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CHILDHOOD VACCINES

Ensuring an Adequate Supply Poses Continuing Challenges



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Abbreviations

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ASTHO	Association of State and Territorial Health Officials
ATSDR	Agency for Toxic Substances and Disease Registry
BLA	biologics license application
CDC	Centers for Disease Control and Prevention
DTaP	diphtheria, tetanus, and acellular pertussis
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
Hep B	hepatitis B
Hib	<i>haemophilus influenzae</i> type b
HHS	Department of Health and Human Services
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPV	inactivated polio vaccine
MMR	measles, mumps, and rubella
NIH	National Institutes of Health
NIS	National Immunization Survey
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
PCV	pneumococcal conjugate vaccine
PHS	U.S. Public Health Service
Td	tetanus and diphtheria booster
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program



G A O

Accountability * Integrity * Reliability

United States General Accounting Office
Washington, DC 20548

September 13, 2002

Congressional Requesters

Immunizations are widely considered one of the leading public health achievements of the 20th century. Mandatory immunization programs have eradicated polio and smallpox in the United States and reduced the number of deaths from several childhood diseases, such as measles, to near zero. A consistent supply of many different vaccines is needed to support this effort. By 18 months of age, it is recommended that each of the 11,000 babies born each day in the United States receive up to 20 doses of vaccine to protect against 11 diseases.

The federal government plays a variety of roles in immunization programs. Although vaccines are made by private companies and immunization policies are set at the state level, various agencies of the Department of Health and Human Services (HHS) have roles in regulating vaccine production, purchasing vaccines and making them available to states, and making recommendations for states to consider in setting immunization policies, such as those for school and day care enrollment. The federal government also plays a central role in ensuring the adequacy of the nation's vaccine supply—a matter of increasing concern in recent years. Although sporadic interruptions in the supply of vaccines have occurred in the past, these interruptions have become much more pronounced in the past 2 years. In late 2001, the Centers for Disease Control and Prevention (CDC) reported shortages in five of the eight recommended childhood vaccines. Concerned about the increasing frequency of these shortages, you asked that we answer the following questions:

1. To what extent have recent childhood vaccine shortages affected immunization policies and programs?
2. What factors have contributed to the recent shortages, and have they been resolved?
3. What strategies are federal agencies considering to help mitigate disruptions in the vaccine supply?

To assess the effect of vaccine shortages on immunization policies and programs, we surveyed 64 state, territorial, and local immunization programs supported by CDC,¹ examined recent changes in recommended immunization schedules, and reviewed studies of past outbreaks. To identify the factors that contributed to shortages and determine if they are being resolved, we visited the four primary vaccine manufacturers, determined how federal regulatory procedures affect vaccine production, and reviewed various analyses of vaccine supply problems by HHS agencies and other entities. To identify strategies being considered by federal authorities to help prevent or mitigate vaccine shortages, we reviewed studies and recommendations to strengthen the vaccine supply, attended advisory panel meetings examining vaccine shortages, and interviewed agency officials and other vaccine experts. We conducted our work from November 2001 through July 2002 in accordance with generally accepted government auditing standards.

Results in Brief

Recent childhood vaccine shortages have prompted federal authorities to recommend deferring some immunizations and have caused states to reduce immunization requirements. The federal Advisory Committee on Immunization Practices (ACIP) and CDC, which recommend immunization standards for the nation, have recommended that physicians defer immunizations for vaccines in short supply, so that the vaccines will continue to be available to those at highest risk. At the state and local levels, 49 state immunization programs reported rationing one or more vaccines. Shortages have also prompted the majority of states to waive or change immunization requirements for school and day care programs so that children who had received fewer than the mandatory immunizations could enroll. States reported that vaccine shortages and missed make-up vaccinations may reduce coverage and increase the potential for disease to spread; however, data are not currently available to measure these effects.

Multiple factors contributed to recent vaccine shortages, and while these have largely been resolved, the potential exists for shortages to recur. The shortages stemmed from a number of factors that affected both supply and demand. On the supply side, for example, some manufacturers had production problems that caused them to fall below their expected output,

¹CDC supports 64 immunization programs nationwide—50 states, 8 territories, 5 cities, and the District of Columbia. For simplicity, throughout this report we refer to them as state immunization programs. Fifty-two of the 64 state immunization programs responded to our survey.

while others discontinued making some vaccines altogether. On the demand side, one manufacturer could not keep pace with the greater-than-expected demand for a new recommended vaccine. CDC reported supplies for all but one vaccine were beginning to return to normal by July 2002. However, the potential for recurring shortages will remain because the complex nature and often year-long production schedule of vaccine manufacturing will continue to make it difficult for the supply system to respond rapidly to sudden changes in supply or demand. Additionally, with so few firms making each vaccine (five of the eight recommended childhood vaccines have only one manufacturer each), production problems or a manufacturer's decision to withdraw may leave few or no alternative sources of vaccine. One development that may help add greater capacity in meeting future needs is that a number of new vaccine products that could be used to meet the existing childhood immunization schedule are in varying stages of development, ranging from clinical testing to review by the Food and Drug Administration (FDA). However, the process to complete clinical trials and undergo FDA review likely will take several years, and these products generally do not qualify for expedited review under FDA policies.

Federal agencies and advisory committees are exploring options to help stabilize the nation's vaccine supply, but few long-term solutions have emerged. One option, expanding vaccine stockpiles, is receiving wide consideration as a short-term strategy that could help cushion disruptions in vaccine supply. Stockpiles have been used successfully to help mitigate supply disruptions in the past. While CDC is required by law to stockpile a 6-month supply of recommended childhood vaccines and has the necessary funding, it currently has established partial stockpiles for only two—one for measles, mumps, and rubella and one for polio. In light of the recent shortages, CDC is now considering plans to expand the stockpile to include additional vaccines. Stockpiling vaccines, however, has its limitations. While stockpiling can provide a cushion in the event of a supply disruption, limited supply and manufacturing capacity will restrict CDC's ability to build certain stockpiles in the near term. In addition, it is unclear whether the authority that CDC is using to establish these stockpiles provides for their use for all children. Another problem in expanding stockpiles is that CDC lacks a strategy for determining such things as how much vaccine to stockpile, where it should be stored, and how to ensure that the stockpile is additional to a manufacturer's normal inventory. CDC also lacks important information from FDA, manufacturers, and states needed to anticipate and manage supply disruptions.

We are making several recommendations to the Secretary of HHS to help promote the availability of vaccine products. These recommendations include adding vaccines to the types of products that can be considered under FDA's authority to expedite the approval of products in development trials and directing CDC to address several operational and strategic issues in expanding childhood vaccine stockpiles. In its general comments on a draft of this report, HHS stated that it agrees with the report's findings and has initiated actions to implement the recommendations. The report also contains a matter for congressional consideration to address the extent to which currently stockpiled vaccines are available for use by all children in the event of a shortage.

Background

CDC currently recommends routine immunizations against 11 childhood diseases: diphtheria, tetanus, pertussis (whooping cough), *haemophilus influenzae* type b (most commonly meningitis), hepatitis B, measles, mumps, rubella (German measles), invasive pneumococcal disease, polio, and varicella (chicken pox).² Some vaccines protect against multiple diseases. By combining antigens (the component of a vaccine that triggers an immune response), a single injection of a combination vaccine can protect against multiple diseases. Examples include the MMR vaccine (for measles, mumps, and rubella) and the DTaP vaccine (for diphtheria, tetanus, and pertussis). As a result of these combinations, eight vaccines are normally used to provide protection against the 11 childhood diseases. To build and maintain sufficient immunity, multiple doses of each of these vaccines are usually needed through infancy and early childhood. CDC's suggested vaccine timetable calls for children to receive up to 23 doses of these vaccines through the first 6 years of life. An additional tetanus-diphtheria booster is recommended during adolescence.

When very large shares of the general population are immunized, vaccines are successful at preventing major outbreaks of disease. Vaccines also offer some degree of protection to individuals not immunized, because a high immunization rate in a population gives a disease less opportunity to take hold and spread—a concept known as “herd immunity.” Development of vaccines and establishment of large-scale immunization programs have virtually eliminated some diseases and drastically reduced the impact of

²The CDC recommended immunization schedule comprises the coordinated recommendations approved by the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians.

others. Finally, with the ease of international travel, wide-scale vaccination programs help protect against infected travelers transmitting diseases, such as measles, from foreign countries where the diseases are still common.

Consolidation Resulted in Four Companies Engaged in Vaccine Manufacturing

Making vaccines is a complicated and time-consuming process. In contrast to drug manufacturing, vaccine manufacturing entails the use of biological organisms, including viruses and bacteria, which requires adherence to strict and complex manufacturing controls to ensure that they grow and react during processing as expected. Under current technology, vaccines typically require long production times. Manufacturers report that a typical production schedule, including growing the antigen, purifying, testing, packaging, and performing final quality checks, can exceed a full year for some vaccines.

Virtually all routine childhood vaccines are made by commercial manufacturers.³ Reflecting the challenges of vaccine production, the vaccine-manufacturing base in the United States has been marked by substantial consolidation over the past three decades. According to HHS, there were 26 manufacturers licensed to distribute vaccines in 1967. Due in part to acquisitions and mergers, at present there are 12 manufacturing entities that hold U.S. licenses, four of which produce almost all of the routine childhood vaccines on the U.S. market. Two of these companies—Merck & Company and Wyeth—are headquartered in the United States, and two—Aventis Pasteur and GlaxoSmithKline—are headquartered in Europe.

Federal and State Governments Play Key Roles

The federal government has a role both as a purchaser of vaccines and as a regulator of the industry. The federal government is the largest purchaser of vaccines in the country. CDC negotiates large purchase contracts with manufacturers and makes the vaccines available to public immunization programs under the Vaccines for Children (VFC) program. Under VFC, vaccines are provided for certain children—Native Americans/Alaska Natives, those eligible for Medicaid, those who are uninsured, and, when vaccinated in federally qualified health centers or rural health clinics, those who are not insured with respect to the vaccine. Participating public

³A state-owned facility in Massachusetts produces a limited quantity of tetanus and diphtheria booster.

and private health care providers obtain vaccines through VFC at no charge. Under a second program, known as the section 317 grant program because it was established under section 317 of the Public Health Service Act,⁴ project grants are provided for preventive health services including immunization programs. Currently, participants include 64 state, local, and territorial immunization programs. These grants are intended to help states maintain immunization infrastructures or purchase vaccines not covered by private insurance or not available through VFC. In addition, state immunization programs can use their own funds to buy vaccines through CDC contracts. In total, about 50 percent of all the childhood vaccines administered in the United States each year are obtained by public immunization programs through CDC contracts.

The cost of the full schedule of recommended vaccines under the CDC contracts has increased substantially in recent years, with a large share attributable to new higher-cost vaccines that have been added to the childhood immunization schedule.⁵ For example, as of May 2002, the CDC contract price for vaccine doses needed to complete the immunization schedule was about \$413.⁶ Over half of this amount is attributable to the most recent ACIP-recommended vaccines—varicella (recommended in 1996) and pneumococcal conjugate vaccine (recommended in 2001).

In addition to purchasing vaccines, the federal government is responsible for ensuring the safety of the nation's vaccine supply. FDA, an agency within HHS, regulates the production of vaccines. It licenses all vaccines sold in the United States, requiring clinical trials to demonstrate that a vaccine is safe and effective, and thoroughly reviews the manufacturing process to ensure that vaccines are made consistently in compliance with current good manufacturing practices. Once vaccines are licensed, FDA also conducts periodic inspections of production facilities to ensure that

⁴42 U.S.C. sec. 247b.

⁵In 1993, legislation was enacted that established price caps for vaccines purchased through existing CDC contracts. Of the eight currently recommended vaccines, two (polio and *haemophilus influenzae* type b) are selling below their price caps, one (MMR) is selling at its cap, and one (tetanus and diphtheria booster) is not available because manufacturers are not willing to sell it to CDC at its price cap; the remaining four are not subject to price caps because CDC had not contracted for them prior to May 1993.

⁶This total is based on the minimum price of vaccines under CDC contracts needed to complete CDC's suggested normal immunization timetable for children through 6 years of age (excludes adolescent tetanus and diphtheria booster).

manufacturers maintain compliance with FDA manufacturing requirements.

Other HHS agencies and programs also provide support for national, state, and local immunization efforts nationwide. The National Vaccine Program Office (NVPO), within the Assistant Secretary for Health’s office, is responsible for coordinating the efforts of all federal agencies, states, providers, industry, and other stakeholders involved in immunization activities. CDC’s National Immunization Program, in addition to purchasing vaccines for VFC, conducts a number of activities to strengthen the nation’s immunization infrastructure, such as monitoring the delivery of vaccines to state immunization programs and providing technical assistance to help health departments implement immunization programs. In times of vaccine shortages, several federal agencies and advisory committees play key roles (see table 1).

Table 1: Functions of Federal Agencies and Committees to Address Vaccine Shortages

Agency/committee	Functions that help avert or mitigate vaccine shortages
ACIP	Evaluate and recommend changes in the immunization schedule to accommodate reduced supplies.
CDC	Monitor production, monitor inventories of state immunization programs, manage distribution of public supplies, administer stockpiles, track back orders, and work with ACIP to modify immunization schedules in order to respond to vaccine shortages.
FDA	Accelerate review of revisions to existing licenses and vaccine lots submitted for release. Work with manufacturers to correct violations of good manufacturing practices that could disrupt production.
NVPO	Facilitate development of contingency plans, identify the reasons for shortages and options to address them, and identify strategies to prevent future shortages.
National Vaccine Advisory Committee (NVAC)	Study and make recommendations to the HHS Assistant Secretary for Health on ways to achieve an adequate supply of safe and effective vaccines.

Source: ACIP, CDC, FDA, NVPO, and NVAC.

States also have an important role in setting immunization policy and establishing an immunization infrastructure. Policies for immunization requirements, including minimum school and day care entry requirements, are made almost exclusively at the state level, although cities occasionally impose additional requirements. For example, the state of New York

requires students to have three doses of DTaP upon entering day care or school, while New York City requires an additional fourth dose. Each state also establishes an immunization infrastructure to monitor infectious disease outbreaks, administer federal immunization grants, manage centralized supplies of vaccine, direct professional and public education efforts, and otherwise promote immunization policies.

Vaccine Shortages Have Peaked and Most Supplies Are Returning to Normal

The recent incidents of vaccine shortages began in fall 2000 when supplies of the tetanus and diphtheria booster (Td) fell short. Over the course of a year, supplies of other vaccines also declined and by fall 2001, CDC reported shortages of five vaccines that, because some are combination vaccines, protect against eight childhood diseases (see table 2). In July 2002, updated CDC data indicated supplies were returning to normal for most vaccines. The shortage of pneumococcal conjugate vaccine (PCV), however, was expected to continue through at least late 2002.

Table 2: Duration of CDC-Reported Childhood Vaccine Shortages

	Vaccine	Approximate start of shortage	Actual or projected end of shortage
In short supply	Tetanus and diphtheria booster (Td)	November 2000	Ended June 2002
	Diphtheria, tetanus, and acellular pertussis (DTaP)	January 2001	Ended June 2002 ^a
	Pneumococcal conjugate vaccine (PCV)	September 2001 ^b	Continue through at least late 2002
	Measles, mumps, and rubella (MMR)	October 2001	Ended June 2002 ^a
	Varicella	October 2001	Ended July 2002
Adequate supply	Hepatitis B (Hep B)		
	<i>Haemophilus influenzae</i> type b (Hib) ^c		
	Inactivated polio vaccine (IPV)		

^aSupplies of DTaP and MMR are sufficient to meet demand for routine use, but not yet sufficient for extensive make-up initiatives.

^bCDC reported shortages of PCV existed throughout most of 2001, but intensified in September 2001.

^cNot considered a shortage by CDC; however, two of three manufacturers reported shipment delays up to 60 days. A third manufacturer had product available.

Source: CDC vaccine shortage reports, July 2002.

Shortages Prompt Actions to Reduce Immunization Requirements

Recent vaccine shortages have necessitated temporary modifications to the recommended immunization schedule and have caused states to scale back immunization requirements. Federal health officials and experts responsible for the development of immunization guidelines have temporarily scaled back their recommendations regarding the timing of immunizations for vaccines in short supply. At the state level, immunization programs are rationing the amount of vaccines distributed to providers. Many states have also suspended existing immunization requirements, allowing children who have received fewer than the previously recommended number of vaccinations to attend day care or school. Data to capture the full impact of the shortages on vaccination coverage are not yet available; however, public health officials are concerned that shortages raise the potential for disease outbreaks.

Federal Immunization Recommendations Scaled Back

In response to recent vaccine shortages, ACIP and CDC issued temporary recommendations to defer immunizations for some groups of children, so that the available supply can be directed to those considered at higher risk for contracting vaccine-preventable diseases.⁷ Five vaccines are included: Td, DTaP, PCV, MMR, and varicella (see table 3). The revisions give guidance to providers that are facing shortages and are intended to help ensure vaccine availability for priority needs. For example, the shortage of PCV, which began in 2001, prompted ACIP to recommend that the full series of doses be given only to high-risk children, such as those with chronic diseases, and that fewer doses be given to healthy children. In the case of varicella immunizations, where only one dose is generally needed to confer long-term immunity, ACIP has recommended that doses be delayed.

⁷The guidelines for the prioritization of Td and DTaP were issued by CDC and were approved by ACIP. Initially these shortages were anticipated to be brief, and therefore no official modifications were made to the immunization schedule by ACIP.

Table 3: Modification of Immunization Schedule during Vaccine Shortages

Vaccine	Recommended schedule	Age at vaccination	Revised recommendations	Date of revision
Td	Routine booster every 10 years	11–15 years and every 10 years thereafter	Defer routine boosters; prioritize vaccine from highest to lowest risk groups ^a	November 2000
DTaP	5 doses	2 months 4 months 6 months 15–18 months 4–6 years	Defer fourth dose; also defer fifth dose, if necessary	March 2001
PCV	4 doses; a fifth dose is recommended for certain high-risk groups ^b	2 months 4 months 6 months 12–15 months 24–59 months	Recommendations vary according to severity of shortage ^c	December 2001
MMR	2 doses	12–15 months 4–6 years	Defer second dose	March 2002
Varicella	1 dose; 2 doses are recommended for high-risk groups ^d	12–18 months 13 years or older	Delay until 18–24 months; prioritize to high-risk groups if shortage persists ^e	March 2002

^aRecommendations for use (highest to lowest priority) of Td are those traveling to countries where the risk for diphtheria is high, those requiring tetanus vaccination for wound management, those who have received fewer than three doses of vaccine containing Td, pregnant women, those at occupational risk for tetanus-prone injuries, and those who have not been vaccinated within the preceding 10 years.

^bHigh-risk children include those with sickle-cell disease, human immunodeficiency virus infection, and other immunocompromising or chronic medical conditions.

^cIn December 2001, ACIP issued updated recommendations for PCV use for healthy children during moderate and severe shortages. For infants who receive their first dose before age 6 months, vaccination with a maximum of three doses is recommended during a moderate shortage, and two doses are recommended during a severe shortage. All health care providers have been asked to reduce the number of doses used and ordered, regardless of their current supply, so that vaccine is more widely available until supplies are adequate.

^dSusceptible individuals aged 13 years or older should receive two doses spaced at least 4 weeks apart.

^eRecommendations for use (highest to lowest priority) of varicella vaccine are health care workers, family contacts of immunocompromised persons, individuals aged 13 years or older, and adults with high-risk children (for example, children infected with human immunodeficiency virus and children with asthma or eczema).

Source: ACIP and CDC recommendations.

States Reduce Immunization Requirements

The shortages that prompted federal officials to scale back their immunization recommendations have also affected programs at the state level. In our survey of 64 state immunization programs, administered through the Association for State and Territorial Health Officials (ASTHO), all 52 responding programs indicated that they had experienced shortages of two or more vaccines and had taken some form of action to deal with the shortages (see table 4).⁸ Officials from 31 of these 52 programs indicated that they had experienced shortages of five or more of the vaccines routinely recommended for children. The most frequently cited vaccines in short supply—DTaP, Td, varicella, MMR, and PCV—protect against eight diseases: diphtheria, tetanus, pertussis, varicella, measles, mumps, rubella, and pneumococcal disease.

Table 4: Extent of Vaccine Shortages in State Immunization Programs

Extent of vaccine shortages	Number of state immunization programs reporting
Shortages of two or more vaccines	52
Shortages of five or more vaccines	31
Shortages of one or more vaccines for 12 months or longer	9
Ration vaccines to providers	49
Allow children to attend school with fewer than recommended number of vaccinations ^a	35

Note: Information is based on responses from 52 state immunization programs.

^aWhile states set the minimum immunization requirements for school and day care entry, local immunization programs have the option to establish additional requirements according to local needs.

Source: GAO survey of 64 state immunization programs.

Forty-nine state immunization programs reported taking steps to ration the vaccines they distribute to providers due to the shortages. Under normal supply conditions, states maintain vaccine inventories that allow providers to keep at least a 1-month supply on hand. With a limited supply of vaccine available, states reported not receiving enough vaccine to maintain ideal inventories, and filling only partial orders to ship to providers. For example, in March 2002 officials from the immunization program in Arkansas reported that they planned to cut the size of vaccine shipments to public and private providers by 50 to 80 percent, with the

⁸We distributed the survey in February 2002 and conducted follow-up on the results through May 2002.

percentage reduction depending on the supply of vaccine in the state depot. The cuts are made to ensure an even distribution of vaccine among providers throughout the state. Officials from nine states reported being short of vaccines for 12 months or longer, and in some cases states reported having been completely out of certain vaccines for months at a time. For example, the immunization program in Philadelphia reported it had been unable to supply its health care providers with varicella and PCV for a 3-month period, and the program in Illinois reported that it had ordered over 70,000 doses of PCV since January 2002 but had received no doses as of the end of May 2002.

Vaccine shortages experienced at the state level have, in turn, prompted cutbacks in immunization requirements for admission to day care or school. Thirty-five states reported putting into effect new, less stringent immunization requirements that allow children who have received fewer than the recommended number of vaccinations to attend school.⁹ In general, these states have reduced the immunization requirements for day care and/or school entry or have temporarily suspended enforcement of those requirements until vaccine supplies are replenished. For example, the Minnesota Department of Health suspended the school and postsecondary immunization laws for Td vaccine for the second year in a row, with the suspension extending through the 2002-2003 school year. Other states, including Washington and South Carolina, reported allowing children to attend day care or school even if they were not immunized in compliance with immunization requirements, under the condition that they be recalled for vaccinations when supplies became available.

Deferred Immunizations Likely to Lower Vaccination Coverage and May Increase the Risk of Outbreaks

While it is too early to measure the effect of deferred vaccinations on immunization rates, a number of states reported that vaccine shortages and missed make-up vaccinations may take a toll on coverage and, as such, increase the potential for infectious disease outbreaks. The full impact of vaccine shortages is difficult to measure, for several reasons. First, none of the surveys that estimate immunization coverage at the national level measures the rate of age-recommended immunizations among children under the age of 18 months—the age cohort receiving the majority of vaccinations. Second, although the National Immunization

⁹A CDC survey that was limited to three vaccines and conducted in fall 2001 showed comparable results. For example, 48 percent of the state immunization programs surveyed reported that they had reduced immunization requirements for tetanus and diphtheria boosters in schools.

Survey (NIS)¹⁰ measures vaccination coverage among children aged 19 to 35 months, it does not inquire why children are not immunized. A reported decrease in coverage for any given year may be due to a number of factors, such as parental concerns about vaccine safety. Third, it would take some time after the shortages have ended to determine how many children were not recalled for missed vaccinations, a measure that could be useful in evaluating the impact of the shortages.¹¹

High vaccination rates from recent years could delay the immediate effects of deferred immunizations, but underimmunization destabilizes population immunity and may lead to outbreaks. Immunization rates for children receiving the series of all recommended vaccinations have been rising steadily since the inception of the NIS in 1994—from 55 percent in 1995 to 74 percent in 2001 for children aged 19 to 35 months.¹² Coverage with three or more doses of DTaP alone was approximately 94 percent in the most recent survey. Immunization experts generally agree that the residual effects of such high levels of population immunity may afford temporary protection for underimmunized children against communicable, vaccine-preventable diseases; however, the more numerous the population of susceptible individuals becomes, the greater the probability that those who are susceptible will come into contact with an infected person. Past outbreaks demonstrated this concept and highlight the importance of giving all recommended doses according to schedule. For example, a CDC analysis of a 1998 outbreak of measles in an Anchorage, Alaska, school showed that only 51 percent of the 2,186 children exposed had received the requisite two doses of measles-containing vaccine. This and other studies of measles outbreaks cited by CDC underscore the potential ramifications of deferring the second dose of MMR vaccine.

¹⁰NIS is a random-digit-dialing telephone survey sponsored by the National Immunization Program and conducted by CDC's National Center for Health Statistics.

¹¹In August 2002, CDC reported that a limited study in Puerto Rico found a marked decrease in DTaP coverage consistent with CDC's recommendation to defer the fourth dose of DTaP. See Centers for Disease Control and Prevention, "Impact of Vaccine Shortage on Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Coverage Rates Among Children Aged 24 Months—Puerto Rico, 2002," *Morbidity and Mortality Weekly Report*, vol. 51, no. 30 (2002): 667-668

¹²NIS statistics reflect national coverage rates for the following immunization series: four or more doses of DTaP, three or more doses of IPV, one or more doses of any measles-containing vaccine, three or more doses of Hib, and three or more doses of Hep B vaccine. NIS does not include varicella or PCV in the combined series. NIS began in 1994; however, we only reviewed years 1995 through 2001 because the 1994 survey did not include coverage of Hep B in the combined series.

In addition to the potential for vaccine shortages to reduce coverage, public health officials are concerned that the deferment of immunizations undermines years of efforts to educate parents and physicians about the importance of vaccinating children as recommended. Although providers are being asked to set up recall systems for children who have been turned away for needed vaccinations, immunization officials are concerned that some children will not be recalled and therefore will remain underimmunized.

Problems Causing Shortages Largely Resolved, but Shortages Could Recur

The problems causing most of the recent vaccine shortages have largely been resolved, but the potential exists for other, similar problems to bring about a recurrence of shortages. The recent shortages stemmed from a number of largely unforeseen factors that affected both supply and demand. By July 2002, the supplies for many vaccines were becoming sufficient to return to the recommended immunization schedule, but the complex nature of vaccine manufacturing and the limited vaccine manufacturing base make it difficult to respond rapidly if similar problems should occur in the future. Thus, any of the variety of technical difficulties that can occur with vaccine production—including those that contributed to recent shortages or other problems, such as a major product recall or catastrophic event like a vaccine plant fire—could trigger shortages again. One prospect that may help alleviate the potential for shortages is that several new vaccines under development could possibly add to the supply of existing childhood vaccines. However, clinical trials and FDA review of these products still need to be completed. These steps usually take several years, and under FDA policies, these products generally do not qualify for expedited review.

Many Factors Affected Supply of and Demand for Vaccine

No single reason explains the rash of recent vaccine shortages; rather, multiple factors coincided that affected both the supply of and demand for vaccines. We identified four key factors: production problems, calls by immunization policy-making bodies to remove a preservative from vaccines as a precautionary measure, a manufacturer's decision to cease production of some vaccines, and greater-than-expected demand for a vaccine that had recently been added to the immunization schedule.

Production Problems

Manufacturing production problems contributed to reductions in the supply of certain vaccines. In some cases, production slowdowns or interruptions occurred as manufacturers addressed problems identified in FDA inspections; in other cases, production was affected when planned maintenance activities took longer than expected. For example, the

shortages of MMR and varicella vaccines (which are produced by the same manufacturer) were brought about by two voluntary interruptions to production. In August 2001, the manufacturer temporarily suspended operations in one of its manufacturing facilities to address issues raised by FDA inspectors during a routine plant inspection. The production halt continued while the manufacturer made scheduled modifications to its facility. These modifications took longer than anticipated and had a substantial impact on production. In the months immediately following the interruptions, supply levels of MMR and varicella vaccines dropped by about 45 percent. Supplies remained low for the next several months, then significantly improved in the spring. In late June, CDC announced that the supply of MMR was sufficient to return to the recommended immunization schedule, although enough vaccine was not available for aggressive efforts to recall children for missed vaccinations. In July 2002, CDC announced that supplies of varicella were sufficient to return to the recommended immunization schedule. Difficulties meeting FDA manufacturing requirements also contributed to supply problems with DTaP, Td, and PCV.

Changes in FDA inspection practices may have resulted in the identification of more or different instances of manufacturers' noncompliance with FDA manufacturing requirements. In 1997, FDA implemented a new program for inspecting the biologics industry (including vaccines), called Team Biologics. This new approach emphasizes a more complete assessment of manufacturers' compliance with current good manufacturing practices, which are the agency's regulatory requirements for ensuring that biological products remain safe, pure, and potent through the entire manufacturing process. These requirements address a broad range of issues, such as quality assurance, recordkeeping, personnel qualifications, equipment cleaning, and laboratory controls. Team Biologics was phased in starting with plasma fractionation products and moved to vaccines in October 1999. Prior to this change, biologics inspections were generally shorter and involved smaller inspection teams, according to FDA officials. The inspections also tended to focus primarily on scientific or technical issues and less on compliance with good manufacturing practices and documentation issues. Several manufacturers confirmed that under this new approach, inspections have intensified and the emphasis on compliance has increased, making it more difficult for manufacturers to be considered in compliance.

FDA did take some steps to inform manufacturers about the program changes; however, some manufacturers reported problems related to how well the changes were communicated. An official at one company said the manufacturer was not well informed of the new expectations and officials at another company said the change in FDA's inspection approach created a gap in perception of what was needed to be considered in compliance. Manufacturers underscored the importance of clear guidance from FDA to help them understand evolving expectations. FDA's efforts to inform manufacturers about the new inspection approach did include numerous presentations made by agency personnel at a variety of meetings and conferences since 1997. In addition, in October 1999, when FDA was beginning to apply Team Biologics to vaccines, FDA issued a compliance program guidance manual detailing the new protocol for conducting inspections. Although this manual is intended for FDA's staff, the information in it could have provided manufacturers a better understanding of the scope of the inspections. However, the manual was not made widely available—only upon request. FDA has made compliance manuals for other biologic areas available on the Internet, but the manual for licensed vaccines is still not available on line, well over 2 years after its issuance, nor is it included in FDA's annual comprehensive list of guidance documents published in the *Federal Register*.

Removal of Thimerosal

Calls for the removal of the preservative thimerosal from childhood vaccines illustrate the effect that policy changes can have on the supply of vaccine. Efforts to remove thimerosal affected the production of several vaccines and contributed in particular to the shortage of DTaP. Thimerosal is a mercury-containing preservative that has been used as an additive in vaccines for over 60 years. Its presence in vaccines reduces the risk of bacterial contamination when providers draw individual doses from multidose vials. Few data are available on the effects of exposure to ethyl mercury (the form of mercury in thimerosal) at the levels introduced by vaccines. However, exposure to mercury-containing compounds, including ethyl and methyl mercury, at sufficiently high doses has the potential to produce adverse health effects, including effects on the nervous system.¹³ The Food and Drug Administration Modernization Act of 1997 required FDA to identify and provide an analysis of foods and drugs containing intentionally introduced mercury compounds. As a result of its review, in

¹³For a review of studies of health effects of ethyl and methyl mercury, see Institute of Medicine, *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders* (Washington, D.C.: 2001).

1999, FDA determined that under the existing recommended immunization schedule, some children over the first 6 months of life could be exposed to a cumulative level of mercury from vaccines exceeding one of the three existing federal guidelines for safe exposure to methyl mercury.¹⁴ As a precautionary measure, in July 1999, the American Academy of Pediatrics (AAP) and the U.S. Public Health Service (PHS) issued a joint statement advising that thimerosal in vaccines be eliminated or reduced as soon as possible.¹⁵

While thimerosal was present in several vaccines, removing it from some vaccines was more complex than for others. Thimerosal was introduced in the latter stages of production in one manufacturer's hepatitis B vaccine, and removing it was fairly straightforward. In contrast, thimerosal was used to help stabilize one company's formulation of DTaP, and the manufacturer said it was not able to completely eliminate it. This contributed to the manufacturer's decision to cease production of the vaccine, initiating the shortage of DTaP. The shortage was exacerbated when one of the remaining manufacturers of DTaP had to switch its packaging from multidose to single-dose vials due to the removal of the preservative, reducing its output of vaccine by 25 percent, according to the manufacturer.

For manufacturers, reformulating existing vaccines without the preservative required taking the product through the regulatory approval process, with the attendant establishment of new procedures, validation, testing, and labeling. Manufacturers acknowledged that FDA worked hard to get thimerosal-free vaccines approved, but the process, involving both FDA and manufacturers, of getting these products onto the market still took about 10 months for one formulation of hepatitis B vaccine and approximately 2 years for one manufacturer's formulation of DTaP.

¹⁴FDA, the Environmental Protection Agency (EPA), and the Agency for Toxic Substances and Disease Registry (ATSDR) have developed guidelines for safe exposure to *methyl* mercury. Thimerosal contains *ethyl* mercury, but since no federal guidelines exist for safe exposure to ethyl mercury, FDA used the guidelines for methyl mercury. FDA found that the cumulative amount of mercury a child could be exposed to from vaccines exceeded EPA's guidelines for safe exposure to methyl mercury but were below those of FDA and ATSDR.

¹⁵The joint statement by AAP and PHS also stated that the large risk of not vaccinating children far outweighs the unknown and probably much smaller risk, if any, of cumulative exposure to thimerosal-containing vaccines in the first 6 months of life.

Manufacturer's Decision to Discontinue Production

Another major factor in the shortage of DTaP, and also Td, was the decision of one manufacturer to discontinue production of all products containing tetanus toxoid. With little advance warning, the company announced in January 2001 that it had ceased production of these vaccines. According to the manufacturer, prior to its decision, it produced approximately one-quarter of all Td and 25 to 30 percent of all DTaP distributed in the United States, so the company's departure from these markets was significant. In the previous year, another manufacturer that supplied a relatively small portion of DTaP also had stopped producing this vaccine. Together, these decisions decreased the number of major manufacturers of DTaP from four to two and of Td from two to one.¹⁶

For the manufacturer involved in the most recent departure, a number of factors were involved in its decision. According to company officials, the manufacturer was already planning to discontinue its DTaP vaccine in a few years because it did not think it would be able to compete with companies developing new DTaP combination vaccines. The company's decision was accelerated when it experienced difficulties eliminating thimerosal from its vaccine, as noted earlier. Company officials said the timing of its decision was also triggered by the need to respond to requirements set forth in a consent decree with the federal government.¹⁷ To comply with these requirements, the company faced making significant upgrades to its facilities where tetanus-toxoid was manufactured. For these reasons, the manufacturer had already stopped releasing vaccine prior to announcing its decision. The manufacturer added that had the company decided to stay in the DTaP and Td market, it would have been several years before it could produce vaccines meeting FDA requirements.

Unanticipated Demand

The addition of new vaccines to the recommended immunization schedule can also result in shortages if the demand for vaccine outstrips the predicted need and production levels. This was the case with a newly licensed vaccine, PCV, which protects against invasive pneumococcal diseases in young children. PCV was licensed by FDA in February 2000 and formally added to the recommended schedule in January 2001. CDC

¹⁶In addition to the one major nationwide supplier of Td, a second manufacturer produces a small amount of Td, primarily for local distribution, and makes some available for nationwide distribution.

¹⁷The company had entered into a consent decree in October 2000 in which it agreed to implement a series of measures aimed at ensuring that products manufactured at two of its facilities are in compliance with FDA good manufacturing practices regulations.

estimates the monthly national need for this vaccine to be 1.3 million doses, but the manufacturer was only able to provide about half the needed doses during the first 5 months of 2002. Company officials said an extensive preeducation campaign resulted in record-breaking adoption of the vaccine. The company's production of vaccine was also hampered by ongoing manufacturing problems. Changes made in the company's quality assurance procedures, partly to comply with the terms of a consent decree with the federal government, resulted in delays in the release of vaccine. Manufacturing equipment problems also affected the manufacturer's ability to meet demand. As of July 2002, both of these conditions continued to affect the supply of this vaccine.

Underlying Factors Could Allow Shortages to Recur

While the recent shortages have been largely resolved, the vaccine supply remains vulnerable to any number of disruptions that could occur in the future—including those that contributed to recent shortages and other potential problems, such as a catastrophic plant fire. One key reason is that the nature of vaccine manufacturing prevents the quick production of more vaccine when disruptions occur. Manufacturing a vaccine is a complex, highly controlled process that can take several months to over a year. Unlike pharmaceuticals, which are usually synthesized from chemicals, most vaccines are produced from or use living biological organisms. Strict control is needed over the entire manufacturing process, and each lot of vaccine is carefully tested for its purity and potency. To illustrate the lengthy production times that can be involved, one manufacturer said it takes about 11 months to produce Td, including almost 7 to 8 months to produce purified vaccine, followed by 8 to 10 weeks of testing, and another 4 to 6 weeks of filling, packaging, and final approvals. With such long production times, it is difficult for the industry to provide a quick response to major disruptions. Some manufacturing plants are dedicated facilities, built and maintained to produce a specific vaccine, and cannot be easily expanded or switched to produce other vaccines. For example, when one of the two major producers of Td ceased production last year, both the long production time and fixed capacity left the remaining manufacturer unable to meet the unexpected drop in supply. The supply of Td only recently returned to levels sufficient to resume routine administration, over a year and a half after the shortage began.

The Td vaccine example illustrates another underlying problem: routine childhood vaccines are available from a limited number of manufacturers. Of the eight recommended routine childhood vaccines, five are made by a single major manufacturer; the remainder are made by two, or in one case,

three manufacturers (see table 5). Consequently, if there are interruptions in supply or if a manufacturer ceases production, there may be few or no alternative sources of vaccine.

Table 5: Number of Manufacturers Producing Routine Childhood Vaccines in the United States

Vaccine ^a	Number of manufacturers
Hib	3
DTaP	2 ^b
Hep B	2
IPV	1
MMR	1
PCV	1
Td	1 ^c
Varicella	1

^aNot shown are two combination vaccines, which can be used to meet the recommended immunization schedule but are generally used much less often. DTaP-Hib can be used for booster doses but is not recommended for primary immunization in infants; this vaccine is made by one company. Hep B-Hib can be used for all but the birth dose of Hep B and is made by one company.

^bOne manufacturer has licenses for two different formulations of DTaP vaccine (produced in geographically separate facilities), so there are actually three DTaP vaccines currently available on the U.S. market.

^cIn addition to the one major nationwide manufacturer of Td, the University of Massachusetts produces a small amount of Td vaccine and makes some available for nationwide distribution.

Vaccines on Horizon May Increase Supply

New vaccines in development could potentially add to the supply of existing vaccines. An example is a new formulation of DTaP that recently received FDA approval and has helped ease the shortage of DTaP. We identified 11 routine vaccines in development that could help meet the current recommended immunization schedule. These vaccines are in varying stages of development, ranging from clinical testing to FDA review. Included are the following types of products:

New brands of existing vaccines: About half of the vaccines in the pipeline represent new sources of existing vaccines. If approved, several of these vaccines would expand the number of suppliers for these products.

New combinations of existing vaccines: Some of the vaccines under development represent new combinations of existing vaccines; for example, one company is developing a DTaP-IPV-Hib vaccine that protects against diphtheria, tetanus, pertussis, polio, and *haemophilus influenzae*

type b. If approved, how these new combination vaccines will be used and whether they will expand supply or simply replace existing vaccines depends on several factors. The first determinant will be the use for which the company seeks licensure. New vaccines could be licensed for use in all doses or just in some doses in an immunization series. For example, when one acellular version of diphtheria, tetanus, pertussis vaccine was first licensed, the company conducted studies and sought licensure for only the fourth and fifth doses of the five-dose series. It was eventually licensed for use in all five doses. ACIP has encouraged the use of combination vaccines over equivalent component vaccines when possible in order to minimize the number of injections children receive. In some cases, however, individual vaccines are used more often than related combination vaccines.¹⁸ Combination vaccines also tend to sell at a premium price compared to the individual component vaccines, which may affect their market acceptance. Provider and parental preferences for vaccines can also come into play.

New vaccines for certain age groups: Some vaccines in the pipeline are vaccines formulated for new age groups. According to a manufacturer, one vaccine includes a pertussis component for adolescents and adults, which is not currently available or included in the recommended schedule.

FDA Policies Restrict Use of Expedited Approval Processes

Completing clinical testing and FDA review of these new vaccines can be a lengthy process, but FDA has a number of procedures for facilitating the development and expediting the review of new pharmaceutical and biologic products. Clinical testing of a vaccine in humans is typically done in three phases to establish the product's safety and efficacy and to determine dosing. Once clinical trials are completed, the manufacturer may submit a biologics license application (BLA) to FDA that assembles evidence on the vaccine's safety, purity, and potency and whether the manufacturing process can ensure its quality. Based on its review of the information in the application and any supplemental information it requests, FDA makes a decision on whether to license the vaccine. In total, completing clinical trials and FDA review for vaccines generally takes over 5 years. However, FDA has a number of mechanisms available to help expedite this process for certain products, including the following two:

¹⁸For example, in the case of the combination vaccine that protects against hepatitis B and *Haemophilus influenzae* type b (Hep B-Hib), CDC data show that about 4.8 million doses of the combination vaccine were distributed in calendar year 2000, compared to 23.7 million doses of hepatitis B vaccine and 11.4 million doses of Hib vaccine.

Fast Track: A manufacturer can request fast track designation if the product is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs. As clinical testing nears completion, and preliminary data support a determination that a fast track product may be effective, FDA may begin accepting portions of the BLA for review before a complete application is submitted.¹⁹

Priority Review: A product may be eligible for priority review status if the product is a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening disease.²⁰ FDA's goals are to review and take action on priority submissions in 6 months, compared to 10 months for standard reviews.²¹

These mechanisms are not available for use with many vaccines in the pipeline because FDA policies preclude their application to products that are essentially new forms of existing vaccines. The Food and Drug Administration Modernization Act of 1997 requires that fast track products demonstrate the potential to address unmet medical needs. While the statute did not define “unmet medical need” or provide criteria for analyzing the need, FDA has established criteria stating that an unmet medical need is one that is not adequately addressed by existing therapies. FDA officials pointed out that a temporary vaccine shortage would not meet the criterion of an unmet medical need, because by the time a new source of vaccine was approved (even under expedited procedures), the shortage would be expected to be over and the condition of unmet need would no longer exist. In addition, because many of the products in development are either new brands or new combinations of existing vaccines, an FDA official said that under current policy they would not meet the agency's criteria for fast track (products address an unmet

¹⁹See 21 U.S.C. sec. 356. Acceptance of a portion of the application does not necessarily mean that the review will start before a complete application is received. According to FDA, when the review is started will depend on many factors including staffing, competing priorities, and the perceived efficiency of starting the review before the submission of the complete application.

²⁰Priority review is ordinarily open to fast track products as well as non-fast-track products.

²¹FDA's review time is the actual amount of time FDA spends reviewing a new drug or BLA. The approval time—from first submission of the BLA to BLA approval—could be much longer. The approval time includes the sum of FDA review time for the first submission of the BLA, plus any subsequent time during which a sponsor addresses deficiencies in the BLA and resubmits the application, plus subsequent FDA review time.

medical need) or priority review (products represent a significant improvement). These expedited processes are applicable mainly to vaccines that offer protection against diseases for which there are no existing vaccines. This was the case with PCV. At the time, no vaccines that protected against invasive pneumococcal disease were licensed for use in children under 2 years of age, so PCV was eligible to be designated as a fast track product and to receive priority review. As a result, the review and approval of PCV took about 8.5 months, compared with the median time of 18.5 months for vaccines.

Product Approval
Requirements Are Not
Standardized among Countries

Some of the vaccines in the pipeline are already licensed products in other countries, including Canada and various countries in Europe. FDA accepts foreign clinical studies in support of U.S. licensure; however, agency officials stated that if foreign data are used to support the safety, purity, or potency of a vaccine, FDA would need to independently assess the information and would usually require additional data. For example, the manufacturer might be required to provide evidence demonstrating that the product elicits a comparable immune response in a U.S. population. These studies can take additional time to complete. Part of the problem is that regulatory requirements for product registration often differ among countries. Standardizing these requirements, a process referred to as “harmonization,” is being discussed, but does not appear to be a near-term solution for vaccines. Harmonization efforts through the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH) involve Europe, Japan, and the United States. According to FDA, at the outset of the harmonization initiative, all ICH parties agreed to exclude from its scope certain biological products, including conventional vaccines, in part because of the complex nature of vaccines.²²

²²At a recent hearing, the Deputy Commissioner of FDA suggested that if a vaccine were approved in another country and CDC indicated its use would help ameliorate shortages in the United States, FDA would consider requests to make these products available as investigational vaccines. Under FDA regulations, these vaccines could be administered to children in the United States with informed consent from their parents. However, the Director of the National Immunization Program within CDC said the use of investigational vaccines in a routine vaccination program could pose problems in achieving public acceptance.

No Clear Path Yet to Resolve Ongoing Supply Issues

Federal agencies and advisory committees are exploring options to help stabilize the nation's vaccine supply, but few long-term solutions have emerged. Earlier this year, the National Vaccine Advisory Committee (NVAC) convened a meeting of vaccine experts to discuss supply problems and develop formal recommendations for further HHS consideration. The preliminary conclusion of the NVAC work group was that further study was needed of strategies, such as additional financial incentives for manufacturers and streamlining the regulatory process. CDC vaccine stockpiles have been used successfully to help mitigate temporary supply disruptions in the past and were considered a priority strategy by workshop participants. While CDC is required by law to stockpile a 6-month supply of recommended childhood vaccines and has the necessary funding to do so, it currently maintains partial stockpiles for only two. In light of the recent shortages, CDC is considering expanding the stockpiles to include additional vaccines. While stockpiling vaccines can provide a cushion in the event of a supply disruption, limited supply and manufacturing capacity will restrict CDC's ability to build certain stockpiles in the near term. In addition, CDC lacks a comprehensive strategy and important information needed to effectively plan and manage the stockpile.

NVAC Studying Strategies to Strengthen Vaccine Supply

Federal efforts to strengthen the nation's vaccine supply have taken on greater urgency with the recent incidents of shortages. A major effort by NVAC has been under way since mid-2001. As part of its mandate to study and recommend ways to encourage the availability of safe and effective vaccines, NVAC formed a Vaccine Supply Work Group to explore the issues surrounding vaccine shortages and identify strategies for further consideration by HHS. In February 2002, the work group convened a meeting of principal stakeholders—federal and state governments, vaccine manufacturers, health care providers, legislators, and academic researchers—to determine the scope and identify contributing causes of vaccine shortages and develop strategies to strengthen the vaccine supply. The work group presented its preliminary findings and recommendations in June 2002.

In its preliminary report, work group members identified several strategies that hold promise, such as providing financial incentives for vaccine development, strengthening manufacturers' liability protection, and streamlining the regulatory process, but they concluded that these strategies needed further study. In regard to liability protections, the work group did make recommendations to strengthen the Vaccine Injury Compensation Program (VICP). VICP is a federal program authorized in

1986 to reduce vaccine manufacturers' liability by directly compensating individuals for childhood-vaccine-related injuries from a VICP trust fund. It was established, in part, to help stem the exodus of manufacturers from the vaccine business due to liability concerns. Manufacturers, however, reported a recent resurgence of childhood-vaccine-related lawsuits—including class action lawsuits related to past use of thimerosal—which allege that they are not subject to VICP. In the manufacturers' view, these lawsuits once again threaten the stability of the industry by creating disincentives to produce vaccines. While the work group acknowledged that recent vaccine shortages do not appear to be related to liability issues, it indicated that strengthening VICP would encourage manufacturers to enter, or remain in, the vaccine production business. Legislation has been introduced for the purpose of clarifying and modifying the VICP program.²³ In response to the work group's finding that streamlining the regulatory process needed further study, FDA recently announced that it is examining regulations governing manufacturing processes in both drugs and vaccine products to determine if reform is needed. However, FDA officials told us it is too early to define the scope and time frame for this reexamination.

The NVAC work group expressed little support for constructing government-owned production facilities to produce routine childhood vaccines. One concern raised by the work group was that vaccine manufacturers might not be able to compete with a government-subsidized program—potentially causing private manufacturers to withdraw from the U.S. market, further shrinking the number of manufacturers, and reducing the level of innovation and introduction of new products. In addition, government-owned facilities would be subject to many of the same limitations—such as long production times and stringent quality control standards—that private manufacturers face. NVAC work group members concluded that stockpiling vaccines, while having some limitations, should receive priority consideration to provide temporary relief during shortages.

Expansion of Stockpiles Is under Consideration

CDC is considering whether additional vaccine stockpiles will help stabilize the nation's vaccine supply. CDC vaccine stockpiles have been used to mitigate supply disruptions on at least seven occasions since they were first established nearly 20 years ago. In 1993, with the establishment

²³See S. 2053, H.R. 1287, and H.R. 3741.

of the VFC program, CDC was required to purchase sufficient quantities of pediatric vaccines not only to meet normal usage, but also to provide an additional 6-month supply to meet unanticipated needs. Further, to ensure funding, CDC was authorized to make such purchases in advance of appropriations. Despite this requirement, to date, CDC has established partial stockpiles for only two—MMR and IPV—of the eight routinely recommended pediatric vaccines.²⁴

CDC's past decisions to stockpile these two vaccines were based on a number of factors. First, CDC considered the number of suppliers of each vaccine—vaccines from a single source were considered at greater risk and were the highest priority for stockpiling. Second, CDC assessed the likelihood that changing technology or immunization schedules could make stockpiled vaccines obsolete—new combination vaccines or revised ACIP recommendations reduce the priority of stockpiling older vaccines. CDC officials noted the importance of balancing the cost of establishing a stockpile versus the risk that the stockpiled vaccine might soon become obsolete. Third, CDC officials stated that because the demand for newer vaccines is unknown, manufacturers might not have excess capacity to create stockpile inventory. In light of recent shortages, CDC is reevaluating its criteria for setting priorities for which vaccines to stockpile. For example, limiting stockpiles to vaccines produced by sole manufacturers may no longer be appropriate.

Even if CDC decides to stockpile additional vaccines, the currently limited supply of several vaccines will restrict CDC's ability to build certain stockpiles in the near term. CDC estimates it could take 4 to 5 years to build stockpiles for all the currently recommend childhood vaccines—at a cost of \$705 million. Past experience also demonstrates the difficulty of rapidly building stockpiles. Neither the current IPV nor MMR stockpiles have ever achieved target levels because of limited manufacturing capacity. As of July 2002, the IPV stockpile stood at 3.7 million doses, less than half of the 8 million doses on order. Similarly, the MMR stockpile has never reached its target of 4 million—coming as close as 3.1 million doses in late 2001.

Another issue that will need to be addressed is the extent to which stockpiled vaccines purchased with VFC funds can be used for non-VFC-

²⁴CDC also maintains small stockpiles of pediatric DT and oral polio (neither recommended for routine use) for use in the event of outbreaks.

eligible children. In 1993, the Congress passed legislation requiring the Secretary of HHS to negotiate for a 6-month supply of vaccines to meet unanticipated needs in connection with the VFC program. The legislation directed the Secretary to consider the potential for outbreaks of vaccine-preventable diseases in carrying out this stockpile requirement.²⁵ CDC bases the target levels of its current stockpiles on the number of children in the general population and has allowed manufacturers to borrow from stockpiled vaccines for releases to this population. We note that the legislation does not state that the supply of stockpiled vaccines may be made available for children not otherwise eligible through the VFC program. CDC officials said that the VFC legislation is unclear as to whether stockpiled vaccines can be used for these children.

There are other authorities under which CDC could procure stockpiles of vaccines for children. CDC may develop vaccine stockpiles under its authority to respond to public health emergencies and is required to maintain vaccine stockpiles under the National Vaccine Program (NVP). NVP is not limited to childhood vaccines, but appropriations were authorized only through 1995. CDC has identified several other provisions of the Public Health Service Act that would authorize expenditures for vaccine stockpiles. For example, section 352 authorizes HHS to produce products for use by the public and private sectors when they are unavailable from licensed sources. Section 311 of the act authorizes HHS to work closely with the states and provide “medical supplies” in the prevention and control of communicable diseases and to address other health emergencies.²⁶

CDC Lacks a Comprehensive Strategy for Expanded Use of Stockpiles

Expanding the number of CDC vaccine stockpiles will require a substantial planning effort—an effort that is not yet complete. CDC has not yet determined key aspects of vaccine stockpiles to ensure their ready release, including the quantity of each vaccine to stockpile, the form of storage, and storage locations. Also, to ensure that use of a stockpile does not disrupt supply to other purchasers, procedures would need to be developed to ensure that stockpiles are additional to a manufacturer’s

²⁵Td is not available for stockpiling under this mechanism because, as previously noted, manufacturers are not willing to sell it to CDC under the VFC price cap.

²⁶CDC also identified section 317 of the Public Health Service Act, which, as mentioned earlier, authorizes state grants for preventive health services, as additional authority to stockpile vaccines.

normal inventory. CDC's current approach to stockpiling lacks clear direction on the following fronts:

Quantity to stockpile: CDC officials have not yet determined what quantity of vaccine most accurately constitutes a 6-month supply. To date, stockpile purchases have been based on estimates of the U.S. birth cohort (about 4 million babies per year) and ACIP recommendations—but this may not be enough to cover the actual need. For example, for each child to receive the recommended two doses of MMR, roughly 8 million doses of MMR would be needed annually. However, manufacturers report nearly 12.7 million doses were distributed in 2001. Overvaccination due to lost immunization records, wastage from refrigerator outages or multiple dose packaging, and make-up immunizations could account for the difference.

Vaccine experts are also beginning to consider whether stockpiles should be expanded to include more than a 6-month supply. Recent shortages have lasted from 9 to 20 months. A catastrophic event, such as a major plant fire, could disrupt production for several years while a plant is being reconstructed. CDC has not yet fully evaluated the logistics of maintaining larger stockpiles or developed contingency plans for major supply disruptions.

Form and location of storage:²⁷ Stockpiled vaccines can be held in three forms: labeled (ready to ship), unlabeled (in vials, but not ready to ship), or bulk (product still must undergo final lot testing, filling, and labeling). Stockpiled vaccines requiring additional processing or packaging need to be closer to the manufacturing facility and require more time for release. Each storage method has advantages and disadvantages. For example, while labeled vaccine can be stored off site and distributed most rapidly, changes in package inserts could require a labor-intensive task of opening all the packages to replace the insert. Label changes are less of an issue for vaccines in unlabeled or bulk form, but these vaccines must still undergo additional processing, making them vulnerable to plant disruptions. This became apparent in fall 2001, when modifications at the manufacturing

²⁷To establish a stockpile, CDC contracts with a qualified manufacturer to purchase the vaccine. CDC then pays the manufacturer an annual fee to store and rotate the stockpile. As portions of the stockpile approach 12 months of remaining shelf life, the manufacturer will rotate the stockpile into normal distribution and replace it with stock having a more distant expiration date. Because stockpiled vaccines are often stored in unfinished form and are periodically rotated with newer lots, stockpiles are typically held at the manufacturer's production location.

plant necessitated shutdowns that delayed the release of the MMR vaccine held in stockpile. In response, CDC is reevaluating the amount of stockpiled vaccines required to be stored in final form and the location of storage.

Maintenance of effort: CDC's current stockpile program is designed to ensure a quantity of vaccine in addition to manufacturers' normal inventory. However, current CDC stockpile contracts do not contain a "maintenance of effort" requirement to ensure that production for the stockpile is additional to normal production levels. Without such a requirement, CDC efforts to use a stockpile could simply result in stock being drawn from a manufacturer's normal deliveries, without an overall increase in the amount of product being available for release into the market in times of shortage.²⁸

During the MMR shortage, CDC became aware that the manufacturer could not release more of the MMR stockpile without affecting its deliveries to the private sector. The manufacturer used nearly 1 million doses from the stockpile during the winter of 2001-2002 (leaving about 2 million doses remaining), but was unable to release more vaccine needed to ease the shortage. The manufacturer had recently adopted additional quality control procedures that temporarily limited the amount of vaccine that could be released during that period. CDC officials said that the recent MMR experience points to the need for additional contractual assurances that stockpiling represents a ready reserve of additional vaccine, and they are considering including maintenance of effort provisions in future stockpile contracts.

Critical Information Needed to Manage Stockpiles Is Lacking

Once sufficient quantities of vaccines are stockpiled in the appropriate form, CDC needs to make wise decisions on when to deploy the stockpiles. However, CDC currently lacks important information to help do so. Timely release of the stockpile requires accurate prediction of a number of variables related to the early identification, severity, and duration of the supply disruption. CDC currently has data that it uses to screen for disruptions in vaccine supply to state immunization programs, but does not have data to anticipate a supply disruption or to fully evaluate the potential severity and duration of a supply disruption, especially to

²⁸Maintenance of effort requirements are particularly important for manufacturers that have multiple products that share the same production facilities, because efforts to use a stockpiled vaccine during a time of shortage could create or exacerbate a shortage of other important drugs or vaccines that would be displaced by shifting production resources.

private providers. With such information, CDC could set priorities for or resize states' orders and determine how much stockpiled vaccine to release and when to release it. Timely information is important, because releasing vaccine from a stockpile can take up to 30 days. Some of this information may already be available within HHS, but other information is available only from manufacturers or state immunization programs.

Information from FDA: FDA has important information about manufacturers' levels of vaccine production and plant conditions that could affect production through its facility inspections and approval of each production lot.²⁹ On occasion, this information could help CDC anticipate supply disruptions and independently assess their potential severity, but it is only available to CDC by written request. Because of the lack of routine sharing of FDA information, CDC would likely be unaware of problems identified in FDA inspections that could cause the manufacturer to temporarily shut down a production line, unless notified by the manufacturer. This communication may not occur. For example, when FDA inspectors identified potential sterility issues at one facility, the manufacturer temporarily stopped production during the inspection, which eventually led to a shortage. But FDA did not inform CDC of the disruption. CDC officials told us they were first made aware of the disruption through media reports several weeks later.

Information from manufacturers: There is no formal mechanism in place for CDC to obtain critical information from manufacturers on prolonged vaccine production disruptions, such as shutdowns due to maintenance or repairs, that could precipitate the need to use the stockpile. CDC officials cite the value of having timely information on manufacturers' capacity, current and future production levels, and any circumstances that could affect production—information that is often considered proprietary by manufacturers. Particularly during shortages, CDC does obtain some supply information from manufacturers, but they do not always provide it consistently or promptly. In addition, there is no requirement for vaccine manufacturers to notify CDC or FDA of business decisions to withdraw vaccines from the market. Although the Food and Drug Administration Modernization Act of 1997 requires sole manufacturers of a drug that is lifesaving or prevents a debilitating disease to give FDA a 6-month

²⁹FDA also secures some supply information through reports it requires manufacturers to submit on the quantity of vaccines they distribute (see 21 C.F.R. sec. 600.81). Currently, such reports are required every 6 months.

notification prior to discontinuance,³⁰ this requirement does not extend to vaccines. The four major vaccine manufacturers told us they would not object to a similar requirement that they give FDA a 6-month notification of their intent to cease production of a vaccine.³¹

Information from states: To identify critical shortages and manage distribution of public supplies, CDC needs an accurate, ongoing accounting of state inventories. State immunization programs can provide early indications of supply problems if states accumulate back orders. State immunization programs also maintain working inventories (often a 3-month or greater supply), which during times of nationwide vaccine shortages could also help cushion supply disruptions. Prior to the recent vaccine shortages, CDC did not routinely monitor the vaccine inventory levels in state depots. In response to recent shortages, CDC instructed state immunization programs to inventory their stock-on-hand and submit monthly reports. CDC program managers are considering monitoring states' inventory levels in nonshortage periods, but automated systems to facilitate uniform and timely reporting are still under development. In order to help ensure that inventories in excess of state needs are not maintained, CDC is also recommending that states maintain a 3-month inventory during normal supply situations, decreasing to a 1-month inventory during shortages, thus providing a 2-month cushion.

Conclusions

A steady and reliable supply of childhood vaccines is critical to maintain the substantial U.S. public health achievements in combating infectious diseases. However, the vaccine shortages experienced over the last 2 years demonstrate the vulnerability of the vaccine supply. Long lead times, sometimes a year or more, are needed to produce vaccines and alter existing production volumes. Because there are so few manufacturers (and increasingly, just one) producing a particular vaccine, even short-term disruptions in a manufacturer's production volume can create a shortage. This condition is not likely to change in the near term. Therefore, federal agencies are continually challenged to take a proactive approach

³⁰The 6-month notification requirement may be reduced if a public health problem could result from continued production, manufacturers face financial loss, there is a shortage of drug components, or other hardship would occur. 21 U.S.C. sec. 356c.

³¹A bill was recently introduced in the Senate (S. 2049) that would amend the notification provision by requiring manufacturers to give FDA at least a 12-month notice before discontinuing biological products, including vaccines.

within their existing missions to help mitigate the effects of future disruptions to the vaccine supply.

An often-cited approach that can help provide a cushion against disruptive effects of future shortages is to expand CDC's reserves, or stockpiles, of childhood vaccines. While CDC is required to stockpile childhood vaccines under the VFC program, authorizing legislation does not address the extent that stockpiles can be used to support the needs of children not eligible under the program. In addition, stockpiling vaccines is not a panacea and, if poorly implemented, may provide little in the way of value. Expanding the stockpiles poses operational challenges that need to be addressed through strategic planning. For example, there is a need to establish a timetable for purchasing vaccines in a way that does not disrupt normal distribution, as well as a need to make decisions on the most desirable form and storage location for each vaccine. Implicit in these efforts to expand and manage a stockpile is the need for more timely information on the nature and extent of possible shortages. While working with manufacturers has shown some promise, opportunities exist to leverage other sources of available information, such as the results of FDA vaccine plant inspections and state vaccine inventory levels.

Although disruptions in supply can occur when manufacturers must stop production in order to bring their facilities into compliance with FDA standards, these standards are critical to helping ensure the safety, purity, and potency of vaccines. As FDA strengthens its process for measuring compliance with these standards, communication of expectations with manufacturers is important. FDA should provide manufacturers with available guidance about the expectations of what constitutes compliance—a situation that has not always occurred in the past.

The prospect of additional vaccine products has potential to help reduce the intensity of future disruptions to the supply of existing vaccines, but introduction of new products faces challenges. On one hand, manufacturers have economic incentives to bring new childhood vaccines to market. For example, introduction of new vaccines against additional childhood diseases or new combinations of existing vaccines traditionally sell for higher prices and offer manufacturers new opportunities to compete for market share. On the other hand, it is an involved and time-consuming process, often taking several years, to obtain a license to sell these products in the U.S. market, even if the products are licensed for use in other countries. A substantial number of vaccines are in the development pipeline. While FDA has mechanisms available to shorten the review process, they are not used for most vaccines under development.

FDA's policy, in effect, applies the expedited processes to address an unmet medical need for a new product, while childhood vaccines under development often involve not new products, but existing vaccines or combinations of existing vaccines. However, the fragility of the vaccine supply itself demonstrates an unmet medical need because when supplies are lacking, children may become more vulnerable to the spread of disease. This possibility warrants FDA's reconsidering its policy regarding expedited review to help prevent or mitigate vaccine shortages.

Matter for Congressional Consideration

To help ensure that stockpiled vaccines are available for use by all children, and in light of CDC's development of vaccine stockpiles under the VFC program, the Congress may wish to consider amending the program legislation to specifically address whether vaccines stockpiled under this program may be made available to children not otherwise eligible.

Recommendations for Executive Action

To ensure a well implemented strategy for expanding HHS's stockpiles of childhood vaccines, we recommend that the Secretary of HHS direct the Director of CDC to develop a strategic plan that addresses the operational difficulties involved. At a minimum, such a plan should include

- a timetable, developed with manufacturers' input, for the purchase of specific quantities of vaccine;
- a determination of form and location of storage of the vaccine;
- procedures to ensure that stockpiles of vaccines are incremental to manufacturers' normal inventory levels;
- procedures for systematic interchange of information between FDA and CDC on potential childhood vaccine manufacturing interruptions; and
- steps for monitoring childhood vaccine inventory in state VFC depots.

To help strengthen the vaccine supply without compromising standards that ensure safety, we recommend that the Secretary direct the Commissioner of FDA to

- take steps to ensure widespread distribution of all forms of compliance guidelines to vaccine manufacturers and ensure that these guidelines are kept up-to-date and

-
- consider revising FDA policies for fast track and priority review approval of vaccines currently under development to allow their use, even in periods of nonshortage, in cases where FDA determines that applying them would help address the unmet need of a stable and sufficient overall vaccine supply.

Agency Comments and Our Evaluation

We obtained comments on our draft report from HHS. In its general comments, the department stated that it agrees with the report's findings and that it has initiated action to implement the report's recommendations. In regard to our recommendation on the need for HHS to develop a strategic plan for stockpiling childhood vaccines, HHS stated that CDC has arranged site visits to manufacturers for the purpose of discussing the specific stockpiling issues raised in the report. Further, after these site visits are completed, CDC would develop a comprehensive vaccine stockpiling program strategy. HHS also cited actions it was taking in regard to our recommendations that FDA be directed to ensure the widespread distribution of all forms of compliance guidelines to manufacturers. HHS stated that FDA was working with a contractor to post all Vaccine Compliance Program guidance on its Web site.

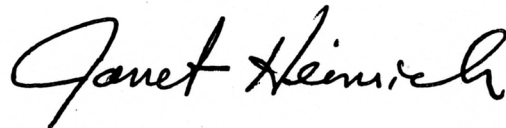
HHS expressed some reservations in its comments about our recommendation that the Secretary direct FDA to consider revising FDA policies for fast track and priority review approval of vaccine products currently under development. HHS stated that in shortage situations, FDA has the flexibility to work as expeditiously as possible with manufacturers of new or existing vaccines to alleviate the shortage. It also stated that critical vaccine shortages could allow for the designation of a vaccine as a fast track product. Often, however, shortages are temporary and are over before even the most expeditious review can be completed. As a result, HHS indicated that formal designation for expedited review process would have little impact on relieving the shortage.

We did not intend that our recommendation apply only in times of existing vaccine shortages. Rather, the purpose of the recommendation is to provide HHS with another option to help prevent or mitigate the effects of future shortages. The potential exists to strengthen the childhood vaccine supply by selectively using the expedited review procedures to increase, as quickly as possible, the number of alternative vaccine products and suppliers. As a result of the department's comments, we have modified the wording of our recommendation to make it clearer that it is directed at using existing expedited review tools as a strategic approach to help strengthen the overall vaccine supply.

HHS did not comment on our matter for congressional consideration concerning amending legislation under the VFC program, but did provide technical comments, which we incorporated in the final report where appropriate. We also provided sections of the draft report on factors that contributed to vaccine shortages and new vaccine products under development to the four major vaccine manufacturers. We incorporated their technical and clarifying comments where appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days after its issue date. At that time, we will send copies of this report to the Secretary of HHS, the Director of CDC, the Deputy Commissioner of FDA, and other interested parties. We will also make copies available to others on request. Copies of this report will also be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staffs have any questions, please contact me at (202) 512-7119. Other contacts and major contributors are included in appendix II.



Janet Heinrich
Director, Health Care—Public Health Issues

List of Requesters

The Honorable Edward M. Kennedy
Chairman
Committee on Health, Education,
Labor, and Pensions
United States Senate

The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
House of Representatives

The Honorable Jeff Bingaman
The Honorable Hillary Rodham Clinton
The Honorable Richard J. Durbin
The Honorable Bill Frist
The Honorable Jack Reed
United States Senate

The Honorable Gary A. Condit
House of Representatives

Appendix I: Comments from the Department of Health & Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

SEP 4 2002

Ms. Janet Heinrich
Director, Health Care - Public Health Issues
United States General
Accounting Office
Washington, D.C. 20548

Dear Ms. Heinrich:

Enclosed are the department's comments on your draft report entitled, "Childhood Vaccines: Ensuring an Adequate Supply Poses Continuing Challenges." The comments represent the tentative position of the department and are subject to reevaluation when the final version of this report is received.

The department also provided several technical comments directly to your staff.

The department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,

A handwritten signature in black ink that reads "Janet Rehnquist".

Janet Rehnquist
Inspector General

Enclosure

The Office of Inspector General (OIG) is transmitting the department's response to this draft report in our capacity as the department's designated focal point and coordinator for General Accounting Office reports. The OIG has not conducted an independent assessment of these comments and therefore expresses no opinion on them.

Comments of the Department of Health and Human Services on the General Accounting Office's Draft Report, "Childhood Vaccines: Ensuring an Adequate Supply Poses Continuing Challenges" (GAO-02-987)

The Department of Health and Human Services (department) thanks the General Accounting Office (GAO) for undertaking this important study and providing the department with the opportunity to comment on the draft report. In general, the report calls needed attention to the challenges and resource needs of mounting an effective response to assure an adequate supply of childhood vaccines. The department agrees with the GAO report, which generally presents an accurate and informative summary of the key issues that impact on vaccine shortages.

Immunization is considered one of ten great public health achievements of the 20th Century. Indeed, vaccine preventable disease levels are currently at or near all-time lows, and childhood immunization coverage levels have been at all-time high levels during the last several years. This success is in no small part due to the innovative and highly effective role of the private sector (often in partnership with innovators in academia and government) in vaccine development and production in the United States and abroad, and the widespread use of licensed vaccines. Many of the childhood vaccines routinely recommended in the U.S. and elsewhere in the world, such as Polio, Measles, Mumps, and Rubella (MMR), *Haemophilus influenzae* type b (Hib), hepatitis B, and Pneumococcal conjugate vaccines, were first brought to the market by private companies. Furthermore, competition among private pharmaceutical companies has resulted in substantial innovation, such as new and safer vaccines, which saves lives and prevents disease and disability.

For more than 15 years, our nation's children have had steady access to vaccines. The minor disruptions in production that have occasionally occurred in the past have been resolved through mobilizing vaccine from national stockpiles, and through the department's Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC), and partners working with manufacturers to increase vaccine supplies. Nevertheless, the unprecedented recent disruption in supply documents that vaccine supply cannot be taken for granted and that critical actions are needed to avert future shortages.

Below are general comments on the GAO report and specific comments to GAO's executive recommendations.

General Comments

The department agrees with the GAO's findings and has initiated actions to implement their recommendations. The department agrees that the Vaccines for Children (VFC) Stockpile authority in section 1928(d)(6) of the Social Security Act (42 U.S.C. 1396s(d)(6)), requires that stockpiles of childhood vaccines be maintained. Several programmatic reasons occurred that have slowed the development of CDC stockpiles. These include the following:

- Implementation of the VFC program took considerable time and resources. Priority was given to recruiting providers to serve eligible children and establishing new contracts with vaccine manufacturers to supply vaccine to the eligible children.
- The CDC had prioritized acquisition to establish stockpiles in a systematic and efficient manner. One year after fully implementing the VFC program, CDC began to expand its stockpile program utilizing VFC program funds. In the late 1990s, CDC focused its efforts on fully establishing single source vaccine stockpiles for highly contagious diseases such as polio and measles. Historical experience with multiple manufacturers indicated that it might not be efficient to have government-funded stockpiles in all instances due to the following: changing market shares, evolving vaccine technology (i.e. new combination vaccines), and open market.
- Any changes to the already complicated vaccine schedule or abrupt and unanticipated changes to the vaccines themselves, such as removal of thimerosal, require concomitant adjustments in stockpiles either by stockpiling new vaccines, drawing down existing stockpiles while increasing stockpiles of new vaccines, or changing existing stockpiled vaccines. Contracts used to establish the stockpiles had previously not had the flexibility to rapidly respond to such changes.

In light of the recent vaccine shortages, as well as the GAO recommendations, CDC is undertaking steps to establish and expand stockpiles as soon as feasible.

Comments on Recommendations for Executive Action

GAO Recommendation

To ensure a well-implemented strategy for expanding HHS's stockpiles of childhood vaccines, we recommend that the Secretary of HHS direct the Director of CDC to develop a strategic plan that addresses the operational difficulties involved. At a minimum such a plan should include:

- A timetable, developed with manufacturers' input, for the purchase of specific quantities of vaccine,
- A determination of form and location of storage of vaccine,
- Procedures for systematic interchange of information between FDA and CDC on potential childhood vaccine manufacturing interruptions, and
- Steps for monitoring of childhood vaccine inventory in state VFC depots.

Department Comment

The department agrees with GAO's recommendation to develop a strategic plan to expand stockpiles of childhood vaccines. Stockpiles have been very effective in the past in alleviating brief disruptions in vaccine supply and are an important resource to maintain. The CDC has already been engaged in a reassessment of its vaccine stockpile and has initiated discussions with the manufacturers to determine their projections of product availability for establishment/expansion of vaccine stockpiles. Site visits to manufacturers have been arranged to discuss issues raised in the GAO recommendation related to timetable, stockpile form, storage location and maintenance. The CDC will develop a comprehensive vaccine stockpile program strategy after the site visits are completed.

GAO Recommendation

To help promote the availability of existing and future vaccine products without compromising standards that help assure safety, we recommend that the Secretary direct the Commissioner of FDA to take steps to ensure widespread distribution of all forms of compliance guidelines to vaccine manufacturers and ensure that these guidelines are kept up-to-date.

Department Comment

Compliance guidance directed to vaccine manufacturers has been made available to them through public postings on the FDA website and through many outreach meetings held with industry and their trade associations. The FDA is working with a contractor to post all compliance programs, including the Vaccine Compliance Program, on its website. In the meantime, inspectional guidance for FDA investigators concerning vaccine-manufacturing inspections will continue to be available in the Vaccine Compliance Program through the Freedom of Information Act.

GAO Recommendation

To help promote the availability of existing and future vaccine products without compromising standards that help assure safety, we recommend that the Secretary direct the Commissioner of FDA to consider revising FDA policies for fast-tracking and priority review approval of vaccine products currently under development to allow their use in cases where FDA determines that applying them is in the public health interest to address the unmet need of strengthening the overall vaccine supply.

Department Comment

There appears to be some confusion about "fast track" and "priority reviews" and how these might or might not speed up the approval time for the licensing of new vaccines or existing vaccines that are in short supply.

The department recognizes the seriousness of vaccine shortages or potential vaccine shortages and, in either the presence or absence of any given formal expedited approval process (i.e., fast track or priority review), FDA has reviewed, and will continue to review, license applications or their supplements in the most expeditious manner possible. The FDA does and will continue to organize priorities based on medical need. For example, FDA expedited the review of influenza vaccine supplements because of shortage situations or to avert potential shortage situations and, recently, the review of Daptacel (Aventis Pasteur's diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed [DtaP]) was conducted as expeditiously as possible.

Biologic License Applications (BLA) may be formally designated for a *priority review*. The FDA has 6 months to complete its review for a new BLA; in contrast, it has 10 months for a so-called *standard review*. A BLA for vaccines in short supply would qualify for a *priority review*. However, even in the absence of a formal designation for a priority review, the application would be reviewed as expeditiously as possible. *Fast track*, which applies to products that are intended to treat or prevent life-threatening or serious conditions, allows for submission of a partial application that can be reviewed before the entire license application is complete. Most fast track products are eligible for priority, 6-month review. Critical vaccine shortages could allow for designation of a vaccine as a fast track product.

It is necessary to consider the practical aspects of priority and fast track reviews. Often, shortages are temporary and are over before even the most expeditious review can be completed; in such cases, the formal designation for the review process has little impact on the shortage. Thus, as a practical matter, it will be infrequent that a new vaccine will become licensed expressly and in time to alleviate a shortage. During the recent shortage of DTaP, Daptacel was approved. The review of this application was a priority for the FDA's Center for Biologics Evaluation & Research (CBER), and this was consistent with a previous determination, stemming from several years ago, that all acellular pertussis vaccines would be considered a priority, and reviewed expeditiously. The message that we wish to stress is that in a shortage situation CBER has the flexibility to work as expeditiously as possible with manufacturers of new or existing vaccines to alleviate the shortage.

As an aside, Prevnar, the pneumococcal conjugate vaccine, was designated as a fast track drug product and the sponsor was allowed to submit a partial application for review before submitting their entire marketing application. This was done because there was a clear unmet medical need, viz., no existing vaccine for the prevention of invasive pneumococcal disease, a serious disease, in infants (< 2 years of age).

Conclusion

The department appreciates the attention the GAO has brought to the issue of childhood vaccine shortages. The GAO's stockpile recommendation will be a useful tool in ensuring an adequate supply of childhood vaccines. The CDC has begun the planning process to address the recommendation regarding stockpiles.

Appendix II: GAO Contacts and Staff Acknowledgments

GAO Contacts

Frank Pasquier, (206) 287-4861
Terry Saiki, (206) 287-4819

Acknowledgments

In addition to those named above, Julian Klazkin, Jennifer Major, Linda McIver, Leslie Spangler, and Stan Stenersen made key contributions to this report.

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