Increased demand for the influenza vaccine may lead to additional increases in price and, hence, profits for producers.

### *3.2.3 Production Costs for the Influenza Vaccine*

The cost of producing the influenza vaccine consists of the ongoing cost of all inputs, such as the eggs required to grow the vaccine, the labor required to produce and manage the quality of the vaccine, and the energy and other ongoing costs required to keep the production facility running. As mentioned previously, manufacturers must incur large upfront—or sunk—costs to produce the influenza vaccine, such as the costs of clinical trials and FDA licensing and the cost of building or purchasing and upgrading a vaccine production facility to meet FDA requirements for vaccine production. Although these sunk costs are large, they serve primarily as barriers to entry—once firms have made these investments (incurring costs that cannot be recouped), decisions about whether revenues from the influenza vaccine are high enough to cover costs focus primarily on day-to-day production costs.

Any increase in the ongoing costs of production will lead to a decrease in firm profits. In the case of the influenza vaccine, the costs of complying with cGMPs increased in the late 1990s, which tended to reduce vaccine profitability. However, one industry informant reported that the per-dose cost of complying with cGMPs is relatively low, suggesting that these costs had a minimal impact on reducing the profits for producing the influenza vaccine.

### *3.2.4 Investments in New Technology for Producing Influenza Vaccine*

Additional indirect evidence that the influenza vaccine is indeed profitable is seen in the growing number of firms pursuing new technologies for producing the vaccine. Data from Finkelstein (2004) indicate that there were no clinical trials for influenza vaccine products between 1983 and 1989. From 1990 through 1993, there were 4 clinical trials for new influenza vaccine products, and from 1994 through 1999, there were 15 clinical trials—an average of 2.5 per year.

## **3.3 Demand for Influenza Vaccine**

The demand for the influenza vaccine may be viewed by producers as too low to make it profitable to enter the market. Most informants interviewed indicated that about 80 million doses of influenza vaccine are demanded in a typical year, not considering year-to-year fluctuations in

demand. Even if everyone in targeted groups were to seek out the influenza vaccine, the number of doses demanded would be approximately 183.3 million per year, or 62 percent of the estimated total U.S. population of 297.2 million in 2005 (CDC, 2005b). If demand for the influenza vaccine were to increase dramatically, additional firms may choose to enter the market. In fact, expected increases in demand may be an important factor behind the decisions of GlaxoSmithKline (GSK) and ID Biomedical to enter the U.S. influenza vaccine market in 2005 and 2007, respectively. On the other hand, it is also possible that no new firms would enter the market, and expected increases in demand would be met by existing firms through expanded production.

One federal expert expressed the belief that increased demand for the influenza vaccine was a critical component to encouraging new firms to enter the influenza vaccine market and limiting future shortages. Another remarked that even increased U.S. demand for the influenza vaccine would not necessarily lead to the entry of new firms to the market. This expert explained that the large vaccine manufacturers have an incentive to split the business so that each has monopoly control over one or two vaccines. The expert stated that financial reports indicate that Merck has come to a legal agreement to give GSK a percentage of Merck profits on Merck's new human papillomavirus (HPV) vaccine. Such an agreement essentially "give[s] over the HPV vaccine as a monopoly to Merck" and creates an incentive for GSK to stop the process of developing an alternative HPV vaccine. Such an outcome may be particularly likely where the capacity to produce has not yet been created. Because several companies worldwide have the capacity and the licensing in place to produce the influenza vaccine for specific markets, it may be less likely that any one or two manufacturers would attempt to monopolize the U.S. market. Indeed, we found no evidence of collusion among firms currently operating in the U.S. influenza vaccine market.

#### **4. Vaccine Supplier Decisions**

In the previous section, we discussed factors that may limit the number of producers of influenza vaccine for the U.S. market, including barriers to entry, low profits, and low demand for the influenza vaccine. In this section, we consider the question of how each influenza vaccine manufacturer decides on the amount of vaccine to make each year and the factors that influence this decision, such as perceptions about competitors' output levels and demand.

##### ***4.1 Profit-Maximizing Decision Making***

In economics, firm behavior is typically modeled as the decision of how much of a product to make to maximize firm profits. In the case of only two firms (i.e., a duopoly), such as

in the U.S. market for TIVs, each firm's decision about how much vaccine to produce depends on the level of production expected from the other firm (Gibbons, 1992).<sup>3</sup> Although each firm could maximize profits by acting jointly as a monopoly and splitting the market to obtain monopoly prices on all the output produced, economic game theory suggests that each firm, acting simultaneously and with perfect knowledge of the other's cost structure, will in fact decide to produce more than one-half the monopoly output, which serves to drive down the market-clearing price and raise the total industry output.<sup>4</sup> Although the total output from both firms is likely to be lower than what would be expected in a perfectly competitive market with many firms producing identical vaccine products, it is nonetheless unlikely that the duopoly market structure is leading to significant underproduction of the influenza vaccine and driving recent shortages.

#### **4.2 *Uncertain Demand***

Although demand for the influenza vaccine has grown significantly over the past 20 years, demand still fluctuates from year to year, depending on many factors that are difficult to predict and impossible to control, such as the timing of influenza outbreaks in a season and the perceived severity of the disease. If the public perceives that the influenza strain is mild or if outbreaks of the disease do not occur until January or later, an excess supply of the vaccine is likely. Further, if the prior season was mild and if many individuals who went without influenza vaccine in the prior season remained healthy, demand in the current season is likely to be relatively low. In contrast, producers of children's vaccines can typically predict demand based on the size of a given birth cohort.

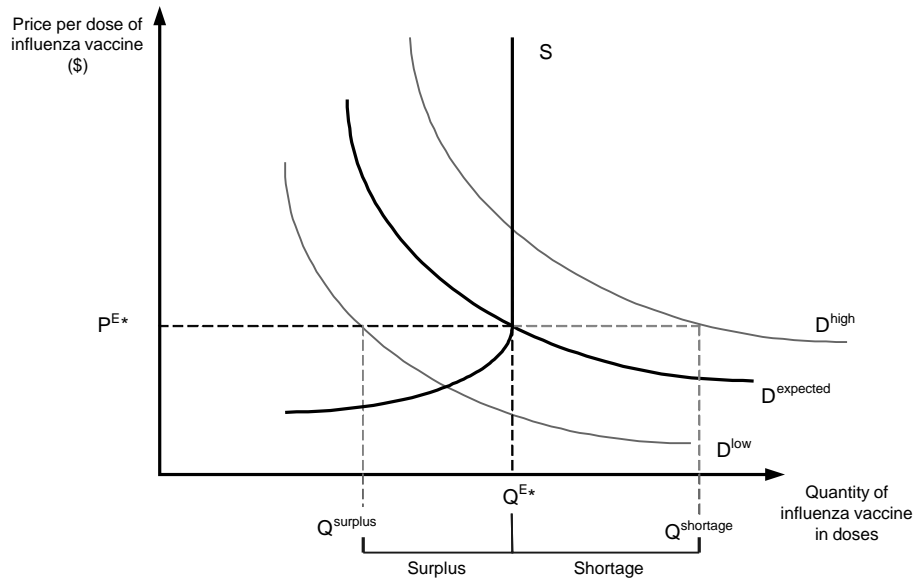
An additional challenge for influenza vaccine manufacturers is that decisions about how much vaccine to produce for the coming influenza season must be made at least 6 months in advance. At that early stage, it is especially difficult for manufacturers to predict demand for the vaccine, although orders placed at that time by providers, pharmacies, governments, and others help manufacturers determine how much vaccine to produce for the fall. Such "prebooked" vaccine orders help manufacturers estimate the expected demand for influenza vaccine. In Figure 1, market supply of the influenza vaccine is  $Q^{E*}$ , an amount that is selected based in part on the number of doses that are prebooked in the spring.

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<sup>3</sup>Each firm's profits are a function of its own output level and the output level of its competitor. Profits for firm  $i = P(q_i + q_j) * q_i - c_i$ , where  $q_i$  is the output level for firm  $i$ ,  $c_i$  represents firm  $i$ 's costs, and  $P(q_i + q_j)$  is the market price, which is higher when total market output is low and lower when total market output is high.

<sup>4</sup>This simplified discussion ignores the difficulty of predicting market size in any given year (i.e., assumes a stationary demand curve).

**Figure 1. Market Output with Uncertain Demand**



$D^{\text{expected}}$  = expected demand curve ;  $D^{\text{high}}$  = curve when demand is high;  $D^{\text{low}}$  = curve when demand is low;  $P^{E*}$  = price;  $Q^{E*}$  = quantity expected;  $Q^{\text{shortage}}$  = quantity when a shortage occurs;  $Q^{\text{surplus}}$  = quantity when a surplus occurs;  $S$  = market supply

However, demand for the influenza vaccine often deviates from the expected demand. Figure 1 depicts the problems that can arise when producers over- or underestimate demand for the influenza season. In Figure 1, producers expect that demand for the influenza vaccine will follow curve  $D^{\text{expected}}$ , and market supply is given by curve  $S$ . Market output is then  $Q^{E*}$  doses of the influenza vaccine sold at a price of  $P^{E*}$  (dollars per dose). If demand turns out to be higher than expected, as shown by curve  $D^{\text{high}}$ , then the public will wish to purchase  $Q^{\text{shortage}}$  doses of the vaccine at  $P^{E*}$ . However, because output is essentially fixed at  $Q^{E*}$  due to the long production process for the influenza vaccine, a shortage occurs.

If demand is lower than expected, as represented by curve  $D^{\text{low}}$ , then the public will be willing to purchase only  $Q^{\text{surplus}}$  doses of the vaccine at  $P^{E*}$ , leading to a surplus. Although the manufacturers may have some flexibility to lower their prices and sell additional doses of the vaccine, they are still likely to end up with extra doses, which have essentially no value by the middle of the influenza season. Dr. Peter Paridiso, Vice President for New Business and Scientific Affairs at Wyeth, reported that Wyeth had to throw out half of the doses it produced in 2002 (Grady, 2004). Wyeth exited the industry in 2002 after being fined \$30 million for cGMP violations (Danzon et al., 2005). MedImmune had to discard 5 million doses in 2003, and Sanofi Pasteur destroys about 15 percent of the vaccines it makes each year (Brown, 2004a). Even during the 2004–2005 influenza season, in which there was a shortage, approximately 5 million

doses of vaccine went unused. The possibility of producing too much vaccine and losing money on the doses that must be thrown out may lead manufacturers to err on the low side when predicting demand for a season. Consequently, if demand turns out to be high, vaccine shortages may be large.

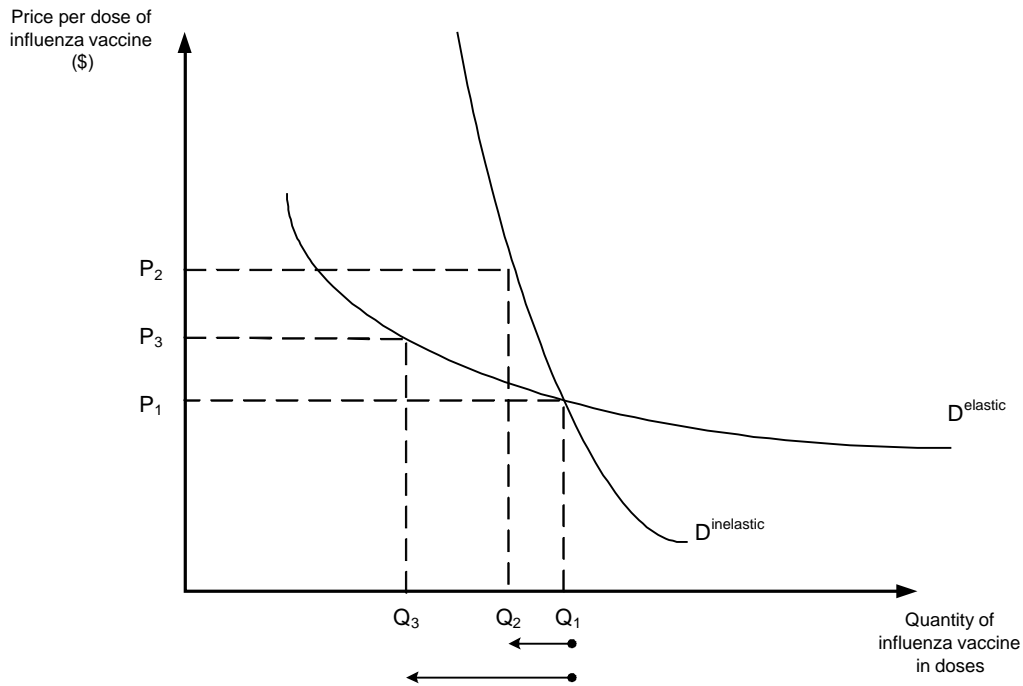
#### *4.2.1 Pricing Decisions*

Although industry informants were unable to shed much light on the pricing decisions of influenza vaccine manufacturers, we can infer that the federal government price charged for the influenza vaccine (about \$6.80 in 2004–2005) at least covers the cost of producing a single dose of the vaccine. We can further infer that the wholesale price of approximately \$8.50 in 2004–2005 was the highest price for which firms believed they could sell all of the doses produced (Figure 1). Reimbursement rates offered by Medicare or private insurance companies could influence the price of the influenza vaccine, but none of the industry informants indicated that reimbursement affected their firm’s pricing decisions. However, higher reimbursement rates, which cover the costs of the vaccine and its administration, may provide an incentive for more health care providers to purchase the vaccine and encourage their patients to get vaccinated.

Firms’ decisions about what price to charge for the influenza vaccine are based in part on perceptions about the price elasticity of demand for the vaccine. If demand for the influenza vaccine is relatively price inelastic—that is, consumption changes very little in response to changes in price (Figure 2)—then manufacturers could raise the price of the vaccine and still sell about the same number of doses. One informant indicated that demand for the influenza vaccine is probably highly inelastic with respect to changes in price, and recent experiences in the United States support this assertion. In the case of inelastic demand, surpluses of the vaccine could not be fully eliminated by price reductions. However, vaccine shortages could drive prices up considerably. During the 2000–2001 influenza season, when vaccine shortfalls arose because of manufacturing delays, one provider reported paying as much as \$12.80 per dose for influenza vaccine purchased in November, although the same provider had been able to order vaccine in spring 2000 for only \$2.87 per dose (Heinrich, 2004). In anticipation of price gouging in 2004–2005, the Federal Inspector General and several state inspectors general notified sellers that those participating in price gouging would be severely prosecuted. If demand is highly elastic, then even small price increases (decreases) could lead to large reductions (increases) in the number of doses sold (Figure 2).



**Figure 2. Price Elasticity of Demand for the Influenza Vaccine**



With elastic demand, a small increase in price ( $P_1$  to  $P_3$ ) will cause a large reduction in quantity demanded ( $Q_1$  to  $Q_3$ ). With inelastic demand, a large increase in price ( $P_1$  to  $P_2$ ) will cause only a small decrease in quantity demanded ( $Q_1$  to  $Q_2$ ).

#### 4.2.2 Vaccine Distribution

The system for distributing vaccines may offer some protection from the risk of profit losses associated with surpluses of the influenza vaccine. Manufacturers typically accept “prebooked” orders for the influenza vaccine in the spring before the influenza season, which establishes a baseline level of demand. Producers then sell vaccines either directly to providers or pharmacies (generally through prebooked contracts that specify the price and quantity in advance), wholesalers (companies that provide a broad range of medical supplies to doctors’ offices and other health care providers), or governments (local, state, and federal).

MedImmune offers buyers the option of returning unsold vaccine if they pay a higher upfront price per dose. In the 2004–2005 influenza season, MedImmune sold its nasal vaccine, FluMist, for \$24.50 per dose with the option of returning unsold doses, and for \$19 to \$20 per dose for doses that could not be returned if not used. Such a practice means that the manufacturer bears virtually all of the risk of profit loss in a low-demand season, which is probably why the practice was abandoned by other influenza vaccine producers following the 2000–2001 influenza season.

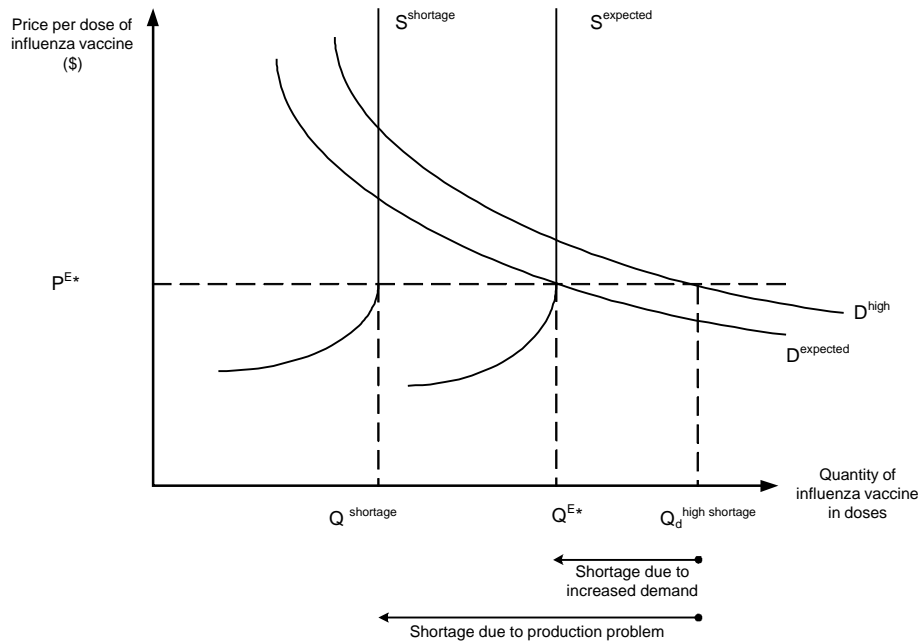
## 5. Summary and Conclusions

In this brief, we have considered several possible explanations for recent shortages or shortfalls of influenza vaccine to the U.S. market. We first addressed the question of why there are so few producers of the vaccine for the United States. The small number of producers and the lengthy production process mean that manufacturing problems for any one producer are likely to cause a shortage. Possible reasons for the small number of producers of influenza vaccine for the U.S. market are barriers to entry, low profits, and low demand for the vaccine. We found evidence that FDA requirements for licensing and production, especially the requirements that clinical trials be conducted on U.S. subjects and that production facilities be up and running before licensure, likely limit competition in the influenza vaccine industry by preventing new firms from entering. We also considered whether low profits and low demand for the influenza vaccine help to explain the small number of producers. There is evidence that the influenza vaccine is profitable, because annual vaccination is needed and because the size of the market is growing. However, it is unclear whether profits are high enough to induce pharmaceutical companies to invest in producing the influenza vaccine rather than investing in the development of drugs. We also found evidence that efforts to increase the demand for influenza vaccine might lead to the entry of new firms to the market. On the other hand, it is also possible that increases in demand would be met by expanded production on the part of existing manufacturers.

The second question we considered was how each firm in the influenza vaccine industry makes output and pricing decisions and the extent to which the decisions of individual firms may lead to too little output and ensuing shortages of vaccine. In markets with only a few producers, such as the influenza vaccine market, economic theory suggests that output will likely exceed the monopoly output level but will nonetheless be lower than in a perfectly competitive market, where no single firm exercises control over prices. Consequently, market structure does not appear to limit influenza vaccine output significantly. Uncertain demand for the influenza vaccine does tend to limit vaccine production. Because influenza vaccine makers are unable to sell excess output, they have an incentive to limit supply, which may lead to a small shortage in years where the demand for vaccines is greater than anticipated and a much larger shortage in years where one or more firms experience production problems (Figure 3).

In this final section, we briefly describe possible strategies to reduce or eliminate influenza vaccine shortages. We focus on policies that address the factors, such as barriers to entry and demand uncertainty, that appear to be key reasons for recent shortages or shortfalls in influenza vaccine supply. Although CDC has published recommendations about priority

**Figure 3. Market Output with Uncertain Demand and a Supply Shortage**



$D^{\text{expected}}$  = expected demand curve ;  $D^{\text{high}}$  = curve when demand is high;  $D^{\text{low}}$  = curve when demand is low;  $P^{E*}$  = price;  $Q^{E*}$  = quantity expected;  $Q^{\text{shortage}}$  = quantity when a shortage occurs;  $Q^{\text{surplus}}$  = quantity when a surplus occurs;  $S$  = market supply

Increased demand will cause a shortage under expected supply conditions. If supply is disrupted, consumers will face an even greater shortage.

groups to receive the influenza vaccine in the event of a vaccine delay or shortage (Harper et al., 2005), strategies to prevent, and not just cope with, future vaccine shortfalls are needed.

Some strategies to increase the output of influenza vaccine and prevent future shortages, particularly in the event of a pandemic, are to

- § harmonize licensing requirements for influenza vaccine producers across international markets;
- § increase demand for the vaccine;
- § develop government buy-back or guaranteed purchase programs;
- § create strategic reserves;<sup>5</sup> and
- § encourage and speed the development and implementation of new technologies for producing influenza vaccine.

Table 1 summarizes the advantages and disadvantages of each approach.

<sup>5</sup>We use the term “strategic reserve” rather than “stockpile” because under current licensing, influenza vaccine can be used for only one season and, thus, cannot be stockpiled.

**Table 1. Key Strategies to Stabilize Influenza Vaccine Supply**

| <b>Strategy</b>                                      | <b>Description</b>  | <b>Advantages</b>   | <b>Disadvantages</b>  | <b>Responsible Entity</b>  |
|--|---|---|---|--|
| Harmonize international standards                    | Harmonizing licensing requirements across international markets would allow entry of licensed producers from non-U.S. markets                           | Provides easier entry to U.S. market for current influenza vaccine producers  | Safety concerns   | Federal government   |
| Shorten FDA approval process for new vaccines        | Streamline FDA processes to reduce the approval time for a new vaccine application  | Encourages entry of new firms   | Safety concerns<br>Licensing and approval process would still take many years   | Federal government   |
| Implement purchase or buy-back guarantees            | Government purchases a set amount of vaccine or purchases a portion of excess supply  | Limits producer losses due to uncertain demand<br>Allows for use of unsold vaccines, which cannot be distributed to the public in future years, in research | Government costs due to sharing in financial risk of oversupply   | Federal government   |
| Increase demand                                      | Methods to stimulate demand, such as a national adult immunization program, provider incentives and education, or requiring coverage under health plans | Increase in market size may encourage additional manufacturers to enter the market  | Increased demand could drive prices up  | Federal government<br>Health care providers<br>State and local governments<br>Health insurers<br>Consumers |
| Create a strategic reserve                           | Purchase a portion of the vaccine produced by all manufacturers   | Provides protection against shortages   | Costly<br>May not be possible if production problems arise<br>Must be replaced annually, unlike stockpiles for other vaccines   | Federal government<br>State and local governments<br>Health care providers                                 |
| Encourage cell-based vaccine production technologies | Cell-based vaccines use mammalian cells rather than eggs; currently under clinical trial in the United States   | Is less susceptible to contamination, which may reduce the frequency of production problems   | Production takes almost as long as egg-based processes  | Manufacturers<br>Federal government  |
| Encourage reverse genetics technologies              | Method of creating the influenza vaccine using genome cloning after the proper strain is identified   | Decreases production time of reference viruses (to about 2 to 3 weeks), allowing for quicker response to shortages (Fedson, 2005)                           | Technology under development<br>Consumer acceptance may be a problem because the process involves a genetically modified organism<br>Legal concerns regarding intellectual property | Manufacturers<br>Federal government  |

One strategy that seems to have a great deal of promise is to harmonize licensing requirements so that firms that are licensed to produce influenza vaccine for another country could more easily become licensed to produce for the United States (Milstein & Candries, 2000). A related suggestion is to streamline the FDA regulatory process so that it would take much less than the typical 5 to 7 years for a firm to enter the influenza vaccine market (Sloan, Berman, Rosenbaum, Chalk, & Giffin, 2004). Such approaches could help reduce the considerable barriers to entry in the influenza vaccine market and encourage new suppliers to enter the market, making the overall supply of vaccine less vulnerable to production problems for any single firm. This strategy could also shorten the time for making vaccine products based on newer technologies available to the public.

Another promising strategy that could limit the extent to which uncertain demand drives shortages of the influenza vaccine is a government buy-back or guaranteed purchase program. Under a buy-back program, the federal government would agree to purchase some portion of each firm's surplus of the vaccine for a reduced price. This approach would limit the financial risk associated with overproduction for each firm, but would not provide an incentive for the firm to significantly overproduce, because the buy-back would cover only a portion of overproduction at a reduced price. Under the guaranteed purchase strategy, the federal government would agree in advance to purchase a set amount of vaccine from each producer, which could then be sold to the public in the event of a vaccine shortage.

The creation of strategic reserves would also eliminate the risk borne by influenza vaccine manufacturers because any shortages that arose could probably be eliminated or reduced by using vaccines from the reserves. This strategy is similar to the government guaranteed purchase program, although the parties responsible for creating the vaccine reserve could include all levels of government, providers, and nonprofit organizations.

Other possible strategies—although perhaps less effective than those that specifically reduce barriers to entry and uncertainty in demand—are to increase demand and encourage new technology. Many different strategies could be implemented to increase demand, including incentives for providers to vaccinate (such as the increased reimbursement levels established by Medicare for the 2005–2006 season), expanded coverage of vaccines by health insurers, and mass campaigns to increase public awareness of the burden of influenza and the effectiveness of the vaccine. Increased demand for the vaccine could encourage new firms to enter the market, and almost certainly would do so in conjunction with harmonization of international standards. However, it is also possible that increased demand would simply lead the existing manufacturers

to increase production levels, leaving the public vulnerable to shortages due to production problems experienced by any single manufacturer.

Although encouraging the approval and use of new technologies is an important long-term strategy for reducing influenza vaccine shortages, cell-based and reverse genetics processes are years away from approval in the United States. Immediate actions to encourage the entry of new influenza vaccine producers and limit the impacts of uncertain demand on producers are needed to prevent future shortages of influenza vaccine.

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