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The development of global vaccine stockpiles

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Abstract

Global vaccine stockpiles, in which vaccines are reserved for use when needed for emergencies or supply shortages, have effectively provided countries with the capacity for rapid response to emergency situations, such as outbreaks of yellow fever and meningococcal meningitis. The high cost and insufficient supply of many vaccines, including oral cholera vaccine and pandemic

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For more on **monovalent serogroup A meningococcal vaccines** see http://www.meningvax.org/partners.php

Contributors

CY did the literature search; AJC, PD, KF, and CY collected the data; AJC, KF, and CY drafted the table, panel, and figure; BTB, AJC, PD, KF, AMH, JST, and CY interpreted the data and drafted the report; and BTB, AJC, VJD, PD, KF, SH, AMH, TBH, JST, and CY critically revised the report.

Declaration of interests

We declare no competing interests. AJC, KF, SH, AMH, JST, PD, and BTB are staff members of WHO. The authors alone are responsible for the views expressed in this publication, and they do not necessarily represent the decisions, policy, or views of WHO. The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

influenza vaccine, have prompted discussion on expansion of the use of vaccine stockpiles to address a wider range of emerging and re-emerging diseases. However, the decision to establish and maintain a vaccine stockpile is complex and must take account of disease and vaccine characteristics, stockpile management, funding, and ethical concerns, such as equity. Past experience with global vaccine stockpiles provide valuable information about the processes for their establishment and maintenance. In this Review we explored existing literature and stockpile data to discuss the lessons learned and to inform the development of future vaccine stockpiles.

Introduction

Historically, stockpiles have been established to create reserves of commodities ranging from weapons, to oil, food, and relief supplies. In public health, global vaccine stockpiles have been established for a few selected vaccines, mainly to provide a ready supply in case of epidemics. The restricted supply of affordable vaccines has prompted discussions about expansion of the number and use of vaccine stockpiles to both alleviate stockouts and address a wider range of diseases.[1] The result of one such discussion was the decision by WHO to establish a global stockpile of oral cholera vaccine for use in epidemic situations, as part of an integrated, comprehensive strategy for cholera prevention and control.[2] The decision to establish this stockpile was complex, and involved factors such as disease epidemiology, recommendations for oral cholera vaccine use, the cost and restricted supply of vaccine doses available worldwide, and, notably, past experience with other vaccine stockpiles. The knowledge gained from the review of these experiences was crucial to inform the planning process, and probably resulted in the oral cholera vaccine stockpile being made operational more rapidly.

Based on a review of scientific literature and pre sentations on vaccine stockpiles and interviews with experts, we describe the general uses and functions of some major global vaccine stockpiles, review lessons learned from establishment and maintenance of these stockpiles, and examine factors that will aid the development of future stockpiles.

Uses of vaccine stockpiles

A vaccine stockpile can be generally defined as an accumulated supply of vaccines held in reserve for use at a later time. This reserve of vaccines might either be a physical stockpile held in a discrete location or a virtual stockpile, such as an agreed-upon quantity of vaccine set aside by vaccine manufacturers for emergency allocation that can be deployed on request. Since vaccine production generally requires substantial lead time, provision of the capacity for rapid mobilisation in response to a proven need is a key underlying objective for all stockpiles.

Vaccines can be stockpiled for worldwide distribution or maintained by individual countries for national use. Uses can involve a range of situations, such as emergency response, disease prevention in non-emergent situations, and filling of gaps during supply shortages.[3,4] For emergency response, vaccine stockpiles can be used to respond to confirmed or predicted epidemics at local or regional levels (or both), worldwide pandemics, or bioterrorist threats.[5] Historically, quantities of vaccines for epidemic-prone diseases (eg, yellow fever and

meningococcal meningitis) that were not readily available for individual countries, because of expense or worldwide supply shortages, have been kept in reserve for distribution to targeted areas in response to confirmed emergencies.[1,6–8] Other worldwide and national stockpiles have been created as precautionary measures for emergency response to either predicted major outbreaks or pandemics (eg, highly pathogenic avian influenza A H5N1) or feared bioterrorism (eg, smallpox).[3,9,10] Vaccine stockpiles can be used for disease prevention through provision of supplies for routine immunisation programmes or vaccination campaigns.[4,7,11] Generally, this purpose is secondary for stockpiles. Vaccine supplies which are not used in epidemic situations in a specified time period can be given to countries to use in disease prevention programmes, which makes efficient use of the vaccines before they expire, such as with yellow fever vaccine.[11] Finally, vaccine stockpiles can be used to fill gaps during supply shortages.[4,12] Stockpiles for this purpose are usually established at the national level. The US Pediatric Vaccine Stockpile Program, for example, maintains a 6 month supply of routine childhood vaccines in the event of disruptions in national vaccine supply.[4]

Global vaccine stockpiles

Overview

At present, four global vaccine stockpiles are maintained, mainly for emergency response situations (table). These include stockpiles of smallpox vaccine, meningococcal vaccine, yellow fever and oral cholera vaccines. A fifth global vaccine stockpile—with vaccine doses pledged by manufacturers—was recommended for pandemic influenza in 2007, but never became operational. In 2013, the WHO Strategic Advisory Group of Experts on immunisation concluded that the stockpile should not be established since it was not needed.[9]

Smallpox vaccine stockpile

A previously deadly and endemic disease worldwide, smallpox was declared eradicated in 1980 by the World Health Assembly.[13] This declaration called for the cessation of routine smallpox vaccination of children and the maintenance of reserve stocks of smallpox vaccine. By 1983, all member nations had ceased routine smallpox vaccination, and some had established their own vaccine stockpiles in the event of an outbreak or bioterrorist attack.[3,13] Subsequently, a global stockpile of live-attenuated first, second, and third generation smallpox vaccines was created, with donations from WHO member states for use in emergency responses, and this stockpile is managed by WHO (table).[9] In 2004, the Ad Hoc Committee on Orthopoxvirus Infections recommended that the stockpile contain 200 million doses of smallpox vaccine, most of which would be held as national stocks until released from the donating countries.[14] However, in the next year, a simulated bioterrorism exercise involving several European and North American cities estimated that smallpox vaccine availability in 31 countries and the WHO international stockpile was enough to cover about 10% of the population worldwide.[15] Only eight of the countries involved had sufficient supplies to cover 100% of their own populations, which raised the question of who should receive a vaccine if an event were to occur. In 2013, the WHO Strategic Advisory Group of Experts was asked to provide a recommendation for the size of the stockpile. At that time,

the WHO global stockpile contained 2·4 million doses of vaccine maintained in a physical stockpile in Switzerland, and 33 million doses kept within donating countries.[9] The WHO Strategic Advisory Group of Experts reviewed existing data for vaccine availability, immunogenicity, effectiveness, and safety, and provided advice on an optimum stockpile size.[9] The group concluded that, although determination of an optimum size is difficult, the estimated 600–700 million doses of smallpox vaccine available through the WHO stockpile and national stocks worldwide would be sufficient for response to an epidemic.[9] In September, 2014, the WHO smallpox vaccine stockpile contained 35 million doses located in Switzerland and donating countries (table). No doses have been deployed since the establishment of the stockpile.

Meningococcal vaccine stockpile

Meningococcal disease, a leading cause of bacterial meningitis in children and young adults worldwide, has an estimated case fatality rate of 5–10%, even when detected early and appropriately treated, and can cause substantial and permanent neurological sequelae among survivors.[16–18] Large scale epidemics occur regularly in the African meningitis belt, which spans the continent from Senegal to Ethiopia.[18] Several vaccines, including polysaccharide and conjugate vaccines, are licensed worldwide, since several serogroups might cause epidemic disease in an unpredictable manner. Polysaccharide meningococcal vaccines are poorly immunogenic in children younger than 2 years, and provide a relatively short duration of protection in children younger than 4 years.[19–21] These vaccines are used mainly for outbreak response. Conjugate vaccines, which confer long lasting immunity, are used in preventive immunisation campaigns, and plans exist for their introduction into routine immunisation programmes.

In 1997, an international polysaccharide meningococcal vaccine stockpile was established by the International Coordinating Group (ICG) on Vaccine Provision for Epidemic Meningitis Control, a partnership between WHO, UNICEF, Médecins Sans Frontières, and the International Federation of the Red Cross. This stockpile was created to provide a rapid, globally coordinated, emergency response to epidemic disease and initially included about 5 million doses, bundled with injection materials.[6,7] By September 2003, the stockpile contained around 6 million doses; the increased volume was partly spurred on by a 2001–02 W135 meningococcal epidemic in Africa, during which the worldwide supply of the appropriate vaccine was inadequate and unaffordable.[1] This epidemic also prompted rapid development and production of an affordable, trivalent polysaccharide vaccine exclusively for the ICG stockpile.[1] The rotating stockpile currently contains trivalent and quadrivalent polysaccharide and monovalent serogroup A (MenA) conjugate vaccines and is managed by the ICG (table).[6] Vaccine doses are maintained in a virtual stockpile at the vaccine manufacturer sites.

The ICG deploys vaccines as follows (figure). First, a country or non-government organisation working within the country must submit a vaccine request and meet the criteria for release (ie, evidence of an epidemic situation with laboratory confirmation, preparedness to conduct a mass vaccination campaign, and availability of standard storage conditions and material resources).[22] The ICG secretariat at WHO then circulates this request to UNICEF,

Médecins Sans Frontières, the International Federation of the Red Cross, and WHO technical counterparts for assessment, and requests additional information if needed. The ICG approves or disapproves the request within 48 h if provided with sufficient information. If approved, UNICEF procures vaccines and injection materials and organises delivery of vaccines to the country, ideally in 7 days or less after the approval. The ICG decides how to manage stocks of polysaccharide vaccine that are nearing expiry. For example, the ICG can donate the vaccines for pre-emptive vaccination in at-risk populations. In the case of MenA conjugate vaccines not used in epidemic situations during a specified time period, the ICG releases the remaining vaccine doses for use in the preventive vaccination campaigns planned for that year. Since 1997, more than 50 million doses of vaccines have been given to countries for outbreak response, and around 5–15 million vaccine doses are made available every year (table).[22–26]

The emergency vaccine stockpile was financed through ICG appeals to donors in 1997 and 2002. In 2003, the ICG started a reimbursement request system, by which countries or donors were asked to replenish the costs. This system allowed countries facing outbreaks to receive vaccines quickly, regardless of their ability to pay, while they raised funds from emergency response donors with the support of the ICG agencies. However, since reimbursement was not a precondition for vaccine release, actual reimbursement was not sufficient to maintain long-term stockpile funding. Since 2009, the meningococcal vaccine stockpile has been financed by GAVI, the vaccine alliance and a revolving fund held by WHO, by which supplies can be advanced all year round, with later cost replenishment by ministries of health, donors, and ICG partners. The revolving fund, which is separate from the mechanism used for vaccine procurement by the Pan American Health Organization, ensures that the supply of vaccines is sustained should a long-term funding shortage occur,[1] and has proven to be sustainable and effective, since donors whose mandates do not allow them to fund preventive mechanisms are willing to contribute to epidemic responses. For the 2014 meningitis season, the stockpile contained around 7 million doses (WHO, unpublished data).

Yellow fever vaccine stockpile

Yellow fever, a mosquito-borne, viral haemorrhagic fever that occurs in tropical South America and sub-Saharan Africa, can cause both endemic and epidemic disease. An estimated 84 000–170 000 severe cases and 29 000–60 000 deaths caused by yellow fever occurred in Africa in 2013.[27] In 1988, a joint UNICEF and WHO Technical Group and the Expanded Programme on Immunization Global Advisory Group recommended that yellow fever vaccine be included in their schedule for countries with endemic yellow fever.[8] However, because of the scarcity of donor funding for vaccine purchasing, only low vaccination coverage was achieved, and disease burden remained high in at-risk countries.[8] In 1998, the WHO Technical Consensus Meeting about yellow fever recommended that an emergency vaccine stockpile of 1 million doses be created and located with vaccine manufacturers in South America and Africa for deployment during epidemics (table).[8] The stockpile was established in 2001 and contained 2 million doses (WHO, unpublished data).

The yellow fever vaccine stockpile functions as a rotating stockpile for epidemic response. Vaccines not used for epidemic response during a specified time period can be provided to at-risk countries for use in disease prevention campaigns.[11] In 2003, similar principles to those of the ICG on Vaccine Provision for Epidemic Meningitis Control were applied to the governance of the yellow fever vaccine stockpile within the Yellow Fever Initiative, financed by the GAVI alliance. As such, the ICG for the yellow fever vaccine stockpile follows the same vaccine request submission and decision-making process as the meningococcal vaccine stockpile; vaccines can be accessed free of charge after meeting the ICG criteria for epidemic response.

In 2010, at the recommendation of the ICG and to ensure the sustainability of the yellow fever emergency vaccine stockpile, the ICG secretariat established an additional revolving fund mechanism for the stockpile, similar to that for the meningococcal vaccine stockpile. Since then, the management, governance, and release of vaccines from the stockpile has been the same as that described for the meningococcal stockpile (figure).[11,22] Between 2001 and 2013, more than 65 million doses of yellow fever vaccine were distributed, with a yearly average of 5 million doses (table). In 2014, the stockpile contained around 6 million doses (WHO, unpublished data).

Oral cholera vaccine stockpile

Worldwide, an estimated 1·4–4·3 million cases of cholera and 28 000–142 000 deaths caused by cholera occur every year.[28] Slow progress in the extension of access to safe water and sanitation to underserved populations, limitations of surveillance systems for early detection of cholera outbreaks, and scarcity of access to timely and appropriate health care have contributed to this burden of disease.[2]

In May 2011, the World Health Assembly adopted a resolution that calls for the implementation of an integrated and comprehensive approach to cholera control, which might include use of oral cholera vaccines “where appropriate, in conjunction with other recommended prevention and control methods and not as a substitute for such methods”.[29] As part of a response to this resolution, and in the setting of an insufficient worldwide supply of cholera vaccine, WHO and partners proposed the establishment of a stockpile of inactivated oral cholera vaccine for use in emergency response situations, to help to reduce cholera morbidity and mortality in epidemic situations.

In April, 2012, WHO convened a technical working group to address the creation of the oral cholera vaccine stockpile and develop a stockpile implementation framework. The working group reviewed relevant data and lessons learned from other established vaccine stockpiles and made recommendations for the use, management, and monitoring of the stockpile.[2] The decision was made that the governance structure for this stockpile would be the ICG model already used to help countries with the control of epidemic meningococcal meningitis and yellow fever. Specific criteria for vaccine deployment, vaccine supply, and funding mechanisms were discussed.[2] In view of the insufficient supply of the vaccine, an initial stockpile size of 2 million doses was recommended, to be stored at vaccine manufacturer sites, with a total of 6 million doses to be made available over a 3 year period. Initial investments were placed in a revolving fund to guarantee sustainability, and monitoring and

assessment of operations will occur regularly to ensure improvements are made as the stockpile mechanism evolves. As of September, 2014, 1·5 million doses (WHO, unpublished data) have been deployed to respond to emergencies (table).

Pandemic influenza vaccine stockpile

Influenza viruses cause seasonal disease and have the potential to cause pandemic disease. The main purpose of a pandemic influenza vaccine stockpile is to provide inactivated and live-attenuated vaccines for emergency response, and to delay or prevent pandemic spread of a specific influenza strain. However, stockpiling of vaccines for use in either seasonal or pandemic influenza is generally not feasible because of seasonal changes in circulating viruses and the inability to predict which pandemic virus will emerge. The only possible exception is the highly pathogenic avian influenza A H5N1 virus, which continues to cause infections in human beings and retains the potential to cause high mortality if it were to become a pandemic virus. In May, 2007, the World Health Assembly recommended that a highly pathogenic avian influenza A H5N1 vaccine stockpile be established for emergency response.[10] Later, in November that year, the WHO Strategic Advisory Group of Experts recommended that this stockpile include 150 million doses of influenza A H5N1 vaccine for use in the context of rapid response and pandemic preparedness.[30] In line with these recommendations, vaccine manufacturers agreed to pledge up to 110 million doses of influenza A H5N1 vaccine to an international stockpile, with doses to be held at vaccine manufacturer sites.[31] The ensuing discussions outlined issues related to vaccine manufacturing capacity, vaccine quality, efficacy and safety, regulatory pathways, ethical distribution, liability, and operationalisation and maintenance of the stockpile, in addition to vaccine access and risk manage ment.[32] In 2009, the influenza A H1N1 pandemic occurred, which showed the complexities involved in selection of an influenza strain for the vaccine stockpile. With a view to increase equity of access to supplies of influenza A H1N1 pandemic vaccine to countries without access, WHO initiated the A H1N1 pandemic vaccine deployment programme with donated vaccines from manufacturers and countries. For this programme, vaccine manu facturers that had pledged influenza A H5N1 vaccine agreed to convert their pledges to influenza A H1N1 pandemic vaccine for deployment by WHO.[33] Influenza A H1N1 vaccine reserves not later deployed by WHO were reconverted to pledges of influenza A H5N1 vaccines (or other future pandemic vaccines).

In May 2011, the Pandemic Influenza Preparedness Framework was adopted by WHO to improve pandemic preparedness and response, through the sharing of influenza viruses with human pandemic potential and improved access to vaccines and other benefits.[33] Subsequently, in November, 2013, the WHO Strategic Advisory Group of Experts agreed that, in the setting of relatively stable influenza A H5N1 epidemiology and with the risk of poor antigen or strain match between an actual pandemic virus and stockpiled influenza A H5N1 vaccine, WHO should not establish a stockpile of A H5N1 vaccine.[9] This decision was made because of the adoption of the Pandemic Influenza Preparedness Framework, and based on the recognition that it would secure real-time access to predictable percentages of pandemic influenza vaccines at the time of a pandemic. Therefore, the stockpile never became operational.

Factors to consider in stockpile development

Overview

An actual vaccine stockpile is one element of the complex process involved in the surveillance, risk assessment, logistics, interventions, and monitoring and assessment of any vaccination campaign.[34] An ideal vaccine stockpile would have guaranteed long-term funding and would include immediately accessible, inexpensive vaccines that are highly effective, safe, easy to administer, thermostable with a long shelf life, and available for all target populations. However, this ideal is not feasible under real-world conditions. Therefore, based on these considerations and lessons learned from global vaccine stockpiles, several factors should be thought of in the determination of whether to establish, and how to maintain, a vaccine stockpile (panel). These factors are related to the disease, the vaccine type, the management of the stockpile, and ethical considerations.

The disease

Characteristics of the disease—Characteristics of the disease in question, such as the epidemic potential or endemicity, seasonality, and geographical distribution (eg, worldwide ***vs*** regional), will help to establish the mechanism of vaccine distribution, the maintenance and physical location of the stockpile, and the target population for vaccination. Some disease characteristics might add complexity to decisions about stockpile development. For example, antigenic drift and shift in influenza strain predominance make determination of whether a strain-specific vaccine stockpile will be useful for an emergency response difficult.[9] In the case of the influenza A H1N1 pandemic, a stockpile of highly pathogenic avian influenza A H5N1 vaccine would not have been useful in an emergency response to the pandemic.

Panel: **Factors for establishment of a vaccine stockpile**

Vaccine preventable diseases

Characteristics of the disease

- What is the epidemiology of the disease?
- What is the geographical distribution of the disease and which countries are at risk?

Capacity to detect the disease

- What type of surveillance exists for the disease?

Prevention and treatment of the disease

- Are other preventive or treatment interventions available?

The vaccine

Characteristics of the vaccine

- How effective are the vaccines?
- How quickly can vaccination provide protection against disease?

- In what formulation is the vaccine available and how is it administered?
- How safe is the vaccine?
- What is this dosing schedule?
- What is the shelf life of the vaccine?
- Is the vaccine WHO-prequalified or licensed within the country receiving it?

Capacity for vaccine production

- How many manufacturers are there for the vaccine?
- How many vaccine doses are available?
- What is the production capacity of the vaccine manufacturers?

Management of the stockpile

Funding

- Who will fund the stockpile in the short-term and long-term?

Forecasting need for vaccines

- How many doses should the stockpile contain?
- What is the contingency plan for the occurrence of a vaccine shortage?
- Is the vaccine used routinely in national immunisation programmes or preventive mass vaccination campaigns?

Criteria for release of vaccines

- What epidemiological criteria are needed for release of vaccine doses?
- Who is involved in the decision-making process for release of vaccine?
- What is the plan for vaccine procurement and shipment?
- What is the plan for vaccination?
- What is the plan for storage of additional vaccine doses and related supplies?

Monitoring and evaluation

- What is the plan for monitoring and evaluation of the stockpile.

Ethical considerations

- If the number of vaccine doses is insufficient, who will be prioritised to receive the vaccine?

Capacity to detect the disease—For effective use of a vaccine stockpile, surveillance systems must have the capacity to rapidly detect an increase in the disease and, in an emergency response, establish whether the intervention threshold for vaccine release has been reached. Therefore, a sensitive surveillance system allows for timely delivery of vaccines and appropriate vaccine selection, as with meningococcal vaccines, which results in improved disease prevention.[35]

Prevention and treatment of the disease—A vaccine stockpile should be established with knowledge of other preventive and treatment interventions for the disease. Thought must be given to whether and how vaccination can complement, not replace, life-saving interventions. For example, cholera treatment centres, appropriate treatment protocols, and plans to improve access to safe water and sanitation should be in place during a cholera epidemic, despite the existence of a cholera vaccination campaign.[2]

The vaccine

Characteristics of the vaccine—Vaccine characteristics help to establish whether the vaccine will be useful in a stockpile and how it can be administered effectively. Vaccine efficacy and effectiveness can confirm the usefulness of vaccination and identify the target populations for vaccination. Vaccine formulation, administration, and storage requirements all affect the feasibility of vaccine use in specific settings, and the dosing schedule will help to forecast the number of doses needed for the stockpile and vaccination campaigns.[5] The safety profile and contraindications to vaccination should be noted, to prevent harm to individuals, and issues of liability for adverse events after immunisation should be addressed, especially in the context of donated vaccines. For example, during discussions regarding the deployment of the influenza A H1N1 pandemic influenza vaccine, vaccine manu facturers wanted assurance that they would not be liable for adverse events that occur during an emergency response for which they had donated vaccines, which were outside their control.[36] However, they did agree to accept liability for events that were within their control, such as compliance with good manufacturing practices.[36]

Regulatory issues must also be thought of for all stockpiled vaccines, especially if a vaccine has not been prequalified by WHO. WHO prequalification is a procedure that assesses the quality of vaccines for purchase by UN agencies.[37] Prequalification status can help to fast-track licensing and importation of vaccines not licensed in a receiving country where the absence of licensure can result in hesitancy to use a potentially lifesaving vaccine during a public health emergency. For example, most available smallpox vaccines are either no longer licensed (first generation vaccines) or not widely licensed (second and third generation vaccines)[9] and this might be a barrier to vaccine acceptance in the event of an epidemic. WHO is working to establish comprehensive fast-track regulatory pathways and emergency options within the WHO prequalification processes to provide provisional approvals of unlicensed vaccines during a public health emergency, similar to the approach used during the influenza A H1N1 pandemic.[36]

Capacity for vaccine production—The number and production capacity of vaccine manufacturers and the number of available doses will help with planning for stockpile size and maintenance, and affect the capacity for increased vaccine dose production should demand be greater than anticipated. For example, the initial oral cholera vaccine stockpile size of 2 million doses per year was recommended with insufficient vaccine manufacturing capacity in mind.[38]

Management of the stockpile

Funding—Short-term and long-term plans for funding must be in place to establish and maintain the stockpile without interruption. In some cases, public–private partnerships might be necessary, as was the case for production of MenA vaccine. In other cases, revolving fund mechanisms have allowed sustainability of the vaccine stockpile by providing longer term funding for short-term and future epidemic response (WHO, unpublished data). These mechanisms give manufacturers improved capacity to plan vaccine production and supply, since financing for future procurement is assured. Additionally, different procurement mechanisms can ensure main tenance of vaccine supplies. For example, the polysaccharide meningococcal vaccine uses two procurement mechanisms: a purchase commitment (reserved stockpile, later payment) or an advanced payment (prepaid stockpile) to manufacturers to maintain the stockpile (WHO, unpublished). With the reserved stockpile, all financial risks are borne by the manufacturers. With the prepaid stockpile, the ICG assumes all risks and absorbs financial losses in cases in which expiring vaccine stocks result in wastage or donations for preventive vaccination.

Prediction of need for vaccines—Forecasting of vaccine demand can be difficult.[39] Best guesses are based on historic disease burden data and epidemiology, and adjustments might be needed as an epidemic evolves. For example, the vaccine shortages that occurred in 2000 during an outbreak in Guinea, and in 2001 in an outbreak in Abidjan, Côte d'Ivoire, triggered the creation of a 2 million dose yellow fever vaccine stockpile to avoid acute supply disruptions.[40] Over time, the stockpile has increased to 6 million doses per year through support from the GAVI Alliance. Accurate vaccine forecasting and a contingency plan for vaccine shortages developed during the establishment of the stockpile, rather than in the midst of an emergency response or actual vaccine shortage, will in our view result in more efficient stockpile management. Additionally, information on whether the vaccine is used in routine immunisation or vaccination campaigns will help to identify how unused doses can be used. Routine yellow fever vaccination and preventive vaccination campaigns in some countries, for example, permit the use of unused vaccine stockpile doses for preventive immunisation.[11]

Criteria for release of vaccines—Specific criteria for the release of vaccine doses will allow for timely, consistent, and transparent distribution of vaccines in emergency responses. These criteria include identification of who will decide whether to distribute vaccines and who will manage vaccine procurement and shipment, whether a vaccination plan has been prepared, and whether this plan includes in-country storage of vaccine doses and related supplies. Not only are these components crucial for vaccine deployment, but so is their coordination. For example, before the establishment of the ICG meningococcal vaccine stockpile coordinated response, some countries bought substantial quantities of meningococcal vaccines independently, which made coordination and forecasting of vaccine demand difficult (ICG Secretariat communication with partners and manufacturer). This independent purchasing resulted in situations in which some countries had insufficient vaccine supply to meet epidemic demand, while other countries had to manage expiring vaccine stockpiles.[41]

WHO has developed a framework to help with the complex decision making required for vaccination in humanitarian emergencies.[42] Although the implementation of these decisions will not always require use of vaccine stockpiles, similar criteria and considerations should be thought of regardless of the source of the vaccines.

Monitoring and assessment—A plan for monitoring and assessment of the operations of the vaccine stockpile should be discussed at the time that decisions about management of the stockpile are being made. Such a process, in conjunction with reporting of findings to all stakeholders, can provide information to improve the functionality of the stockpile and contribute to the wider body of evidence on vaccination responses and vaccine stockpiles.[2]

Ethical considerations

Careful assessment of risks and benefits related to disease and vaccination are needed to ensure the fairest distribution of vaccines. However, in settings short of resources, equitable distribution of vaccines might not happen. Allocation of vaccines might occur, for example, in specific countries or population groups (eg, age or occupational groups), especially if the goal is to maximise the benefits of vaccination to contain an outbreak and reduce mortality.[43] Transparency in the decision-making process for vaccine allocation is crucial to ensure trust and confidence in the stockpile mechanism, since complex ethical, political, and logistical issues might arise. Such issues were discussed for the oral cholera vaccine stockpile.[2] In view of the insufficient worldwide supply of cholera vaccines, difficult decisions will have to be made about who will receive the cholera vaccine through the stockpile, with the equity and utility of vaccination taken into account.

Search strategy and selection criteria

We identified references for this Review through searches of the following sources: PubMed articles published from Jan 1, 1946 to Aug 31, 2014, using the terms “stockpile”, “vaccine stockpile”, “yellow fever stockpile”, “meningitis stockpile”, “meningococcal vaccine stockpile”, “influenza stockpile”, “smallpox stockpile”, “Strategic National Stockpile”, and “Pediatric Vaccine Stockpile Program”; publicly available presentations regarding specific vaccine stockpiles; grey published by WHO; and information publicly available on the GAVI Alliance, PATH, UNICEF, US Centers for Disease Control and Prevention, and WHO websites as of Aug 31, 2014. We reviewed articles and presentations from these searches and relevant references cited in those articles. We only included articles published in English.

Conclusion

Vaccine stockpiles have been part of the response to vaccine-preventable disease outbreaks for several decades, and opportunities for their use are likely to increase.[42] This Review provides a general overview of the complexity involved in the decision to establish and maintain a vaccine stockpile, and how the process needs to take account of disease and vaccine characteristics, stockpile management, funding, and ethical issues regarding access to vaccines. Additional in-depth assessments of the operations of each stockpile could

provide further insights into the strengthening of the effectiveness, efficiency, and effect of these important resources. Beyond provision of a crucial supply to respond to vaccine-preventable disease outbreaks, creation of stockpiles can drive innovations for the development of vaccines with longer shelf lives, increased efficacy, and more efficient delivery. Proposed stockpiles, such as those for oral polio vaccine—and inactivated polio vaccine for the post-oral-polio vaccine era—underscore the complexity and opportunities that such reserves can provide.[43] Although lessons learned from establishment and maintenance of existing vaccine stockpiles can help to inform policy, each new vaccine stockpile will probably face additional challenges and costs.

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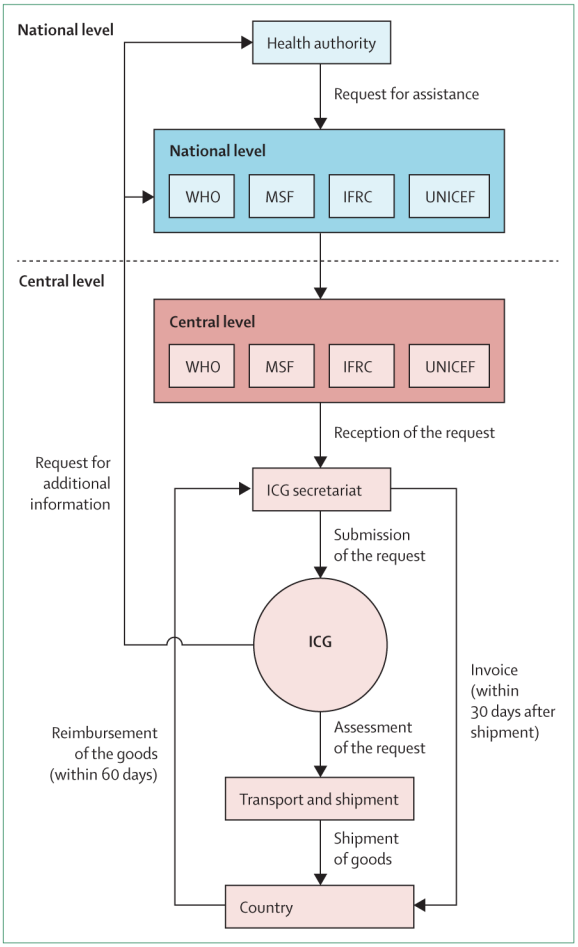

Figure. Operational steps of the ICG mechanism

MSF=Médecins Sans Frontières. IFRC=International Federation of the Red Cross. ICG= International Coordinating Group.

Table

Overview of existing global vaccine stockpiles

	Smallpox vaccine	Meningococcal vaccine	Yellow fever vaccine	Oral cholera vaccine
Year established	1980	1997	2001	2013
Main uses	Emergency response	Emergency response, disease prevention (conjugate)	Emergency response, disease prevention	Emergency response, humanitarian emergencies
Types of vaccine	Live-attenuated	Polysaccharide (bivalent, trivalent, quadrivalent), conjugate (monovalent)	Live-attenuated	Inactivated
Storage	WHO headquarters and multiple nations	Manufacturer	Manufacturer	Manufacturer
Management	WHO	ICG	ICG	ICG
Number of doses available (annual average)	35 million	9 million	5 million	2 million
Number of doses distributed to date (annual average)	None	4 million	5 million	1·5 million
Funding mechanism	Donations, WHO procurement	Donations, revolving fund	Donations, revolving fund	Donations, revolving fund

ICG=International Coordinating Group.