

# Vaccine Supply: A Cross-National Perspective

How do the economics of vaccines differ in the United States from other countries, both industrialized and developing?

by **Patricia M. Danzon, Nuno Sousa Pereira, and Sapna S. Tejwani**

**ABSTRACT:** In U.S. vaccine markets, competing producers with high fixed, sunk costs face relatively concentrated demand. This tends to lead to exit of all but one or very few producers per vaccine. Detailed evidence of exits and shortages in the flu vaccine market demonstrates the importance of high fixed costs, demand uncertainty, and dynamic quality competition. A comparison of vaccine suppliers in four industrialized countries compared with the United States shows that smaller foreign markets often have more and different vaccine suppliers. High, country-specific, fixed costs, combined with price and volume uncertainty, plausibly deters these potential suppliers from attempting to enter the U.S. market.

VACCINES PROVIDE AN EXTREMELY COST-EFFECTIVE technology for dealing with killer diseases, saving lives, and averting millions of dollars of potential health spending. But the U.S. supply of key pediatric vaccines is precarious, with a declining number of producers and products, leading to periodic supply interruptions and shortages. In 1967 there were twenty-six licensed manufacturers of such vaccines; in 2002 there were only twelve. Five firms produce almost all routine childhood vaccines, and five of the eight currently recommended pediatric vaccines have a single supplier.<sup>1</sup> Supply shortages can lead to children's not being immunized, while flu vaccine shortages pose risks to vulnerable populations because of the narrow window for effective administration.

Not all is gloom and doom in the vaccine business, however. Global vaccine sales doubled during the 1990s, from \$2.9 billion in 1992 to more than \$6 billion in 2000.<sup>2</sup> This revenue growth reflects new pediatric vaccines, including varicella and childhood pneumococcal vaccines, in addition to adult and travel vaccines. Over the same period, the global market value of basic vaccines dropped 40 percent.<sup>3</sup> In 2000, vaccine manufacturers spent about 16 percent of sales on research and development (R&D), a comparable ratio to that spent by the pharmaceutical industry. Roughly 350 compounds are under investigation, including 188 projects

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*Patricia Danzon (danzon@wharton.upenn.edu) is the Celia Moh Professor of Health Care Systems at the Wharton School, University of Pennsylvania, in Philadelphia. Nuno Sousa Pereira is an assistant professor in the Economics Department at the Universidade do Porto, Portugal. Sapna Tejwani is a research associate in the Health Care Systems Department at the Wharton School.*

in preclinical development and 158 in clinical trials, involving both the established vaccine producers and many new biotech entrants.<sup>4</sup> This R&D targets primarily vaccines for untreated diseases, such as cancer, HIV, and other sexually transmitted diseases (STDs), in addition to new technologies for some existing vaccines.

However, we argue that survival of only one or two producers of each vaccine is likely to be the norm in U.S. vaccine markets. We first outline the demand and supply characteristics that lead to this conclusion. Evidence on vaccine availability in Canada, France, Portugal, and the United Kingdom, compared with the United States, is consistent with our thesis. A case study of the flu vaccine in the United States illustrates the importance of high fixed costs and demand uncertainty.

## The Market For Vaccines

■ **United States.** *Small markets.* Vaccines are subject to a winner's curse: The longer the efficacy, the smaller the demand. Thus, for most pediatric vaccines, annual sales volume is limited by the size of the birth cohort, which implies vastly fewer doses than for drugs intended for chronic illnesses. Given the relatively small market in any country, one might expect vaccines to be marketed globally, to exploit scale economies. In fact, whereas most effective drugs are sold in most major markets of the world, vaccine markets remain regional and even country-specific, for reasons we discuss below.

*Government role.* Governments in all industrialized countries require and often subsidize vaccination against major contagious diseases. The rationale is that social benefits of vaccination exceed private benefits (because of reduced probability of transmission) and that individuals have incentives to "ride free" if vaccination rates for others ensure herd immunity. Government intervention has multiple effects: Government recommendations and mandates increase the volume sold for recommended products, but with opposite effects for competing, nonrecommended products. But government purchasing tends to concentrate demand and reduce prices, depending on procurement strategies and the extent of competition. The U.S. Centers for Disease Control and Prevention (CDC) began purchasing vaccines for low-income children in 1966. During the 1980s the CDC's share increased with variation across years and vaccines, ranging around 30–40 percent for diphtheria-tetanus-pertussis (DTP) and polio, and 40–50 percent and higher for measles-mumps-rubella (MMR). In 1993 the Vaccines for Children (VFC) program increased the public share of childhood vaccines to more than 50 percent.

Prior to 1993, the CDC used a winner-take-all strategy, awarding all sales to the lowest bidder. This resulted in low prices and great uncertainty for suppliers. Since 1998, the CDC solicits bids annually but does not directly purchase vaccines. Rather, it posts bid prices of firms with which it has negotiated contracts, usually with a near-zero minimum and a negotiated maximum quantity, and bidders can adjust prices quarterly. State and local grantees that receive budgets for

vaccine purchase decide which suppliers to use. States may also purchase vaccines at CDC prices for non-VFC programs that are federally authorized, including using their own funds to supply all vaccines used within the state (“universal purchase”). Vaccines with federal contracts in 1993 are subject to a cap on price increases equal to the Consumer Price Index (CPI). This created incentives to develop new variants of existing vaccines—such as combination products—which are not subject to the price cap.<sup>5</sup>

The CDC discounts have decreased over time, averaging 75 percent off catalog price in 1987 and 50 percent in 1997 and with smaller discounts on the newest, single-manufacturer vaccines, such as varicella (9 percent) and pneumococcal conjugate (22 percent).<sup>6</sup> A sole supplier of a mandated childhood vaccine faces reduced quantity uncertainty, because the government is committed to supplying the vaccine; however, the government also has bargaining power because the manufacturer has incurred sizable sunk costs and has no other purchasers of comparable size. In the private sector, vaccines are purchased directly by individual providers—physicians, hospitals, and their group purchasing organizations (GPOs). These are sophisticated, price-sensitive buyers whose ability to negotiate discounts is greater the larger the number of suppliers of a particular product.

Although the dominant government role in purchasing pediatric vaccines may contribute to low prices, particularly if multiple suppliers compete for the business, the net effect on producers’ willingness to enter this market is unclear because government recommendation also increases total units sold and reduces volume uncertainty. Moreover, the fact that supplier exit and supply disruptions have occurred for flu vaccine, for which government is a minor purchaser and does not set prices, suggests that government purchase is not a necessary condition for supply problems, as discussed below.

*Liability risks.* Tort liability has been a more severe risk for vaccines than for most therapeutic drugs, because vaccines treat large numbers of healthy people, usually children, and risks are correlated. Following exits of several manufacturers, in 1986 the Vaccine Injury Compensation Fund was established to provide no-fault compensation to children injured as a result of pediatric vaccines. However, vaccine manufacturers have still faced tort claims, most recently claims related to thimerosal, a mercury-based preservative used in several pediatric vaccines. Although these claims have so far generally not succeeded, the defense costs remain, as does the risk that some may eventually succeed.

*Barriers to generic entry.* For older vaccines, product patents are less common than process patents, which are easy to invent around. But the absence of an abbreviated application process for biologics, comparable to the abbreviated new drug application (ANDA) for generic drugs, means that a generic entrant would have to undertake costly clinical trials to demonstrate safety and efficacy, just as an originator would. Small markets and the proprietary nature of some vaccine strains may be additional factors discouraging generic entry.

*Dynamic product competition.* Although originator vaccines do not face a generic threat in the United States, their economic value is continually open to challenge by new, improved products. Many vaccine exits reflect the withdrawal of older products following entry of superior products that offered advantages in safety, efficacy, or convenience. For example, acellular pertussis replaced whole-cell pertussis; inactivated polio replaced oral (live) polio; and combination products have replaced single-product forms for most pediatric vaccines. Anticipation of improved technologies undermines incentives to invest in new variants of older technologies or plants, particularly when such investments have long lead times. Although the dynamic competition from new, improved technologies also characterizes pharmaceutical markets, for vaccines the displacement of old technologies is more rapid and complete, because of more concentrated public and private purchasing, reinforced by government recommendations.

■ **Global markets.** In Europe, Japan, and other industrialized countries, governments play a dominant role in vaccine procurement and price setting, as they do for most pharmaceuticals and health services. In Europe, many vaccines submit for market approval through the European Medicines Agency; however, vaccine schedules and pricing are determined by each country.

Vaccine purchase for the Latin America public sector is managed by the Pan American Health Organization (PAHO). Although individual countries decide which vaccines to purchase, procurement and price negotiations are coordinated through PAHO, using competitive bidding. For developing countries, including purchases financed through the Global Alliance for Vaccines and Immunization (GAVI), the United Nations Children's Fund (UNICEF) serves as the procurement agency. For basic pediatric vaccines, UNICEF accounts for 40 percent of global volume but only 5 percent of market value. Between 1992 and 2002, the number of manufacturers offering UNICEF its key DTP, bacille Calmette-Guérin (BCG, for tuberculosis), tetanus toxoid (TT), and measles vaccines dwindled to three or four for each vaccine.<sup>7</sup> UNICEF has switched from winner-take-all procurement to spreading its demand across several suppliers, to keep them in the market and defend against supply interruptions. Most of the supply to UNICEF is now from Indian, Korean, and other developing country suppliers, rather than from multinationals. This partly reflects the growing divergence between the vaccines purchased for developing countries and those purchased for industrialized countries, particularly the United States, as the latter have moved toward combination products, acellular pertussis, inactivated polio vaccine (IPV), and thimerosal-free products.

Given the tight budget constraints and the consequent focus of UNICEF and PAHO on low prices, these markets do not offer much revenue opportunity for multinational companies. A major hope is that differential pricing will permit the new and improved vaccines to recoup their fixed costs in high-income markets while being priced affordably in low-income countries. How far this will be feasi-

ble depends on the willingness of high-income countries to accept differential pricing and on whether the higher manufacturing costs of new vaccines makes them unaffordable, even at marginal cost prices, compared with older vaccines.

### **Vaccine Cost Structure And Regulation**

Bringing a new vaccine to market entails a sequence of high fixed investments in R&D, manufacturing capacity, and batch costs. Although failure rates in clinical trials may be lower for vaccines than for drugs, trial size may be larger to demonstrate absence of very rare events. For example, trials for a rotavirus vaccine have involved 70,000 patients. A vaccine Biologics License Application (BLA) includes review of both clinical data and the manufacturing plant. A full-scale production facility costs millions of dollars.<sup>8</sup> Fixed costs related to quality assurance, administration, depreciation, and other elements are estimated to account for 60 percent of total production costs.<sup>9</sup> In addition, the batch process required for vaccines entails fixed costs per batch. A batch may take six to eighteen months to produce, depending on the type of vaccine. Thus, production is characterized by very high fixed, sunk costs and low marginal cost per unit within each batch. Changing to a technology with larger scale could take years, including new approval from the U.S. Food and Drug Administration (FDA). Similarly, modifying the production process, if regulatory standards change, is costly and time-consuming. Consequently, innovation costs may be worth incurring only if costs can be recouped over several years of sales.

This structure of high fixed costs and low marginal costs, which reflects both the regulatory requirements and the technology of vaccine production, explains some of the key problems of vaccine supply. First, high regulatory costs of market approval, including many that are country-specific, plausibly contribute to the reluctance of some foreign manufacturers to launch some of their vaccines in the United States and to the absence of generic entrants.<sup>10</sup> Second, required production improvements entail high costs of retrofitting an old plant and have contributed to disruptions of supply and revenue loss for manufacturers. Costly product and plant upgrade requirements appear to have contributed to a number of vaccine exits, including the requirements to remove thimerosal in 1989 and plant-specific problems of the flu vaccine manufacturers Parkedale and Wyeth. The 1972 regulations, which required that vaccines be effective as well as safe, led to the exit of several products that had not demonstrated efficacy. Third, increasing production quickly from a given plant is limited by the batch process; in the longer term, expanding output beyond the capacity of existing plant requires building a new plant, which is extremely costly and takes several years. Consequently, one supplier cannot easily ramp up supply to fill gaps left when another experiences problems or exits the market.

High fixed costs of regulation and production are not barriers to entry if these costs can, with reasonable certainty, be recouped over large volume or high mar-

gins, or both. But the interaction of high fixed costs with relatively small and concentrated demand is likely to result in a market equilibrium that supports only one or two suppliers in most markets at any point in time. At the limit, if there are multiple firms and each faces constant or decreasing per unit costs, models of independent (noncooperative) pricing imply that price will fall to marginal cost. The intuition is simple: Having incurred the high fixed costs and having limited possibility of storing output for future use, each firm would rationally be willing to supply at marginal cost, since any excess of price above marginal cost contributes to covering the fixed costs. If such pricing is anticipated, all but one firm will eventually exit and new entry will not occur, except by a superior product. This outcome is more likely the higher the fixed costs relative to market size, the more concentrated the market demand, and the more limited the potential for storage.

Exit of established products is more likely following entry of new, superior products, particularly if superiority is reinforced by government recommendations. Thus, in the United States, acellular pertussis displaced whole-cell pertussis and IPV displaced oral (live) polio vaccine (OPV) because of safety factors that triggered changes in Advisory Committee on Immunization Practices (ACIP) recommendations; combination products have displaced the single component or smaller combinations for reasons of convenience and compliance. Multiple products may coexist if they differ in efficacy or safety for different patient groups—for example, if some patients cannot tolerate one component of a combination, a variant that excludes that component may survive, as in the case of DTP and DT (diphtheria-tetanus only).<sup>11</sup> Even then, a single firm may dominate if it has scope economies—that is, cost savings from producing both the combination and its component products. Thus, market dominance in vaccines is related to product superiority for the majority of patients, not to first-mover advantage. By contrast, in many drug classes, multiple products coexist because each product works best for a subset of patients; markets are generally larger; purchasing is less concentrated and not driven by government recommendation; and the greater potential for storage enables manufacturers to inventory excess output for future sale.

The number of vaccine manufacturers has also been reduced through mergers, including the acquisition of Connaught Laboratories by the Mériex Institute in 1989 and Chiron's purchase of Sclavo in 1998 and Powderject in 2003. How far these mergers were motivated by high fixed costs and the potential for scale economies is not explored here.

## Empirical Evidence

■ **United States versus other industrialized countries.** High fixed costs would be spread most widely if each vaccine were distributed globally. In fact, the diffusion of vaccines appears to be more limited than that of many drugs, even across industrialized countries. Licensed producers of each of the major pediatric vaccines and several adult vaccines in five countries (United States, United Kingdom, Can-

ada, France, and Portugal) are listed in online Supplemental Exhibit 1.<sup>12</sup> These data are broadly consistent with the hypotheses outlined here: that vaccine production entails high country-specific fixed costs and concentrated demand, such that each market supports only one or at most a few producers. Each country has few producers of each vaccine. However, for several vaccine types, the United States has fewer producers than other countries, despite their smaller potential volumes and dominant government purchase.<sup>13</sup> The fact that several products that are available in other countries are not available in the United States suggests that entry into the United States is not worthwhile, given the additional fixed costs combined with the price and volume uncertainty of competing with established products.

The number of licenses per manufacturer and vaccine is also often higher in Canada and Europe than in the United States. This suggests that the cost of compliance with more stringent regulatory requirements may contribute to fewer licensed products' being maintained in the United States.<sup>14</sup>

The data also indicate that although national immunization plans are similar across developed countries, the specific vaccines recommended within each category still vary—for example, in the use of combination vaccines. Diversity persists within the European Union (EU), where despite the possible use of the centralized approval process, each country's health authority still exerts choices that make each country a specific market. In 2000, for example, while Austria, Denmark, Germany, Ireland, Luxembourg, and Norway had adopted the exclusive use of acellular pertussis, Belgium and the Netherlands were only licensing whole-cell pertussis, and Finland and Portugal were recommending acellular pertussis vaccines only if whole-cell was contraindicated.<sup>15</sup> Country-specific requirements limit the potential for manufacturing economies of scale and may require the development of country-specific products.

■ **Flu vaccine: a case study.** A brief history of the supply of flu vaccine in the United States illustrates how fixed costs, dynamic competition, and preemptive effects of superior products can lead to few suppliers, despite a limited role for government purchase. Influenza is an extreme case of limited storability. The influenza virus has two strains: Type A, which has several subtypes, and Type B. Because these types undergo antigenic "drift," the influenza vaccine must be reconstituted each year to match the circulating strains. Since 1998, the World Health Organization (WHO) has issued separate recommendations in February and September for the Northern and Southern Hemispheres, respectively.<sup>16</sup> In the United States the vaccine composition for the upcoming flu season is determined between February and March. Since the peak flu season is November–March, manufacturers must supply the vaccine by October to early November.

The injectable vaccine is traditionally cultured on embryonic eggs; sterilized, monovalent concentrates are produced and then combined into the trivalent form, with comprehensive quality control at each step in the process. This time-consuming process requires that supply be estimated almost a year in advance and that

quick ramping up of production is impossible. A newer method of culturing the viruses using mammalian cells is not yet approved in the United States.

There has been a major increase in flu vaccine production since the approximately twenty million doses distributed annually in the mid-1980s.<sup>17</sup> In 1993, flu vaccine was covered under Medicaid and Medicare Part B. Before 2000, ACIP recommended vaccination primarily of elderly and other high-risk people. The ACIP recommendation was extended to people ages 50–65 years in 2000 and to infants ages 6–23 months in 2002. In 2003, pediatric vaccination was approved for use of VFC funds.

Actual uptake has increased but remained unpredictable at less than 50 percent of the recommended population. In 2001, only 87.7 million of the recommended 152 million people were vaccinated.<sup>18</sup> In 2003, although recommended recipients increased to 182 million, manufacturers distributed only 83 million doses.<sup>19</sup>

In 1999, there were four manufacturers in the United States producing a total of 77.9 million doses: Aventis Pasteur, Wyeth, Parkedale (owned by King Pharmaceuticals), and Powderject (now Chiron). In October 1999 Parkedale was cited by the FDA for current Good Manufacturing Practices (cGMP) violations. Six months later the company was ordered to halt production and distribution because it remained out of compliance. On 27 September 2000 the FDA again ordered operations halted, giving the company thirty days to implement changes. But given the short window for effective vaccination, it was unlikely that the necessary changes could be completed for that year's season. Instead, Parkedale announced its withdrawal from the flu vaccine business, writing off some \$45 million instead of incurring the costs of upgrading. Wyeth had produced influenza vaccine for the U.S. market for more than two decades. In October 2000 Wyeth was fined \$30 million for cGMP violations and an additional \$15,000 per day it remained out of compliance (capped at \$5 million).<sup>20</sup> In November 2002 Wyeth announced that it would exit, which left only two manufacturers of injectible influenza vaccine.<sup>21</sup>

In December 2002, shortly after Wyeth's exit, Aventis pledged an \$80 million investment to increase filling and formulation capacity, in addition to sizable capital investments in 2001 to increase its capacity by 20 percent.<sup>22</sup> In early 2003 Chiron acquired its Liverpool (England) plant from Powderject and began aggressive expansion to serve the expected growth in U.S. demand. Chiron produced 25.6 million doses in 2002 and 35.6 million in 2003. Before being shut down by the U.K. regulatory authorities just weeks before the 2004 influenza season, Chiron estimated it would produce 46–48 million doses for the United States. It has been suggested this rapid expansion at an aging factory contributed to the contamination problems that occurred there.<sup>23</sup> About \$75 million has been spent to upgrade the factory in the past five years. In addition, Chiron committed to spending another \$100 million to replace part of the plant.<sup>24</sup>



Only one new influenza vaccine has entered the U.S. market recently. In July 2003, FluMist, an intranasally administered, live attenuated influenza vaccine (LAIV) produced by MedImmune, was approved. But because of its restricted indications (for use in healthy people ages 5–50 years) and its relatively high price, FluMist captured only a small share of the expanding market. More generally, LAIV products are unlikely to alleviate vaccine shortages because they are restricted to low-risk people and because they rely on the same embryonic egg-based process. For 2004–2005, MedImmune planned to make only two million doses, despite a capacity to make twenty million.<sup>25</sup>

This shrinkage of the number of flu vaccine suppliers cannot be blamed on government purchase and price controls. Less than 20 percent is publicly purchased.<sup>26</sup> Medicare reimbursement for flu vaccine is at 95 percent of average wholesale price (AWP), which is a list price set by manufacturers.<sup>27</sup> Although provider reimbursement is at 95 percent of AWP, manufacturer prices are determined by competitive bids for the business of physicians, hospitals, and others who dispense flu vaccine. Thus, manufacturer prices reflect competition rather than regulation. Given the high fixed costs and low marginal costs and the total absence of storability of flu vaccine, it is not surprising that competition leads to low prices. Faced with low prices and volatile demand, manufacturers have chosen to exit rather than to incur the sizable costs of bringing manufacturing capacity up to the high standards required. Unpredictability resulting from the production technology and the very short demand window are also critical. Despite the reality of repeated shortages, millions of doses are wasted each year, because of overall demand uncertainty and mismatch of supply to meet the narrow demand window.<sup>28</sup>

But the U.S. flu market also illustrates the importance of threat of dynamic competition from superior products in vaccine investment decisions. Although manufacturers are reluctant to invest additional capacity based on current embryonic egg-based methods, several are developing mammalian cell-based vaccines. Such vaccines are expected to provide equivalent or better efficacy, with lower contamination risk, less wastage, and shorter production time.<sup>29</sup>

In 2003 Solvay's Influvac TC (cell culture) product was approved in the Netherlands, with the rest of the EU expected to follow with approval shortly. No cell-culture influenza vaccine is yet approved in the United States, but several are in clinical trials.<sup>30</sup> Given the potential superiority of cell-based products, egg-based products are likely to become obsolete, so further investment in egg-based capacity is not worthwhile without government subsidy.

The global supply of flu vaccines (Exhibit 1) shows a lack of global diffusion similar to other vaccines in Supplemental Exhibit 1. There are currently about sixteen manufacturers of flu vaccine worldwide.<sup>31</sup> Solvay, one of the EU's largest suppliers and the leader in the new cell-based methods, does not have a product approved in the United States. Despite potential for growth in the U.S. market

**EXHIBIT 1**  
**Major World Health Organization (WHO)-Approved Global Manufacturers Of**  
**Inactivated Influenza Vaccine**

<b>Company<sup>a</sup></b>	<b>Country where manufactured</b>	<b>Product name</b>	<b>Market</b>
CSL Ltd.	Australia	Fluvax	Australia
Baxter Vaccine AG	Austria	Inflexal V	Austria
ID Biomedical Corporation	Canada	Fluviral	Canada
Typharm	China	Influenza vaccine	China
Aventis Pasteur SA	France	Fluzone Vaxigrip (Merck) <sup>b</sup> Mutagrip Imovax Gripe	U.S. Globally outside U.S./U.K. Europe, South Africa South America
GlaxoSmithKline Biologicals	Germany	Fluarix	Globally outside U.S.
Istituto Vaccinogeno Pozzi SPA	Italy	Influpozzi	Italy
Denka Seiken Co. Ltd.	Japan	Influenza vaccine DKNA	Japan
Chemo-Sero-Therapeutic Research Institute	Japan	Influenza vaccine	Japan
Kitasato Institute	Japan	Influenza vaccine (KITA)	Japan
Biken, Research Foundation for Microbial Diseases of Osaka University	Japan	Influenza vaccine	Japan
Dong Shin Pharmaceutical Co. Ltd.	Republic of Korea	Dong Shin influenza HA	Republic of Korea
Solvay Pharmaceuticals BV	Netherlands	Influvac Influvac TC (cell-culture) <sup>c</sup> Invivac <sup>c</sup>	Globally outside U.S. Netherlands Europe
Cantacuzino Institute	Romania	Influenza vaccine	Romania
Berna Biotech Ltd.	Switzerland	Inflexal V	Europe
Chiron Vaccines	United Kingdom	Fluvirin Aggripal S1 Begrivac Fluad	Europe, U.S. Europe, South Africa Europe Europe
MedImmune	United States	FluMist	U.S.

**SOURCES:** World Health Organization: "Influenza Vaccine Manufacturers," [www.who.int/csr/disease/influenza/manulist/en](http://www.who.int/csr/disease/influenza/manulist/en) (1 March 2005); IMS vaccine sales data, 2002; and corresponding company Web sites.

<sup>a</sup> Crucell was omitted because it markets a platform technology versus an actual influenza vaccine.

<sup>b</sup> Distribution agreement with Merck.

<sup>c</sup> Recently approved, not yet distributed, as of 15 November 2004.

and lack of government price controls, there is little incentive for other companies to enter using the old technology, which will soon be rendered obsolete.

## Concluding Comments

This analysis suggests that U.S. vaccine markets are likely to reach equilibrium with only one or at most a few suppliers of each vaccine type. This reflects the interaction of high fixed costs with concentrated, price-sensitive demand and dynamic quality competition in which product superiority is reinforced by govern-

ment recommendation. In such conditions, there is little incentive to introduce “me-too” vaccines. Consequently, new vaccine R&D targets improved technologies for existing vaccines or new vaccine categories. The entry of superior products in turn leads to the exit of now-obsolete inferior products. Many vaccines that are approved in other industrialized markets have not applied to enter the United States, presumably in part because of the high costs of regulatory approval and manufacturing compliance, combined with relatively low and risky demand, with both price and volume uncertainty if multiple firms are competing for the business. The flu vaccine illustrates the contribution to supply problems of high regulatory hurdles, fixed costs, demand uncertainty, and the threat of dynamic competition in a context of extreme unstorability. Pediatric vaccines face similar regulatory, cost, and dynamic competitive conditions; in addition, pricing is more controlled, but volume is more predictable, at least for sole-supplier products, and storability is somewhat greater.

These economic realities pose difficult policy challenges. Harmonization of country-specific regulatory requirements might increase the diffusion of products across the industrialized markets, particularly between the EU, Canada, and the United States. However, given the importance of vaccine policy to public health, national health authorities are unlikely to delegate autonomy on vaccine recommendations and schedules. Perhaps the best hope comes from scientific advances that may improve the storability of vaccines or reduce the lead time required for production. Such improvements would mitigate temporary supply disruptions. Although stockpiles would not protect against withdrawal of a sole supplier, both theory and evidence suggest that a sole supplier faces less demand uncertainty and hence is less likely to exit, unless a superior product enters the market. But while new technologies are our best hope in the long run, new technologies may exacerbate supply shortages in the short run, by undermining incentives to invest in older plants that are destined to become obsolete.

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## NOTES

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4. Mercer Management Consulting, *Lessons Learned*.
5. Of the vaccines listed in Supplemental Exhibit 1, seventeen of the forty-eight valid licenses were issued after 1993. The exhibit is available online at [content.healthaffairs.org/cgi/content/full/24/3/706/DC1](http://content.healthaffairs.org/cgi/content/full/24/3/706/DC1).

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10. See Supplemental Exhibit 1, online at [content.healthaffairs.org/cgi/content/full/24/3/706/DC1](http://content.healthaffairs.org/cgi/content/full/24/3/706/DC1).
11. The pertussis component is usually not given to adults because whooping cough is less severe in older people while the vaccine side effects may be more severe. Patients also receive diphtheria and tetanus boosters every ten years. Nidus Information Services Inc., "What Are the Vaccines for Diphtheria, Tetanus, and Pertussis?" 2001, [www.nym.org/healthinfo/docs/090/doc90diphtheria.html](http://www.nym.org/healthinfo/docs/090/doc90diphtheria.html) (15 November 2004).
12. See Note 10.
13. Although we were unable to obtain reliable price data, the limited data available to us indicate that foreign prices are no higher and usually lower than U.S. prices.
14. In Supplemental Exhibit 1, the U.S. licenses include some that are inactive and some for further manufacturing only, so this count of licenses overstates the number of active producers in the United States compared with, say, Canada. See [content.healthaffairs.org/cgi/content/full/24/3/706/DC1](http://content.healthaffairs.org/cgi/content/full/24/3/706/DC1).
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25. "Using Live, Attenuated Influenza Vaccine for Prevention and Control of Influenza: Supplemental Recommendations of the Advisory Committee on Immunization Practices (ACIP)," *Morbidity and Mortality Weekly Report* 52, no. RR13 (2003): 1–8.
26. P. Hosbach, "Aventis Pasteur Perspective" (Presentation to the National Influenza Summit, Chicago, 20–22 May 2003).
27. Although Medicare reimbursement for other Part B drugs changed in 2004 to average selling price (ASP) plus 6 percent, reimbursement for flu, pneumococcal, and Hepatitis B vaccines remains at 95 percent of AWP.
28. See Supplemental Exhibit 2, available at [content.healthaffairs.org/cgi/content/full/24/3/706/DC1](http://content.healthaffairs.org/cgi/content/full/24/3/706/DC1).
29. J.A. Tree et al., "Comparison of Large-Scale Mammalian Cell Culture Systems with Egg Culture for the Production of Influenza Virus A Vaccine Strains," *Vaccines* 19, no. 25–26 (2001): 3444–3450.
30. These include small new entrants to the flu vaccine business, such as Protein Sciences, BioDiem, and Vaxin Technology, some with funding from the National Institutes of Health (NIH), as well as Sanofi Aventis and GlaxoSmithKline. Chiron's influenza cell-culture research program has completed Phase II clinical trials in Europe.
31. World Health Organization, "Influenza Vaccine Manufacturers," [www.who.int/csr/disease/influenza/manulist/en](http://www.who.int/csr/disease/influenza/manulist/en) (15 November 2004).