Strengthening the Supply of Routinely Administered Vaccines in the United States: Problems and Proposed Solutions

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At the request of the Assistant Secretary for Health of the United States Department of Health and Human Services, the National Vaccine Advisory Committee organized workshops in February 2002 and January 2005 to identify the reasons for vaccine shortages and to develop strategies to prevent shortages in the future. This supplement to Clinical Infectious Diseases includes presentations outlining the problems associated with and proposed solutions for strengthening the supply of routinely administered vaccines in the United States.

In the fall of 2001, 8 of the 11 universally recommended vaccines for infants and children were unavailable or in short supply in the United States. Supplies of most vaccines returned to levels sufficient to meet national needs (table 1) in 2002, but continued shortages of pneumococcal heptavalent conjugate vaccine created concern among parents and physicians. The shortage of influenza virus vaccine in the fall of 2004 led to consumer anxiety and political uproar. Although there have been short-term shortages in the past, those shortages were usually resolved without public knowledge or clamor. The concurrent shortages of 2001 lead to recognition of the vulnerability of the supply of vaccines in the United States. At the request of the Assistant Secretary for Health of the US Department of Health and Human Services, the National Vaccine Advisory Committee (NVAC) organized workshops in February 2002 and January 2005 to identify the reasons for vaccine shortages and to develop strategies and solutions to prevent shortages in the future. The NVAC workshops brought together members of the various constituencies involved in vaccine supply (e.g., manufacturers, regulatory authorities, purchasers, distributors, consumers, state and local public health authorities, scientists, advocacy groups, and legislators) and identified 5 general issues that need to be addressed to strengthen the vaccine supply in the United States: (1) providing incentives to maintain current vaccine manufacturers and encourage new manufacturers to enter the market; (2) streamlining regulatory authority, to ensure reliable production of safe and effective vaccines; (3) strengthening liability protections for consumers, manufacturers, and providers; (4) implementing a more comprehensive program of vaccine stockpiles; and (5) developing an educational program that would provide information to parents and vaccine recipients about the usage and value of approved vaccines. A summary of the first workshop was published in December 2003 [2]. This supplement to Clinical Infectious Diseases includes this overview of the problems and proposed solutions to strengthen the vaccine supply, selected manuscripts from the first workshop, and a summary of the proceedings of the second workshop.

DEVELOPING FINANCIAL INCENTIVES: VACCINES NEED TO BE PROFITABLE

Problems

The United States has lost its capability to manufacture vaccines domestically. In 1967, there were 26 licensed manufacturers of vaccines in the United States; now, there are only 6 licensed manufacturers: Wyeth, Merck, Sanofi Pasteur, MedImmune, Chiron, and GlaxoSmithKline Biologics. The merging of manufacturers is one reason for the decreased number of manufacturers, but the dominant reason that manufacturers left the market was decreased profitability. In some instances, adherence to current Good Manufacturing Practices (cGMPs)
Table 1. Average monthly need for selected vaccines for the US market, 2003.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Average national monthly need, millions of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria and tetanus toxoids and acellular pertussis</td>
<td>1.7</td>
</tr>
<tr>
<td>Measles-mumps-rubella</td>
<td>1.1</td>
</tr>
<tr>
<td>Varicella</td>
<td>0.55</td>
</tr>
<tr>
<td>Pneumococcal conjugate</td>
<td>1.33</td>
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</table>

Note: Data are from Mason [1].

of the US Food and Drug Administration (FDA) required renovation of plant facilities that was too costly to warrant the expenditure, and the companies ceased production of those vaccines. The decision of the American Academy of Pediatrics and the Advisory Committee on Immunization Practices to recommend removal or reduction of thimerosal as a preservative in vaccines forced Wyeth to stop producing diphtheria and tetanus toxoids and acellular pertussis vaccine, because thimerosal was an early part of the manufacturing process and because a new formulation would have required extensive development (P. Paradiso, personal communication). The transition to thimerosal preservative–free vaccines required the remaining manufacturers to use single-dose packaging for most vaccines. Filling vials with a single dose is less efficient than filling vials with multiple doses, because it requires more time and more vaccine to ensure that the person administering the vaccine can remove a full dose.

The reduced number of domestic manufacturers led to 2 problems with regard to vaccine supply. First, many vaccines are produced by only one manufacturer (e.g., measles-mumps-rubella, varicella, inactivated poliovirus, and pneumococcal and meningococcal polysaccharide and conjugate vaccines), so a halt in production for any reason results in an immediate loss of supply. Second, when a manufacturer voluntarily ceases production, there may not be sufficient supply from the other manufacturers to avoid a shortage. As a result of cessation of production by a major manufacturer, the national distribution of tetanus and diphtheria toxoids for adults decreased from 16.1 million doses in 1998 to 9.7 million doses in 2001.

New capital is available only for products that provide an appropriate return on investment. The fiduciary responsibility of publicly held vaccine manufacturers is no different from that of other businesses; the companies must identify optimal return on invested capital. New capital is available only for products that will provide adequate profitability. The increased production costs for products with a low profit margin may lead to the withdrawal of such products from the market. Vaccines are typically developed and produced by companies that manufacture a number of other products. Within the company, vaccines are in competition for funding with the other products in the company portfolio (e.g., over-the-counter medications, consumer products, and therapeutic drugs). Priority for maintenance or development of new facilities will go to the products that provide maximum return on investment. The relatively long research and development period and the fixed market size (because vaccines are generally given to an individual only once or a few times) place vaccines at a competitive disadvantage against other products that are administered frequently or on a regular schedule.

Paul [3] noted at the first workshop that higher profits lead to more research and development, because higher prospective profits motivate investment. An innovative and vigorous vaccine industry is promoted by maximizing profit.

Cost of approved vaccines must include losses incurred by failed vaccines. Many promising vaccines fail to achieve the expected result of safety or efficacy in the preapproval stages. The cost of approved vaccines must incorporate the losses incurred by failed products and support a continued innovative research and development program.

Vaccines are complex to develop and manufacture. Vaccines are complex to manufacture and require prolonged periods of preparation. The time needed to prepare the pneumococcal heptavalent conjugate vaccine, from start to finish, can be as long as 50 weeks [4]. Influenza virus vaccines pose unique problems, because the composition changes almost every year, the yield of candidate strains sometimes is not as high as desired (which results in fewer doses), or strains may take additional time to obtain optimal yields, resulting in delays in the availability of the vaccine.

The manufacturer of a new vaccine has to determine during the clinical trial whether the market for the vaccine is likely to be sufficient for the vaccine to be worthy of the investment of hundreds of millions of dollars for the construction of new plants and the renovation of old plants. Clinical trial costs have increased, and cost per enrollee is now many thousands of dollars. It can cost $700 million or more to bring a new vaccine from the conceptual stage to market. [5]

Manufacturer costs and the market are relatively fixed. Zoon [6], who represented the FDA perspective at the first workshop, pointed out that there are limits to the profitability of vaccines: infrastructure costs are relatively fixed, production costs are relatively fixed, and the market or demand is relatively fixed. The profitability of vaccines can be increased only by increasing the price or developing new markets.

Vaccines may be withdrawn even after FDA approval and introduction. A vaccine program may fail with substantial financial loss, even after FDA ap-
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proval has been received and the product has been introduced. Two recent examples, the rotavirus vaccine and the Lyme disease vaccine, illustrate this financial hazard. A rotavirus tetravalent vaccine (RotaShield; Wyeth) was approved by the FDA in August 1998 and was incorporated into the routine immunization schedule in 1999. Because of an association of the vaccine with intussusception, the recommendation for use of the vaccine was withdrawn, and the manufacturer ceased production of vaccine in October 1999. A Lyme disease vaccine (Lymerix; GlaxoSmithKline Biologics) was approved in 1998. Although the vaccine was considered to be safe and effective, the manufacturer ceased production of the vaccine in 2002 because of low market demand.

Solutions

The successful resolution of current concerns about financing vaccines will be a complex process that can be achieved only over time and with sustained effort. The NVAC workshops identified the following principles for increasing financial incentives [2]:

1. Manufacturers should be able to obtain an appropriate profit for the research, development, approval, and distribution of vaccines for the public well-being. Pricing of the product must include costs of failed products.

2. Financial incentives for manufacturers may be made available by means other than increased price, such as tax relief for new facilities or reconstruction of old facilities.

3. A guaranteed market and price would encourage manufacturers to invest in new or renovated facilities. The government is the largest purchaser of vaccines, providing a guaranteed market at a negotiated price. As Paul noted at the first workshop [3], government purchase represents a major presence of an “economizing” public buyer presenting a push to get the lowest price that can be negotiated and the pull to maintain a healthy, vigorous, and profitable vaccine industry.

4. The development of contracts between the government and manufacturers that reward performance, such as delivering an adequate supply of vaccine in a predictable manner, should be explored.

5. Increasing market size, such as promoting more-effective delivery of immunizations to adolescents and adults, would provide new sources of funding.

APPROPRIATE COMPENSATION FOR THOSE WHO ADMINISTER VACCINES

Problems

Physicians and health care workers must be champions of immunization programs. Most health care providers have a public health perspective that promotes immunizations, but the limited administration fees paid by Medicare (and Medicaid and insurance companies, which base their reimbursements on those set by Medicare) have been disincentives to successful immunization programs. Although the Vaccines for Children (VFC) Act of 1992 provided an entitlement for vaccine availability for many underinsured children, its implementation often removes vaccine administration from the child’s medical home. Many other underinsured families with children may fall outside the VFC program’s financial eligibility requirements.

A successful office practice or community clinic requires the development of an infrastructure with dedicated facilities and personnel. Each step in the vaccine program requires attention to multiple details: vaccine supply has to be ordered, recorded, and appropriately stored; capital needs to be available to pay up front for vaccine; supplies (e.g., syringes and needles) need to be available; the staff must be knowledgeable enough to discuss questions prompted by the mandated vaccine information sheet and to screen for vaccine indications and contraindications; a skilled health care worker needs to administer vaccine as painlessly as possible; after immunization, questions from the concerned parent or patient must be appropriately answered; and, if adverse events occur, the case must be reported to both the manufacturer and the Vaccine Adverse Event Reporting System. Until recently, the compensation for administration has been <$5 per vaccine. Some physicians with a limited pediatric practice would likely refer the patient to clinic, rather than invest in the infrastructure necessary for a successful vaccine program.

Solutions

Administration fees should be appropriate for the structure, effort, and time required for a successful immunization program. In recent years, Medicare has responded with increased compensation for those who administer vaccines. Insurance programs have followed with higher fees. For example, current compensation for administration of vaccines in pediatric practices in Massachusetts is $8–$15 per product (R. Earle, personal communication). As costs increase in the future, there will be a need to reassess the vaccine administration schedule to be sure that compensation is appropriate for the required effort.

VACCINE PURCHASING PRACTICES OF THE CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

Problems

The CDC purchases >50% of routinely administered vaccines in the United States through the Vaccination Assistance Act (Section 317 of the Public Health Service Act, 1963) and through the VFC program, which was established in 1994. In 2002, 41% of vaccines administered to children in the United States were purchased through the VFC program, 11% were purchased through Section 317 funds, 5% were purchased through state
and local governments, and 43% were purchased through the private sector [7].

The CDC is expected to pay as little for vaccines as it is able to negotiate, which likely reduces the potential profit for producers (table 2). In contrast, if newly licensed vaccines are recommended for universal use, they become covered by the VFC program and must be purchased by the CDC at prices close to those asked by the producer; this creates a powerful incentive to the industry to concentrate on new vaccines, rather than on the production of older, less profitable vaccines.

Solutions
Manufacturers need to be able to increase the price per dose for older “commodity” vaccines as their production costs increase over time in response to changing cGMPs. Over the past several years, increases in the price per dose of influenza virus vaccine have gone unchallenged, attracting new producers to the US market.

REGULATORY OVERSIGHT NEEDS TO BE STREAMLINED

The FDA has the responsibility to ensure the safety and effectiveness of biologic products intended for use in humans. This includes the regulation of vaccine development, testing, and licensure. After licensure of a vaccine, the FDA monitors the product and its production facilities, including periodic inspections of facilities. Prior to licensure of a vaccine, the FDA may request that the sponsor conduct postmarketing studies to monitor for potential adverse events.

Problems
cGMPs. FDA oversight of vaccine production requires manufacturers to maintain cGMPs. cGMPs are evolving standards of practices used by industry. As manufacturing practices change, the FDA monitors that vaccines are being manufactured according to these standards. Changing standards represent increasing costs for vaccine production over time.

Historically, inspections of production processes and facilities were done by FDA-based scientists. To make the process more standardized, Team Biologics was created to perform these activities. Manufacturers complain that this new inspection process has imposed excessive record-keeping and administrative requirements. The result has been a shift to more druglike standards of manufacturing, with more-stringent guidelines for systems. Ultimately, as cGMPs change, the manufacturer must decide whether it is cost effective to continue to upgrade production practices or to cease production. Thus, in some instances, vaccine manufacturers have chosen to leave the vaccine marketplace, rather than invest in new or renovated vaccine facilities. For example, Wyeth ceased production of diphtheria and tetanus toxoids and acellular pertussis vaccine in 2001, in part because of the increasing costs of maintaining cGMPs. In addition, the need to reduce the thimerosal content would have substantially altered the production process. The company also stopped production of pneumococcal polysaccharide and influenza virus vaccines, because significant investment in facilities could not be justified by their market potential.

Center for Biologics Evaluation and Research (CBER). The FDA CBER is a national resource for vaccine development, evaluation, regulation, and research. The CBER plays a critical role in the translation of basic research to licensed products through applied research. For example, scientists at the CBER have developed assays for standardization of the potency of vaccines, have made improvements in neurovirulence testing for viral vaccines, and have developed novel methods for the detection of adventitious agents in vaccines.

Differing national regulatory entities. Each country regulates drugs and biologics for use by its citizens. For manufacturers, this represents great complexity and expense to bring products to multiple markets and presents barriers to responding to vaccine shortages. For example, during the shortage of influenza virus vaccine in the United States in 2004–2005, there were ample supplies available in other countries that could not be utilized because the vaccines had not been submitted for review by the FDA.

Solutions
Streamlining FDA regulations. The FDA is charged to ensure the safety of vaccines. Vaccines and biologics are very different than drugs, and their regulation should be different as well. Definition of cGMP standards should be evidence based and should be subject to external review, perhaps by the Vaccines and Related Biologic Products Advisory Committee. Standards should be dynamic, with changes that incorporate both technological advances and facilities that are in

Table 2. Federal contract and catalog prices of selected vaccines, 2002 [7].

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Federal contract price, US$</th>
<th>Catalog price, US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria and tetanus toxoids and acellular pertussis</td>
<td>10.58–10.65</td>
<td>17.12–18.50</td>
</tr>
<tr>
<td>Measles-mumps-rubella</td>
<td>15.53</td>
<td>28.35</td>
</tr>
<tr>
<td>Varicella</td>
<td>39.14</td>
<td>49.13</td>
</tr>
<tr>
<td>Pneumococcal conjugate–7</td>
<td>45.99</td>
<td>49.13</td>
</tr>
<tr>
<td>Inactivated poliovirus</td>
<td>8.25</td>
<td>15.42</td>
</tr>
<tr>
<td>Haemophilus influenzae b</td>
<td>5.75–8.00</td>
<td>15.25–18.95</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>9.00</td>
<td>21.40–24.20</td>
</tr>
</tbody>
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Vaccine safety research is not adequately funded. This type of research does not compete well with discovery research of the type sponsored by the National Institutes of Health, and neither the CBER nor the CDC has sufficient funding to conduct anticipatory vaccine safety research. As a consequence, when a hypothesis, such as a causal relationship between autism and administration of measles-mumps-rubella vaccine or thimerosal, is suggested, years are required to collect sufficient evidence to test the hypothesis and reassure the public of vaccine safety.

Solutions
The NVAC workshops considered the following remedies:

1. Strengthen legislative language to ensure that VICP remains the primary mechanism for the adjudication of vaccine injury claims. For example, VICP legislation should recognize that the term “vaccine” includes all ingredients in the formulation of the vaccine, including preservatives, additives, and excipients.

2. Expand the VICP to include additional vaccines as they are recommended for routine administration to children.

3. Utilize a portion of the trust fund for vaccine safety research. Priorities for vaccine safety research could be formulated with public input in a fashion similar to the process whereby NVAC advised the Secretary on the selection of topics for the Institute of Medicine Vaccine Safety Review Committee.

STRATEGIC VACCINE INVENTORIES (STOCKPILES)
Stockpiles could be one of the most effective solutions to alleviate short-term vaccine shortages. The stockpile project was initiated in 1986, with the goal of the availability of a 6-month supply of selected vaccines.

Increased funding for the CBER.
The Administration and Congress need to recognize the unique aspects of the research activities conducted by the CBER. They should greatly expand the funding for the CBER so that highly qualified scientists can be retained and new scientists can be attracted to this important division of the FDA. The FDA budget should reflect the strategies that have enhanced the efficiency of vaccine evaluation in the past and can accelerate the process in the future.

Harmonization.
Harmonization of regulatory requirements across countries and regions would greatly reduce the complexity and expense of bringing a product to international markets. This is an important goal for the FDA, which is an active participant in the International Committee on Harmonization, an organization that attempts to achieve common regulatory procedures. These activities need to be greatly enhanced. The FDA needs to accelerate the effort to coordinate activities with other national regulatory authorities, to achieve mutual recognition of evaluation of the safety and efficacy of specific vaccines so that there are uniform criteria for approval in the United States and elsewhere. In addition, when unexpected vaccine shortages occur, there need to be emergency regulatory procedures in place to permit temporary licensure of products that have undergone similar regulatory review in other countries.

VACCINE LIABILITY
The National Childhood Vaccine Injury Act of 1986 established a no-fault compensation program through the Vaccine Injury Compensation Program (VICP). The program removed a financial burden from manufacturers and health care workers who administer vaccines. The program has been successful in providing appropriate compensation for the few individuals who have sustained injuries associated with receipt of a vaccine, thus ensuring that protection provided by the vaccine will be available to the majority of children. The process has been effective because it adheres to the principle of no fault; involves short informal hearings; and has established annullities, trusts, and guardianships to help ensure the safety of the benefit stream. The trust fund was established by a tax of $0.75 on each dose (or disease prevented) of vaccine that the CDC recommends for routine administration to children. More than $1.5 billion has been awarded to individuals and families, with an average of 3 years per case for adjudication. Plaintiffs’ attorney fees are determined by the court and reimbursed from the trust fund. This legislation and the VICP greatly stabilized the marketplace by reducing financial risks to the vaccine producers and to providers who administer the vaccines, while recognizing the need to compensate individuals injured by vaccine.

Problems
Current concerns with regard to maintenance of the effectiveness of the VICP include attempts by plaintiffs’ attorneys to circumvent the VICP. For example, class action lawsuits focused on thimerosal, in particular, as a cause of autism have been filed in a number of jurisdictions, despite a comprehensive review by the Institute of Medicine Vaccine Safety Review Committee that favored rejection of such an association [9].

Compliance with current standards but that allow sufficient flexibility to ensure continued vaccine production within the context of safety and effectiveness. Efforts to increase efficiency of the regulatory process should include early and frequent communication between the FDA and sponsors with regard to the conduct of research that facilitates accelerated development and approval, as well as anticipated changes in cGMPs. Further study is needed to determine whether current legislation is optimal to ensure these solutions or whether additional legislation is needed. In 2002, the FDA undertook such a review as part of an initiative called “Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach” [8].
vaccines. The CDC received funds to begin purchasing vaccines and toxoids for a 6-month strategic stockpile [10]. The government has gone into the stockpile on at least 12 occasions since it was established to respond to surges in demand and to stem short-term shortages [7]. Under the plan, vaccine is purchased by the CDC from the manufacturer, is stored by the manufacturer, and, if unused, is rotated out of the stockpile with a shelf life of at least 6 months for use in the private and public sectors. Because vaccine was constantly being rotated out of the stockpile when new vaccine was added, funding for the purchase of vaccine was needed only for the initial purchase and for maintenance costs. The companies were paid at the time of delivery of the vaccine into the stockpile. A separate fee was paid to the manufacturer by CDC to rotate the stockpile and keep it fresh.

In 2003, at the recommendation of the NVAC, President Bush, with the support of Congress, called for the development and maintenance of a robust vaccine stockpile program. As a result, the CDC asked for a 6-month stockpile of all recommended pediatric vaccines. For fiscal year 2005, $248 million in funding was proposed by Congress, but no new vaccines have been added to the stockpile program.

**Problem**
The obstacle to implementing the stockpile expansion has been a Securities and Exchange Commission (SEC) ruling on “revenue recognition.” In December 1999, the SEC issued Staff Accounting Bulletin #101, which was intended to address the timing of revenue recognition. The SEC established criteria for such “bill and hold arrangements.” Although there had been 20 years of problem-free purchase of vaccine for the stockpile, with revenue recognized when the orders were fulfilled, in accordance with the CDC contract, the SEC ruling voided these arrangements. Beginning in 1999, manufacturers could not count payments for the stockpile as revenue until the vaccine was taken out of the stockpile for use; withdrawal could be delayed by up to 1 year or might not occur (e.g., unused influenza virus vaccine). Some manufacturers are not participating in the new program because the delay in declaring revenue would decrease current reported earnings. The revenue recognition problem for expanding the stockpile program has been under negotiation by the CDC, Congress, and the SEC for several years, without resolution. In addition, some manufacturers believe that their creation and maintenance of these strategic inventories should be compensated to a greater degree than the CDC has offered.

**Solution**
There is no clear understanding of the delay in modifying the “revenue recognition” issue so that the expanded stockpile program can be implemented. It may be that only a public outcry initiated by newspaper articles, such as those that appeared in a United Press International dispatch in June 2004 [11] and in the Washington Post in April 2005 [12], can bring sufficient pressure on the involved parties to come to resolution on this universally supported program. Congressman Waxman has recommended legislation to make a legal exception that would allow companies to “recognize” revenue from sales to the vaccine stockpile [13].

**WHAT NEEDS TO HAPPEN NOW TO FIX PROBLEMS OF VACCINE SUPPLY?**

In recent years, a number of organizations, including the United States General Accounting Office [12], the Institute of Medicine of the National Academies [5], the Sabin Vaccine Institute [14], and the Center for Global Development [15], have examined the problems of vaccine supply. Interesting and innovative solutions of value have been proposed, but there has been little follow-through to develop concrete proposals that could be presented to the public and their representatives.

A sustained effort to address each of the facets of vaccine supply is required. Representatives of each of the vaccine con-
stituencies are represented on the NVAC, which could take a major role in leading these activities and keeping the public aware of its activities. Thus, to develop a sustained effort, the NVAC has established a subcommittee that will meet frequently to monitor progress in developing solutions to the vaccine supply issues. Members of the various vaccine constituencies are to be invited to discuss specific proposals that will be presented to the members of NVAC to be forwarded to the Assistant Secretary of Health.

Acknowledgments


References


Addendum. On 5 December 2005, the Securities and Exchange Commission said that vaccine manufacturers could recognize revenue on vaccines placed into government stockpiles instead of waiting to count payment when the vaccine was taken out of the stockpile (SEC releases 33-8642, 34-52885, and IC-27178: Commission Guidance Regarding Accounting for Sales of Vaccines and Bioterror Countermeasures to the Federal Government for Placement into the Pediatric Vaccine Stockpile or the Strategic National Stockpile).