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Vaccine supply, demand, and policy: A primer

Jagannath M. Muzumdar and Richard R. Cline

Abstract

Objective: To provide an overview of supply and demand issues in the vaccine industry and the policy options that have been implemented to resolve these issues.

Data sources: Medline, Policy File, and International Pharmaceutical Abstracts were searched to locate academic journal articles. Other sources reviewed included texts on the topics of vaccine history and policy, government agency reports, and reports from independent think tanks. Keywords included *vaccines*, *immunizations*, *supply*, *demand*, and *policy*.

Study selection: Search criteria were limited to English language and human studies. Articles pertaining to vaccine demand, supply, and public policy were selected and reviewed for inclusion.

Data extraction: By the authors.

Data synthesis: Vaccines are biologic medications, therefore making their development and production more difficult and costly compared with “small-molecule” drugs. Research and development costs for vaccines can exceed \$800 million, and development may require 10 years or more. Strict manufacturing regulations and facility upgrades add to these costs. Policy options to increase and stabilize the supply of vaccines include those aimed at increasing supply, such as government subsidies for basic vaccine research, liability protection for manufacturers, and fast-track approval for new vaccines. Options to increase vaccine demand include advance purchase commitments, government stockpiles, and government financing for select populations.

Conclusion: High development costs and multiple barriers to entry have led to a decline in the number of vaccine manufacturers. Although a number of vaccine policies have met with mixed success in increasing the supply of and demand for vaccines, a variety of concerns remain, including developing vaccines for complex pathogens and increasing immunization rates with available vaccines. New policy innovations such as advance market commitments and Medicare Part D vaccine coverage have been implemented and may aid in resolving some of the problems in the vaccine industry.

Keywords: Vaccines, medication supply, medication demand, drug policy.

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Jagannath M. Muzumdar, MS, is a graduate student in Social and Administrative Pharmacy, College of Pharmacy, and **Richard R. Cline, PhD**, is Associate Professor, Department of Pharmaceutical Care & Health Systems, College of Pharmacy, University of Minnesota, Minneapolis.

Correspondence: Jagannath M. Muzumdar, MS, College of Pharmacy, University of Minnesota, 7-170 Weaver Densford Hall, 308 Harvard St SE, Minneapolis, MN 55455. Fax: 612-625-9931. E-mail: muzum002@umn.edu

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Learning objectives

- Describe the vaccine research and development process.
- List three factors that have affected vaccine supply.
- List three factors that have affected vaccine demand.
- Describe at least three “push” strategies in vaccine policy.
- Describe at least three “pull” strategies in vaccine policy.

ACPE Activity Type: Knowledge-Based

Currently, vaccine-preventable disease levels are at near record lows.¹ This was not the case at the beginning of the 20th century, when infectious diseases were the greatest threat to public health and the leading cause of death in the United States and elsewhere.² During that period, few effective treatments or measures were available for preventing large numbers of deaths from these diseases, despite the fact that in 1796, Edward Jenner performed the Western world's first vaccination.³ During the 20th century, the "Golden Age" of vaccines³ witnessed the development and acceptance of vaccines for diphtheria (discovered in 1921, but not used widely until the 1930s), tetanus toxoids (1924), influenza vaccine (first used in 1945), polio vaccine with inactive virus (1955) and live attenuated virus (1961), measles (1963), and combination measles–mumps–rubella (MMR) vaccine (1971). Estimates indicate that these vaccines have prevented more than 3 million deaths per year worldwide from infectious diseases.⁴

Vaccines have been well documented as one of the greatest achievements of medicine and are among the most cost-effective interventions in public health. For example, Zhou et al.⁵ evaluated the economic impact of the routine U.S. childhood immunization schedule. They reported that for every dollar invested in childhood vaccination against nine vaccine-preventable diseases, \$5.80 was saved in direct medical care costs. Further, when indirect benefits were taken into account, such as parental absenteeism costs incurred in caring for ill chil-

dren, the amount saved rose to \$17.70. Salo et al.⁶ assessed the cost effectiveness of influenza vaccination of children aged 6 months to 13 years and found that influenza vaccination for healthy children (all age groups) was more effective and less costly than not vaccinating children against influenza. These findings are due in part to the fact that many vaccines result in long-term or lifelong protection of the recipient and people they contact. Through the process of "herd immunity" and "herd effect,"^{7a} vaccines protect not only those who receive them but also those who cannot or do not receive the vaccine because of medical conditions, parental indifference, or religious or philosophical objections to vaccinations.^{7,8} ("The probability of unvaccinated individuals contracting a disease when part of a larger group with a certain seroprevalence [herd immunity] is called the herd effect.") However, of note, if a susceptible person strays outside the herd or if the herd changes, that person is still susceptible. Compared with pharmaceutical products, the number of lives saved per invested dollar is substantial. Economists have reported that this increased life expectancy has made a considerable contribution to economic growth.^{9,10} In fact, it has been argued that more than one-half of the growth in real income in the first half of the 20th century is attributable to the declining mortality associated with the discovery of vaccines.^{11,12}

Mass immunization programs have resulted in 100% eradication of smallpox from the world, elimination of diphtheria and polio, and 99% eradication of measles, mumps, and rubella in the United States.¹ *Haemophilus influenzae* type b (Hib) vaccines have been successful in reducing childhood mortality.¹³ In addition, vaccination of healthy adults has resulted in decreased work absenteeism and decreased use of health care resources, including less use of antibiotics.^{14,15}

Nevertheless, this success of vaccines is threatened because of several factors. Problems related to vaccine research and development (R&D), manufacturing complexities, supply and distribution, safety issues, and financing have become areas of major concern. Symptoms of this crisis include a decline in the number of vaccine producers from 26 in 1967 to 5 in 2004¹⁶ and a decline in the number of licensed vaccine products from 380 in 1967 to 51 in 2005. (Some of these are combination products.)^{16,17} Eight of these vaccine products are currently produced by five major companies: Sanofi Pasteur, Chiron (a business unit of Novartis Vaccines and Diagnostics), GlaxoSmithKline, Merck Vaccines & Infectious Diseases, and Wyeth Vaccines.¹⁸ Should any one of these suppliers cease production, it could take years for a replacement vaccine to be licensed and become available publicly.

Beginning in late 2000, the United States faced shortages of 8 of the 11 recommended childhood vaccines.¹⁹ Affected vaccines included diphtheria–tetanus–acellular pertussis (DTaP), MMR, varicella, and pneumococcal conjugate vaccines.²⁰ Suspension of production of PedvaxHIB and COMVAX by Merck and a subsequent voluntary recall of certain lots of both vaccines on December 13, 2007, led to a considerable disruption in the supply of Hib-containing vaccines.²¹ Thus, the dearth of suppliers appears to have affected the stability of vaccine supply.²²

At a Glance

Synopsis: Supply and demand issues in the vaccine industry and the policy options that have been implemented to resolve these issues are reviewed in the current work. Although vaccines have been responsible for some of the greatest successes in public health, the vaccine market is fragile and requires both supply- and demand-side interventions. Vaccine availability has been limited by the number of suppliers, high research and development and production costs, and safety problems leading to increased regulatory requirements. Demand for vaccines has been constrained by rapidly increasing vaccine costs, financing issues that have hindered efforts to achieve targets set for population immunization rates, and parental attitudes regarding the safety and efficacy of vaccine products.

Analysis: To date, a patchwork of policies to make the vaccine market more attractive for private firms and to increase patient access to these products has been implemented by the U.S. government and private philanthropies. According to the authors, an integrated policy approach that preserves incentives for market entry and innovation in the vaccine industry while addressing parental vaccine concerns and increasing immunization funding and reimbursement for both providers and patients is needed.

Compounding these problems, the epidemiology of several diseases is changing. West Nile virus killed at least 98 people in the United States in 2007,²³ and cases of Dengue fever, formerly known only in tropical areas, have been reported in Texas.²³ The Centers for Disease Control and Prevention (CDC) received reports of 1,528 cases of malaria in 2005 among individuals in the United States or its territories. This total represents an increase of 15.4% from the 1,324 cases reported for 2004.²⁴ With rapid intercontinental transportation and a larger global population, diseases can travel and spread to many countries in little time. CDC issued a health advisory on April 2, 2008, regarding a measles outbreak in Arizona that was linked to importation of the measles virus from Switzerland.²⁵ The first case, with rash onset on February 12, 2008, occurred in an adult visitor from Switzerland who was hospitalized with measles and pneumonia. In another dramatic example, severe acute respiratory syndrome spread from Asia to North America quickly, eventually infecting 8,098 people worldwide, of whom 774 died,²⁶ when a 78-year-old woman carried the infection from Hong Kong to Toronto, where it eventually caused 44 deaths.^{8,26}

Objectives

The current report seeks to provide an overview of the vaccine industry and public policy affecting it. Specifically, we sought to (1) highlight issues faced by vaccine manufacturers that make the vaccine industry a unique segment of the prescription drug industry, (2) provide an overview of the vaccine market with regards to vaccine supply and demand, and (3) provide an overview and critical evaluation of policy options proposed and implemented by various parties to address vaccine supply and demand problems.

Methods

This research consists of a narrative literature review and critical analysis of the information retrieved. Search criteria were limited to English language and human studies. Keywords used for the search included *vaccines*, *immunizations*, *supply*, *manufacturing*, *demand*, *policies*, and *push-pull solutions*. Indices such as Medline, Policy File, and International Pharmaceutical Abstracts were searched and the results augmented with reports produced by government agencies (e.g., Government Accountability Office) and independent think tanks. A variety of sources were reviewed, including reports from academic journals and current texts on vaccine history and policy. Articles pertaining to vaccine demand, supply, and public policy were selected and reviewed for inclusion in the current work.

Vaccine supply

Vaccines are biologics that introduce “weakened or killed disease-causing bacteria, viruses, and/or their components”²⁷ or toxoids into a person or animal to stimulate an immune reaction that the body will remember if exposed to the same pathogen in the future.²⁸ This unique property sets them apart from other segments of the pharmaceutical industry, such as “small-molecule” or products derived from traditional organic

chemistry methods and from other biologically derived products used in a therapeutic capacity. As such, when a private firm considers entering the vaccine market, they face several important barriers to entry, some of which are shared with these product segments and others that are unique to vaccines. These are discussed in detail below.

Vaccine R&D

New vaccines begin with the recognition of an infectious disease burden worth preventing.²⁹ Basic research regarding pathogens and immune responses, often funded by the National Institutes of Health (NIH), vaccine manufacturers, and non-profit organizations such as the Bill & Melinda Gates Foundation, is performed mainly at universities.¹ Certain vaccines for yellow fever, typhoid, and anthrax are funded and developed in the Department of Defense. Before entering clinical trials, prototype vaccines undergo toxicology testing that is conducted in a Good Laboratory Practice-compliant laboratory. Private firms then build on this knowledge to develop clinically feasible vaccine products and shepherd them through clinical testing. The vaccine’s manufacturer then must submit a Biological License Application (BLA) to the Food and Drug Administration (FDA) for evaluation and approval before marketing. The approval process tests extensively for safety and efficacy, along with purity and absence of contaminants. If data raise serious concerns about product safety or efficacy during any phase, FDA may request additional information or studies or may halt ongoing clinical studies.³⁰ The entire research, development, and approval process may require 10 years or more.³¹ Estimates of the cost of this process range from \$110 million to \$802 million (\$US 2000).^{1,32} Table 1 summarizes information on the different phases in vaccine research.

Manufacturing complexities. Although vaccine manufacturing regulation originally was controlled by the U.S. Public Health Service under the Biologics Control Act of 1902, this authority now rests with FDA. The majority of vaccines approved by FDA are manufactured from live (attenuated) or killed (inactivated) organisms. Some are based on partially purified components of an organism such as diphtheria and tetanus, and a handful are recombinantly produced, such as the hepatitis B vaccine.⁴ Vaccines are manufactured by at least three methods: egg-based (e.g., influenza vaccine), cell-derived (e.g., polio vaccine), or recombinant (e.g., hepatitis B vaccine). For bacterial vaccines, the bacterial pathogens are grown in bioreactors using media developed for optimizing the yield of the antigen (e.g., Hib)³¹ (Figure 1).

As such, small deviations in the manufacturing process can have a major impact on the potency and/or purity of these products. Thus, FDA production facility requirements are rigorous, and these stringent regulatory hurdles add to the production costs of vaccines. Because new vaccines generally are more complex than older products, vaccine suppliers face increasingly stringent regulation of manufacturing facilities even after a vaccine is approved. Suppliers undergo frequent inspections of their production facilities by each country in which the vaccine product is licensed and by FDA. Individual product batches require separate approval for release, and slight modifications

to production processes or the packaging of products may trigger expensive and time-consuming product reviews.³³ FDA also requires frequent upgrades of vaccine production facilities to reflect state-of-the-art manufacturing processes. Recently, FDA quality control inspections led to Merck's recall of 1.2 million doses of childhood vaccines to protect against meningitis, pneumonia, and hepatitis B because of contaminated manufacturing equipment.^{21,34} The recall involved 11 lots of the Hib vaccine Pedvaxhib and two lots of a combination vaccine for both Hib and hepatitis B sold under the brand name Comvax.³⁴

Market size problems

Most vaccine manufacturers are profit-seeking firms, not public health agencies. As such, they are not obligated to develop vaccines.¹⁸ These manufacturers face the decision of whether to invest large amounts of capital in vaccine R&D for a small portion of the global pharmaceutical market representing approximately 1.5% of all pharmaceutical revenues.³⁵ Most vaccines are not "blockbuster" pharmaceuticals that yield large profits or returns on investment. Although pharmaceuticals in the aggregate are a large market representing approximately \$340 billion annually (\$US 2000) worldwide, sales of vaccines are estimated at just \$4.8 billion to \$6 billion per year, with about one-quarter of total sales in the United States.³⁶ This \$6-billion market is controlled primarily by the five major manufacturers. Moreover, most vaccines are used at most several times in a lifetime, whereas therapeutic biologics and small-molecule drugs often are used every day. Thus, markets for small-molecule and biotechnology drugs treating chronic diseases are considerably more attractive to investors than vaccines.

Safety and liability issues

Safety concerns, both real and unsubstantiated, continue to be a threat to the present vaccine market. Vaccines are biologics and therefore are more difficult to produce with consistent precision than small-molecule drugs. They are subject to variability in the manufacturing process and require careful handling.¹⁷ Despite intensive quality regulation, the biologic

nature of vaccines, inherent uncertainties in manufacturing, and safety concerns make vaccine manufacturers targets for tort litigation for patients suffering an illness after vaccination. A surge of lawsuits in the 1980s resulted in serious concerns regarding the supply of the DTaP combination vaccine, as well as other vaccines.³³

Concerns have been raised in the United States regarding the safety of thimerosal, which is a mercury-containing preservative used in some vaccines. Another concern is with the false association of MMR combination vaccine and autism in children. However, to date, studies have not shown an association between neurodevelopmental disorders and thimerosal.^{37,38} In addition, no evidence has been found demonstrating a link between vaccination with the MMR vaccine and autism in children.³⁹

Rotashield, a rotavirus vaccine licensed in 1998, was permanently withdrawn in 1999 when it was found to cause a rare but serious intestinal obstruction in some recipients.⁴⁰ These safety concerns have been a reason for a change in the attitudes of some parents regarding having their children immunized.³ Taken together, liability issues and safety concerns provide important disincentives to manufacturers considering developing and manufacturing vaccines.

Vaccine demand

Immunization rates for recommended vaccines among children in the United States have been consistently high. The immunization regimen was simple, costs incurred were small, and many (if not most) public schools required proof of immunization as a condition of attendance.^{35,41} Most children received vaccines from private practitioners with their parents paying for this service through third-party insurance or out of pocket. Underprivileged children often received free immunizations from local health departments, with costs paid from general revenue funds at the local and state level.

Vaccine costs

In the 1990s, the cost of recommended immunizations began to increase, primarily as a result of the introduction of

Table 1. Phases in vaccine research

Phase	Purpose	Approximate time required (years in each phase)
Preclinical phase (animal studies)	Help in evaluating dosing and schedules	5
Phase I	Safety and immunogenicity studies performed in a small number of closely monitored patients	4
Phase II	Dose-ranging studies; may enroll hundreds of patients	
Phase III	Studies typically enroll thousands of patients and provide the critical documentation of effectiveness and important additional safety data required for licensing	3
BLA	During this stage, the proposed manufacturing facility undergoes a preapproval inspection during which production of the vaccine as it is in progress is examined in detail.	1

Abbreviation used: BLA, Biological License Application. Adapted from references 2 and 30.

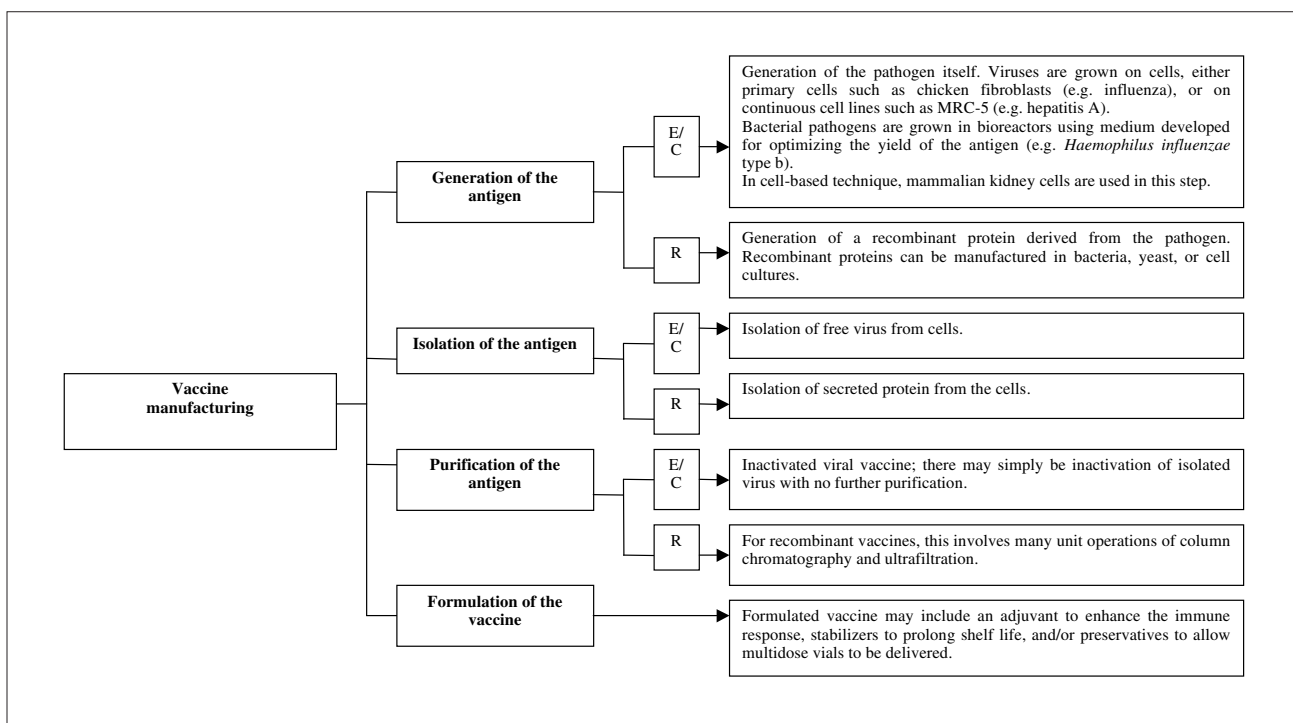


Figure 1. General steps in vaccine manufacturing

Abbreviations used: C, cell-derived; E, egg-based; R, recombinant.

Adapted from references 4 and 31.

new vaccines (e.g., acellular pertussis vaccines, varicella vaccine).⁴² These costs increased more in the early years of the current decade with the introduction of pneumococcal vaccine and meningococcal conjugate vaccine. The cost of the rotavirus vaccine from Merck is \$69.59 per dose (three doses recommended). Table 2 displays a comparison of the costs for recommended vaccines for children 0 to 6 years of age for 1987 and 2008. According to the 2007 National Immunization Survey (NIS) for children, although the number of children vaccinated had reached record highs, for some vaccines, coverage among children was lower and varied with poverty level.⁴³ Also, according to recent CDC data, substantial gaps continue to remain in vaccination coverage for adults.⁴⁴ These shortcomings may be due in part to the increasing costs of vaccines.

Vaccine financing

Given the increasing costs associated with vaccination and the increasing number of vaccine doses, financing for this service has taken on greater importance. Currently, U.S. vaccine financing is a joint responsibility shared by the private and public sectors. As of 2002, more than one-half of the vaccines recommended for children were purchased through federal contract,⁴⁵ whereas vaccines for adults typically are covered by private insurance. Private health plans often have insurance coverage for vaccines. However, some children enrolled in private health plans do not have coverage for vaccines and are considered underinsured for immunization.⁴⁶

Finally, some studies have shown that health care provid-

ers have concerns regarding the costs of purchasing and administering vaccines and their level of reimbursement from public and private insurers.⁴⁷ Providers must order and purchase many vaccines (e.g., influenza) months before they are administered, resulting in substantial capital outlay coupled with delayed reimbursement.⁴⁷ Recently, Freed et al.⁴⁸ conducted a survey exploring physicians' perspectives on reimbursement for childhood immunizations. Approximately one-half of the study respondents reported financial reasons and low profit margins from immunizations as factors affecting their purchase and administration of vaccines. These authors concluded that physicians who provide vaccines to children and adolescents are dissatisfied with third-party reimbursement levels and the increasing financial strain on their practices from immunizations. Thus, increasing vaccine prices, a greater number of vaccine doses, and declining provider reimbursement for these products appear to be factors constraining both patient and provider demand for these products.

Parental attitudes toward vaccine safety

Parental beliefs regarding vaccine safety and efficacy have led to a decrease in the demand for recommended vaccines.^{3,49-51} For example, Kennedy et al.⁵⁰ reported that 12% of parents with a child still living at home in 2002 were opposed to compulsory vaccination laws and that this opposition was associated significantly with beliefs in the safety and efficacy of vaccines. In an analysis of the 2003-2004 NIS, Gust et al.⁵¹ found that more than 13% of parents had delayed their child's

first vaccination and that 6% had refused vaccination. Concerns about vaccine safety were associated significantly with both of these behaviors.

Vaccine policy

As described above, at least two important positive externalities (i.e., benefits accruing to individuals other than the original supplier and patient)⁵² can be attributed to vaccines: (1) vaccination helps protect even those individuals not receiving the vaccine by reducing the transmission of a given disease and (2) reductions in the burden of infectious disease in the 20th century have been linked to considerable economic expansion during that period. However, vaccine manufacturers cannot capture these third-party benefits. This problem, together with other supply-side (e.g., barriers to entry) and demand-side (e.g., vaccine financing) issues have resulted in market failure (i.e., a quantity and variety of vaccine products supplied that is below the social optimum) in the vaccine market. Thus, both government policy makers and various health philanthropies have implemented a number of proposals aimed at overcoming these issues. These policies can be described as either “push” or “pull” strategies.² Push strategies seek to address supply-side issues in the vaccine market by providing direct assistance to ease the burden of research, development, and production costs, whereas pull strategies are designed to manipulate demand for vaccines, thereby improving the likelihood of a return on investment by increasing the number of immunizations administered. Thus, push mechanisms can be thought of as funding inputs, while pull mechanisms can be thought of as paying for outputs.

Push mechanisms

Financial incentives. Large, government-funded research and academic institutions play a vital role in basic vaccine research. Public funding of vaccine discovery and early developmental efforts coupled with tax subsidies to private firms can reduce manufacturers’ upfront financial outlays substantially and alter return on investment calculations for vaccine research favorably.^{2,28} For example, NIH sponsors approximately one-third of all vaccine-related basic research. Most of this funding is in the form of grants to academic institutions and health-related agencies.

The Bioshield Act of 2004 (P.L. 108-276) conferred more authority and leadership in the vaccine development effort on the National Institutes of Allergy and Infectious Diseases (NIAID).⁵³ The law increased the federal share of bioterrorism projects and allowed NIAID to hire technical experts and to award grants and contracts for advancing R&D efforts for specific vaccines. To date, funds from the act have provided support for the R&D of new smallpox and anthrax vaccines.⁵⁴ After the Bioshield Act, in 2006, Congress enacted the Pandemic and All-Hazards Preparedness Act (P.L. 109-417).⁵⁵ This act gave authority for the advanced development and acquisitions of medical countermeasures to the Biomedical Advanced Research and Development Authority.⁵⁵

FDA fast-track mechanism. The FDA Modernization Act of

1997 (P.L. 105-115) directed FDA to issue guidance describing its policies and procedures pertaining to fast-track products.⁵⁶ FDA’s fast-track mechanism is designed to facilitate the development and expedite the review of new vaccines intended to treat serious or life-threatening conditions.⁵⁶ The mechanism emphasizes early communication between the manufacturer and FDA. This allows the manufacturer and FDA to discuss development plans and strategies that can improve the efficiency of preclinical studies of the drug and focus efforts on the design of the major clinical efficacy studies before a formal submission of a BLA.⁵⁶ This early interaction can help clarify goals and plan early for obstacles that might delay approval decisions for a new vaccine. Biovest International Inc.’s BiovaxID (a therapeutic vaccine focused on follicular non-Hodgkin’s lymphoma)⁵⁷ and Intracel’s OncoVAX vaccine (designed to prevent recurrence in stage 2 colon cancer)⁵⁸ are recent examples of vaccines that have been granted fast-track status.

FDA accelerated approval. For certain biological products that are being tested for treatment of a serious or life-threatening illness, FDA regulations allow “accelerated approval” of the biologic product based on the biologic products’ “meaningful therapeutic benefit over existing treatments.”^{59,60} FDA grants this approval on the basis of adequate and well-controlled clini-

Table 2. Comparison of vaccine prices, 1987 and 2008

Year/product	No. of doses	Private sector cost	
		Cost per dose (\$)	Total cost (\$)
1987			
DTaP	5	8.67	34.68
OPV	4	11.22	56.10
MMR	1	17.88	17.88
Hib	1	0.68	6.68
Td	1	0.65	0.65
Total for 1987			115.99
2008^a			
DTaP ^b	5	20.96	104.80
IPV ^c	4	22.80	91.20
MMR ^b	2	46.54	93.08
Hib ^c	3	22.77	68.31
Hepatitis B ^c	3	64.11	64.11
Rotavirus ^c	3	69.59	208.77
Pneumococcal ^b	4	78.44	313.76
Influenza ^c	1	11.72	11.72
Varicella ^c	1	77.51	77.51
Hepatitis A	2	27.41	54.82
Meningococcal ^c	1	93.87	93.87
Total for 2008			1181.95

Abbreviations used: DTaP, diphtheria–tetanus–acellular pertussis; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus; MMR, measles–mumps–rubella; OPV, oral poliovirus; Td, tetanus–diphtheria toxoids.

Source: Centers for Disease Control and Prevention (prices as of February 23, 1987, and April 10, 2008).

^aRecommended vaccines for individuals aged 0–6 years.

^bVaccine cost includes \$2.25/dose federal excise tax.

^cVaccine cost includes \$0.75/dose federal excise tax.

cal trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.⁶⁰ For example, in an effort to meet the increasing need for a flu vaccine, the FDA approved Fluarix, an influenza vaccine for adults that contains inactivated virus through this mechanism. The manufacturer demonstrated that after vaccination with Fluarix, adults made levels of protective antibodies in the blood that FDA believes are likely to be effective in preventing influenza.⁶¹ Fluarix was the first vaccine approved using the accelerated approval process.

FDA priority review. Under the FDA Modernization Act, reviews for New Drug Applications (NDAs) or BLAs are designated as either standard or priority.⁶² The review period changes depending on the designation given to the drug. Drugs given a standard designation usually require 10 months to more than 1 year for review. The priority designation can, however, shorten the anticipated amount of time until approval decision from 10 months to 6 months for some products. The priority review process begins only when a manufacturer officially submits a BLA (or an NDA). Priority review, therefore, does not alter the steps taken in a vaccine's development or testing for safety and effectiveness.⁶² Merck's human papillomavirus vaccine—the first developed to prevent cervical cancer—was evaluated and approved in 6 months under the priority review process.⁶³

Liability protections and safety solutions. Because pharmaceutical manufacturers have expressed liability concerns as an important reason for abstaining from vaccine development, proposals addressing these concerns have been seen as necessary incentives to participation in vaccine development.²⁸ In response to the safety concerns and the lawsuits against vaccine manufacturers, Congress enacted the National Childhood Vaccine Injury Act of 1986 (P.L. 99-660).⁶⁴ This legislation established the Vaccine Injury Compensation Program in 1988, which ensures that individuals or families of individuals who may have been injured as a result of a routinely recommended vaccine are quickly, easily, and appropriately compensated.⁶⁴ An individual claiming injury or death from a vaccine files a petition for compensation with the court. The petition is reviewed to determine whether it meets the criteria for compensation. A vaccine injury table lists and explains injuries/conditions that are presumed to be caused by vaccines. It also lists time periods in which the first symptom of these injuries/conditions must occur after receiving the vaccine. To qualify for compensation, a petitioner must show that an injury found in the vaccine injury table occurred or must prove that the vaccine caused the condition. A case found eligible for compensation is scheduled for a hearing to assess the amount of compensation. Most noncompensable claims receive awards for attorney fees and costs. Congressional approval of this act also set in motion the Vaccine Adverse Event Reporting System for monitoring vaccine adverse events.

The Homeland Security Act of 2002 (P.L. 107-296) protects manufacturers and health care workers who administer the smallpox vaccine from tort liability and restricts the liability assumed by the United States to negligence of those parties.⁶⁵ The Smallpox Emergency Personnel Protection Act of 2003

(P.L. 108-20) created a mechanism to compensate individuals who, in response to a Secretarial request for smallpox vaccine preparedness, are injured by the vaccinia virus used in the smallpox vaccine. Vaccine recipients and individuals contacted by them are eligible for medical care expense reimbursement, lost income benefits, and death benefits, administered through the Health Resources and Services Administration.⁶⁶

The Public Readiness and Emergency Preparedness Act of 2006, (P.L. 109-148) is a tort liability shield that immunizes vaccine manufacturers, distributors, program planners, and administrators.⁶⁷ The act protects these entities from financial risk in the event of any loss related to the manufacture, testing, development, distribution, administration, and use of countermeasures against chemical, biological, radiological, and nuclear agents of terrorism, epidemics, and pandemics.⁶⁷

Public-private partnerships. Donors, foundations, and other partners have created a public-private partnership known as the Global Alliance for Vaccines and Immunization (GAVI), the mission of which is to save children's lives and protect people's health through the widespread use of vaccines.⁶⁸ As a GAVI partner, the Bill and Melinda Gates Foundation has invested millions of dollars in R&D for vaccines for diseases such as malaria and human immunodeficiency virus, currently the leading killers of children and adults around the world. GAVI has established public-private partnerships to accelerate late-stage development and introduction of priority vaccines against disease such as rotavirus and pneumococcus.⁶⁹

Pull mechanisms

Stockpiles. Stockpiles are, put simply, an artificial enhancement to current market demand levels in anticipation of periods when supply will be insufficient to meet demand.² Government funding of vendor-managed stockpiles of childhood vaccines ensures that some excess vaccine supply is always available to buffer supply problems when they occur. Currently, the United States has a large enough stockpile of smallpox vaccine to vaccinate every person in the country who might need it in the event of an emergency.⁷⁰ The government also expects to stockpile nearly 8 million doses of an investigational vaccine against pandemic influenza, and studies are under way to develop mechanisms that could stretch that supply to cover more than one-third of the population.⁷¹ CDC also maintains a large anthrax vaccine stockpile.

Advance market commitments. Advance market commitments involve donors who commit to buying yet-to-be-developed vaccines in bulk for poor nations if drug makers are able to deliver a vaccine that meets specifications and a price can be settled on in advance.⁷² Supporters of advance market commitments range from the GAVI partners to Pope Benedict XVI. Donors have agreed to test this mechanism for a vaccine for pneumococcal disease. To date, the Gates Foundation, the United Kingdom, Italy, Canada, Norway, and Russia have committed a total of \$1.5 billion for the project.

Vaccine bonds. The United Kingdom has taken a lead in promoting an International Financing Facility for Immunization (IFFIm)⁶⁹ IFFIm has raised more than \$1 billion in capital markets to immunize poor children in developing nations against

vaccine-preventable diseases.⁷³ IFFIm plans to invest \$4 billion over the next decade to immunize 500 million people who would not otherwise be protected from diseases that no longer represent public health threats in developed countries.⁷³ The IFFIm mechanism concentrates on the funding for vaccine research by using long-term government commitments as security bonds issued in the capital markets. The cash received for the bonds then can be used for research and future purchase of vaccines. Whenever the bonds are issued, IFFIm pays bondholders a modest rate of interest. As money pledged by donor governments becomes available gradually over 30 years, these funds will be used to repay the capital value of the bonds.⁶⁹ IFFIm was able to double the resources GAVI has been able to allocate—\$945.6 million in 2007 compared with \$418.3 million in 2006.⁷⁴

Vaccine financing programs. Historically, the U.S. immunization system has been financed through public-private sector partnerships. The public sector purchases vaccines for approximately 55% of the birth cohort.⁷⁵ Section 317 (a federal discretionary grant program to all states), the Vaccines for Children (VFC) Act of 1993 (P.L. 103-66), and state funds are major public sector sources for vaccine financing. Private sector vaccine purchases are covered through private health insurance and account for 45% to 50% of the pediatric vaccines sold annually in the United States.⁷⁵

The federal government has played an evolving role in building the immunization structure in the United States. The earliest legislation pertaining to vaccine financing is the Social Security Act of 1935. Title V of this act pertains to immunization services for children and their mothers. In 1963, Congress enacted the Vaccine Assistance Act (Section 317 of the Public Health Service Act). This legislation provided grants to social service agencies and local health departments for immunization infrastructure and vaccine purchases.⁴¹ However, barriers to immunization access still remained in some areas as a result of considerable variability in immunization efforts by state and local governments.

The deficiencies in this legislation were highlighted by the measles epidemic of 1989–1991, which involved more than 55,000 cases and led to 123 deaths.^{35,76} Substantial numbers of unimmunized preschool children, particularly in inner-city areas, contributed to this event.⁷⁶ To ensure that vulnerable children had more reliable access to vaccines, the government re-focused their funding resources on helping individual states in building immunization infrastructure. VFC is a state-operated federal entitlement program that provides free Advisory Committee on Immunization Practices–recommended vaccines to children 18 years of age or younger who are uninsured, Alaska Native or Native American, eligible for Medicaid, or receive their vaccines in a federally qualified health center.⁷⁷

At the state level, funds are earmarked for vaccine purchase and immunization programs.³⁵ State funds also have been used to purchase vaccines for children and adolescents not eligible for VFC. A combination of VFC, state/local, and Section 317 program funds (i.e., VFC only, VFC and Underinsured, VFC and Underinsured Select, Universal, and Universal

Select) has been used by a number of states to purchase all recommended vaccines for children in the state, including the privately insured.⁷⁸

Many states use universal programs that expand the eligibility for VFC vaccines by supplementing VFC purchases at federally discounted prices. The universal purchase states have been successful in raising vaccination rates among the underinsured⁷⁹ and increasing access to newer and more expensive vaccines for children without insurance.⁷⁵ However, criticisms of the universal purchase programs have been raised, including (1) vaccine manufacturers' claims that universal purchase programs unfairly provide for the purchase of all vaccines at lower government contract prices, thus eliminating the private market for vaccines and decreasing revenue; (2) although immunization charges are reduced under this program, patients still pay for the vaccine administration fee; and (3) some contend that taxpayer money should not be spent to provide free vaccines for children whose insurance would otherwise pay for it.⁷⁹ State Medicaid and State Children's Health Insurance Program funds also are provided for vaccine purchase, although the level of Medicaid funding varies from state to state.

In contrast to vaccine coverage for children, adults are far less likely to be covered for immunization services and frequently face a problem of underinsurance. The federal Medicare program covers some immunizations for all eligible beneficiaries through the Medicare Part B program.⁸⁰ The selected immunizations include influenza, pneumococcal, and hepatitis B vaccinations. Certain other vaccines (e.g., tetanus toxoid) also are covered if their administration is considered necessary in the treatment of another covered illness.⁸⁰ The Part D program generally covers those vaccines not available for reimbursement under Medicare Parts A or B when administration is reasonable and necessary for the prevention of illness. Private insurance coverage of immunizations for working-age adults varies widely by the type of health plan.³⁵ For example, health maintenance organizations typically have the highest coverage levels, while preferred provider organizations and indemnity plans historically have covered immunization services less frequently.

Conclusion

By saving millions of lives and millions of dollars, vaccines have been responsible for some of the greatest successes in public health. However, the struggle against infectious disease is a continual process requiring new vaccines for the challenges that may confront human health in the future. The vaccine market is fragile and requires both supply- and demand-side interventions. Vaccine availability has been limited by the number of suppliers, high R&D and production costs, and safety problems leading to increased regulatory requirements. Demand has been constrained by rapidly increasing vaccine costs, financing issues that have constrained efforts to achieve targets set for population immunization rates, and parental attitudes regarding the safety and efficacy of vaccine products. To date, the U.S. government, in concert with private philanthro-

Table 3. Selected vaccine legislation

Year	Legislation	Description
1813	The Vaccine Act	The first federal law dealing with patient protection and therapeutic substances. An agent to be appointed for preserving the genuine vaccine matter and to furnish the same to any citizen of the United States, whenever it may be applied for, through the medium of the post office. Packets not exceeding half an ounce and relating to vaccination to go free of postage to and from the agent.
1902	Biologics Control Act	In addition to the testing of the final product, this act also mandated the testing and control of manufacturing materials and establishments.
1963	Vaccine Assistance Act (Section 317 of the Public Health Service Act)	Infrastructure support for preventive health services such as immunization activities, including vaccine purchase assistance, is provided under Section 317 of the Public Health Service Act.
1986	National Childhood Vaccine Injury Act	Ensures that children who might be injured as a result of a routinely recommended vaccine are quickly, easily, and appropriately compensated. This act set into motion VAERS for monitoring vaccine adverse events.
1993	Vaccines for Children Act	State-operated federal entitlement program that provides free ACIP-recommended vaccines to eligible children through age 18 years.
1997	FDA Modernization Act: fast-track mechanism	The mechanism is designed to facilitate the development and expedite the review of new potential vaccines intended to treat serious or life-threatening conditions.
1998	FDA Modernization Act: priority review	Reviews for NDAs or BLAs are designated as either standard or priority. The review period changes depending on the designation given to the drug.
2002	Homeland Security Act	Protects manufacturers and health care workers who administer the smallpox vaccine from tort liability and restricts that liability assumed by the United States to negligence of those parties.
2003	Smallpox Emergency Personnel Protection Act	Mechanism to compensate individuals who, in response to a Secretarial request for smallpox vaccine preparedness, are injured by the vaccinia virus used in smallpox vaccines. Vaccine recipients and their contacts are eligible for medical care expense reimbursement, lost income benefit, and death benefits, administered through HRSA.
2004	Project Bioshield Act	Increased the federal share of bioterrorism projects and allowed NIAID to hire technical experts and to award grants and contracts for advancing the research and development efforts in vaccine areas.
2006	Pandemic and All-Hazards Preparedness Act	Intended to improve U.S. public health and medical preparedness and response capabilities for emergencies, whether deliberate, accidental, or natural.
2006	Public Readiness and Emergency Preparedness Act	Tort liability shield intended to protect vaccine manufacturers, distributors, program planners, and administrators of vaccines from financial risk in the event of a loss from vaccines.

Abbreviations used: ACIP, Advisory Committee on Immunization Practices; BLA, Biological License Application; HRSA, Health Resources and Services Administration; NDA, New Drug Application; NIAID, National Institutes of Allergy and Infectious Diseases; VAERS, Vaccine Adverse Event Reporting System.

pies, has implemented a patchwork of policies to make the vaccine market more attractive for private firms and to increase access to these products for individuals. We would argue that what is needed is an integrated policy approach that preserves incentives for market entry and innovation in the vaccine industry while simultaneously addressing parental vaccine concerns and increasing immunization funding and reimbursement for both providers and patients.

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Assessment Questions

Instructions: The assessment test for this activity must be taken online; please see “CPE processing” below for further instructions. There is only one correct answer to each question. This CPE will be available at www.pharmacist.com no later than July 31, 2009.

1. Which of the following is the process by which vaccines protect not only those who receive them but also those who cannot or do not receive the vaccine?
 - a. Passive immunization
 - b. Active immunization
 - c. Herd immunity
 - d. Mass immunization
2. After successful completion of clinical testing, the vaccine’s manufacturer must submit which of the following to the Food and Drug Administration (FDA) for evaluation and approval before marketing?
 - a. Biological License Application
 - b. Investigational New Drug Application
 - c. New Drug Application
 - d. Abbreviated New Drug Application
3. Which of these is *not* a vaccine manufacturing method?
 - a. Egg-based
 - b. Recombinant technique
 - c. Cell-derived
 - d. Mix method
4. Which of the following has led to a decrease in the number of pharmaceutical manufacturers producing vaccines?
 - a. A large number of new brand-name drug manufacturers entering the market during this period
 - b. The large proportion of revenue vaccines are responsible for at most drug manufacturers
 - c. The difficulty involved in keeping vaccine production facilities up to current regulatory standards
 - d. The National Childhood Vaccine Injury Act of 1986
5. Which of the following vaccines was withdrawn in 1999 when it was found to cause a rare but serious intestinal obstruction in some recipients?
 - a. Prevnar
 - b. Rotashield
 - c. Pneumovax
 - d. Diphtheria–tetanus–acellular pertussis
6. In the 1990s, the cost of recommended immunizations began to increase, primarily as a result of which of the following?
 - a. Vaccines for Children Act
 - b. Vaccine awareness programs
 - c. Herd immunity
 - d. Introduction of new vaccines
7. Which of the following strategies seeks to address supply-side issues in the vaccine market by providing direct assistance to ease the burden of research, development, and production costs?
 - a. Push
 - b. Active immunization
 - c. Pull
 - d. Positive market
8. Which of the following is *not* a push mechanism?
 - a. Fast-track mechanism
 - b. Accelerated approval
 - c. Vaccine bonds
 - d. Vaccine Adverse Event Reporting System

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- 9. Which of the following conferred more authority and leadership in the vaccine development effort on Biomedical Advanced Research and Development Authority?**
- Pandemic and All-Hazards Preparedness Act
 - Project Bioshield Act
 - Biologics Control Act
 - Homeland Security Act
- 10. Which of the following directed FDA to issue guidance describing its policies and procedures pertaining to fast-track products?**
- FDA Modernization Act
 - Project Bioshield Act
 - Biologics Control Act
 - Homeland Security Act
- 11. Which of the following vaccines has received fast-track status?**
- BiovaxID
 - Menactra
 - Gardasil
 - Cervarix
- 12. Which of the following is the first vaccine approved using the accelerated approval process?**
- OncoVAX
 - Fluarix
 - Gardasil
 - BiovaxID
- 13. Which of the following vaccines was approved using the priority review process?**
- BiovaxID
 - Menactra
 - Fluarix
 - Gardasil
- 14. Which of the following established the Vaccine Injury Compensation Program?**
- Biologics Control Act
 - The Vaccine Act
 - National Childhood Vaccine Injury Act
 - Homeland Security Act
- 15. Which of the following can be considered a pull mechanism?**
- The Public Readiness and Emergency Preparedness Act
 - National Childhood Vaccine Injury Act
 - Homeland Security Act
 - Vaccine Assistance Act
- 16. Which of the following is a pull mechanism?**
- Priority review for human papillomavirus vaccine
 - Stockpiles of anthrax vaccines
 - Fast-track mechanism for stage 2 colon cancer vaccine
 - Accelerated approval process for influenza vaccine
- 17. Which of the following involves donors who commit to buying yet-to-be-developed vaccines in bulk for poor nations?**
- Stockpiles
 - Advance market commitments
 - Vaccines for children
 - Generic Open
- 18. A combination of VFC, state/local, and Section 317 program funds for vaccines is called?**
- Stockpiles
 - Universal purchase
 - Vaccine assistance
 - Generic Open
- 19. Which of the following was enacted after the measles epidemic of 1989–1991, which involved more than 55,000 cases and led to 123 deaths?**
- Vaccine Assistance Act
 - Section 317 of the Public Health Service Act
 - Vaccines for Children Act
 - State Children's Health Insurance Program
- 20. Which of the following tend to provide the highest levels of immunization coverage for working-age adults?**
- Universal purchase programs
 - Health maintenance organizations
 - Vaccines for children programs
 - Advance purchase commitment programs

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