



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Optimal vaccine stockpile design for an eradicated disease: Application to polio

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ARTICLE INFO

Article history:

Received 3 September 2009

Received in revised form 31 March 2010

Accepted 3 April 2010

Available online 27 April 2010

Keywords:

Vaccine stockpile

Optimization

Dynamics

Polio eradication

ABSTRACT

Eradication of a disease promises significant health and financial benefits. Preserving those benefits, hopefully in perpetuity, requires preparing for the possibility that the causal agent could re-emerge (unintentionally or intentionally). In the case of a vaccine-preventable disease, creation and planning for the use of a vaccine stockpile becomes a primary concern. Doing so requires consideration of the dynamics at different levels, including the stockpile supply chain and transmission of the causal agent. This paper develops a mathematical framework for determining the optimal management of a vaccine stockpile over time. We apply the framework to the polio vaccine stockpile for the post-eradication era and present examples of solutions to one possible framing of the optimization problem. We use the framework to discuss issues relevant to the development and use of the polio vaccine stockpile, including capacity constraints, production and filling delays, risks associated with the stockpile, dynamics and uncertainty of vaccine needs, issues of funding, location, and serotype dependent behavior, and the implications of likely changes over time that might occur. This framework serves as a helpful context for discussions and analyses related to the process of designing and maintaining a stockpile for an eradicated disease.

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1. Introduction

Global eradication of infectious diseases offers the promise of substantial health and financial benefits due to the prevention of cases of disease and the reduction of costs for disease control and treatment after eradication. Recognizing the humanitarian and economical benefits of eradication, the international public health community successfully eradicated smallpox, and is currently attempting to eradicate the transmission of wild polioviruses, dracunculiasis (guinea worm), and rinderpest (an animal disease) [1,2]. Eradication of other diseases, including measles and malaria, represents a continuing topic of discussion [3–5]. Preserving the benefits achieved through eradication requires preparing for the possibility that the causal agent could re-emerge (unintentionally or intentionally). In the case of a vaccine-preventable disease, creation and planning for the use of a vaccine stockpile becomes a primary concern, particularly when achieving the goal of eradication leads to expectations and demands to stop vaccination. For example, following smallpox eradication, national and international public health agencies prepared to respond to potential but unlikely reintroductions of smallpox after the cessation of vaccination for smallpox by creating vaccine stockpiles. Milstien

conducted an extensive review of the smallpox vaccine stockpile and other stockpiles for non-eradicated diseases (i.e., meningitis, yellow fever, influenza, and anthrax), and offered lessons learned related to the establishment, maintenance, governance, financing, regulation, implementation, and use of a post-eradication stockpile (Table 1) [6]. Emergency antigen and vaccine banks also exist for foot and mouth disease and other animal diseases [7].

Stockpiles for eradicated diseases, for which routine vaccination with a vaccine used to achieve eradication will cease, differ from those for non-eradicated diseases in two important ways. First, while the perceived risk of reintroduction of the causal agent remains small for an eradicated disease, population immunity will likely decrease substantially after reduced agent vaccination, leading to a situation in which a reintroduction can potentially spread very rapidly. This means that the speed of deployment of the vaccine becomes a key requirement of the stockpile and that the possible consequences of insufficient quantities of vaccine in the stockpile become very important. Second, the stockpile may contain a no longer routinely used vaccine, making a rotating stock procurement strategy impossible, with implications for vaccine licensing, testing, expiry, and storage. Thus, managing the stockpile requires consideration of the dynamic interactions between the vaccine supply chain and disease transmission in a highly uncertain environment. The complexity of the issues suggests the need for quantitative analysis to inform the process of developing and maintaining a post-eradication stockpile for a vaccine that will cease to be used for routine vaccination following eradication. While

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Table 1
Lessons learned from prior stockpiles (adapted from Milstien [6]).

Aspect of the stockpile	Lessons learned
Establishment	Need for more than one manufacturer Need to keep stocks in more than one format
Maintenance	Need to make provisions for potential advances in the field Need for strategies to handle intellectual property rights issues
Governance	Need of an independent oversight committee Need for permanent institutional memory provisions Manufacturing facilities may provide the best storage possibilities in terms of oversight Importance of well-designed and implemented quality assurance and quality control
Financing	Need for advance funding for procurement Funding must cover storage, transport, quality assurance and quality control, and other costs
Regulation	Possible need for innovative regulatory approaches WHO prequalification is essential Importance of national acceptance of the stockpile
Implementation	Need for liability indemnification Need for criteria for trigger events and distribution, including epidemiological and laboratory confirmation

several mathematical models of stockpiles of antiviral drugs for influenza contributed to the evolving discussions of preparedness for an influenza pandemic [8–10], to our knowledge no quantitative model exists for analyzing stockpiles for eradicated diseases. This paper formulates a mathematical framework for optimizing the management of a stockpile for an eradicated disease. We focus on the current development of the polio vaccine stockpile for the post-eradication era [11], and anticipate that this framework will provide helpful context for discussions and analyses related to the process of its design, use, and maintenance. Building on our prior work exploring responses to outbreaks [12,13], we use the framework to discuss numerous issues, including capacity constraints, production and filling delays and the expiry process, risks associated with the stockpile, dynamics and uncertainty of vaccine needs, issues of funding, location, and serotype dependent behavior, and the implications of likely changes over time that might occur.

The following section presents a general framework for stockpile optimization, with two distinct formulations of the optimization problem. The next section provides background related to the polio vaccine stockpile and then presents the supply chain model for this study. We then present a hypothetical example to illustrate some of the dynamics and present variations of the optimization model that highlight different issues with respect to a polio vaccine stockpile to demonstrate the value of the framework. Finally, we discuss insights we derived from developing the framework and analyzing the example, and we suggest the need for continued work on this topic.

2. General optimization framework

While optimizing the use of scarce health resources typically relies on relatively static tools such as cost-effectiveness analyses, mathematical optimization offers opportunities to further improve resource allocation decisions [14–17]. In the case of a vaccine stockpile, optimization requires an understanding of the dynamics of the supply chain and the nature of the demand [18–20]. In this section, we formulate optimization problems for a simplified, abstract stockpile to illustrate the general framework.

We consider the simplified stock-and-flow diagram for the stockpile depicted in Fig. 1. A stock-and-flow diagram consists of stocks (shown as boxes) whose levels can change over time, inflows and outflows (shown as arrows with valves) that control the levels in the stocks, and intermediate variables (shown as text connected with arrows) that may contain constants or calculations and influence the flows [21]. The arrows show direct influences between stocks, flows, and intermediate variables. In text discussing the stock-and-flow figures, we refer to stocks using bold text and flows or other variables using italics. The box **stockpile** in Fig. 1 represents the quantity of vaccine readily available for use. The **stockpile** size gets drawn down as a result of *expiry and loss* due to a finite shelf-life or wastage in storage, or *deployment* in response to *vaccine demand*. *Vaccine demand* depends on how quickly we can vaccinate people (captured in the *distribution constraints*). The amount of vaccine in the **stockpile** and the time needed to deploy vaccine from the **stockpile**, captured in the *deployment constraints*, together determine the *maximum deployment rate* (e.g., the *maximum deployment rate* becomes 0 if the amount of vaccine from the **stockpile** is 0). The **stockpile** size may increase as a result of a nonnegative *order rate*, but due to the production process, newly ordered vaccine first accumulates in the stock **vaccine in production** through the *production starts* flow before arriving in the **stockpile** through the *production flow*. The stock **vaccine in production** in reality includes many intermediate stocks representing different stages in the production pipeline, including vaccine orders waiting to enter the production pipeline, production of bulk, storage of bulk, vaccine being filled, and vaccine waiting to be tested. For simplicity, we represent them here all in one stock, **vaccine in production**, and show the box in bold face to indicate that this stock in reality consists of multiple stages. We capture the delays and capacity constraint of the production process in *production constraints*. The *production constraints* and amount of **vaccine in production** determine the *maximum production rate*, and *loss* may occur as a result of wastage during the production process. Managers place orders at a certain *order rate* following their *ordering strategy*, although a delay may exist between setting the strategy and executing it, as shown by the delay mark (double line) in the arrow from *ordering strategy* to *order rate*. The *ordering strategy* at any given time t may be subject to *financial constraints* and use information about the **stockpile** size at time t (both shown by the dotted arrows) and other information about the current state of the stockpile (arrows not shown). *Production* leads to *vaccine costs* and *unmet vaccine needs* lead to sub-optimal outbreak response and thus to *public health costs*. Whenever *deployment* cannot meet the *vaccine demand* due to insufficient vaccine available from the **stockpile**, this leads to *unmet vaccine needs*.

Optimizing the vaccine stockpile involves balancing the trade-off between *vaccine costs* and *public health costs*. We formulate two different framings of the optimization problem.

Framing 1: Minimize the present value of total costs over all feasible ordering strategies, assuming no financial constraints:

$$\text{Minimize } C = \int_{t_0}^{\infty} (c_p(t) + c_v(t))e^{-rt} dt$$

$$\text{s.t. } o(t) \geq 0$$

where C is the net present value of the total costs, c_p and c_v are the *order rate* dependent annual *public health costs* and annual *vaccine costs*, respectively, r is the discount rate, and o is the *order rate*. It follows from the constraint that any *ordering strategy* that leads to nonnegative *order rate* is feasible. If the *order rate* exceeds the *maximum production rate*, excess orders will simply remain in the stock **vaccine in production** as backlog and the *production constraints* will govern the rate at which these orders ultimately flow to the **stockpile**.

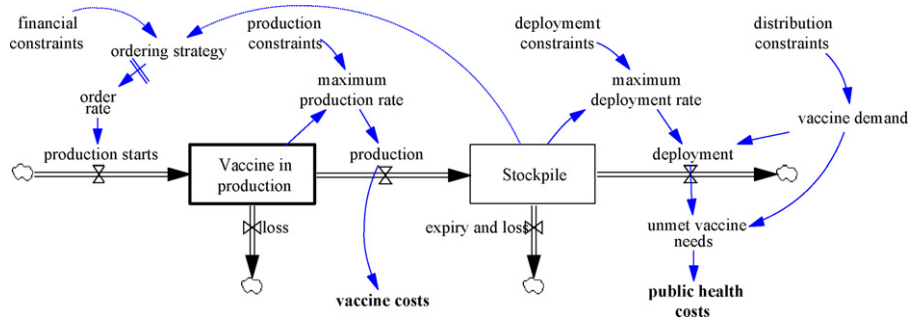


Fig. 1. Stylized general stockpile model.

Framing 2: Minimize the present value of public health costs over all feasible ordering strategies subject to the financial constraints:

$$\begin{aligned} \text{Minimize } C_p &= \int_{t_0}^{\infty} c_p(t)e^{-rt} dt \\ \text{s.t. } o(t) &\geq 0 \\ 0 &\leq \int_{t_0}^{\infty} c_v(t)e^{-rt} dt \leq F \end{aligned}$$

where C_p is the net present value of the public health costs, F represents the *financial constraints* as a total amount of available funds (alternatively, the financial constraint could consist of variable maximum funds available over different time periods), and all other symbols are as in framing 1. Under framing 2 the available funds determine the lowest possible health costs, while under framing 1 the potential public health costs determine the amount of funds available for the stockpile.

3. Vaccine stockpile model: disease-specific context for polio

Before formulating the polio vaccine stockpile model and presenting a hypothetical example, the following subsection provides background on polio eradication and stockpiles.

3.1. Background

3.1.1. Global polio eradication

The Global Polio Eradication Initiative (GPEI) anticipates successful interruption of wild poliovirus transmission in the next few years, given sufficient financial resources, at which time it will begin implementation of post-eradication risk management strategies [11]. The benefits of the successful polio immunization program in the United States include preventing large numbers of cases of paralytic polio and overwhelming economic savings due to avoided treatment costs [22]. Similarly, finishing polio eradication globally promises large long-term net benefits [23] as long as the GPEI can successfully contain the post-eradication outbreaks that likely will occur due to the possibility of circulating vaccine-derived polioviruses (cVDPVs) [24]. Other potential outbreak risks include, unintentional or intentional poliovirus reintroductions, VDPVs from immunodeficient long-term excretors, and any polioviruses circulating after apparent interruption of transmission or remaining in the environment [24]. The World Health Organization (WHO) currently plans for the cessation of routine use of the live, oral poliovirus vaccine (OPV) several years after wild poliovirus eradication to minimize the risk of generating new VDPVs [25]. Following global eradication, national and global policy makers will face numerous choices [26,27], including creation and maintenance of one or more vaccine stockpiles. All of these choices, including whether to use IPV for routine immuniza-

tion, and the surveillance and response policies, influence the risks and epidemiology of outbreaks and hence the size of the optimal stockpile.

3.1.2. US polio vaccine stockpile

The current vaccine tools to respond to polio outbreaks include OPV, with trivalent (tOPV), bivalent (bOPV, types 1 and 3), and monovalent (mOPV) OPV formulations currently available, inactivated poliovirus vaccine (IPV), a combination of these, or doing nothing. Jenkins and Modlin performed a decision analysis to evaluate these options in the context of a potential future outbreak in the US and they identified mOPV as the vaccine of choice if a supply exists, although they recognized that IPV is currently the only licensed polio vaccine in the US and carries no risk of causing vaccine-associated paralytic polio (VAPP) or cVDPVs [28]. In February 2004, a joint National Vaccine Advisory Committee and Advisory Committee on Immunization Practices work group concluded that an 8 million dose stock of IPV represents a necessary component of a US stockpile for polio, and that this size would be adequate in the event of a short-term disruption of the routine IPV supply or to control an outbreak given current and anticipated continued high population immunity [29,30]. However, questions remain about the efficacy of IPV in outbreak response, and as a result the committee also stated that prudent preparedness requires access to 8 million doses of tOPV or 8 million doses of mOPV of each serotype. It recommended that the US “work with the WHO and other international partners to help finance, create, and maintain a global poliovirus vaccine stockpile that provides the US with immediate and guaranteed access.” [29, p. 1110] Given the desire to contain or avoid the spread of viruses derived from OPV used in outbreak response, a report from the international Committee on Development of a Polio Antiviral and Its Potential Role in Global Poliomyelitis Eradication recommended rapid development of at least one and preferably two polio antiviral compounds as an additional tool for outbreak response [31]. The US now has partially filled the recommended stockpile of 8 million doses of IPV, and the current plan for an international stockpile includes ensured universal access to mOPV [32]. The size and composition of the US stockpile, however, might need to change over time, as the risks of polio outbreaks and the availability of IPV and OPV change.

3.1.3. Global polio vaccine stockpile

WHO plans to establish a global polio vaccine stockpile as a prerequisite for OPV cessation [33,34]. Currently, development of the global polio vaccine stockpile centers on the requirement that the stockpile contain sufficient doses either to re-interrupt poliovirus transmission following any post-eradication outbreaks, or if unable to stop transmission, to vaccinate until OPV production restarts assuming insufficient IPV production capacity for universal use [32]. Based on analysis and a review of prior stockpiles,

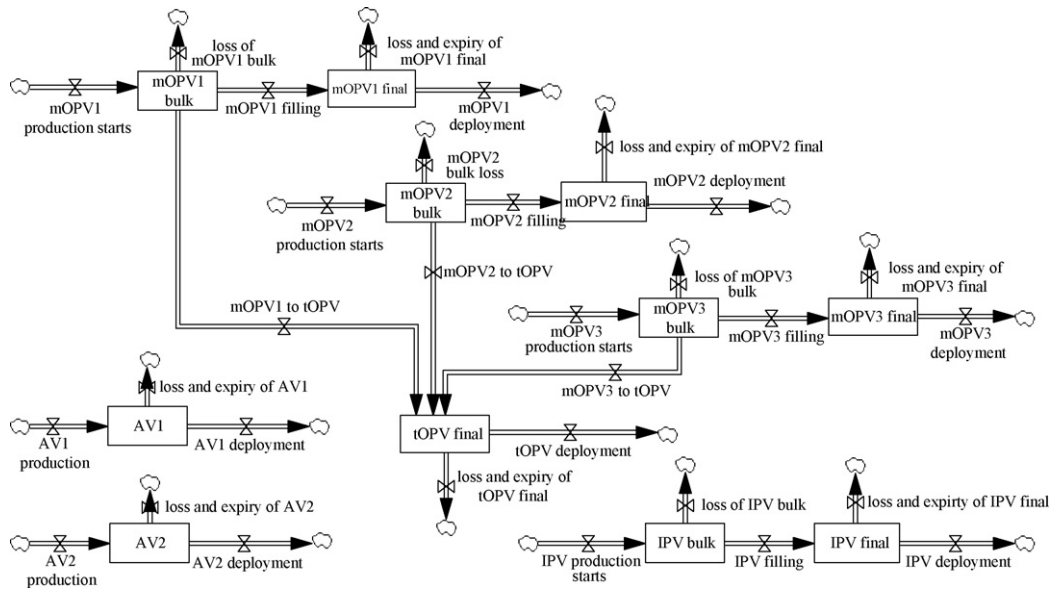


Fig. 2. High-level stock-and-flow representation of the polio vaccine and antiviral stockpile. Acronyms: AV1, AV2: two different (trivalent) antiviral products; IPV: (trivalent) inactivated poliovirus vaccine; mOPV1, mOPV2, mOPV3: monovalent oral poliovirus vaccine types 1, 2, and 3, respectively; tOPV: trivalent oral poliovirus vaccine.

recommendations in 2004 for a polio vaccine stockpile included establishment of an independent oversight commission, international financing, periodic assessment of costs, ensured access for all countries without regulatory hurdles or import/export barriers, and liability protection [6]. Current WHO standard operating procedures (SOPs) call for a stockpile of 750 million doses of each mOPV serotype, including 250 million doses of each serotype stored as finished product at the time of OPV cessation and a minimum balance of 100 million at any time, with the remaining mOPV stored as bulk [32]. The SOPs further state that UNICEF would maintain ownership of the international stockpile to ensure universal access and coherent use for response to an outbreak. The SOPs also established release criteria involving timely assessment of the trigger event by the independent oversight commission and subsequent recommendations regarding release of vaccine by the WHO Director-General.

The process of filling OPV vaccine involves handling live polioviruses. In an increasingly susceptible world after OPV cessation, reintroduction of any live poliovirus presents an important risk to maintaining a polio-free world [35]. To minimize this risk, strict biocontainment requirements and the requirement of very high population immunity in the area surrounding the production facility could substantially increase the production and filling costs. In this context, the SOPs recommend physical storage and maintenance of the stockpile at two or more distinct vaccine production facilities that comply with these requirements to reduce the risk of an inadvertent poliovirus reintroduction [36]. Consequently, some current conceptions of the stockpile envision all procurement to occur prior to OPV cessation while covering the anticipated needs to respond to likely cVDPV outbreaks in the time period immediately following OPV cessation.

While current efforts represent significant progress, many issues related to this stockpile remain open, and optimization of the stockpile design offers the potential to reduce costs while ensuring preparedness. Developed countries continue their efforts to evaluate the adequacy and accessibility of the global stockpile for domestic needs. Presumably, WHO might also consider the existence of national vaccine stockpiles in evaluating development of the global vaccine stockpile. We previously concluded that international cooperation represents a key requirement to optimize the global use of resources for polio vaccine stockpiles [37].

3.2. Polio vaccine stockpile supply chain

Fig. 2 visualizes the different stocks and flows in a polio vaccine stockpile at the highest level. The stocks of mOPV bulk (any type) and IPV bulk increase through orders resulting in production and decrease either through filling or loss (wastage). We assume that the shelf-life of the vaccine bulk product is infinite for all practical purposes [32]. Filling is the only flow into mOPV final (any type) or IPV final, while the outflows from final vaccine include deployment, loss, and expiry. In a post-OPV cessation context, OPV deployment would only result in the event of outbreaks, but for IPV some deployment may also result from routine usage in the event of routine vaccine shortage. As shown, tOPV does not exist in bulk form, but gets filled from the three mOPV bulk types. In addition, Fig. 2 shows two stocks of antiviral drugs, which may become a possibility in the future [31].

Fig. 3 shows the stock-and-flow diagram for optimizing framing 1, focusing on a single mOPV type. We focus on framing 1 for the example below and refer to Appendix A.3 for a similar diagram reflecting framing 2, and expand on the general model shown in Fig. 1 to explicitly distinguish bulk and final vaccine components. In Fig. 3, both the **vaccine in bulk production pipeline** and **vaccine in filling pipeline** stocks use bold faced box edges to indicate the possible subdivision into multiple stocks reflecting different stages in the production process. The number of subdivided stages depends on the actual properties of the bulk production and filling processes, including the number and location of production and filling lines and procedures for virus growth and testing. These properties determine the appropriate way to model the delay, ranging from a simple first-order delay (reflecting no intermediate stages and multiple parallel filling and production lines) and yielding the largest variance around the mean of the eventual outflow from the process, to a fixed (pipeline) delay yielding no variance around the mean [21]. In addition, capacity constraints in any of the stages in the pipeline can increase the actual duration of the process. Fig. 3 also explicitly shows the accumulation of vaccine costs from *bulk production*, *filling*, and maintenance of the stockpile, the accumulation of *public health costs* due to excess cases and political costs associated with *unmet vaccine needs*, and all the inputs determining the flows (e.g., the different wastage rates that determine loss outflows). The *ordering strategy* here determines both *bulk production*

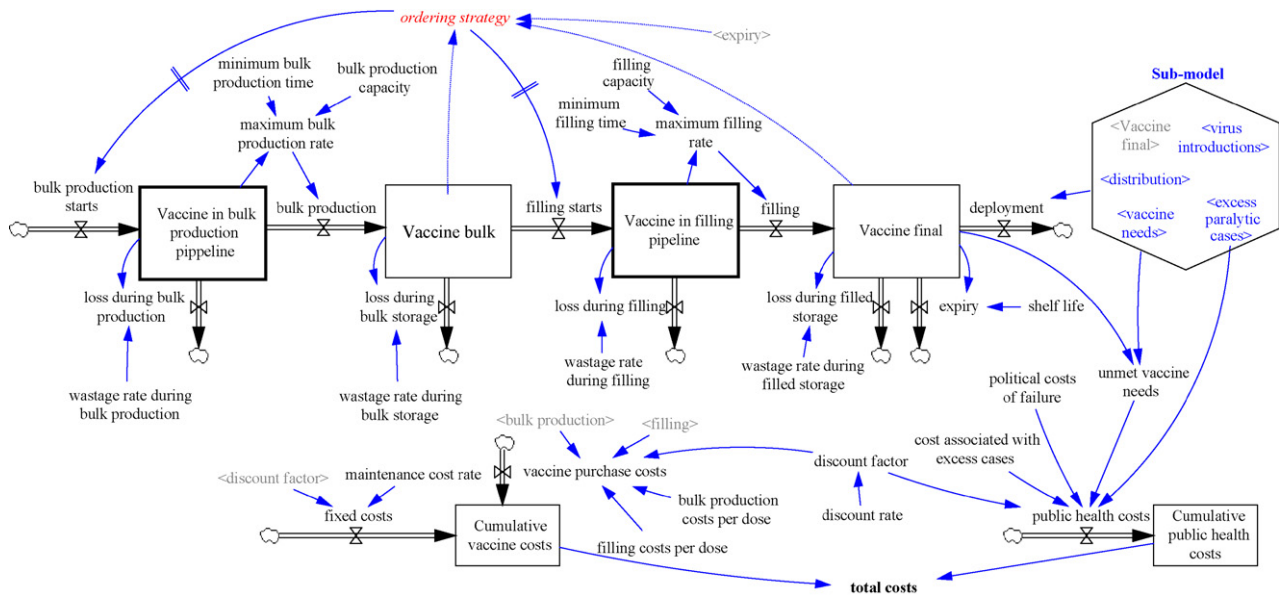


Fig. 3. Stock-and-flow diagram for the minimization of the total costs with no financial constraints (framing 1) for a single serotype stockpile.

starts and filling starts and may use information about current levels of vaccine bulk and vaccine final as well as the predictable expiry of vaccine final. Finally, Fig. 3 explicitly shows the interaction of the stockpile supply chain with an outbreak sub-model that determines the vaccine needs and deployment resulting from virus introductions as well as the excess paralytic cases in the event of unmet vaccine needs. Consistent with the general framings, optimization framing 1 for this model entails minimizing the total costs (i.e., sum of cumulative vaccine costs and cumulative public health costs) over all feasible ordering strategies.

Trade-offs in the model center around the costs of producing and filling bulk vaccine doses vs. the costs associated with excess paralytic polio cases that might occur in the event of an outbreak due to a delayed or reduced outbreak response [12]. This includes both the medical and societal costs of excess cases and the political costs of stockpile “failure” (i.e., of facing unmet vaccine needs during an outbreak). The number of excess paralytic cases must also include cases of VAPP resulting from OPV use, which may increase as the fraction of susceptibles in the population increases and protection due to maternal antibodies declines [24].

4. Hypothetical example for polio

This section presents an example of solutions for framing 1 based on hypothetical model inputs to demonstrate the utility of the framework. The example focuses on the primary objective of the global polio vaccine stockpile to respond to outbreaks during the time immediately after OPV cessation. Appendix A includes examples for framing 2 and some variations on the assumptions. The example illustrates the key dynamics and raises a number of important considerations in the design of an optimal vaccine stockpile for polio, although future analyses should address the specific choices made as the process for developing the poliovirus vaccine stockpile evolves. We use an outbreak sub-model that generates vaccine needs and excess paralytic cases associated with any unmet vaccine needs implemented using Mathematica™ (see Appendix A.1–3 for details of the outbreak sub-model and derivations of the solutions to the different framings of the optimization problem using linear programming methods). For simplicity, the example assumes a deterministic stream of vaccine needs that result from a deterministic number of virus introductions over time. For ease of

presentation, we further assume no wastage or maintenance costs, because these only scale the total costs but have essentially no impact on the optimization algorithm. Table 2 provides the hypothetical values of constants used in the example for the stockpile supply chain model. While we assume first-order delay processes in the outbreak sub-model, we assume fixed delays in the stockpile supply chain. We further consider first-order delays in Appendix A.2 to explore the possible spectrum of delay types in the stockpile.

4.1. Illustration of outbreak sub-model dynamics

The outbreak sub-model simulates the diffusion of poliovirus following an initial introduction through a finite number of population blocks. Once infected, population blocks eventually control the outbreak by increasing the level of population immunity. This occurs due to either natural burnout, which leads to many paralytic polio cases, or due to outbreak response immunization, which controls the outbreak more rapidly and requires vaccine from the stockpile. Given that population blocks interact dynamically, the amount of vaccine available from the stockpile itself determines the future vaccine needs. For example, with insufficient vaccine from the stockpile, an outbreak may spread to new population blocks and consequently generate additional vaccine needs. Thus, the outbreak sub-model requires input from the stockpile supply chain model (i.e., vaccine final) and at the same time generates output that feeds into the stockpile supply chain model (i.e., distribution as a result of vaccine demand, vaccine needs, and excess paralytic cases), as shown in Fig. 3. Virus introductions in this simple model consist of exogenously generated increments in the numbers of infected populations. To illustrate the dynamics in the sub-model, Fig. 4 shows the vaccine needs arising from an exponentially decreasing number of virus introductions starting in year 3 with a half-life of 2 years and totaling 10 introductions as a simplified scenario roughly consistent with the expected decrease in initiating cVDPV events [24,27,38]. Year 3 represents the point in time when outbreak response activities would begin using vaccine from the stockpile (i.e., OPV cessation), while bulk production and filling may already occur before year 3. Fig. 4 shows the vaccine demand over time, either with no stockpile or response, or with sufficient vaccine in the stockpile to cover all vaccine needs. With sufficient vaccine, the response leads to rapid control of all the out-

Table 2
Stockpile supply chain model constants used for the demonstrative example (including initial values for vaccine stocks)^a.

Symbol in equations	Name in Fig. 3	Value
V_b^p	Vaccine in bulk production pipeline	0 doses (initial value)
V_b	Vaccine bulk	0 doses (initial value)
V_f^p	Vaccine in filling pipeline	0 doses (initial value)
V_f	Vaccine final	0 doses (initial value)
t_b	Minimum bulk production time	18 months
bc	Bulk production capacity	100 million doses/month
t_f	Minimum filling time	3 months
fc	Filling capacity	10 million doses/month
t_s	Shelf-life	60 months
w_1, w_2, w_3, w_4	Wastage rates	0 1/month
r	Discount rate	0.0025 1/month (=3% per year)
c_b	Bulk production costs per dose	0.2\$/dose
c_f	Filling cost per dose	0.1\$/dose
c_{case}	Cost associated with excess cases	1000\$/case
c_{pol}	Political costs of failure	100 million \$/month with unmet vaccine needs
c_m	Maintenance cost rate	0\$/month

^a While we emphasize the hypothetical nature of the examples and choices of input values, most values represent informed choices based on prior work [27].

breaks. With no stockpile, virus exportations to other populations occur over time and outbreaks continue to increase until no more at-risk populations remain (i.e., populations with sufficient susceptibles to sustain outbreaks); correspondingly, vaccine demand rises until it eventually plateaus. Thus, if we stop routine vaccination and do nothing to respond to outbreaks, then any small risk of outbreaks results in an eventual return to uncontrolled poliovirus circulation.

4.2. Illustration of optimal solution for framing 1

Appendix A.2 describes how we obtained an optimal solution for framing 1 using standard linear programming methods. The solution relies on the plausible assumption that the penalty (i.e., costs) associated with each dose of unmet vaccine needs exceeds the costs of stockpiling a dose. If this assumption does not hold, then no economic justification exists for the stockpile, because the costs of the consequences do not exceed the stockpile costs. In addition, we ignored expiry by assuming that we use vaccines for outbreak response soon after they enter the stock of final vaccine, which is possible if vaccine demand is deterministic and filling capacity is sufficiently high.

Fig. 5 shows the optimal solution assuming fixed delays for the bulk production, filling, and expiry processes. Due to discounting in the objective function, the optimal solution delivers vaccine as late as possible to incur costs as late as possible. This means that it does not start accumulating vaccine final until year 2, although it must start filling before the actual vaccine needs arise in year 3

because of the filling capacity constraint and delay. Similarly, the optimal solution requires that we build the stock of vaccine bulk as late as we can and only up to the level required to be able to fill at maximum capacity when needed. Once we start bringing the outbreak under control, the vaccine needs decrease (Fig. 4), deployment of vaccine final diminishes, and as a result filling can decrease and both vaccine stocks deplete to (almost) 0. The amount of vaccine bulk needed depends on the time period over which we plan orders (i.e., the planning period). In the example, the planning period equals half a month, so the stock of vaccine bulk at any time must hold sufficient vaccine to cover the total filling needed for the next half month (e.g., 0.5 months × 10 million doses per month = 5 million doses when filling occurs at maximum capacity in year 3 (Table 2)). Thus, the choice of planning period impacts the required level of vaccine bulk, which in the case of deterministic demand with fixed delays becomes zero as the planning period approaches 0. The (discounted) cumulative costs reflect the same two waves of production and filling activity and in this example amount to approximately \$55 million over 23 years based on the hypothetical model inputs from Table 2.

5. Variations of the optimization models

The example in the prior section represents only one of many possible variations of the optimization models. These variations may reflect different practical realities and we discuss these

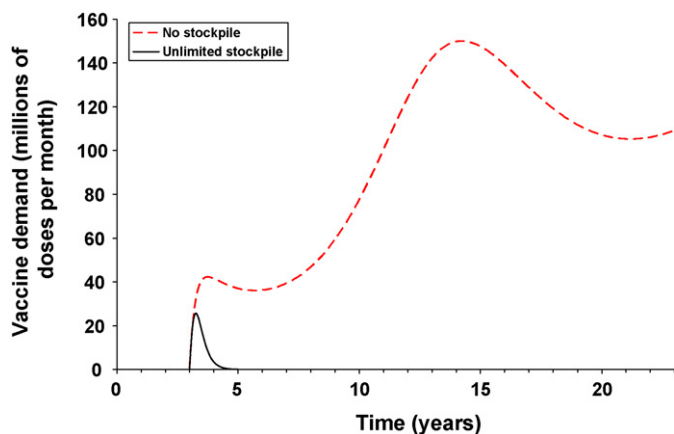


Fig. 4. Forecast of the vaccine demand assuming an exponential decay in virus introductions, starting in year 3.

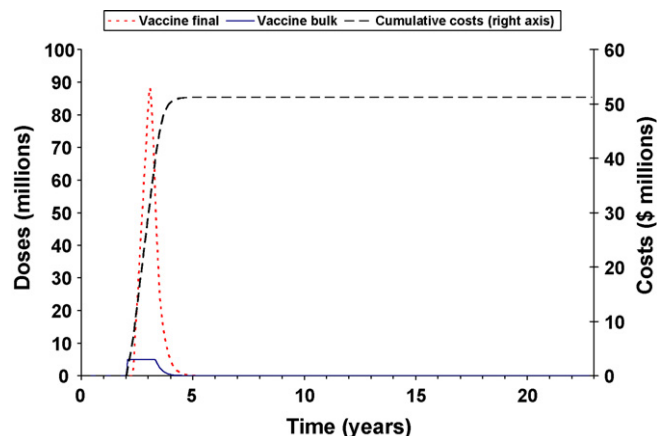


Fig. 5. Vaccine stocks and cumulative costs (discounted) for the optimal solution of framing 1 assuming fixed delays in the stockpile supply chain and an exponential decay in virus introductions, starting in year 3.

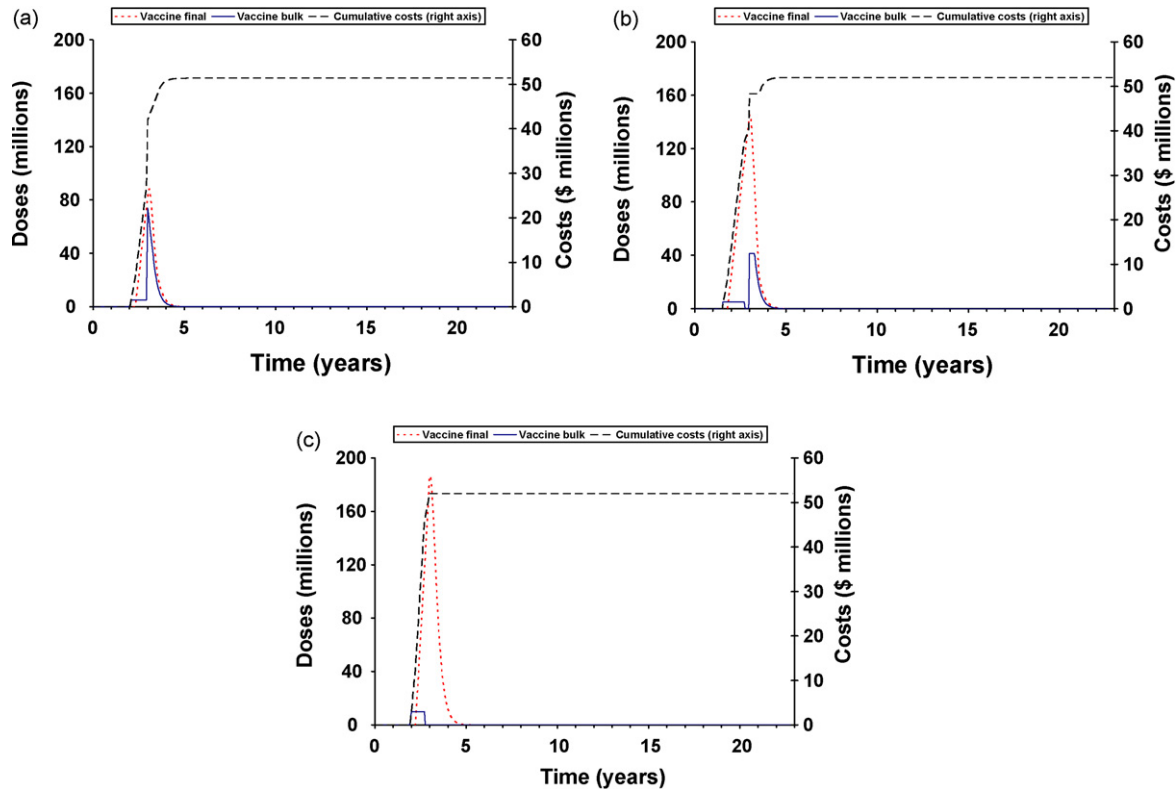


Fig. 6. Optimal solution assuming a sudden and permanent doubling of the bulk production and/or filling costs in year 3: (a) only bulk production cost doubled; (b) both bulk production and filling costs doubled; (c) both bulk production and filling costs doubled and filling capacity constraint relaxed.

qualitatively here to expose important issues that need explicit discussion in the process of designing the poliovirus vaccine stockpile.

5.1. Risks and costs of vaccine production after OPV cessation

As mentioned, the risks associated with OPV production after OPV cessation might effectively imply an increase in vaccine production costs due to constraints on the physical location of production facilities as well as containment requirements. To explore this possibility, Fig. 6 shows the effect of a sudden and permanent doubling of the production costs per dose in year 3. In Fig. 6a, we only doubled the bulk production costs, presumably because bulk production requires the most stringent and expensive biosafety precautions. As a result of the cost increase, in the optimal solution all bulk accumulation occurs before year 3, while the vaccine final levels remain unchanged compared to Fig. 5. In Fig. 6b, we explored the effect of simultaneously doubling the filling costs from year 3 forward. This results in an optimal solution that acquires all needed vaccine final before year 3, which due to the capacity constraint involves earlier accumulation of vaccine final than in Fig. 6a. This in turn requires production of most vaccine bulk early on, with one last order of vaccine bulk occurring just before year 3. If we relax the filling constraint, then the optimal solution orders as much as possible of both bulk and final vaccine just before year 3 (Fig. 6c).

While the practical effect of the risk associated with producing poliovirus after OPV cessation is a sudden increase in production costs at OPV cessation, in reality there exists a trade-off between the costs of containment measures and the risk associated with production after OPV cessation. An extension of the model might consider whether the expected excess cases resulting from the risk of releases from vaccine production facilities justify the costs of containment. Such an extension would explicitly consider geographical locations of the stockpile to link virus introductions to production and would need to consider immunity level in the pop-

ulation surrounding the production facility as it affects the risk of new virus introductions and excess cases.

5.2. Expiry of filled vaccine

The assumption of a fixed delay process for expiry, as in the example, is appropriate if disposal of expired vaccine lots occurs on the basis of expiry dates set at the time of filling, which is current practice. Alternatively, in the future random tests may possibly determine the disposal of lots or batches. In that case, a more appropriate model would disaggregate the stock by age, with the hazard of expiry increasing with age. In the example, we neglected expiry by assuming that we could receive newly filled vaccine only a short time before its required use, but this assumption does not hold if filling capacity is low relative to vaccine demand, filling and production costs increase over time, or vaccine demand is highly stochastic. As an extreme departure away from the assumption of a fixed delay in expiry, Appendix A.2.1 considers a first-order expiry process and shows that this drives up the costs, because a fixed fraction of filled vaccine expires before deployment. The expiry of vaccine occurs primarily due to the loss of efficacy resulting from a decrease in vaccine virus titers over time, and consequently one approach to increasing the vaccine shelf-life might include beginning with higher initial titers. Modeling this option would necessitate including a decision about the desired titer for filling in the diagram along with the associated costs, and possibly some influence of the titers on the risks associated with the vaccine.

5.3. Nature of production and filling delays

Like the nature of the expiry process, the technical characteristics of the bulk production and filling processes also determine the appropriate model for the filling and bulk production delays (see Appendix A.4. From the perspective of the stockpile owner, the

production delay might look like a fixed delay, with no distribution around the time that doses arrive due to a single time of delivery. From the manufacturer's perspective, however, a given order of bulk vaccine might potentially get produced over time, with production of some doses completing before others, which would suggest a first- or low-order delay. Filling involves a relatively fixed delay associated with testing batches of final product, but if many filling lines exist, each line might become available at a different point in time such that the delay could look more like a low-order delay. Given that the exact time that vaccine becomes available plays an important role in the event of potential shortage of vaccine, the choice of the delay in the model should reflect the physical reality of the process and the relevant perspective of the analysis (i.e., stockpile user vs. manufacturer). We mention it explicitly here since different stakeholders involved in discussions about the stockpile design might implicitly assume different types of delays, and we anticipate that explicit discussions might prove helpful.

5.4. Production and filling capacity over time

Depending on the implementation of OPV cessation, a "warm base" of OPV production may or may not continue to exist (e.g., continued routine use of IPV based on Sabin OPV seed strains might offer a warm base) [39]. Our model did not explicitly include the cost of maintaining or increasing this capacity, but at the very least maintaining capacity to produce and fill a vaccine no longer routinely used presents economic challenges from the manufacturer's perspective. To model the manufacturer's perspective, the costs of maintaining capacity would be linked to the expected demand. From the stockpile owner's perspective, things could look different. While all bulk production may occur before OPV cessation (given practical unlimited shelf-life of the bulk product), the only way to maintain a long-term OPV stockpile, if so desired, involves filling at multiple points after OPV cessation, unless the shelf-life of filled vaccine increases dramatically. Given the substantial societal cost of excess cases, the stockpile owner's incentives to maintain some filling capacity remains much stronger than those of the manufacturer. The difference in incentives calls for continuing dialogue between owners and manufacturers and contractual mechanisms to better align the incentives.

5.5. Forecasting vaccine demand

The forecast of vaccine demand represents the key driver of decisions regarding the stockpile. Prior work suggests that the likelihood of outbreaks remains greatest immediately after OPV cessation [24], but small risks exist of potentially much larger outbreaks in the long-term [12,27]. Combined with changes in costs and risks of filling and production, changing vaccine demand implies that the optimal allocation policy will also change over time (see Appendix A.5). Thus, the optimization problem becomes stochastic and dynamic. Moreover, the vaccine demand depends on both the stochastic risks and the stock of vaccine final, and in two different ways. First, if the vaccine demand exceeds the maximum output of filled vaccine, then this will likely create new demand due to the natural expansion of the ongoing outbreak. This leads to a positive (reinforcing) feedback loop around vaccine demand, since the likelihood of unmet vaccine needs lead to more demand which leads to greater likelihood of unmet vaccine needs. Second, the use of OPV to respond to outbreaks carries a risk of generating new cVDPV outbreaks, leading to another positive feedback loop involving vaccine demand, since more vaccine demand leads to more distribution, which leads to a higher probability of virus introductions, creating new vaccine demand. The strength of this feedback increases over time as global population immunity decreases and depends on the specifics of the outbreak response. This remains a

topic of further research, including more mathematical modeling of poliovirus outbreak spread.

5.6. Excess paralytic cases

Realistically estimating the excess paralytic cases associated with unmet vaccine needs requires a more detailed dynamic outbreak and response model [12,13]. Such a model requires specific assumptions about the response strategy, including the time from detection until the first mass immunization response, target populations and coverage of the immunization rounds, and number of immunization rounds. The model must include this information both for the response strategy when sufficient vaccine is available and for the response strategy in the event of unmet vaccine needs. Thus, discussions of the different response strategies in different outbreak scenarios remain an important factor that will determine the ultimate quality of the stockpile optimization model.

5.7. Funding stream

Framing 2 minimizes the cumulative public health costs over possible streams of the use of funds over time (see example in Appendix A.3). Due to the risks mentioned above associated with production and filling after OPV cessation, the costs of filling and procurement will likely increase over time. Furthermore, a possible decreasing number of competitors in the market might also reduce supply and increase prices. While this makes upfront funding appear attractive, the finite shelf-life of finished vaccine means that filling must occur to facilitate access to vaccine as needed over time, which necessitates some funds to replenish the stock of final product at a later stage depending on the long-term demand forecast. Under framing 2, the decision maker can flexibly decide when to spend funds over time, but the funding stream may not in fact come with such flexibility. For example, the situation may arise in which the donors of stockpile funds do not provide 100% funding upfront but distribute funds over time. At the other extreme, setting aside funds from donors for an extended period of time may not represent a feasible option. This situation would require use of a *minimum use of funds* variable in the model that further constrains the utilization of funds over time. Moreover, optimizing the utilization of some initial funds in practice involves working with a finite time horizon, which means that the stockpile only covers this finite time period. In reality, provisions are needed beyond any practical time horizon for as long as a risk of virus introductions exists.

Various mechanisms in the model might influence the availability of new funds and would involve new feedback loops in the model. For example, unusually high vaccine needs due to the occurrence of outbreaks might deplete the stocks of vaccine to such low levels that replenishment of the stockpile becomes desirable. The relationship could be a threshold relationship (i.e., if bulk vaccine decreases below a certain level we can raise funds for new vaccine) or more continuous (i.e., the lower the stock of bulk the more pressure on donors to supply new funds). Alternatively, new funds might not actually become available until excess paralytic cases actually occur. A reluctance to use OPV in the long term might favor the use of IPV for outbreak response. This would impact the demand for IPV vs. OPV over time and the availability of new funds.

5.8. Country-dependence

The formulation of the optimization model does not explicitly include the physical location of the stockpile as an additional dimension of the problem. However, the trade-off between costs and risks of the stockpile may depend on the location(s) of the facilities. For example, manufacturing facilities in countries of higher income will most likely offer better secondary safeguards, such as

high IPV coverage [36], but typically produce vaccine at a higher cost than lower income countries [40]. The current SOPs place a greater weight on safety than on the possibility of less expensive vaccine by requiring vaccine storage at manufacturing facilities in locations that comply with the secondary safeguards [32]. Inputs that depend on the location of the outbreak include the forecast of vaccine needs (since risks vary by country [24]), the excess cases associated with unmet vaccine needs (since outbreaks in different countries may vary widely in magnitude [13]), and the valuation of future outcomes [27]. Given the shared global objective of the stockpile [37], one approach might first disaggregate the models by income level to estimate outcomes for each income group and then sum over the income groups to get the totals [13,24,27].

5.9. Serotype dependence

Different poliovirus serotypes vary with respect to vaccine seroconversion, transmission characteristics, and rate of paralysis per infection [41,42]. This means that the vaccine needs and excess paralytic cases depend on serotype, and thus that the optimal content of mOPV stocks may differ by serotype. Under framing 1, the lack of a stockpile cost constraint means that the optimization problems for each serotype remain essentially independent. The optimal quantity of mOPV over time may vary by serotype, but the amount of vaccine of one serotype does not directly impact the resources available for the other serotypes. Under framing 2, the explicit stockpile cost constraint implies that the problems become interdependent and optimal ratios of types 1, 2, and 3 will exist over time.

IPV protects against all 3 serotypes, but with different effectiveness [42]. One approach to optimize an IPV stockpile would base the forecast of the needs and excess paralytic cases on typical “average serotype” behavior [13], or alternatively index by serotype and aggregate the total public health and stockpile cost of each serotype as the basis for the objective functions. Although tOPV also protects against all 3 serotypes, it appears an unlikely candidate for a global polio vaccine stockpile because mOPV yields higher seroconversion than tOPV [13] and using tOPV to respond against an outbreak of one serotype would unnecessarily reintroduce two other serotypes of live poliovirus. Thus, the full optimization problem most likely involves a combined stockpile of mOPV (all three types) and IPV vaccine. For example, with mOPV as the main tool for rapid outbreak response, especially immediately after OPV cessation, IPV might play a role in responding at the edges of the mOPV target population to stop transmission of OPV-derived viruses, perhaps using a form of ring vaccination [43]. Projected future routine use of IPV will also affect outbreak response demands and optimization. In this case, what might seem like a relatively expensive use of IPV could potentially serve to mitigate possible future increases in the needs for more mOPV and IPV, such that the optimization problem will need to determine the optimal balance not only of each serotype of mOPV, but also of mOPV and IPV. Similarly, if antivirals become available, the models must consider their potential roles as well.

6. Discussion

We present a framework for optimizing the supply chain of a polio vaccine stockpile aimed at facilitating the response to polio outbreaks after polio eradication and OPV cessation. This framework helps create a common platform for discussions among the various stakeholders and decision makers who must ultimately design and implement the stockpile. The risks associated with vaccine production after OPV cessation and delays in the production

and filling processes necessitate creation and management of the stockpile in advance of OPV cessation. We demonstrate with a simple example how optimization may lead to useful results in terms of the ordering strategy that minimizes the present value of public health and vaccine costs, although we emphasize that these hypothetical results depend on simplifying assumptions in the stockpile and outbreak model.

We emphasize the need to address various issues in order to fully optimize the stockpile in the context of all its complexities. First, the technical details of the stockpile, such as capacity constraints and delays in the production and expiry processes, impact the dynamics within the supply chain and require careful consideration. Second, the relationships between vaccine production risks and vaccine demand as well as between vaccine demand and financial constraints lead to additional feedback loops that merit further exploration. Third, the perspective (e.g., stockpile owner vs. manufacturers, short term vs. long term) impacts the objectives and therefore the optimal policy for a stockpile. Explicit understanding of the perspectives will help discussions. Fourth, the vaccine demand is inherently stochastic, which implies some probability of unmet vaccine needs even for a very large stockpile. The extent to which the stockpile must cover all possible scenarios depends on the true costs of excess cases and the political costs of failure. Fifth, the serotype dependence and availability of multiple products (mOPVs, IPV, antivirals) add another layer of complexity, as does the geographical dimension. Finally, the use of OPV after OPV cessation carries its own risk, leading to another feedback loop back to the demand. The specifics of the outbreak response remain critical to the actual use and benefits of the stockpile. Further modeling in this area provides an opportunity to better anticipate this risk and determine policies that maximize the probability of successful control and minimize the probability of generating new outbreaks with the response vaccine. We propose a flexible framework that can incorporate all of these complexities, although optimization of the full stochastic and dynamic problem will most likely require heuristics based on simulation rather than relatively straightforward linear programming (see Appendix A.6). Careful examination and discussion of the assumptions and their implications must occur before actual optimization of the full stockpile problem.

We expect that political factors might also play a role in decisions about financial investment in a global stockpile. For example, although we discussed how the location of the stockpile(s) and serotype-variability present additional levels of complexity, we did not explore the political issues that arise in the context of national or other preferences for vaccine suppliers. Logistics related to distribution of the stockpile resources and campaign operational issues also remain an important issue. We implicitly assumed operational readiness and global access to the stockpile, but such access may require negotiation, which we emphasize, must occur early in the process of creating and designing the stockpile. In this regard, we note that the current plans for an international stockpile strive to “ensure that vaccine can be available, if necessary, to any country in the world within 48 hours” [32, p. 2].

While this paper focuses on a polio vaccine stockpile, this approach might prove useful for the design of future stockpiles for eradicated diseases and potentially emerging pathogens. For example, in the case of pandemic flu, the stockpile might contain antivirals and a prototype pandemic flu vaccine to provide first-response interventions during the time needed to develop a more effective vaccine targeting the newly emerged pandemic strain. Explicit consideration of the supply chain and transmission dynamics might also provide helpful input to stockpile decisions in this context. We anticipate that providing a coherent framework represents a significant contribution that will facilitate discussions about many of the assumptions and numerical estimates for key inputs required to perform optimization.

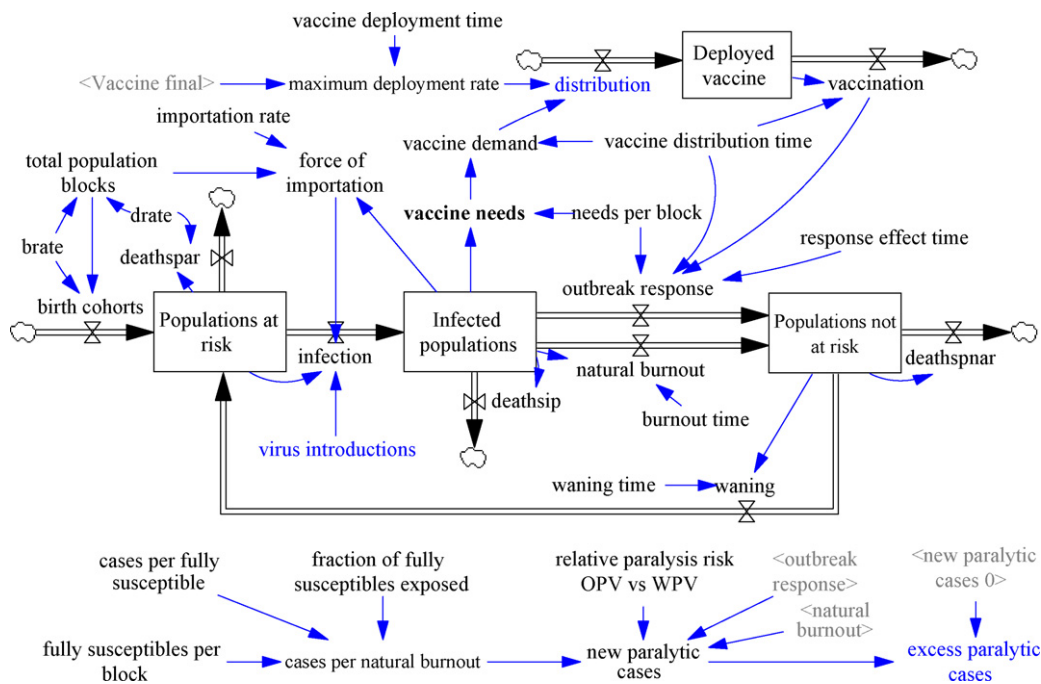


Fig. A1. Stock-and-flow diagram of the simplified outbreak sub-model.

Acknowledgments

Drs. Duintjer Tebbens and Thompson acknowledge support for their work from CDC Grant U01 IP000029 and under NVPO N37 (FY2005). The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. The authors thank Margaret Watkins, Steve Wassilak, and Steve Cochi for helpful comments. We also thank two anonymous reviewers for excellent comments that significantly improved the manuscript.

Appendix A.

This appendix presents technical details about the outbreak sub-model and stockpile supply chain model, derives linear programming formulations of the optimization problems where possible, presents framing 2 of the optimization problem, provides some additional results, and discusses solution strategies for situations in which a standard linear programming approach is not possible.

A.1. The outbreak sub-model

Fig. A1 shows the structure of the outbreak sub-model, which captures the key dynamics at a highly aggregate level but does not account for many of the more detailed level dynamics that must be considered for a more realistic and data-based analysis [13]. Table A1 provides the symbols and hypothetical values of the constants we used for the demonstrative examples.

The input to the sub-model is a given number of virus introductions over time and the main output is the incidence of paralytic polio cases. The sub-model depends on the availability of **vaccine final** in the stockpile supply chain model, but also determines the deployment of **vaccine final** in response to *vaccine demand*, which in turn depends on the diffusion of outbreaks. Unlike a traditional SIR model, to capture the dynamics of virus transmission between populations and vaccine needs at the global level the stocks here represent numbers of population blocks rather than

numbers of individuals. **Populations at risk** are those in which the proportion of susceptibles is high enough to allow significant poliovirus transmission. **Infected populations** are those with an ongoing outbreak. **Populations not at risk** are populations with sufficient herd immunity to prevent outbreaks. New births increase the number of **populations at risk**, and **populations not at risk** can again become susceptible through waning of immunity. We assume deaths reduce the number of population blocks in each stock at a similar rate.

The rate at which **populations at risk** become **infected populations** depends on the *force of importation*, which is proportional

Table A1

Sub-model constants (including initial values at the top of the table) used for the demonstrative examples^a.

Short symbol	Name in Fig. A1	Value (hypothetical)
<i>P</i>	Population blocks (initial value)	600 ^b (initial value)
PAR	Populations at risk (initial value)	0 (initial value)
IP	Infected populations (initial value)	0 (initial value)
PNAR	Populations not at risk (initial value)	60 (initial value)
DV	Deployed vaccine (initial value)	0 (initial value)
<i>b</i>	brate	0.025/12 per month
<i>μ</i>	drate	0.01/12 per month
<i>β</i>	Importation rate	0.64 per month
<i>v</i>	Needs per block	10 million doses per block
<i>t_{depl}</i>	Vaccine deployment time	1 month
<i>t_{dist}</i>	Vaccine distribution time	1 month
<i>t_r</i>	Response effect time	4 months
<i>t_b</i>	Burnout time	16 months
<i>w</i>	Waning time	1 million months ^c
<i>fsb</i>	Fully susceptibles per block	5 million people
<i>cfs</i>	Cases per fully susceptible exposed	1/200 cases/people
<i>fse</i>	Fraction of fully susceptibles exposed	0.5
<i>ρ</i>	Relative paralysis risk OPV vs. WPV	200/750,000 ^d

^a While we emphasize the hypothetical nature of the examples and choices of input values, most values represent informed choices based on prior work [27].

^b This value implies that the sub-model characterizes the world as 600 identical population blocks with approximately 10 million people.

^c This value essentially ignores waning of immunity in the model.

^d Ratio of typical rate of paralysis per WPV infection to typical rate of VAPP per first OPV dose [42].

to **infected populations**, with *importation rate* as the proportionality constant. In addition, *virus introductions* move populations at risk to the stock of infected populations, and the sum of *virus introductions* and *force of importation* determines the flow *infection*. When infected, populations become more immune and eventually become **populations not at risk** as a result of *natural burnout* and *outbreak response*. *Natural burnout* depends on the average *burnout time* (i.e., the average time a population would remain infected in the absence of a response before natural infections reduce the proportion susceptible to a sufficiently low level to stop the outbreak and become a **population not at risk**). Similarly, *outbreak response* depends on the average *response effect time*, which we assume is shorter than the *natural burnout time*. Every **infected population** gives rise to *vaccine needs* according to an assumed constant (i.e., *needs per block*).

Ideally, an increase in *vaccine needs* immediately leads to vaccination of the newly infected population blocks. In reality, however, detection of the outbreak and subsequent deployment of vaccine takes time, and to represent this delay in the model vaccine resides in a stock **deployed vaccine** before being used for outbreak response. The available amount of **vaccine final** limits the *distribution* (d) of vaccine, which equals $d = \text{Min}(d_{\text{max}}, d^*) = \text{Min}(V_f/t_{\text{depl}}, V_n/t_{\text{dist}})$, where d_{max} is the *maximum deployment rate*, d^* the *vaccine demand* (or desired deployment rate), V_f the amount of **vaccine final**, V_n the *vaccine needs*, t_{depl} the *vaccine deployment time*, and t_{dist} the *vaccine distribution time*. This formulation is consistent with a first-order delay plus a capacity constraint. While the *vaccine deployment time* represents the minimum time to deploy vaccine from the stockpile, the *vaccine distribution time* represents the minimum time to distribute the vaccine in the field. If $V_n/t_{\text{dist}} > V_f/t_{\text{depl}}$, then this leads to *unmet vaccine needs*, which trigger political costs of failure in the stockpile supply chain model. For simplicity, we assumed that $t_{\text{dist}} = t_{\text{depl}}$ (Table A1) so *unmet vaccine needs* effectively arise whenever *vaccine needs* exceed **vaccine final**. *New paralytic cases* occur both due to *natural burnout* (wild cases) and due to OPV infections associated with *outbreak response* (VAPP cases). Even with sufficient **vaccine final**, wild polio cases occur due to the delay in the response and VAPP cases due to the vaccine used. A model identical to that in Fig. A1, except that $d = \text{Min}(\infty, d^*) = V_n/t_{\text{dist}}$, determines the incidence of paralytic cases given sufficient vaccine (i.e., *new paralytic cases 0*). The incidence of *excess paralytic cases* is the difference between *new paralytic cases* and *new paralytic cases 0*.

The stock-and-flow diagram in Fig. A1 corresponds to the following set of differential equations:

$$\begin{aligned} \frac{d \text{PAR}(t)}{dt} &= bP(t) + \frac{\text{PNAR}(t)}{w} - \mu \text{PAR}(t) - \lambda(t) \text{PAR}(t) \\ \frac{d \text{IP}(t)}{dt} &= \lambda(t) \text{PAR}(t) - \mu \text{IP}(t) - \frac{\text{IP}(t)}{t_b} - \frac{\text{DV}(t)}{t_r \times v} \\ \frac{d \text{PNAR}(t)}{dt} &= \frac{\text{IP}(t)}{t_b} + \frac{\text{DV}(t)}{t_r \times v} - \mu \text{PNAR}(t) - \frac{\text{PNAR}(t)}{w} \\ \frac{d \text{DV}(t)}{dt} &= \text{Min} \left(\frac{V_f}{t_{\text{depl}}}, \frac{v \text{IP}(t)}{t_{\text{dist}}} \right) - \frac{\text{DV}(t)}{t_{\text{dist}}} \\ \lambda(t) &= \frac{\beta \text{IP}(t)}{P(t)} + \alpha(t) \\ \text{Inc}(t) &= \left(\frac{\text{IP}(t)}{t_b} \right) \times \text{fsb} \times \text{cfs} \times \text{fse} + \left(\frac{\text{DV}(t)}{t_r \times v} \right) \times \text{fsb} \times \text{cfs} \times \text{fse} \times \rho \end{aligned} \tag{A1}$$

Here, we use abbreviations for constants and stocks from Table A1 and *Inc* denotes the incidence of paralytic cases (*new paralytic cases* in Fig. A1), λ denotes the force of infection (the flow *infection* in Fig. A1), and α represents an exogenous function that describes the rate of virus introductions per population at risk over time (*virus introductions* in Fig. A1), appropriately scaled relative to the time

step of the integration scheme (we use Euler integration with a time step of $\tau = 0.5$ months for all analyses).

A.2. Solving framing 1 (no financial constraint)

We can solve the optimization problem for framing 1 by making the realistic and mathematically weak assumption that the public health costs associated with each dose of *unmet vaccine needs* exceed the costs of purchasing the vaccine. In other words, we assume that the opportunity costs of not having invested in a needed dose of vaccine for the stockpile outweigh the costs of stockpiling this vaccine dose. If this condition does not hold, then justification for the stockpile becomes questionable in the first place. Thus, we can reformulate the optimization problem as that of finding feasible *bulk production* and *filling* flows that minimize the **cumulative vaccine costs** while avoiding *unmet vaccine needs*. For a given time step τ and using Euler integration, the **vaccine needs** vn_i at step i follow by solving Eqs. (A1) iteratively, assuming infinite **vaccine final** (note that the solution does not depend on **vaccine final**):

$$\begin{aligned} \text{DV}_i &= \text{DV}_{i-1} + \tau \left(\frac{v \text{IP}_{i-1}}{t_{\text{dist}}} - \frac{\text{DV}_{i-1}}{t_{\text{dist}}} \right) \\ \text{PAR}_i &= \text{PAR}_{i-1} + \tau \left(bP_{i-1} + \frac{\text{PNAR}_{i-1}}{w} - \mu \text{PAR}_{i-1} - \lambda_{i-1} \text{PAR}_{i-1} \right) \\ \text{IP}_i &= \text{IP}_{i-1} + \tau \left(\lambda_{i-1} \text{PAR}_{i-1} - \mu \text{IP}_{i-1} - \frac{\text{IP}_{i-1}}{t_b} - \frac{\text{DV}_{i-1}}{t_r \times v} \right) \\ \text{PNAR}_i &= \text{PNAR}_{i-1} + \tau \left(\frac{\text{IP}_{i-1}}{t_b} + \frac{\text{DV}_{i-1}}{t_r \times v} - \mu \text{PNAR}_{i-1} - \frac{\text{PNAR}_{i-1}}{w} \right) \\ vn_i &= v \times \text{IP}_i \end{aligned} \tag{A2}$$

As we will see below, the requirement that *unmet vaccine needs* be avoided imposes linear constraints on *bulk production* and *filling*, allowing us to formulate linear programming (LP) problems, for which well-known iterative solution algorithms exist [44]. The linear programming problem depends on the formulation of the delays in the stockpile supply chain model (Fig. 3). We first describe the case of first-order delays given that it allows the most robust formulation (i.e., requiring no further assumptions), although the case of fixed-order delays probably most closely matches reality and thus appears in the main paper. To simplify equations, we drop terms involving wastage, consistent with the assumption that $w_1 = w_2 = w_3 = w_4 = 0$ in Table 2.

A.2.1. Optimal solution for framing 1 assuming first-order delays

With first-order delays, **vaccine in filling pipeline** in Fig. 3 vanishes and the pipeline **vaccine in bulk production pipeline** consists of one stock. The equations of the stockpile supply chain model for optimization problem 1 become:

$$\begin{aligned} \frac{dV_f(t)}{dt} &= f(t) - d(t) - \frac{V_f(t)}{t_s} \\ \frac{dV_b(t)}{dt} &= b(t) - f(t) \\ \frac{dV_b^p(t)}{dt} &= bs(t) - b(t) \\ \text{total costs}(t) &= (b(t) \times c_b + f(t) \times c_f + c_{\text{pol}} \times 1_{\text{unv}(t)} \\ &\quad \times c_{\text{case}} \times \text{epc}(t))e^{-rt} \end{aligned} \tag{A3}$$

Here, we use abbreviations for constants and stocks from Table 1 and f denotes *filling*, b denotes *bulk production*, ps denotes *bulk production starts*, epc denotes *excess paralytic cases*, and $1_{\text{unv}(t)}$ equals 1 if *unmet vaccine needs* > 0 and 0 otherwise. Also, $d(t)$ is *distribution* which equals *deployment*. The constants in Eqs. (A3) may also change over time without loss of generality (e.g., c_b and c_f). We seek to find filling flows ($f(t)$) and production flow ($b(t)$), $t = 0, \zeta, 2\zeta, \dots$.

where ζ denotes the time period over which we plan orders (i.e., the planning period). Given first-order delays, any desired filling rate (f^*) is constrained by the maximum filling rate (f_{\max}), which depends on the filling capacity (fc), the *minimum filling time* (t_f), and the level of **vaccine bulk** (V_b):

$$f(t) = \text{Min}(f_{\max}(t), f^*(t)) = \text{Min} \left(\text{Min} \left(fc, \frac{V_b(t)}{t_f} \right), f^*(t) \right) \quad (\text{A4})$$

The formulation of f^* determines the decision rule for filling, which might occur as a result of gaps between a desired level of **vaccine final** and the actual level of **vaccine final**, as well as the anticipated drawdown of **vaccine final** due to routine use and expiry (in the case of rotating stocks):

$$f^* = \text{Max} \left(0, u_r + e + \frac{V_f^* - V_f}{t_{vf}} \right)$$

where u_r denotes routine usage, e denotes expiry, V_f^* denotes the desired level of **vaccine final**, and t_{vf} denotes the desired stock adjustment time for **vaccine final**, which determines how quickly we respond to gaps between desired and actual **vaccine final**. Similarly, we could formulate the desired bulk production rate (b^*) as follows:

$$b^* = \text{Max} \left(0, u_r + e + \frac{V_b^* - V_b}{t_{vb}} \right)$$

where V_b^* denotes the desired level of **vaccine bulk**, and t_{vb} denotes the desired stock adjustment time for **vaccine bulk**. These decision rules reflect a stockpile management strategy aimed at avoiding steady state error that might arise as a result of predictable outflows from the stockpile supply chain. However, since we optimize directly to solve for the *filling* and *bulk production* flows, the actual formulation of desired filling and desired bulk production rates do not influence the solution. Instead, once we obtain a solution for *filling* and *bulk production*, we could backtrack to determine the required minimum desired stock levels V_f^* and V_b^* that would lead to the same optimal solution, contingent on the formulation of f^* and b^* .

To simplify notation, we choose $\tau = \zeta$, although we emphasize that our results do not depend on the choice of the numerical integration step size τ as long as τ is sufficiently small. Using Euler integration and the requirement that for the optimal policy we avoid *unmet vaccine needs*, we can rewrite Eqs. (A3) as:

$$V_f(t) = \left(1 - \frac{\tau}{t_s}\right)^n V_f(0) + \tau \sum_{j=1}^t \left(\left(1 - \frac{\tau}{t_s}\right)^{t-j} (f(j-1) - d(j-1)) \right) \quad (\text{A5})$$

$$V_b(t) = V_b(0) + \tau \sum_{j=1}^t (b(j-1) - f(j-1))$$

$$\text{total costs}(t) = (b(t) \times c_b + f(t) \times c_f) e^{-rt}$$

The requirement that we avoid *unmet vaccine needs* translates into the requirement that *distribution* ($=\text{Min}(V_f/t_{\text{depl}}, V_n/t_{\text{dist}})$) is not constrained by the stockpile, or $V_f(t) \geq V_n(t) \times t_{\text{depl}}/t_{\text{dist}}$ at all times. Note that if this condition holds, then $d(t) = V_n(t)/t_{\text{dist}}$. Moreover, per Eq. (A4) *filling* cannot exceed *filling capacity* (fc) at any time. In addition, it follows from Eq. (A4) that given a filling rate $f(t)$, we must have that $V_b(t) \geq f(t) \times t_f$. Finally, *bulk production* cannot exceed *bulk production capacity* (bc) at any time. Combining these conditions with the Eqs. (A5), we obtain the following linear programming

problem:

$$\text{Minimize } \sum_{t=1}^{\tau_{\text{end}}} (b(t-1) \times c_b + f(t-1) \times c_f) e^{-rt} \quad \text{subject to (for } t = 1, \dots, \tau_{\text{end}} \text{):}$$

$$\sum_{j=1}^t \left(\left(1 - \frac{\tau}{t_s}\right)^{t-j} f(j-1) \right) \geq \frac{V_n(t) t_{\text{depl}}}{t_{\text{dist}} \tau} - \frac{(1 - (\tau/t_s))^t V_f(0)}{\tau} + \sum_{j=1}^t \left(\left(1 - \frac{\tau}{t_s}\right)^{t-j} \frac{V_n(j-1)}{t_{\text{dist}}} \right)$$

$$f(t-1) \leq fc$$

$$\sum_{j=1}^t b(j-1) \geq \frac{f(t) t_f}{\tau} - \frac{V_b(0)}{\tau} + \sum_{j=1}^t f(j-1)$$

$$b(t-1) \leq bc$$

We solve the LP problem in Mathematica™ [44] using $V_f(0) = V_b(0) = 0$, $\tau = \zeta = 0.5$ months, and an analytical time horizon of 276 months (23 years), yielding solutions $f(t)$ and $b(t)$, for $t = 0, \dots, t_{\text{end}} - 1$, with $t_{\text{end}} = 552$. To obtain the actual *ordering strategy* from Fig. 3, we must also determine the stock of **vaccine in bulk production** and the flow *bulk production starts* using the constraint that $V_b^p(t) = b(t) \times t_b$, where t_b is the *minimum bulk production time*, with an objective function minimizing the total bulk production (although technically, this need not be minimized for given that in the model in Fig. 3, we only associate costs with *bulk production* and not with *bulk production starts*). However, given our focus on presenting the levels of **vaccine bulk** and **vaccine final** as the main outcome of the optimization, we did not compute the actual *bulk production starts* flow.

Fig. A2 shows the optimal solution assuming first-order delays in the stockpile supply chain. Comparing this result to Fig. 4, which assumes fixed delays but is otherwise equal, we find that the first-order delay assumption entails the need to build more **vaccine bulk** stock than with fixed delays to meet the filling requirements and because the stock of **vaccine final** continuously loses vaccine due to expiry. This leads to somewhat higher cumulative costs, as shown in relation to the *bulk production* and *filling* flows and in direct comparison with the model with fixed delays in Fig. A3. Thus, although the time of orders and the stock levels differ to some extent, the optimal solution varies only minimally in terms of costs between the extremes of the range of possible delay types.

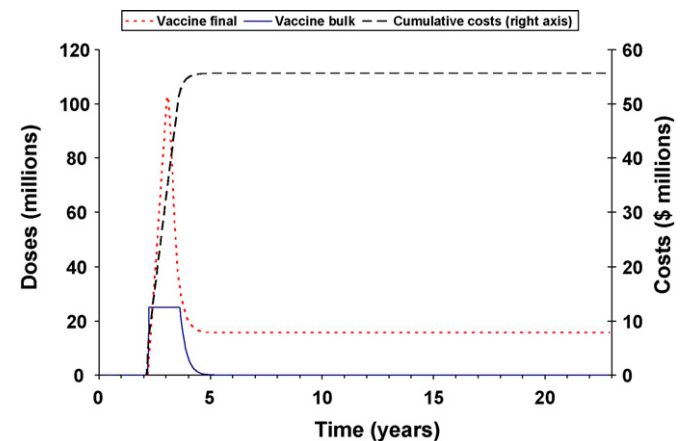


Fig. A2. The optimal solution for framing 1 assuming first-order delays in the stockpile supply chain and an exponential decay in virus introductions, starting in year 3.

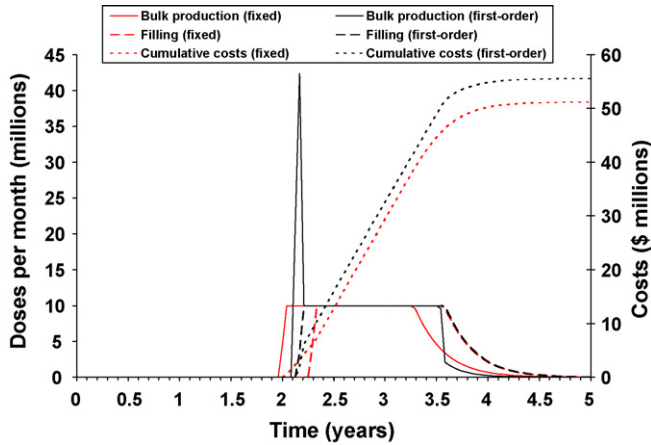


Fig. A3. Comparison of the cumulative costs and bulk production and filling strategy for the optimal solution of framing 1 with fixed delays (solution from Fig. 3) and first-order delays (solution from Fig. A2) during the first 5 years (no further filling or bulk production occurs beyond that time).

A.2.2. Optimal solution for framing 1 assuming fixed delays

In the case of fixed delays, we represent the stockpile model as a set of difference equations rather than differential equations. The following equations describe the stockpile model for optimization problem 1 (with $\tau = \zeta$ to simplify notation):

$$V_f(t) = V_f(t-1) + \tau(f(t-1) - d(t-1)) = V_f(0) + \tau \sum_{j=1}^t (f(j-1) - d(j-1)) \tag{A6}$$

$$V_b(t) = V_b(t-1) + \tau(b(t-1) - fs(t-1)) = V_b(0) + \tau \sum_{j=1}^t (b(j-1) - fs(j-1))$$

Here, in addition to the abbreviations used above, $fs(t) = f(t + \tau_f)$ denotes *filling starts* and $\tau_f = t_f/\tau$ (rounded to nearest integer) denotes the number of time steps in the *minimum filling time*. To simplify calculations, we omit *expiry* from Eqs. (A6). This assumption remains valid if we can deploy vaccine before it expires, corresponding to a situation in which we fill vaccine a short time before it is needed for deployment. This in turn is possible only if filling capacity is sufficiently large (otherwise we would have to stock up vaccine well ahead of its use) and future demand known with sufficient certainty. These conditions hold for the hypothetical example in the main paper. If they do not hold, we can no longer write the problem as an LP problem and we must model the process for expiry in more detail, as discussed in the main paper.

The *total costs* remain as in Eqs. (A5) and the condition for **vaccine final** also remains $V_f(t) \geq V_n(t) \times t_{depl}/t_{dist}$, as with first-order delays, because we did not alter the delay type for the deployment and distribution processes. However, the condition for **vaccine bulk** that it contains sufficient stock to satisfy the outflow translates into $V_b(t) \geq \tau \times fs(t)$ for any t . As with first-order delays, we will optimize over f and b (i.e., not fs and bs), allowing us to keep the same capacity conditions and prompting us to further impose that $b(t) = bs(t - \tau_b) = 0$ for $t = 0, \dots, \tau_b - 1$, where $\tau_b = t_b/\tau$ (rounded to nearest integer) denotes the number of time steps in the *minimum bulk production time*, and that $f(t) = fs(t - \tau_f) = 0$ for $t = 0, \dots, \tau_f - 1$. Using all conditions, we obtain the following LP problem:

$$\text{Minimize } \sum_{t=1}^{\tau_{end}} (b(t-1) \times c_b + f(t-1) \times c_f) e^{-rt} \text{ subject to (for } t = 1, \dots, \tau_{end}) :$$

$$\sum_{j=1}^t f(j-1) \geq \frac{V_n(t)t_{depl}}{t_{dist}\tau} - \frac{V_f(0)}{\tau} + \sum_{j=1}^t \frac{V_n(j-1)}{t_{dist}}$$

$$f(t-1) \leq fc$$

$$\sum_{j=1}^t b(j-1) \geq -\frac{V_b(0)}{\tau} + \sum_{j=1}^{t+1} f(j + \tau_f - 1)$$

$$b(t-1) \leq bc$$

and :

$$f(t) = 0 \text{ for } t = 0, \dots, \tau_f - 1$$

$$b(t) = 0 \text{ for } t = 0, \dots, \tau_b - 1$$

In solving the problem, we shall further effectively assume that $f(t) = 0$ for $t \geq \tau_{end}$ by omitting terms of f beyond the analytical time horizon as they arise in the third condition above.

A.3. Formulation of framing 2 (with financial constraint)

Fig. A4 shows a possible model diagram corresponding to framing 2 of the optimization problem, which seeks to find the feasible ordering strategy that minimizes the total public health costs. Feasibility of the ordering strategy here means that orders satisfy the production and financial constraints (Fig. 1). Given that the production constraints are already embedded in the stockpile supply chain model, the problem essentially consists of determining the optimal *funds allocation strategy* given a certain amount of *total initial stockpile funds*, the initial value of the stock of **stockpile funds**. The *funds allocation strategy* determines both the *use of funds* (i.e., the fraction of remaining **stockpile funds** used for purchase of bulk of filled vaccine), and the fraction of funds for bulk production vs. filling. **Stockpile funds** may increase as a result of interest on the funds as well as the addition of *new funds*. In this formulation, the latter remains an exogenous variable, although future models might examine the dependence of *new funds* on the levels in the stockpile and public health outcomes. The allocation of funds for bulk production triggers the start of production, but the funds accumulate first in the stock of **funds for bulk production**, before actual *spending on bulk production* as *bulk production* completes with a delay. A similar process occurs for filling, although importantly the flow *filling starts* is constrained by **vaccine bulk**, and thus *new funds for filling* and the *funds allocation strategy* must depend on the level of **vaccine bulk**. The remaining structure remains similar to that for framing 1 (Fig. 3), although the **cumulative vaccine costs** become obsolete as we minimize only over the **cumulative public health costs**.

The strategy for solving framing 2 depends on whether sufficient funds exist to avoid *unmet vaccine needs*. If this is the case, then one or more solutions exist that minimize the public health costs to 0, and we can directly determine an optimal solution by computing the *funds allocation strategy* from the optimal solution of framing 1. Using the optimal $bs(t)$ and $fs(t)$ from framing 1, we work backwards to get:

$$\text{New funds for bulk production : } nf_b(t) = bs(t) \times c_b$$

$$\text{New funds for filling : } nf_f(t) = fs(t) \times c_f$$

$$\text{Use of funds : } uf(t) = nf_b(t) + nf_f(t)$$

$$\text{Funds for bulk production : } F_b(t) = F_b(t-1) + \tau(nf_b(t-1) - b(t-1) \times c_b)$$

$$\text{Funds for filling : } F_f(t) = F_f(t-1) + \tau(nf_f(t-1) - f(t-1) \times c_f)$$

$$\text{Stockpile funds : } F(t) = F(t-1) + \tau(nf(t-1) - uf(t-1))$$

where nf denotes the flow *appreciation of funds*. The *funds allocation strategy* might consist of a certain utilization rate of the remaining **stockpile funds** and a certain fraction of the *use of funds* that goes to filling vs. bulk production. Thus, with sufficient funds to avoid *unmet vaccine needs*, this solution simply tells managers how to spend the funds to accomplish the optimal strategy determined in framing 1, as shown in Fig. A5.

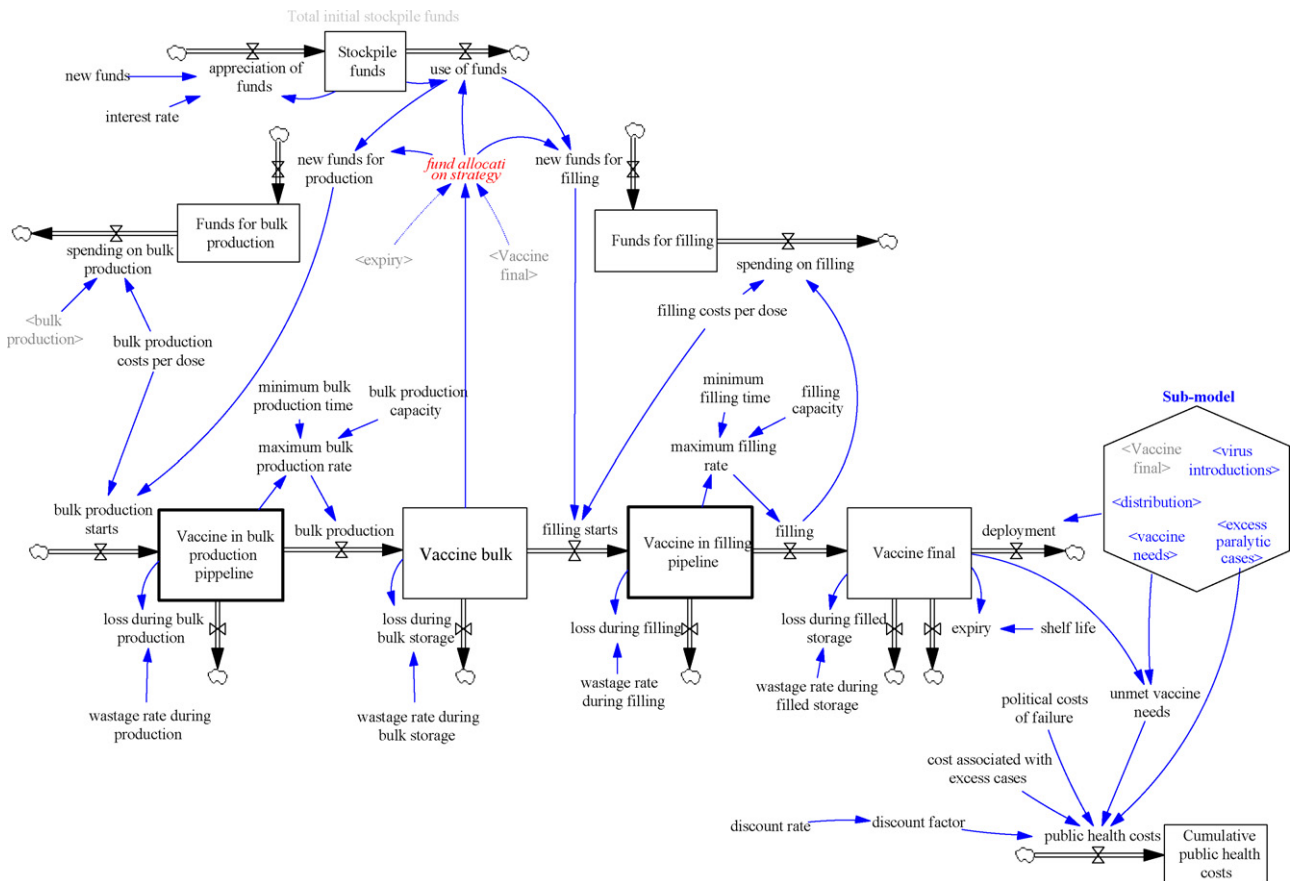


Fig. A4. Stock-and-flow diagram for the minimization of the total costs with no financial constraints (framing 1) for a single serotype stockpile.

Any optimal solution when the stockpile funds remain insufficient to accommodate the vaccine needs invokes the feedback between vaccine final and vaccine needs. As a result, in this case we can no longer transform the optimization problem to a linear programming problem. Thus, determining the optimal solution in this case requires non-linear programming methods or some generic global optimization methods (e.g., evolutionary algorithms, simulated annealing, or other sampling-based optimization methods). Finding or approaching the optimal solution for this case remains beyond the scope of this paper, and we note that the complexity of these problems necessitates development of methods to ensure that the algorithm finds the true global optimum instead of one of

many local optima. In exploratory analyses that we performed, we found that even with initial stockpile funds well above the threshold for maintaining zero public health costs, the conventional global optimization methods used did not find the global optimum, most likely due to the challenges that arise in searching a combination of two noisy dynamic functions within a very large space of possible functions.

If the stockpile funds remain only slightly below the threshold, intuition suggests that the optimal solution might involve following the optimal fund utilization path from the previous section until the stockpile funds are exhausted. This would ensure that unmet vaccine needs occur only at the end of the time horizon, and the effect of exportations would not kick in within the time horizon. However, in reality the stockpile must cover more than a limited time horizon (especially if virus introductions may continue to occur). Moreover, given decreasing global population immunity and potentially increasing procurement or filling costs per dose over time, lower cumulative public health costs may occur by tolerating unmet vaccine needs early on and building up a stockpile for later use when population immunity becomes lower and the ability to respond might prevent more excess paralytic cases. Such a policy obviously implies enormous potential political ramifications, with the risk of escalating the situation and permanent re-establishment of virus transmission. As the latter depends on the dynamics of virus exportations, the dynamics of the sub-model will ultimately determine the optimal spending path in a situation of insufficient stockpile funds.

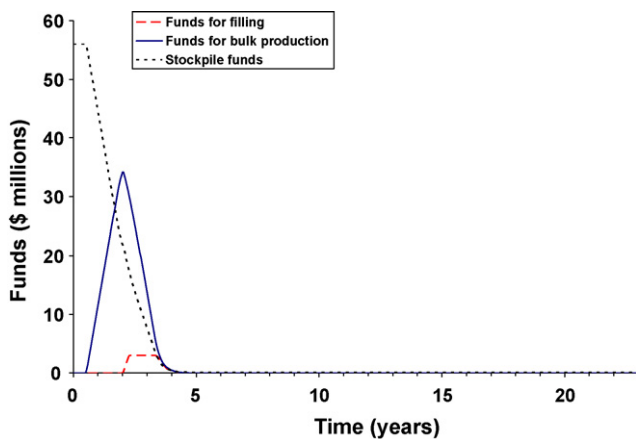


Fig. A5. Solution of framing 2 in the form of required funds, assuming sufficient initial stockpile funds (\$ 56 million) to avoid unmet vaccine needs, and no appreciation of funds. The solution directly follows from the optimal solution of framing 1.

A.4. Possible types of delays in the stockpile supply chain model

Different types of delays exist in dynamic models, and the nature of the delay often significantly impacts results [21]. A fixed delay

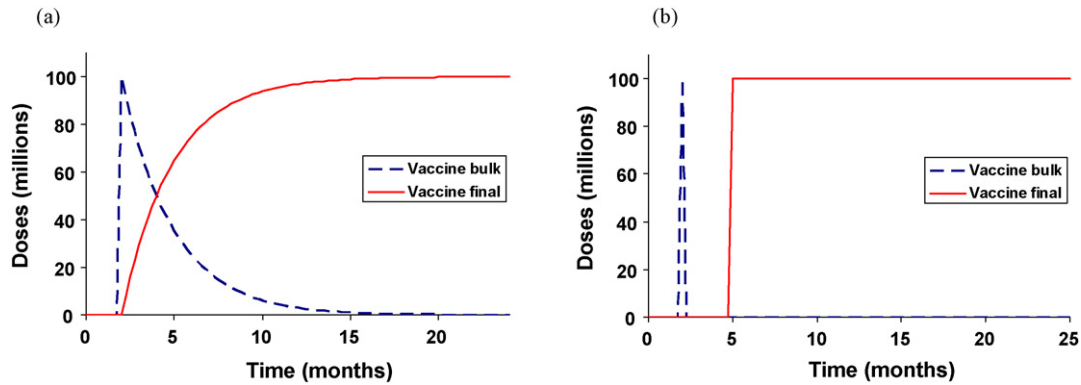


Fig. A6. Kinetics of vaccine bulk and vaccine final in response to an instantaneous infusion of 100 million doses of vaccine bulk at time 2 months, assuming: (a) a first-order filling delay with time constant 3 months and (b) a fixed filling delay with time constant 3 months.

implies that all materials ordered at a given point in time arrive at exactly a fixed amount of time later. In contrast, a first-order delay spreads out the arrival of the materials exponentially, with the mean arrival time equal to the specified delay time. Thus, the materials mix in the process such that some arrive before and some after the average delay time according to an exponential distribution. Higher-order delays may also occur, which will narrow the shape of the distribution of the arrival of materials to concentrate this increasingly around the average delay time, until the distribution approaches a fixed delay. Given the importance of delays in the supply chain of the stockpile and their impact on the supply chain dynamics, we illustrate the difference between first-order and fixed (or pipeline) delays. We consider the effect of an instantaneous infusion of 100 million doses into the stock of **vaccine bulk** in month 2. We assume that at any given time we order as much bulk as available for *filling*, but that *filling* occurs with a delay with time constant equal to $t_f = 3$ months. Fig. A6a shows that with a first-order delay, **vaccine final** immediately starts to increase as soon as bulk becomes available, while the amount of vaccine bulk exponentially decreases to zero. In contrast, Fig. A6b shows that with the fixed delay, the 100 million doses simply do not get filled until 3 months after they enter the stock of **vaccine bulk**. For both delays, the average time at which vaccine gets filled equals month 5 (i.e., 3 months after the time of the infusion).

A.5. Alternative virus introduction scenarios

For illustrational purposes, Fig. A7 shows the optimal solution for framing 1, but with a virus introduction scenario that

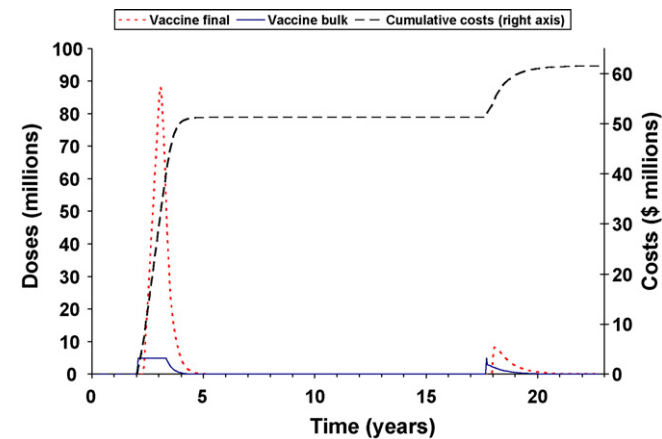


Fig. A7. Optimal solution for framing 1 assuming fixed delays in the stockpile supply chain, with an additional single virus introduction assumed in year 15.

includes one additional introduction in year 15 compared to the base case (Fig. 5). However, we note that this solution depends on the assumption that we can produce and fill vaccine at any time at the same cost. If this is not the case, then we must stock up vaccine earlier, and this raises the possibility of expiry before deployment of vaccine final. Thus, solving for this scenario under realistic conditions requires an extension on the model used for the hypothetical examples (see below).

A.6. Strategy for full optimization

As discussed in the main paper, many potential variations and extensions exist on the model for the hypothetical examples, including additional feedbacks, stochastic variables, and more precise modeling of the expiry process and delays in the stockpile. In addition, the assumption that any optimal policy must avoid unmet vaccine needs implies a loss of generality of the model, for example in the case of stochastic demand or insufficient upfront funding. In light of the limitations on existing global optimization methods discussed above, we suggest the use of safety stocks and heuristics to optimize more general models. A possible heuristic could include:

- (1) Find the optimal solution using the deterministic model for framing 1 using linear programming.
- (2) Choose a safety stock level S , either as constant or fraction of optimal stockpile level over time.
- (3) Compute the total costs for 1 stochastic iteration of the full, stochastic model.
- (4) Repeat step (3) N times to determine the expected total costs for given safety stock level S .
- (5) Repeat steps (2)–(4) to find the expected total costs as a function of S .
- (6) Find the value of S that minimizes the total expected costs.

The heuristically-approximated optimal solution then consists of the optimal stockpile levels from the deterministic model plus the optimal safety stock. While this represents a very simple heuristic, it might offer more robust solutions and be amenable to logical extensions, such as distinct safety stocks for bulk and final, policies using adaptive safety stocks, etc.

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