Abstract

In recent years, several factors have led to pediatric vaccine manufacturers experiencing vaccine production interruptions that resulted in vaccine supply shortages. One unfortunate consequence of such events is that not all children in the United States could be vaccinated on time, as set forth by the Recommended Childhood Immunization Schedule, and hence, created the potential for epidemic outbreaks of several childhood diseases. The Centers for Disease Control and Prevention (CDC) have responded to such events by releasing vaccine supplies from the national pediatric vaccine stockpiles, which were designed to mitigate the impact of vaccine production interruptions. This paper analyzes the CDC-proposed vaccine stockpile levels using a stochastic inventory model. The results from this analysis examine the adequacy of the proposed pediatric vaccine stockpile levels, as well as provide insights into what the appropriate pediatric vaccine stockpile levels should be to achieve prespecified vaccination coverage rates. Given that the average pediatric vaccine production interruption has lasted more than 1 year, the model is used to compute appropriate pediatric vaccine stockpile levels sufficient to absorb the effect of such vaccine production interruptions. The level of funding needed to create such pediatric vaccine stockpile levels is also reported.

Keywords: Pediatric vaccines; Vaccine stockpiles; Pediatric vaccine coverage rates; Pediatric immunization

1. Introduction and background

The Advisory Committee on Immunization Practice (ACIP) establishes pediatric immunization regulations and standards for the United States by managing the Recommended Childhood Immunization Schedule, a comprehensive sequence and timing of pediatric vaccines to protect children from several pediatric diseases that once posed major infectious disease health risks throughout the nation [1]. Immunization is considered by many within the public health community to be one of the great medical advances of the twentieth century. For example, the risk of polio and measles has been almost entirely eradicated through nationwide pediatric immunization programs [2].

Biotechnology advances, educational programs spearheaded by government agencies, the responsible attitude of parents and guardians, and strategic solutions directed to improve vaccine delivery systems have led to significant improvements in pediatric immunization practices. One indicator of such improvements is that vaccination coverage rates are now at all-time highs, which in turn has resulted in record low disease rates [4]. Maintaining such rates requires a safe and reliable pediatric vaccine supply. However, in recent years, different vaccine manufacturers have experienced production interruptions that have led to several pediatric vaccine supply shortages [4] (see Table 1 for a sample of such vaccine production interruptions).

Based on surveys and interviews of immunization program managers and providers of the Vaccine for Children...
Program at the end of 2001, Stokley et al. [3] evaluate the impact of vaccine supply shortages on the immunization programs and providers. They observe that a minority of providers implemented the temporary immunization recommendations, as suggested by the ACIP, which were designed to minimize the negative impacts of the shortages. They also note that after the ACIP calls for the resumption of the recommended vaccine schedule, a certain proportion of children may actually never receive their missed immunization doses.

The National Vaccine Advisory Committee [6] and Santoli et al. [4] describe several contributing factors that have caused vulnerability in the pediatric vaccine supply chain. First, they observe the low valuation of vaccines reflected in the low price that the public and legislators are willing to pay for vaccines. Moreover, the high cost and complexity associated with the development, approval, production, and distribution of pediatric vaccines provides barriers that a shrinking number of vaccine manufacturers are willing to tackle. They also note that confidentiality requirements in communication between key stakeholders in the vaccine industry and the federal government make it difficult to promptly recognize and manage potential shortages. Lastly, Santoli et al. [4] observe that over the past two decades, the number of pediatric vaccine manufacturers in the United States has been decreasing [6], while the number of vaccines in the Recommended Childhood Immunization Schedule has been increasing. This reduction of manufacturers can be blamed, in part, to the pressure on the industry to provide low-price vaccines. For example, the federal government purchases over one-half of all pediatric vaccines that are administered in the United States (in 2001, approximately 57% of all pediatric vaccines were purchased with federal, state and local funds, through the Vaccine for Children program) [4], and negotiated government contract prices are significantly lower than private sector prices [5]. It has been suggested that the resulting low profit margins on pediatric vaccines have made it financially unattractive for vaccine manufacturers to either enter the pediatric vaccine market or increase vaccine production capacity [10]. The small number of vaccine manufacturers is critical, not only since it may lead to insufficient vaccine production capacity, but also because it limits the ability of the health care immunization community to quickly respond to unanticipated changes in market share when one or more vaccine manufacturers experience production problems and/or precipitously cease production. For example, in the Spring of 2001, Wyeth Pharmaceuticals ceased production of diphtheria-tetanus-acellular pertussis (DTaP), leaving the United States with just two manufacturers for this vaccine. Temporary production interruptions in the supply of the measles-mumps-rubella (MMR) and varicella (VAR) vaccines were due to the reconstruction of a vaccine manufacturer’s vaccine filling suite [4]. A shortage of the pneumococcal conjugate (PNU7) vaccine occurred when it was initially introduced because of production problems during the startup period [6].

Based on a request by the United States Department of Health and Human Services (HHS) to investigate the root causes of pediatric vaccine supply shortages, the National Vaccine Advisory Committee (NVAC) formed the working group, “Strengthening the Vaccine Supply of Routinely Recommended Vaccines” [6]. In 2002, this working group held a workshop with industry representatives, regulatory authorities, public health officials, purchasers, providers, consumers, legislators and academic investigators to consider relevant issues surrounding the pediatric vaccine supply shortage problem. This discussion identified several possible solutions, including providing financial incentives to motivate vaccine manufacturers, enacting changes in the vaccine regulatory process, and expanding the rotating pediatric vaccine stockpiles [7]. Sloan et al. [8] discuss the rational implementation of a pediatric vaccine subsidy system that could serve to encourage more pharmaceutical companies to enter the vaccine market, and hence, create a more reliable vaccine supply system for the future. Kuran et al. [9] outlines the position of the American College of Preventive Medicine with respect to the Institute of Medicine [10] and the NVAC reports. They use the arguments posed from both sets of recommendations to align its own position about needed financial changes in the vaccine supply chain system. Hinman [11,12] further clarifies the position of the NVAC towards the Institute of Medicine recommendations in the vaccine financial system.

The General Accounting Office and the Centers for Disease Control and Prevention (CDC) deemed that a national pediatric vaccine stockpile program would provide the most advantageous short-term solution against possible future vaccine supply shortages [7]. Note that the first national pediatric vaccine stockpiles were created in 1983 to address short-term vaccine supply interruptions. According to the CDC, vaccine

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Table 1: Duration of recent pediatric vaccine supply shortages

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Start of shortage</th>
<th>End of shortage</th>
<th>Duration (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined tetanus-diphtheria toxoids (Td)</td>
<td>November, 2000</td>
<td>June, 2002</td>
<td>19</td>
</tr>
<tr>
<td>Diphtheria-tetanus-acellular pertussis (DTaP)</td>
<td>March, 2001</td>
<td>July, 2002</td>
<td>16</td>
</tr>
<tr>
<td>Pneumococcal conjugate (PNU7)</td>
<td>September, 2001</td>
<td>March, 2003</td>
<td>20</td>
</tr>
<tr>
<td>Measles-mumps-rubella (MMR)</td>
<td>October, 2001</td>
<td>July, 2002</td>
<td>9</td>
</tr>
<tr>
<td>Varicella (VAR)</td>
<td>October, 2001</td>
<td>August, 2002</td>
<td>10</td>
</tr>
<tr>
<td>Pneumococcal conjugate (PNU7)</td>
<td>February, 2004</td>
<td>September, 2004</td>
<td>7</td>
</tr>
</tbody>
</table>

* Month and year of publication in Morbidity and Mortality Weekly Report announcing resolution of the shortage.  

b NIP, vaccine shortages archives.
The unreliability of the vaccine production model; see [14] for technical details of this model. The results from this analysis examine the adequacy of the proposed pediatric vaccine stockpile levels, as well as provide insights into appropriate pediatric vaccine stockpile levels as a function of vaccination coverage rates, the time duration of vaccine production interruptions, and the rate at which vaccine production returns to full capacity. The model provides an approximation for the probability that a pediatric vaccine supply shortage will occur, given a specified stockpile of vaccines available when a production interruption occurs. It also uses this probability to quantify appropriate pediatric vaccine stockpile levels for different vaccination coverage rates and vaccine production interruption scenarios. The paper is organized as follows. Section 2 briefly describes the unreliable vaccine production model, including the assumptions used in constructing and applying the model. Section 3 reports the results of the analysis. Section 4 discusses the implications and limitations of the results obtained. Given that the average pediatric vaccine production interruption has lasted more than 1 year, the model is used to compute appropriate pediatric vaccine stockpile levels sufficient to absorb the effect of such vaccine production interruptions. The amount of funds that would be needed to create such pediatric vaccine stockpiles is also reported.

2. Methods: model overview and assumptions

A stochastic inventory model, termed the unreliable vaccine supply model, is used to capture the relationship between vaccine supply and vaccine demand when vaccine production is temporarily interrupted. This model is used to approximate the probability that all children who require immunization with a particular vaccine (i.e., the vaccination coverage rate) can receive all their required doses on schedule, given the following input data: a vaccine stockpile level, a probability distribution for the length of the vaccine production down-time, a function for the vaccine production ramp-up process, and a probability distribution for the number of children born each day. The model considers three phases for the vaccine production process: a steady-state phase during which vaccine production equals the expected vaccine demand; a vaccine production interruption phase; and a vaccine production ramp-up phase. The model analysis focuses on the second and third phases, which captures the vaccine supply/demand relationship when a vaccine manufacturing facility (and hence, the vaccine supply process) fails due to a temporary production interruption, and then ramps-up again to a full vaccine stockpile. For further information on this model, see Jacobson et al. [14], which includes a detailed technical derivation of the model, as well as a description of all the assumptions used in the analysis.

To provide an overview of the model, consider a monovalent vaccine that requires C doses to provide full immunization, as defined by the Recommended Childhood Immunization Schedule [1]. Suppose that the number of children born on day t (and hence, the number of children that require or demand immunization each day) are independently and identically distributed random variables \( \{X_t\} \) with mean

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated polio</td>
<td>8,000,000</td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>4,000,000</td>
</tr>
<tr>
<td>Haemophilus influenzae type B</td>
<td>8,000,000</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>6,000,000</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>4,000,000</td>
</tr>
<tr>
<td>Varicella</td>
<td>2,000,000</td>
</tr>
<tr>
<td>Diphtheria/tetanus-acellular pertussis</td>
<td>10,000,000</td>
</tr>
<tr>
<td>Pneumococcal conjugate</td>
<td>8,000,000</td>
</tr>
</tbody>
</table>
\( \lambda = 11,000 \) and standard deviation \( \sigma = 1,100 \) (both measured in children per day). Without loss of generality, assume that this vaccine is produced by a single source provider (which is the case for three of the eight vaccines listed in Table 2; for vaccines produced by two or more manufacturers, the ensuing analysis can be applied to the vaccine deficit created if one or more of these manufacturers experiences a production interruption). Suppose that the vaccine production is interrupted and remains down during a time period of length \( T \), a positive random variable (measured in days) that is greater than 0 with probability one.

Assume that the initial vaccine stockpile level, \( I \), is known prior to the vaccine production interruption. Suppose that \( t = 0 \) is labeled as the time at which the vaccine manufacturer production operation becomes available and begins a production ramp-up phase, from a production rate of zero to a maximum production capacity rate of \( 1.1C_\lambda \), until the vaccine stockpile is replenished to \( I \) doses, where \( u(t) \) denotes the vaccine production ramp-up rate function at time \( t \). Let \( t_a \) denote the discrete point of time at which the vaccine manufacturer’s production capacity rate returns to its maximum production rate (i.e., \( u(t_a) = 1.1C_\lambda \)), and hence, the vaccine stockpile can be replenished back to \( I \) doses (since vaccine production will exceed vaccine demand). Assume that vaccine demand is tracked once per day (daily) and that the vaccine production rate monotonically increases from time \( t = 0 \) until time \( t = t_a \).

Given the dearth of available data, due to the propriety of vaccine production information, there is no way to know the exact form of \( u(t) \). For example, setting the maximum production capacity rate to be 10% above the demand rate is arbitrary. If this value is set too close to zero, it may be difficult to satisfy the backlog of children requiring immunization and to replenish the vaccine stockpile in a reasonable amount of time (which seems unlikely). If this value is set too high (e.g., 50% above the demand rate), then providing vaccines for the backlog of children requiring immunization and replenishing the vaccine stockpile replenishment could both be done sufficiently fast that there would be a minimal ramp-up time period (which also seems unlikely). In fact, this latter situation would be equivalent to reducing the length of the vaccine production interruption. Therefore, changes in the maximum production capacity rate have the same effect as shortening or lengthening the effective time of a vaccine production interruption. The implication of such an effect is further discussed in Section 4.

To better understand the form of \( u(t) \), two extreme cases are considered, which provide an envelope between the best and worst case scenarios. In particular, a concave and a convex functional form for \( u(t) \) over time period \([0, t_a]\) are proposed as two possible vaccine production ramp-up rate functions, as the supply rate monotonically increases from zero to its maximum production capacity. Note that by considering these two extreme scenarios, a mean or base case can be extracted from this analysis by interpolating between them. The convex vaccine production ramp-up rate function (which corresponds to a pessimistic scenario, since the production rate increases slowly and only accelerates near the end of the time period \([0, t_a]\)) is given by

\[
u(t) = 1.1C_\lambda \left( \frac{t}{t_a} \right)^3, \tag{1}
\]

while the concave vaccine production ramp-up rate function (which corresponds to an optimistic scenario, since the production rate increases rapidly and then levels off near the end of the time period \([0, t_a]\)) is given by

\[
u(t) = 1.1C_\lambda \left( \frac{t}{t_a} \right)^{1/2}. \tag{2}
\]

Define \( S(t) \) to be the vaccine supply level at time \( t \). Fig. 1 depicts the expected vaccine supply level as a function of the initial stockpile level \( I \). Lastly, to determine the probability that at least \( \alpha \) 100% of all children that require vaccination can indeed be immunized, during the time period defined from when the vaccine production is interrupted until time \( t = t_a \), define two extreme random variables \( t_a \), to be the time when the expected vaccine supply reaches its minimum level. Therefore, after the \( T \) days during which the vaccine production interruption occurred, the vaccine production facility then becomes available again and begins a production ramp-up period, from a production rate of zero to its maximum production capacity rate (which is assumed to be \( 110\% \) of the average production rate needed to meet the immunization needs of all children).

The parameter \( \alpha \) denotes the vaccination coverage rate (hence a specified value of \( \alpha \) implies that \( \alpha \) 100% of all children are immunized on schedule). Under these assumptions, define \( P(\alpha, I, T) \) as the probability of achieving a vaccination coverage rate of \( \alpha \) 100% during a vaccine production interruption, as a function of the vaccine stockpile level \( I \) and the probability distribution for the length of the vaccine production interruption period \( T \). Therefore, for each vaccine, the objective is to determine the probability that at least \( \alpha \) 100% of all children that require vaccination during the vaccine production interruption can be immunized on schedule.

\[ \text{Fig. 1. Expected vaccine supply function.} \]
3. Results

This section reports results with the unreliable vaccine supply model described in [14] to evaluate the proposed vaccine stockpile levels (see Table 2) and to determine appropriate pediatric vaccine stockpile levels in the event of production interruptions that last longer than 6 months.

Table 3 reports approximations for $P(\alpha, I, T)$ for the eight vaccines listed in Table 2, for the CDC-proposed values of $I$, for $\alpha = 1.0$, $t_M = 60, 120, 180$, and $T$ distributed as a truncated normal ($\eta T(\eta, \sigma_T)$), with $\eta = 120, 180$, and $\sigma_T = \eta/6$, for both concave (optimistic scenario) and convex (pessimistic scenario) vaccine production ramp-up rate functions. From the definitions and notation described here, complete recovery of the vaccine production facility is assumed to take on average slightly more than $\eta + t_M$ days. Therefore, for $\eta = 180$ and $t_M = 60$, the resulting vaccine production interruption lasts for approximately 8 months (which includes a 2-month production ramp-up period).

For less than 100% vaccination coverage rate, Tables 4 and 5 report initial vaccine stockpile levels (in millions of doses) for each vaccine and each scenario. The optimistic scenario assumes $\eta = 180$ and the pessimistic scenario assumes $\eta = 60$.
stockpile levels that provide a 100% vaccination coverage rates for each pediatric vaccine, $a=0.90, 0.95$ such that $P(x, I, T)=0.99$; these levels are provided for the same set of values for $\eta$ and $\eta_M$ used for Table 3, for both the optimistic and pessimistic scenarios. To provide a frame of reference for these values, they should be compared to the recommended vaccine stockpile levels reported in Table 2. Alternatively, to compute the amount of time it would take for the vaccine stockpile levels reported in Tables 4 and 5 to be depleted (assuming no vaccine production over this time period), the values in Tables 4 and 5 for a given vaccine, would need to be divided by the product of $\lambda = 11,000$ children per day and $C$ doses of the vaccine required for each child. For example, for the value $11.1$ million doses for vaccine IPV in the first row of Table 4, this corresponds to a supply of just over 252 days (since $C=4$). Note that all these results were obtained using Mathematica 5.1.

4. Discussion and recommendations

The results in Table 3 suggest that the CDC-proposed pediatric vaccine stockpile levels for IPV, MMR, Hib, HBV, HAV, VAR, DT,$P$, and PNU) are adequate to absorb the impact of a 6-month vaccine production interruption for these vaccines. In particular, the proposed vaccine stockpile levels for these diseases are moderately likely (i.e., 99% for the optimistic scenario, down to a 0% chance for the pessimistic scenario) to be able to provide all the vaccines needed to fully immunize the nation during a 6-month production interruption. Given that these vaccine stockpile levels have been set for such a production interruption time period, these results are reasonable. What they do provide is some empirical validation for the unreliable vaccine supply model introduced in Jacobson et al. [14].

The results in Table 3 also provide approximations for $P(x, I, T)$ for the proposed vaccine stockpile levels, in the event of longer production interruption periods, as measured by larger values for $\eta$ and $\eta_M$. These results suggest that in the event of a vaccine production interruption for any of the vaccines that lasts for 8 or more months (which has been the case for all but one of the recent production interruptions; see Table 1), there is a reasonably high risk (i.e., between 8% in the optimistic scenario and up to 95% in the pessimistic scenario) that the proposed vaccine stockpile levels will not be adequate to fully vaccinate all children that require immunization during such a production interruption. In the event of a 12-month production interruption, there is a very high risk (i.e., between 95% in the optimistic scenario and up to 100% in the pessimistic scenario) that the proposed vaccine stockpile levels will not be adequate to fully vaccinate all children that require immunization during such a production interruption. In practical terms, this means that the proposed pediatric vaccine stockpile levels are inadequate to mitigate the impact of vaccine production interruptions that last for 8 or more months, which could pose significant risks to children not being fully immunized on schedule.

If a vaccine production interruption lasts longer than 6 months, then vaccine stockpile levels will need to be higher to absorb the impact of the resulting vaccine supply shortage. The values in Tables 4 and 5 report initial vaccine stockpile levels that provide a 100% vaccination coverage rates for each pediatric vaccine, $a=0.90, 0.95$ such that $P(x, I, T)=0.99$; for different sets of values for $\eta$ and $\eta_M$ for both the pessimistic and optimistic scenarios. Note that the goal of the CDC is to achieve 95% vaccination coverage rates [17]. For example, for IPV, with $a=0.95, \eta=120, \eta_M=60$, in the optimistic scenario, a stockpile of 7.7 million doses will be adequate to absorb the impact of a vaccine production interruption of approximately 6 months, with a 4-month down period and a 2-month production ramp-up period. On the other hand, for the same parameter values in the pessimistic scenario, the stockpile level would need to be 8.6 million doses. For $\eta=120$ and $\eta_M=120$, a stockpile of 8.3 million doses will be adequate to absorb the impact of a vaccine production interruption of approximately 8 months, with a 4-month down period and a 4-month (optimistic scenario) production ramp-up period, while for the same parameter values in the pessimistic scenario, the stockpile level would need to be 13.6 million doses. Similar conclusions and insights can be drawn for all the other vaccines. In general, as the length of a vaccine production interruption increases, as measured by the production down time, $\eta$, the length of the ramp-up period, $\eta_M$ and the form of the production ramp-up rate function (i.e., optimistic versus pessimistic scenario), the vaccine stockpile required to absorb the impact of such a production interruption time period must also increase. Moreover, if the maximum production capacity rate is assumed to be 1.5G (i.e., 50% above the demand rate, rather than 10%), then the pediatric vaccine stockpile levels reported in Table 4 would be on the order of 2–7% lower, while the pediatric vaccine stockpile levels reported in Table 5 would be on the order of 2–12% lower. All these results suggest that the proposed stockpile levels will only serve to absorb the impact of a 6-month or shorter vaccine production interruption under the optimistic scenario.

It would be useful to determine the cost of purchasing adequate vaccine stockpiles (see Tables 4 and 5) for the eight vaccines listed in Table 2. Table 6 reports the purchase cost of these eight vaccines (based on various June 15, 2005 federal negotiated contract prices), for $\eta=120$ and $\eta_M=120$, which models an 8-month vaccine production interruption.
with a 4-month down period and a 6-month (optimistic scenario) ramp-up period with maximum production capacity rate of 1.1C, for 90% and 95% vaccination coverage rates (i.e., values for α). In addition, the cost of the CDC-proposed vaccine stockpile levels are also reported (labelled as baseline cost). Similarly, Table 7 reports the purchase cost of these eight vaccines for η = 180 and τ = 180, which models a 12-month vaccine production interruption with a 6-month down period and a 6-month (optimistic scenario) ramp-up period with maximum production capacity rate of 1.1C, for 90% and 95% vaccination coverage rates. The results in Table 6 indicate that to stock sufficient vaccines to achieve a 95% vaccination coverage rate for each of the vaccines would require $1023 M (which is $10 M less than what would be needed to purchase up to the proposed vaccine stockpile levels). Moreover, to achieve a 90% vaccination coverage rates for each of the vaccines would require $1354 M (which is $554 M more than what would be needed to purchase up to the proposed vaccine stockpile levels). If the maximum production capacity rate is assumed to be 1.5C, then these costs would decrease to $1415 and $1337 M, respectively.

The analysis also focuses on the one-time outlay to create pediatric vaccine stockpiles. It does not take into account the costs associated with holding, rotating, maintaining, or transporting vaccines in the stockpile. For example, rotating large quantities of vaccines requires diligent inventory management. In addition, centralized versus localized inventory and distribution systems could have a large impact on overall stockpile management costs. Once a pediatric vaccine stockpile is created, such on-going costs would need to be considered to determine the costs of maintaining the stockpile. As data becomes available to support changes in the assumptions of the unreliable vaccine supply model, or if other assumptions are deemed more appropriate by either public health administrators, CDC personnel, or vaccine manufacturers, they can and will be incorporated into the analysis.

This analysis only considers monovalent vaccines. There are a growing number of combination vaccines that are now available (e.g., HBV-HaB, DTaP-HBV-IPV) that could also be stockpiled. Although it would appear that this would significantly reduce the total number of vaccines that would need to be stockpiled, it would also create a complex dependency between the different vaccines covered in the Recommended Childhood Immunization Schedule. Such a dependency would likely result in the need for a larger stockpile of combination vaccines, which may closely rival the sum
of the monovalent components. Work is in progress to study this highly complex situation.

In conclusion, the results reported suggest that the CDC-proposed pediatric vaccine stockpile levels for IPV, MMR, Hib, HBV, HAV, VAR, DTaP, and PNU7 are adequate to absorb the effect of a vaccine production interruption lasting no more than 6 months. If a vaccine production interruption exceeds 6 months, then modifications to the vaccination guidelines must be instituted to preserve and optimally use existing vaccine stockpiles, and hence, to ensure that all children receive at least some doses of the required vaccines. However, modest increases in the vaccine stockpile levels may have a significant impact to ensure that vaccination coverage rates remain high during vaccine production interruptions [17].

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