Vaccine Supply Problems: A Perspective of the Centers for Disease Control and Prevention

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Although immunization is one of the great public health achievements, continued success depends on an available supply of the vaccines that are recommended for routine use. Beginning in 2000, the United States experienced vaccine supply disruptions of unprecedented scope and magnitude. Although most of the supply disruptions have been resolved, it appears that a fragile vaccine supply will be part of the immunization environment in the United States for the foreseeable future. Here, we describe the perspective of the Centers for Disease Control and Prevention on the recent supply disruptions and the methods used to manage vaccine shortages. The present article focuses on routine pediatric vaccines, including influenza virus vaccine.

Immunization is one of the great success stories in the history of public health [1, 2]. That success is the result of the administration of safe and highly effective vaccines, which are provided through collaboration between government and industry and are used widely in the populations for whom they are indicated. The availability of vaccines is the first critical component of a successful immunization program, and, over the past 5 years, that availability has been compromised. The present article focuses on routine pediatric vaccines, including influenza virus vaccine. Events in recent years have demonstrated that the vaccine supply cannot be taken for granted. By better understanding the problems that cause vaccine supply shortages, we can determine and implement appropriate solutions for those problems.

Table 1 shows the effect of routine childhood immunization on the incidence of vaccine-preventable diseases. On the basis of provisional 2004 data, record or near-record low incidence rates were reported for the 8 diseases listed in table 1, as well as for a disease complication, congenital rubella syndrome. Incidence rates of all of these diseases have been reduced from representative annual 20th-century morbidity rates by >87% [2].

The critical reasons why the incidence rates of those diseases are so low include (1) the high efficacy of the vaccines used to prevent the diseases and (2) the record or near-record high rates of immunization coverage in the United States (table 2). According to the National Immunization Survey [4], coverage rates for most of the vaccines were ≥90% for 19–35-month-old children (median age, 27 months) surveyed during 2004. Coverage rates for varicella vaccine have increased dramatically in recent years, and the coverage rate for the population is now 87.5%. For pneumococcal conjugate vaccine, the coverage rate for the population is 71% [5]. This article will review the vaccines that have recently been in short supply, some potential reasons for the supply disruptions, the relationship between vaccine price and supply problems, the effect of the Centers for Disease Control and Prevention (CDC) on supply, and the use of vaccine stockpiles to mitigate short-term supply disruptions.

Children in the United States should be vaccinated routinely against 14 diseases [6]. There have been supply problems with vaccines that protect against 9 of the diseases. These 9 diseases are covered by 6 vaccines: (1) pneumococcal heptavalent conjugate vaccine, (2) diphtheria and tetanus toxoids and acellular pertussis (DTaP)
Table 1. Average annual morbidity due to vaccine-preventable diseases throughout the 20th century, compared with morbidity in 2004 (for pre-1990 vaccines).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Morbidity in the 20th century, average no. of cases per year&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Morbidity in 2004, no. of cases&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Decrease in no. of deaths, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>48,164</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>175,885</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Measles</td>
<td>503,282</td>
<td>37</td>
<td>99.99</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209</td>
<td>236</td>
<td>99.84</td>
</tr>
<tr>
<td>Pertussis</td>
<td>147,271</td>
<td>18,957</td>
<td>87.13</td>
</tr>
<tr>
<td>Polio (paralytic)</td>
<td>16,316</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>12</td>
<td>99.97</td>
</tr>
<tr>
<td>Congenital rubella syndrome</td>
<td>823</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1314</td>
<td>26</td>
<td>98.02</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are from the Centers for Diseases Control and Prevention [2].

<sup>b</sup> Data are from the Centers for Diseases Control and Prevention [3].

One can estimate the annual need for a vaccine by multiplying the number of doses recommended for that vaccine by the size of the birth cohort. For example, for DTaP vaccine, with a birth cohort of ~4 million and a recommended schedule of 5 doses, the national need is estimated to be 18–20 million doses. The requirements will vary by the number of doses recommended, ranging from 5 for DTaP to 1 for varicella and DTaP; the expected immunization coverage in the absence of a shortage; and extra immunization that results from record-keeping problems [7]. Other factors in determining vaccine needs include wastage, special initiatives or campaigns, outbreaks of disease, the size of the vaccine vial packages, and inventory capacity changes [8]. Despite the shortages, there appeared to be little effect on vaccine coverage rates among 19–35-month-old children, and, although some children may have experienced vaccine-preventable diseases as a result of the shortage, there were no major outbreaks of those diseases because of vaccine supply disruptions.

The CDC maintains a federal contract for the purchase of childhood vaccines [9], and it purchases ~56% of the vaccines distributed in the United States. Problems in meeting vaccine demand can be determined by comparing orders through the federal contract and shipments to cover those orders. The federal contracts require that vaccine be delivered within 15 working days of the order being placed. Any orders not filled within 15 days are considered to be back orders.

For example, between January and August 2001, the manufacturer of pneumococcal heptavalent conjugate vaccine was able to distribute 1–1.5 million doses per month. Distribution decreased to ~700,000 doses in September 2001 and to <600,000 doses in October 2001. By November 2001, there were ~1 million doses on back order (figure 1). Although the number of back orders decreased in December 2001 and January 2002, an increase in the number of back orders occurred again in February 2002. Although the supply of pneumococcal heptavalent conjugate vaccine returned to normal levels at the end of the month, the number of back orders was still high in March 2002.

Table 2. Vaccination coverage levels, according to a 2004 National Immunization Survey [4].

<table>
<thead>
<tr>
<th>Vaccine, no. of doses</th>
<th>Coverage rate, mean ± SD, % of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria and tetanus toxoids and acellular pertussis</td>
<td></td>
</tr>
<tr>
<td>&gt;3 doses</td>
<td>95.9 ± 0.5</td>
</tr>
<tr>
<td>&gt;4 doses</td>
<td>85.5 ± 0.8</td>
</tr>
<tr>
<td>Poliovirus, &gt;3 doses</td>
<td>91.6 ± 0.7</td>
</tr>
<tr>
<td>Measles-mumps-rubella, &gt;1 dose</td>
<td>93.0 ± 0.6</td>
</tr>
<tr>
<td>Haemophilus influenzae type b, &gt;3 doses</td>
<td>93.5 ± 0.6</td>
</tr>
<tr>
<td>Hepatitis B virus, &gt;3 doses</td>
<td>92.4 ± 0.6</td>
</tr>
<tr>
<td>Varicella, &gt;1 dose</td>
<td>87.5 ± 0.7</td>
</tr>
<tr>
<td>Pneumococcal conjugate, &gt;3 doses</td>
<td>73.2 ± 1.0</td>
</tr>
</tbody>
</table>
of 2002, the vaccine was in short supply again within the following year.

At the end of 2000, 2 of the 4 manufacturers of DTaP vaccine stopped distributing the vaccine. This led to a substantial increase in the number of back orders of DTaP vaccine (866,500 doses) in February 2001, because the remaining 2 manufacturers were unable to keep up with the increased demand (figure 2). As those manufacturers increased their production, the number of back orders decreased to 269,000 doses by the middle of June 2001. However, production output decreased when one of the remaining manufacturers switched from a multiple-dose product containing thimerosal as a preservative to a singleshage product without thimerosal as a preservative. The number of back orders increased to 1 million doses in November 2001 and remained high until June 2002. For one of the manufacturers, who provided vaccines primarily to the public sector, the maximum number of DTaP vaccine doses specified by the federal contract was reached in February 2002; thus, a separate emergency contract was required.

The DTaP vaccine supply problem disproportionately affected the public sector and private providers who depend on the public sector for vaccine supply, because one of the companies decided to divert its limited supply primarily to private-sector orders [10]. The licensure of a third DTaP vaccine relieved this shortage [11].

The supply of varicella vaccine deteriorated significantly between November 2001 and January 2002. For January 2001 through October 2001, the average monthly supply was ~600,000 doses. For November 2001 through January 2002, the average monthly supply was 200,000 doses, a 65% decrease. An announcement to resume the routine schedule for varicella vaccine administration was made in August 2002 [12].

Some of the most severe and long-term supply problems have involved Td vaccine. One of the 2 major commercial manufacturers of this vaccine stopped production in 2000, and the second manufacturer was unable to meet the increased demand (figure 3). Total distribution of vaccine in 2001, in both the public and private sectors, was estimated to be <11.2 million doses, compared with the peak distribution of 16.1 million doses in 1998. The schedule for distribution of Td vaccine had to be changed to defer routine boosters for adolescents and adults and to centralize distribution of the remaining Td vaccine supply only to selected providers, including hospitals and emergency departments [13]. A return to the routine schedule, including booster doses, occurred in June 2002 [14].

Measles-mumps-rubella vaccine was in short supply in 2001. In calendar year 2000, ~13 million doses were distributed. In 2001, the number of doses distributed decreased to 10.6 million. Before October 2001, ~1 million doses were distributed each month. In October and November 2001, the average number of doses distributed was <600,000, which represents a 61% decrease in the number of vaccine doses distributed. Measlesmumps-rubella vaccine supply was adequate to return to the routine schedule in July 2002 [15].

The vaccine that most recently was in short supply is influenza virus vaccine. On 5 October 2004, the anticipated 100 million doses of vaccine expected for the influenza season was decreased by nearly 40% when Chiron’s United Kingdom license was suspended by the British regulatory authorities. The Advisory Committee on Immunization Practices (ACIP) recommended restricting vaccine use to high-risk target groups [16], and the sole remaining supplier of inactivated influenza virus vaccine halted shipment of vaccine until plans to distribute the remaining doses could be made in concert with public health officials. Although the restricted recommendations for the vaccine and the distribution of vaccines at the direction of
public health officials were effective in attaining levels of coverage for targeted groups that were near previous levels [17], the longer-term consequences, in terms of demand for influenza virus vaccine, are not yet known.

There is no single unifying reason for the supply disruptions. Four factors, which are somewhat interrelated, appear to be playing a role: (1) business decisions to leave the market, (2) production problems, (3) adherence to requirements for current Good Manufacturing Practices [18], and (4) a recommended change in formulation to remove thimerosal as a preservative. Business decisions affected supplies of both Td and DTaP vaccines. One of the 2 major commercial producers of Td vaccine and 2 of the 4 producers of DTaP vaccine left the market unexpectedly. The remaining manufacturers were unable to compensate for the decreased production. Problems with DTaP vaccine were exacerbated when 1 of the 2 remaining companies changed its formulation from multiple-dose to single-dose packaging to remove thimerosal, a preservative that contains mercury, from their product. This change led to markedly lower yields, which was an unintended consequence of a precautionary recommendation. This recommendation, which was issued in 1999, called for removal of mercury in vaccines, even in the absence of any data indicating that thimerosal had actually caused harm [19].

Economic incentives are critical to the long-term viability of the vaccine industry. Such incentives help companies to enter or remain in the US market and to make changes, including capital improvements in their manufacturing processes to ensure compliance with current Good Manufacturing Practices [20]. However, the role of insufficient economic incentives as an immediate cause of the current shortages is less clear. An analysis of the role of economic incentives for vaccine development and production should take into account development and manufacturing costs, plant maintenance costs, profit margins, and a variety of other factors. Although we do not have access to those data, we can determine the association between vaccine price and supply shortage.

Figure 4 shows federal contract prices for vaccines with or without supply problems during the time that vaccines shortages occurred. For vaccines with multiple manufacturers, average prices were used. There is no apparent association between a low vaccine price and supply disruption.

The 1993 legislation that established the Vaccines for Children (VFC) program instituted a price cap for vaccines covered by federal contracts in effect in August 1993 [21]. Vaccines developed subsequently are not subject to a price cap. The price cap is also removed when vaccine formulations change and the vaccine is licensed under a different US Food and Drug Administration biologics license number. Vaccines for which price caps were in place were no more likely to have supply problems than were vaccines without price caps.

Table 3 shows federal contract prices for vaccines with or without supply problems and the corresponding catalog prices of these vaccines. The differences in price represent the federal discounts. There is no relationship between the magnitude of the discount given to the federal government and supply disruptions. In fact, there have been supply problems associated with the 2 vaccines with the lowest proportionate discount, pneumococcal heptavalent conjugate vaccine and varicella vaccine.

**EFFECT OF THE CDC ON VACCINE SUPPLY**

The CDC can affect vaccine supply in 4 ways. First, the market is heavily influenced by recommendations of the ACIP. Second, the CDC negotiates a federal contract that uses federal and state funds to purchase ~56% of childhood vaccines distributed in the United States, exclusive of influenza virus vaccine, on the basis of 2004 data. Third, the CDC administers grants to states to help in implementing and promoting immunization programs to improve vaccine coverage rates. Fourth, the CDC administers some stockpiles of vaccines to be used for disruptions in production and surges in demand.

In essence, recommendations of the ACIP define the standard of practice for immunization and determine the maximum size of the market. The vaccines universally recommended for children are included in a harmonized schedule that is issued annually by the ACIP in collaboration with the American Academy of Pediatrics and the American Academy of Family Physicians. In addition, the ACIP has the potential to finance the use of a substantial proportion of recommended vaccines, because it can incorporate those vaccines into the VFC program for eligible children. The VFC program provides a vaccine entitlement for some children, and, once a federal contract is negotiated, funds are soon thereafter made available to purchase vaccine for children who are eligible for the VFC program. In 2001 and 2002, 45% of all children were entitled to VFC vaccines [22].

Figure 3. National distribution of tetanus and diphtheria toxoids vaccine, as of 4 June 2002. Data are from the Biologic Surveillance System. All data are provisional until officially published. Because of underreporting, the real national distribution values may be ~18 million doses for calendar years 1997–2001.
In times of vaccine shortage, the CDC and the ACIP will modify recommendations to help health care providers manage shortages and delays. For example, changes made to the recommendations for pneumococcal conjugate vaccine included deferring catch-up immunization for certain groups of children who were considered to be at lower risk for disease and deferring the fourth dose of the 4-dose infant vaccination schedule \[23\]. For DTaP vaccine, similar actions were taken with deferral of the fourth and fifth doses \[24\]. These changes are a last resort and may not work well. Such changes are difficult to communicate, and, often, by the time health care providers realize that they need to make the changes, they may already be out of vaccine. In addition, such changes require moving from optimal protection to a lower degree of protection, so schedule changes are avoided unless absolutely necessary.

The purchase of childhood vaccines, except influenza virus vaccine, through the CDC contract accounts for ~56% of the vaccines purchased in the United States. Approximately 42% of vaccines distributed are purchased with VFC program funds, ~9% are purchased through the 317 Grant Program, which is a federal discretionary program dependent on annual appropriations from the Congress, and 5% are purchased through state-based appropriations (CDC, unpublished data). Because of the large market covered by the CDC contract, there is the potential that some manufacturers would lack access to a large proportion of the total market if they chose not to participate in the contract. Before 1994, contracts were granted according to a “winner-takes-all” strategy. The low bidder for the given product won the total contract, and the manufacturer with the higher bid could focus only on the private-sector market. Since 1994, as a result of guidance in the VFC legislation, the CDC has granted contracts to all licensed manufacturers for a given product, so that each manufacturer could openly compete and have a share of the public-sector market. The CDC still reserves the right not to grant a contract if terms and conditions are unfavorable to the government (i.e., the public-sector market).

Since 1998, the CDC has entered into 1-year consolidated contracts with all licensed manufacturers for each product, which allows the manufacturers to adjust prices during the period covered by the contract to more closely simulate the competition of the private-sector market. Prices can be adjusted twice during the 12-month contract period. The only limitation is that adjusted prices cannot exceed the price established at the beginning of that contract—in other words, prices can only be adjusted downward during a contract year. The CDC also encourages immunization grantees (i.e., state and urban area immunization programs) to allow for provider choice in vaccine product selection. As of 31 December 2002, approximately two-thirds of the 64 immunization grantees had such a policy that allows all or many providers to choose which product, purchased with public funds, that they obtain. The remaining states choose the vaccine brand type at the state or urban level. Because of the high proportion of vaccines purchased through CDC contracts, the CDC can monitor orders, inventories, and distribution and, during times of shortage, can allocate vaccines and prioritize distribution to those most in need.

**STOCKPILES**

Stockpiles can serve as an insurance policy against unanticipated supply problems. Because production problems have occurred, the CDC has maintained vaccine stockpiles for some vaccines since 1983. The original goal was to establish stockpiles containing a 6-month supply of selected vaccines for the nation. These stockpiles are not static, stored quantities of vaccines that are only distributed when needed and are otherwise discarded after their shelf life expires. For most vaccines, such stockpiles...
are not feasible. Instead, the stockpiles are dynamic strategic inventories.

As vaccine is produced, some portion enters the stockpile, and older vaccine is rotated out of the stockpile and placed on the market, so that the minimum shelf life of vaccine that leaves the stockpile is 12 months. Since 1983, CDC stockpiles have been accessed on at least 8 occasions to relieve production disruptions. Stockpiles can also be used to meet surges in demand, such as those that occur during a large epidemic.

Before 2002, the CDC’s strategy for vaccine stockpiling had been to stockpile only those vaccines produced by single manufacturers. The CDC has prioritized its efforts to stockpile single-manufacturer vaccines with mature, predictable markets. Such stockpiles are most efficient, are easiest to maintain, and provide the least financial risk to the federal government. When vaccine needs can be predicted, manufacturers know how much vaccine to produce at steady-state conditions, how much vaccine will be rotated out of the stockpile, and how much vaccine must be produced to replace it. When markets are changing, such as when a new vaccine is introduced, it becomes more difficult to predict vaccine needs and to determine both the amount of vaccine to be rotated out of the stockpile and how much vaccine must be produced to replace it. If too much vaccine is produced, the stockpile increases in size, and valuable shelf life is lost. If too little vaccine is produced, the stockpile decreases in size.

The stockpiles involve advance financial commitment and risks. The appropriation or establishment of funding must be done in advance of granting contracts and building inventory. When newer vaccines replace older vaccines, there is the potential to lose the vaccine doses and resources put into stockpiling the older vaccines. If a stockpile is available for DTaP vaccine in single-dose preparations, if a second stockpile for Hib vaccine is available in single-dose preparations, and if the standard of practice becomes DTaP-Hib vaccine, then either of the inventories of separate DTaP and Hib vaccines can be lost, because there is little demand for them.

Changing market share is a problem when there are multiple manufacturers of individual vaccines. If manufacturer A has 75% of the market and manufacturer B has 25% of the market at the time a stockpile contract is awarded, 75% of the stockpile would go to manufacturer A, and 25% of the stockpile would go to manufacturer B. If that market share reverses, then manufacturer A no longer would have the turnover rate to maintain 75% of the stockpile. The stockpile with manufacturer A would likely have to be reduced, and the CDC would have to renegotiate with manufacturer B to increase its share of the stockpile.

The building of inventory for new vaccines may be a problem, because manufacturers are usually producing at peak capacity and may not have the excess capacity to create a strategic inventory or stockpile. Furthermore, the market may be unpredictable, and a manufacturer may not have the necessary turnover in the vaccines produced to maintain adequate shelf life.

Although stockpiles have many advantages, they do not solve long-term supply disruptions. For example, if the sole supplier of a vaccine leaves the market, a 6-month national supply would probably not be sufficient to cover vaccine needs until a new manufacturer enters the market. Stockpile size needs to be carefully considered.

The current supply problems highlight vulnerabilities in vaccine supply. At this time, there is only a single licensed manufacturer in the United States distributing inactivated poliovirus, measles-mumps-rubella, varicella, Td, quadrivalent meningococcal conjugate vaccine, and pneumococcal conjugate vaccines. Fortunately, no sole manufacturers of vaccines universally recommended for children have ever left the US market. However, if such a manufacturer ever did leave the market, the United States certainly would be vulnerable.

Starting in 2002, the CDC began an effort to develop stockpiles for all vaccines routinely recommended for children. In-

### Table 3. Federal contract and catalog vaccine prices in place at the time of vaccine shortages, as of 4 February 2002.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Federal contract price</th>
<th>Catalog price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined tetanus and diphtheria toxoids</td>
<td>Not availableb</td>
<td>$7.50c</td>
</tr>
<tr>
<td>Diphtheria and tetanus toxoids and acellular pertussis</td>
<td>$10.58–$10.65</td>
<td>$17.12–$18.50</td>
</tr>
<tr>
<td>Measles-mumps-rubellaa</td>
<td>$15.53</td>
<td>$28.35</td>
</tr>
<tr>
<td>Varicella</td>
<td>$39.14</td>
<td>$49.13</td>
</tr>
<tr>
<td>Pneumococcal heptavalent conjugate</td>
<td>$45.99</td>
<td>$58.75</td>
</tr>
<tr>
<td>Inactivated poliovirusa</td>
<td>$8.25</td>
<td>$15.42</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>$5.75–$8.00</td>
<td>$15.25–$18.95</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>$9.00</td>
<td>$21.40–$24.20</td>
</tr>
</tbody>
</table>

a The price of the vaccine was capped, in accordance with the Omnibus Budget Reconciliation Act of 1993.
b No federal contract was in effect. The federal government purchases vaccine through state contracts instead.
c Average state purchase price.
fluoresence virus vaccine is an exception, because the vaccine tends to change each year. The CDC’s pediatric vaccine stockpile program is being built to establish a 6-month supply of vaccines. The status of the stockpile varies by vaccine, but, as of February 2005, 2 of 8 vaccines in the stockpile had met their target amounts [25]. Funding for the stockpiles is provided through VFC program funds.

In conclusion, immunization is one of the most effective disease prevention measures. However, it is dependent on an adequate supply of vaccine, and our supplies are vulnerable. There is no clear single reason for supply problems, and, therefore, the solutions needed are multifaceted. We believe that there is no connection with the recent supply problems and vaccine price. Both short-term and long-term solutions are needed. Stockpiles are probably the best way to meet short-term problems with vaccine production or surges in demand.

Acknowledgments

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References