

**Operational framework for the deployment of
the World Health Organization Smallpox Vaccine
Emergency Stockpile
in response to a smallpox event**



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Table of contents

Acknowledgements	v
List of abbreviations.....	vi
1. Introduction	1
1.1 Purpose	2
1.2 Scope	3
2. WHO process for the request and release of vaccine from the SVES	3
3. Recommended smallpox vaccination strategy	6
4. Legal considerations	6
5. Regulatory considerations	7
6. Logistical considerations.....	8
6.1 Response personnel	8
6.2 Smallpox vaccine packing and cold chain	8
6.3 Smallpox vaccination ancillary supplies	8
6.3.1 Sterile, bifurcated needles or sterile, auto-disable vaccination syringes with attached sterile needles	9
6.3.2 Diluent to reconstitute the freeze-dried vaccine or to dilute the vaccine	9
6.3.3 Materials for medical waste disposal	9
7. Financial considerations.....	9
8. Communications and public information.....	10
9. Smallpox and the IHR (2005)	10
Annexes.....	12
1. Standard operating procedure to request vaccine from the WHO Smallpox Vaccine Emergency Stockpile.....	12
1.1 Smallpox vaccine request form (sections 1.1–1.14)	16
1.1.1 General information	16
1.1.2 Acceptance of request.....	17
1.1.3 Terms and conditions	18
1.1.4 Epidemiological situation in the country.....	22
1.1.5 Laboratory confirmation form.....	23
1.1.6 Affected population in the country.....	24
1.1.7 Organization of the response in the requesting country	25
1.1.8 National vaccine stockpiles in the requesting country	26
1.1.9 Vaccine request for use by the requesting country.....	27
1.1.10 Outline of smallpox vaccination plan.....	28
1.1.11 Request for technical and operational costs support	30
1.1.12 Shipment information.....	31
1.1.13 Information package	32

1.1.14 Signature.....	33
1.2 Feedback report on vaccination campaign.....	34
2. Standard operating procedure for the release and delivery of smallpox vaccine from the donor to WHO	35
2.1 Lines of communication/point of delivery	39
2.2 Pledged smallpox vaccine	40
2.3 Ancillary items	43
2.4 Packing the vaccine.....	44
2.5 Accompanying documents	46
2.6 Smallpox donation and transfer of title document	49
2.7 Smallpox vaccine delivery document	52
2.8 Logistical requirements.....	53
3. Communication challenges with international donation and deployment of smallpox vaccine	54
4. Summary table of vaccines physically stockpiled or pledged to the WHO Smallpox Vaccine Emergency Stockpile (SVES)	57
References for tables 7–9	67

List of tables

Table 1. Epidemiological information per location and per week	22
Table 2. Laboratory confirmation form	23
Table 3. Target population for vaccination and total vaccine requirement.....	24
Table 4. Estimation of vaccines and injection material needed	27
Table 5. Estimation of operational costs	30
Table 6. General characteristics of first-, second-, and third-generation vaccines, by category	58
Table 7. Overview of stockpiled first-generation smallpox vaccines	61
Table 8. Overview of stockpiled second-generation smallpox vaccines	63
Table 9. Overview of stockpiled third-generation smallpox vaccines	65

List of figures

Figure 1. WHO process for the request and release of smallpox vaccine from the SVES	5
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List of abbreviations

DG	Director-General of the WHO
HQ	Headquarters
IHR (2005)	International Health Regulations (2005)
PHEIC	Public Health Emergency of International Concern
SAGE	Strategic Advisory Group of Experts
SOP	Standard Operating Procedure for the Release and Delivery of Smallpox Vaccine from the Donor to the WHO
SVES	Smallpox Vaccine Emergency Stockpile
WHO	World Health Organization

1. Introduction

Smallpox, one of the oldest known human diseases, was declared eradicated by WHO in 1980, following the Intensified Smallpox Eradication Programme in which mass vaccination campaigns were conducted in countries with endemic smallpox infections. However, concern remains that the variola virus, which causes smallpox and still exists in some laboratories, might be deliberately released as a biological weapon or accidentally released from a laboratory. A range of factors – the variola virus' long incubation period and highly contagious nature, coupled with greater population mobility than 40 years' ago, clinicians lacking training and familiarity with the disease, scarce laboratory confirmation capacity, limited availability of medical countermeasures, and a global population with diminishing immunity to this disease – mean that a single smallpox case in any country poses a potential threat to all countries.

Currently, a few countries have the capacity to conduct surveillance, immunization and control campaigns, if smallpox were to reappear. However, most countries do not have their own vaccine stocks or the other resources needed to respond to an outbreak. In the case of a smallpox event, WHO will assume a major role, coordinating the global response and facilitating access to emergency supplies of vaccines, expertise and other technical, logistical, and human resources, consistent with WHO's role under the revised International Health Regulations (2005), known as IHR (2005).¹ Under the IHR (2005) which entered into force in 2007 as a legally binding framework for 195 States Parties, WHO is mandated to coordinate and manage the international assessment of, and public health response to, serious international public health events, whether or not they constitute a public health emergency of international concern (PHEIC) including a release of the smallpox virus.

In 1980, when smallpox eradication was achieved, it was recognized that there was a need for WHO to maintain an emergency reserve of Smallpox Vaccine Emergency Stockpile (SVES). WHO was given a set of formal responsibilities for maintaining capacity and expertise to respond to a re-emergence of smallpox in the post-eradication era as both a preparedness strategy and a possible deterrent to intentional release.

Originally, SVES was created by combining the remaining vaccine that had been donated by WHO Member States with the Intensified Smallpox Eradication Programme. At that time, a global physical stockpile of 200 million doses, maintained by WHO, was considered an adequate safety net. In the late 1980s, the diminished risk of recurrent smallpox and the cost of sustaining the physical stockpile led the Advisory Committee on Orthopoxvirus Infections (the Committee) to recommend that the physical stockpile should be substantially reduced.

In 2002, World Health Assembly (WHA) Resolution 55.16² urged Member States to share expertise, supplies and resources to rapidly contain a public health emergency or mitigate its effects. The resolution further requested the WHO Director-General (DG) to examine the possible development of collaborative mechanisms to prepare and stockpile resources for a potential smallpox emergency for which a PHEIC is declared. In line with this WHA resolution and the IHR (2005), five WHO Member States – France,

¹ <http://www.who.int/ihr/9789241596664/en/> (accessed 1 October 2017).

² http://apps.who.int/gb/archive/pdf_files/WHA55/ewha5516.pdf?ua=1 (accessed 5 October 2017).

Germany, New Zealand, the United Kingdom, and the United States – pledged to make smallpox vaccine immediately available to the SVES upon request.

To ensure that vaccine could be rapidly deployed and administered in response to any future outbreaks, the SVES was further developed as a mechanism to store, maintain and distribute smallpox vaccine internationally during an emergency. The SVES currently consists of two components:

- **A physical stockpile of vaccine held by WHO headquarters in Switzerland.** This is composed of calf lymph smallpox vaccines from a variety of sources dating from the final years of the eradication programme. These are regularly tested for potency. It is estimated that this stockpile will provide approximately 2.4 million doses when reconstituted and delivered by bifurcated needle.
- **A pledged stockpile held by donor countries in their respective national stockpiles for use in time of international need upon request by WHO,** which currently consists of 31.01 million doses of smallpox vaccine held by France, Germany, New Zealand, the United Kingdom, and the United States. Smallpox vaccine manufacturers, and other Member States and donors may augment this with donations in the future.³

Subject to the specific circumstances of an outbreak, **the physical stockpile of the SVES will be used for rapid, short-term and limited interventions. The pledged SVES will be mobilized when it is estimated that the physical stockpile will be exhausted or when vaccine from pledged stocks can be deployed faster. The vaccines that currently make up the SVES are NOT sufficient to vaccinate the entire global population and will instead be used to facilitate the initial response to a smallpox outbreak,** to allow manufacturers to start production of additional vaccine, and for WHO and countries to implement long-term containment/control strategies. **Vaccine from the SVES will only be released to assist containment measures in situations where an outbreak of smallpox has been confirmed by a WHO reference laboratory.** The U.S. Centers for Disease Control and Prevention (CDC) and Russia's State Research Centre of Virology and Biotechnology contain the only two WHO reference laboratories able to confirm a case of smallpox. WHO continues to work to increase international laboratory capacity and will deploy reverse transcription polymerase chain reaction (RT-PCR) reagents to countries during a smallpox emergency. WHO may seek supplementary vaccine from Member States or manufacturers and/or pursue procurement of vaccine from standby production capacity in the case of a sustained, widespread smallpox outbreak.

1.1 Purpose

This operational framework describes the World Health Organization (WHO) Smallpox Vaccine Emergency Stockpile (SVES) and the considerations and processes needed for countries to request vaccine in the event of a smallpox outbreak. It also describes the processes by which donors can deploy vaccine to the WHO SVES, and WHO can deploy vaccine to requesting countries. This document will be updated as needed as preparedness and response planning evolves based on new scientific developments and implementation of new global health security capacities.

³ <http://www.bioline.org.br/request?jp03037> (accessed 2 October 2017).

1.2 Scope

This operational framework discusses the procedures for deployment of smallpox vaccines (including diluent) and ancillary supplies (bifurcated needles and syringes for dilution) in case of a smallpox event. Antiviral drugs and vaccinia immunoglobulin are not included as they are not currently part of the WHO SVES.

2. WHO process for the request and release of vaccine from the SVES

Under IHR (2005),⁴ any case of smallpox is deemed "unusual" or "unexpected" and has the potential to have a "serious public health impact". Accordingly, any one case of smallpox, in any context, must be urgently notified to WHO as an event which may constitute a PHEIC, in accordance with the WHO case definition of smallpox for IHR (2005) notifications⁵

Once a case is reported, samples should be provided to a WHO reference laboratory for confirmation. Following their positive confirmation, and in accordance with any temporary recommendations that may be issued by the WHO under the IHR (2005),⁶ the process for the request and release of smallpox vaccine from the SVES will be triggered (see Figure 1).

Countries should request vaccine from the SVES following the steps outlined in the "Standard Operating Procedure to Request Vaccine from the World Health Organization Smallpox Vaccine Emergency Stockpile" (SOP; Annex 1). This includes completing and returning to WHO the "Request form to obtain emergency smallpox vaccine from the WHO" (Annex 1.1), including countersigning the recipient terms and conditions. WHO will ask countries requesting vaccine to develop and present a smallpox vaccination plan in accordance with the template provided in the SOP (Annex 1).

WHO will make decisions on whether, and how much vaccine, to deploy from the SVES in response to a request based on: epidemiological considerations; laboratory information; the availability of stocks in the affected area; the number of requests received; the ability of the requesting country to accept, distribute, use and mount a vaccination campaign; and other logistical considerations (such as the ability to maintain a cold chain). It should be noted that, given the limited number of doses currently available in the SVES, WHO may not be able to provide vaccine in response to every request and will be extremely limited in its ability to honour requests for a specific vaccine type or category.

If WHO decides to deploy vaccine from the physical SVES, the shipment of the vaccine will be arranged through the Organization's contracting and procurement services. If a decision is made to release vaccine from the SVES-pledged stockpile, the DG will request that one or more donors deploy vaccine according to the SOP (Annex 1).

In addition to vaccine from the SVES, other resources that may be provided or coordinated by WHO include: a WHO-mandated assessment team and training support for the safe implementation of emergency immunization campaigns; public health measures; infection control; and diagnostics for outbreak

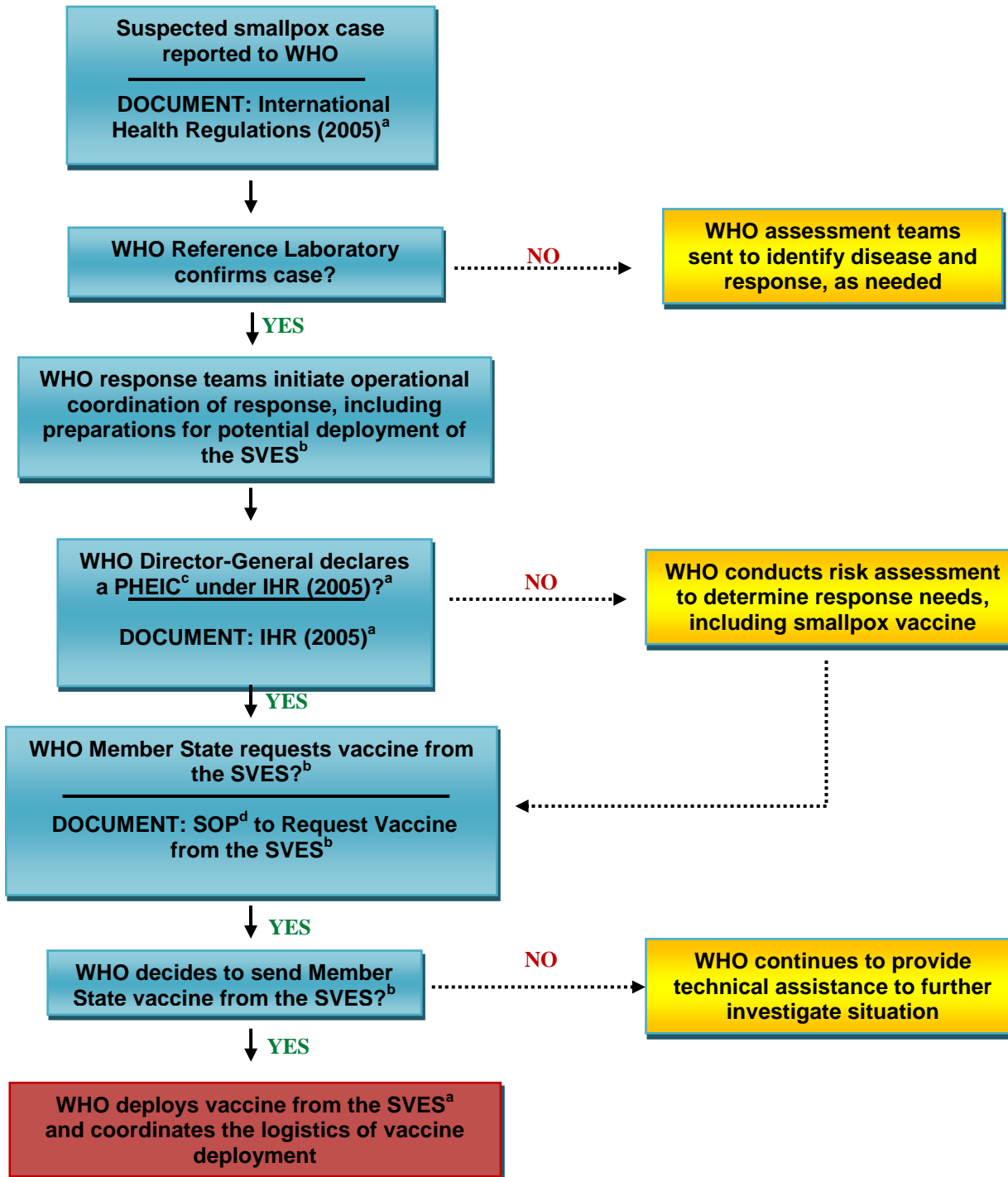
⁴ <http://www.who.int/ihr/9789241596664/en/> (accessed 1 October 2017).

⁵ See: "Case definitions for the four diseases requiring notification to WHO in all circumstances under the IHR (2005)", which includes smallpox (http://www.who.int/ihr/surveillance_response/case_definitions/en/index.html, accessed 30 September 2017).

⁶ <http://www.who.int/ihr/9789241596664/en/> (accessed 1 October 2017).

investigation and control. Implementation of all such plans will be contingent on the availability of the designated transport and resources during an event.

Figure 1. WHO process for the request and release of smallpox vaccine from the SVES



^a International Health Regulations (2005); <http://www.who.int/ihr/9789241596664/en/>, accessed 30 September 2017).

^b Smallpox Vaccine Emergency Stockpile.

^c Public Health Emergency of International Concern.

^d Standard operating procedure for the release and delivery of smallpox vaccine from the donor to the WHO.

^e Public health emergency of international concern.

3. Recommended smallpox vaccination strategy

The Strategic Advisory Group of Experts (SAGE) on Immunization last reviewed the WHO smallpox immunization policy in 2013.⁷

The consensus was that the use of smallpox vaccine should be reserved for the following at risk groups:

1. immediate contact of cases, e.g. personnel caring for smallpox patients should be vaccinated immediately after their initial contact;
2. health-care workers; and
3. first responders who have direct contact with symptomatic patients (such as when interviewing them, escorting them to hospitals or other care facilities, feeding them, etc.).

Contacts of contacts, the so-called “second ring of contacts”, should not be vaccinated. However, second ring contacts should be identified, and communications established, so that they can be vaccinated if the first ring contact actually develops smallpox or symptoms that suggest a smallpox infection. SAGE also recommended vaccinating laboratory or other health-care personnel who collect diagnostic specimens from patients, or who handle or process such specimens.

If a smallpox event is determined to be a PHEIC, any vaccination campaign will furthermore follow the relevant provisions of the IHR (2005).⁸

4. Legal considerations

Any vaccine provided by WHO to a country for emergency response, whether from the physical stockpile or the pledged stockpile will **only** be released on acceptance of the terms and conditions contained in the "Smallpox vaccine request form" (Annex 1.1). These terms and conditions *inter alia* provide that “the government (“the Government”) of the requesting country (“the Country”) shall “be solely responsible for, and accepts, any and all liability for the use of the vaccine [...] and agrees to indemnify, and hold harmless WHO and any (direct or indirect) supplier of the vaccine to WHO or to the Government (including but not limited to any donor country, manufacturer and/or distributor of the vaccine) [...] for any and all costs, expenses and claims of any kind arising from, as a result of, or in connection with the supply, distribution and/or use of the vaccine in the Country [...].”

The smallpox vaccine request form must be signed by the government of each requesting country in order to receive supplies from the SVES. By signing the request form, the government of the requesting country confirms that the vaccine has been authorized by the government for use in the control of a virologically

⁷ http://www.who.int/immunization/sage/meetings/2013/november/1_SAGE_report_consultation_smallpox.pdf/ (accessed 5 October 2017).

⁸ <http://www.who.int/ihr/9789241596664/en/> (accessed 5 October 2017).

and/or epidemiologically⁹ confirmed outbreak of smallpox in the country, and that the government irrevocably and unconditionally accepts and agrees to the terms and conditions contained in the request form.

5. Regulatory considerations

WHO Member States requesting smallpox vaccine and ancillary supplies from the SVES to respond to a smallpox outbreak must be able to arrange for the rapid importation and authorization of these products before they are deployed from the SVES. If vaccines do not have market authorization from the national regulatory authority (NRA) of the requesting country, the NRA must be prepared to conduct an emergency assessment and review of the vaccines based on:

- advice from the IHR Emergency Committee on vaccine deployment in case of a PHEIC declaration;
- recommendations from WHO on emergency use, which will take into account risk/benefit recommendations from vaccine experts based on currently available vaccine data and the risk from the emerging smallpox strain, using a collaborative approach with multilateral stakeholders;
- reliance on regulatory status granted by the NRA of the donor country or country of manufacture.

It is also important to know that, to date, some vaccines in the SVES do not have NRA authorization in the potential donor country or the country of manufacture. Therefore, to assist any requesting WHO Member States to arrange importation and authorization for the use of the SVES smallpox vaccines, WHO developed procedures as follows.

- Determine eligibility of vaccines in the SVES. Physical and pledged vaccines are to be subjected to an assessment for emergency use in preparation for a potential smallpox outbreak based on several factors including: whether the vaccine was used during the smallpox eradication campaign; whether there are potency, storage, safety, and efficacy or effectiveness data available (including in animals); whether the type of vaccine has been included in SAGE recommendations, etc.
- Perform an emergency assessment based on the scientific data available and issue recommendations for emergency use during a smallpox outbreak.
- Work with requesting countries to assess the emergency use of smallpox vaccines and means of importing such vaccines through an importation waiver programme managed by the requesting country's NRA or appropriate national authorities. This will enable countries to understand requesting procedures and their obligations and be prepared to import the requested vaccine legally.

In addition, WHO is focusing on developing sustainable technical capacity to assess vaccine safety and efficacy to facilitate rapid international emergency deployment not only of smallpox vaccine but also of any appropriate public health emergency medical interventions.

⁹ For initial cases in the cluster of cases virological confirmation will be needed. Once laboratory confirmation has been obtained, all new cases within this cluster do not need laboratory confirmation. New outbreaks of cases not linked to previous confirmed cases, will need laboratory confirmation.

6. Logistical considerations

6.1 Response personnel

The resources of the WHO Health Emergency Programme (WHE) will be mobilized to support emergency response to a smallpox outbreak. WHE coordinates response and containment operations for outbreaks of international concern, will use its existing infrastructure and mechanisms to ensure rapid vaccine deployment of the SVES.

6.2 Smallpox vaccine packing and cold chain

Some types of smallpox vaccine require a cold environment. The manufacturers specify required temperatures for both their storage and transport. Donors and WHO should follow appropriate cold-chain packaging and transportation protocols for the smallpox vaccine until the vaccine is delivered to the recipient country to ensure that the appropriate temperature is maintained.¹⁰

Any vaccine donated or purchased for the SVES physical stockpile should have a virus titre of 8.0 log₁₀ pock forming units/ml, or the validated equivalent in plaque forming units or TCID₅₀ units (for first and second generation vaccines). The vaccine should be freeze-dried. Vaccines for the pledged stockpile should meet the same potency criteria but may be either freeze-dried or liquid. The vaccine should be kept at an appropriate temperature for long-term storage, i.e. at -20°C, or lower or according to the manufacturer's recommendations.

6.3 Smallpox vaccination ancillary supplies

In line with the WHO/United Nations Children's Fund (UNICEF)/United Nations Population Fund (UNFPA) joint statement on the use of auto-disable syringes in immunization services, smallpox vaccine from the SVES should be delivered with all the ancillary supplies needed for administering the vaccines.

Most donors to the WHO SVES have pledged vaccine, diluent to reconstitute freeze-dried vaccine, and bifurcated needles. Sharps boxes and materials for medical waste were not included in these pledges. As far as possible, WHO will attempt to ensure that sharps boxes will be available to ensure occupational safety.¹¹ If WHO were not able to provide ancillary items, recipient countries will be responsible for ensuring that they have the necessary items to conduct a vaccination campaign.

WHO will inform Member States receiving vaccine from the SVES of the types and quantities of ancillary supplies that will accompany the vaccine donation. Ancillary items that *may* be delivered with vaccine from the SVES are listed in sections 6.3.1-6.3.3 below.

¹⁰ http://www.who.int/immunization/documents/WHO_IVB_05.01/en/index.html, accessed 30 September 2017.

¹¹ The term “bundling” refers to a conceptual package that contains the pledged smallpox vaccine and all other material required for a vaccination campaign using the pledged smallpox vaccine (for example vaccination materials, sharps boxes, and materials for medical waste). However, “bundling” does not have a physical connotation and does not imply that the items must be physically “packaged” together or must be stored in the same location.

6.3.1 Sterile, bifurcated needles or sterile, auto-disable vaccination syringes with attached sterile needles

Bifurcated needles

Smallpox vaccination using the multiple-puncture technique with bifurcated needles is normally preferred over scarification using normal needles. Bifurcated needles give a better “take rate” and use much less vaccine than normal needles.

Auto-disable syringes with attached needles

The auto-disable syringe with attached needle can be used only once, reducing the risk of person-to-person transmission of bloodborne pathogens. This type of syringe is the equipment of choice for transferring the vaccine diluent to the vaccine vial (also called ampoules) for reconstitution. Injected smallpox vaccines are also administered using an auto-disable vaccination syringe.

6.3.2 Diluent to reconstitute the freeze-dried vaccine or to dilute the vaccine

Some vaccines require liquids – diluents or solvents – to reconstitute the freeze-dried vaccine. If the smallpox vaccine and the required diluent for the vaccine are supplied in ampoules, it may be appropriate to use:

- a. a saw to cut the ampoules; and/or,
- b. a stand for the ampoules so that they are held upright, limiting the chance that they will spill.

6.3.3 Materials for medical waste disposal

Improper disposal of used materials for vaccination poses a direct danger to the vaccination recipient and to the health-care worker. Additionally, improper disposal of used materials for vaccination poses a continuing risk of infection and an environmental hazard to individuals, and to local communities.

Non-reusable sharps safety boxes

All sharps pose a potential hazard and can cause injury through cuts or puncture wounds. In particular, sharps, such as bifurcated needles and auto-disable syringes with attached needles, are capable of cutting or penetrating the skin. The design and construction of non-reusable sharps safety boxes reduce the possibility of injury to health-care workers during disposal and to handlers during the collection and transportation of the boxes. The boxes used in a smallpox vaccination campaign should be properly labelled, colour-coded for medical waste, and have the universal biological hazard symbol printed on them.

Non-reusable medical waste disposal sacks

Medical waste disposal sacks are used for the collection and storage of medical waste other than sharps. Empty smallpox vaccine vials should be placed into plastic non-reusable medical waste disposal sacks. The design and strength of the non-reusable medical waste sacks reduce the possibility of injury to health-care workers when disposing of medical waste during the vaccination campaign, and to handlers collecting and transporting non-reusable medical waste sacks. The non-reusable medical waste sacks designated for use in a smallpox vaccination campaign should be properly labelled, colour-coded for medical waste and have the universal biological hazard symbol printed on them.

7. Financial considerations

All stakeholders involved in the deployment of smallpox vaccine will require funding to support operational costs when responding to a smallpox outbreak.

- Transportation of smallpox vaccine from the donors' stockpile to the point of transfer to WHO (point of departure from the donor or point of arrival in the recipient country).
- Transportation from WHO to the requesting countries.
- International cargo insurance of vaccine from the SVES and/or from the donor to the recipient country. This cost will depend on the location of the outbreak and other factors, such as whether the shipment requires additional security measures.
- Implementation of vaccination campaigns in the recipient country, including the operational costs of deployment and/or training of health-care workers, transportation of vaccines from point-of-arrival within the country to the final destination.

In case of a smallpox outbreak, WHO will request funds for the deployment of smallpox vaccines from the financial mechanism set out under the Emergency Response framework (ERF).¹²

In case of damage to, or loss of, vaccine, WHO will endeavour to obtain a donation or (subject to the availability of funds) procure additional doses of either the same or a different generation vaccine, up to the quantity that has been damaged or lost.

8. Communications and public information

Smallpox vaccines are grouped into “categories” based on when they were first developed and their methods of production. The SVES currently contains a diverse mix of smallpox vaccines, including vaccines of different generations. Annex 4 shows a summary table of vaccines physically stockpiled or pledged to the SVES providing descriptions and general information on the basic characteristics of smallpox vaccines currently available internationally to respond to a smallpox outbreak.

Extensive risk communication research data show that being transparent about difficult situations and unknown factors actually strengthens the public's trust in an organization and enhances its public credibility, especially if further uncertainty or bad news is expected. To this end, transparency in the actions and words of authorities regarding the importance and use of different types of vaccines, throughout the duration of the health emergency is absolutely critical to public confidence and national cohesion.

In order to allow WHO and its Member States to develop communications plans and provide accurate, transparent information on vaccines that may be deployed from the SVES in response to a smallpox outbreak, Annex 3 provides a guidance communication plan template upon which more specific, tailored plans may be developed that will support an entity's communication strategy regarding donating and/or receiving smallpox vaccine.

9. Smallpox and the IHR (2005)¹³

WHO DG may determine that a smallpox outbreak constitutes a PHEIC under the IHR (2005). If such a determination is made, the DG, after taking advice from an IHR Emergency Committee of outside experts,

¹² <http://apps.who.int/iris/bitstream/10665/258604/1/9789241512299-eng.pdf?ua=1> (accessed 14 November 2017).

¹³ <http://www.who.int/ihr/9789241596664/en/> (accessed 5 October 2017).

will issue IHR (2005) “temporary recommendations”¹⁴ of health measures for Member States to implement in order to prevent or reduce the international spread of disease and avoid unnecessary interference with international traffic. These recommendations can involve issues such as the distribution of the vaccine and related activities. It is important to note that even if a PHEIC is not declared under the IHR (2005) (1), WHO (through the DG) can still issue strong advice (and focus attention) concerning the same measures as might be included in temporary recommendations, including aspects concerning the distribution of smallpox vaccine and related issues.

The IHR (2005)¹⁵ outline the criteria for the DG in formulating the temporary recommendations, including: the views of the States Parties concerned; advice of the Emergency Committee; scientific principles, evidence and other relevant information; relevant international standards and instruments; the activities of other intergovernmental organizations (IGOs) and international bodies; and the health measures that are not more restrictive of international traffic or intrusive to persons than reasonably available alternatives that would achieve an appropriate level of health protection. More specifically, information that is most relevant for the development of such recommendations in these circumstances includes:

- health measures in place;
- basic descriptive epidemiology, including population size and structure in affected area(s);
- date of last mass immunization in the affected area, estimation of seroprotection;
- supplies of vaccine available in the country;
- logistics available in the country for securely transporting and administering vaccine;
- approximate number of cases, contacts and first responders (e.g. health-care workers, emergency services staff, etc.) needing immediate vaccination;
- relevant security issues;
- laboratory capacity for diagnosis, or for processing clinical samples for safe forwarding to reference laboratories;
- public health infrastructure for detection and notification of suspected cases;
- information on isolation facilities and policies;
- information on capacity of the public health authorities to identify, manage and follow contacts.

An *outbreak* of smallpox may be considered a PHEIC. However, a minimal, localized and easily contained event may not be considered (and determined) to be a PHEIC, but would be graded, in any event, within all of the other broad provisions in the IHR (2005) and ERF^{16,17} including surveillance, reporting, response and information sharing. As noted above, even in the absence of a PHEIC determination, WHO (through the DG) can still focus global attention and advise States Parties and others on the same kinds of measures that might be included in temporary recommendations.

¹⁴ http://apps.who.int/iris/bitstream/10665/43883/1/9789241580410_eng.pdf (accessed 5 October 2017).

¹⁵ Ibid.

¹⁶ Ibid.

¹⁷ <http://www.who.int/hac/about/erf/en/> (accessed 14 November 2017).

Annexes

1. Standard operating procedure to request vaccine from the WHO Smallpox Vaccine Emergency Stockpile

1. Purpose

This SOP describes the process by which a country can request (“requesting country”) smallpox vaccine from the WHO SVES to respond to a smallpox outbreak. This includes the submission of the completed smallpox vaccine request form (see Annex 1.1) and the steps that requesting countries should follow in order to be eligible to receive smallpox vaccine.

WHO will prioritize the requests for vaccines from the WHO SVES if needed on the advice of relevant expert groups, such as the IHR Emergency Committee and SAGE on Immunization. The decision will be based on:

- epidemiological considerations;
- laboratory information;
- the total number of doses requested from WHO;
- the existence of a planned intervention strategy;
- the local coordination of the epidemic response;
- the operational aspects of the response to the event; and
- the prioritization of the requests received by WHO based on requesting countries’ need to receive smallpox vaccine from WHO.

The submission of the smallpox vaccine request form does not automatically mean that WHO will supply any vaccine and ancillary materials to the requesting country. Similarly, the submission of the smallpox vaccine request form does not automatically mean that WHO will provide any requested technical support or support for operational costs. WHO will communicate to the government of the requesting country details regarding any supply of vaccine and ancillary materials, including the quantities and logistics, such as anticipated delivery timelines and destinations, and details regarding the provision of any requested technical support and support for operational costs.

2. Roles and responsibilities

WHO

The WHO country office¹⁸ must ensure that the smallpox vaccine request is made without unnecessary delay. Upon receipt of the smallpox vaccine request form, the country/regional office:

- determines if the smallpox vaccine request form has been completed correctly and contains all the requested information;

¹⁸ Or where there is no country office to the relevant regional office.

- determines if the smallpox vaccine request form, including the terms and conditions, has been accepted and signed;
- assists the requesting country to obtain the missing information and to complete the smallpox vaccine request form;
- submits the completed smallpox vaccine request form directly to the Smallpox Secretariat at WHO HQ by email at smallpox@who.int to ensure rapid response – the country/regional office may request assistance from the relevant WHO regional office (RO) communicable disease focal point or directly from the WHO Smallpox Secretariat in filling out the request;
- informs the WHO Smallpox Secretariat with copies to RO about the country's storage and cold chain capacities to ensure adequate reception of the supplies;
- sends written confirmation of the final reception of the medical supplies at country level plus a signed copy of the packing list to the Smallpox Secretariat at smallpox@who.int;
- conducts an evaluation of the response with the country's Ministry of Health and informs the WHO Smallpox Secretariat concerning the smallpox outbreak and any vaccination results, including case counts, uptake and the results of the use of the vaccine and incidence of adverse events.

The WHO Smallpox Secretariat at HQ:

- provides support to respond to smallpox outbreaks;
- evaluates the requests to supply smallpox vaccine;
- assesses the available data to determine if the criteria to define a smallpox outbreak/event have been met;
- monitors the status of the requests;
- ensures that sufficient items in the smallpox vaccine are available when required;
- sends the smallpox vaccine request form to the affected countries;
- acknowledges receipt of the completed smallpox vaccine request forms,
- provides technical justification to the DG on the decision about quantity and dose type to be allocated;
- ensures release and delivery of the bundled smallpox vaccine to the requesting country;
- informs donors about the smallpox outbreak and any vaccination results including case counts, uptake and results of the use of the vaccine and the incidence of adverse events.

WHO/HQ logistics:

- manages and organizes deployment of bundled smallpox vaccine and materials to countries;
- provides technical support to countries to improve and facilitate national preparedness and response to a smallpox event.

The requesting country

The requesting country requests vaccine from WHO according to the following procedure.

- Reports any smallpox case as a potential public health emergency of international concern (PHEIC) under the IHR (2005).¹⁹
- Obtains information about smallpox from WHO resources and the IHR website for the case definition (see table below), and additional information from the WHO website at: http://www.who.int/ihr/surveillance_response/case_definitions/en/index.html and <http://www.who.int/csr/disease/smallpox/en/index.html>.
- Establishes a smallpox surveillance system, including contact tracing and monitoring of adverse events following immunization (AEFI).
- Evaluates the number of cases reported and the attack rate and reports on a daily basis.
- Provides laboratory data obtained from WHO reference laboratories to confirm that people suspected as having smallpox are infected with the variola virus.
- Appoints ONE person to liaise with the WHO country office. This person should be an employee of the national IHR focal point (i.e. the national centre designated by each of the States Parties, which shall be accessible at all times for communications with WHO IHR contact points under the IHR (2005)).²⁰
- Requests the smallpox vaccine request form from the WHO Smallpox Secretariat.
- Completes the smallpox vaccine request form.
- Officially signs the completed smallpox vaccine request form, including the terms and conditions section, and returns it to WHO within 24 hours of its receipt.
- Submits the completed and signed smallpox vaccine request form to the WHO Country Office or directly to the WHO Smallpox Secretariat at HQ using email, fax or other acceptable means (e.g. text messages, expedited couriers, etc.) so that it will arrive as soon as possible.
- Sends the signed original copy by courier to the WHO Smallpox Secretariat at HQ.
- Ensures preparation of the vaccination plan while obtaining all the necessary information to complete the smallpox vaccine request form.

¹⁹ http://apps.who.int/iris/bitstream/10665/43883/1/9789241580410_eng.pdf (accessed 5 October 2017).

²⁰ Ibid.

Box 1
Case definition for notification of smallpox under the IHR (2005)

States Parties to the IHR (2005) are required to immediately notify WHO of any confirmed case of smallpox. The case definition for a confirmed smallpox case includes the following.

Confirmed case of smallpox:

an individual of any age presenting with acute onset of fever ($\geq 38.3^{\circ}\text{C}/101^{\circ}\text{F}$), malaise, and severe prostration with headache and backache occurring 2–4 days before rash onset

AND

subsequent development of a maculopapular rash starting on the face and forearms, then spreading to the trunk and legs, and evolving within 48 hours to deep-seated, firm/hard and round well-circumscribed vesicles and later pustules, which may become umbilicated or confluent

AND

lesions that appear in the same stage of development (i.e. all are vesicles or all are pustules) on any given part of the body (e.g. the face or arm)

AND

no alternative diagnosis explaining the illness

AND

laboratory confirmation.

Note:

In contrast to the varicella (chickenpox) infection with centripetal and more superficial lesions, the majority of smallpox cases present with a characteristic rash that evolves slowly over days (with each stage lasting 1–2 days) at the same rate and is centrifugal in distribution, i.e. predominantly concentrated on the face and extremities with usual involvement of the palms and soles of the feet.

More information and illustrative examples to differentiate smallpox from chickenpox can be found at <http://www.who.int/csr/disease/smallpox/preparedness/en/index.html>

The risk of not identifying atypical presentations of smallpox is weighed against the extremely low risk of reintroduction of the disease and the very high risk of obtaining a false-positive laboratory result. In view of this, laboratory tests to confirm smallpox should be limited to individuals that match the above clinical case definition. Should a single, laboratory-confirmed case of smallpox ever occur, it would be considered an outbreak since smallpox no longer exists as a naturally occurring disease.

1.1 Smallpox vaccine request form (sections 1.1–1.14)

1.1.1 General information

Date of the request:
Country:
Region/state:
Affected areas (towns/districts/divisions):
Name of Ministry:.....("the Government")
Name of Minister:.....
Address:.....
Postcode.....City.....
Country..... ("the Country")
Telephone No.....Facsimile No.....
E-mail.....

To activate the request process, the requesting country should carefully read sections I to XIV, complete all the required information, check the boxes below and submit sections I to XIV to the address below. Please ensure that all required information and documentation is provided (tick the box if filled out/attached)

The Government of (fill in requesting country) has:

- ☐ Read sections I to XIV
- ☐ Completed Section IV – Epidemiological situation in the Country
- ☐ Completed Section V – Laboratory confirmation form
- ☐ Completed Section VI – Affected population in the Country
- ☐ Completed Section VII – Organization of the Response in the Country
- ☐ Completed Section VIII – National vaccine stockpile in the Country
- ☐ Completed Section IX – Vaccine request for use in Country
- ☐ Completed Section X – Outline of smallpox vaccination plan
- ☐ Completed Section XI – Request for technical and operational costs support
- ☐ Completed Section XII – Shipment information
- ☐ Read Section XIII – Additional information
- ☐ Signed Section XIV

Address signed Vaccine Request Form and required documentation to:

WHO Smallpox Secretariat

20 Avenue Appia

1211 Geneva 27

Switzerland

Fax + 41 22 791 4198; email at smallpox@who.int

cc: WHO country office.

1.1.2 Acceptance of request

WHO will prioritize the requests for vaccines from the WHO Smallpox Vaccine Emergency Stockpile (SVES) based on the recommendations of the International Health Regulations (IHR) Emergency Committee and of the Strategic Advisory Group of Experts (SAGE) on Immunization.²¹ The decision will be based on epidemiological considerations, the laboratory information provided, the total number of doses requested from WHO, the total number of doses in the WHO SVES, and the prioritization of the requests received by WHO based on requesting countries' need to receive smallpox vaccine from WHO.

In this regard, it should be noted that the submission of this request form does not automatically mean that WHO will actually supply any vaccine and ancillary materials to the requesting country, or that WHO will supply the quantities requested and/or supply the vaccine and ancillary materials by the requested delivery date. Similarly, the submission of this request form does not automatically mean that WHO will actually provide any requested technical support and support for operational costs. The decisions on whether to supply any vaccine and ancillary materials to the requesting country, which type of vaccine and ancillary materials to supply and in which quantities, and whether to provide any requested technical support and support for operational costs, will be taken by WHO in its sole discretion based on the recommendations of the IHR Emergency Committee and the SAGE and the above-mentioned considerations. Details regarding any supply of vaccine and ancillary materials, including the quantities and logistics, such as anticipated delivery timelines and destinations, and details regarding the provision of any requested technical support and support for operational costs will be communicated by WHO to the government of the requesting country at the contact details indicated above.

The availability of the WHO SVES is not a replacement for national stockpiles, which should be considered as one of a number of measures of national preparedness consistent with the national priorities of the requesting country.

The vaccines in the stockpile are intended for outbreak response. The SAGE recommended to WHO that, for outbreak response stockpile, both licensed ACAM2000 and LC16m8 are preferred. If they are not available, vaccine used during the eradication programme (lymph, skin from animals) can be used.

Vaccines recommended for use in the case of smallpox outbreaks should be lyophilized, administered via bifurcated needles (which allows a reduction of the vaccine dose) and produce a visible major cutaneous reaction as a correlation for protection (i.e. "take"). In controlling an outbreak, countries should use any smallpox vaccine on hand that meets the standards for potency, purity and stability as laid out in WHO/TRS No. 926. 2004.

Should a smallpox outbreak occur and a country requests vaccine, WHO will provide information about the vaccines available in its stockpile, the SAGE recommendations, as well as the advantages and disadvantages of each vaccine with up-to-date safety and efficacy/effectiveness information.

In any situation of a suspected or a confirmed case, WHO will assist the country to prepare the smallpox vaccine request form and the requesting country will receive confirmation from WHO whether the request has been accepted and, if so, which vaccine will be shipped.

²¹ <http://www.who.int/wer/2014/wer8901.pdf> (accessed 14 November 2017).

1.1.3 Terms and conditions

The supply of smallpox vaccine is to be used with the diluent provided, or with equivalent diluent as recommended by the manufacturer (if any) or with diluent consistent with the standards and use during the smallpox eradication programme or standards subsequently recommended by WHO. The vaccine, the diluent and other ancillary materials (bifurcated needles and safety boxes) supplied by WHO from the Smallpox Vaccine Emergency Stockpile (SVES) are hereinafter severally and jointly referred to as “the smallpox vaccine” or “the vaccine”.

By signing the smallpox vaccine request form, the Government (“the Government”) of the Requesting Country (“the Country”) accepts and agrees that the supply of vaccine from the WHO SVES will be subject to the following terms and conditions:

The vaccine is being supplied to the Government exclusively for emergency use under the control of the Government, in the event of a WHO confirmed outbreak of smallpox in the Country. Although it is generally believed that the vaccine may be useful in case of emergency, the Government confirms that it has full knowledge of:

- the known side effects of the vaccine, as described in the relevant and most recent literature (it being understood that the Government shall be responsible for identifying such literature, to the extent it is not contained in the information package provided by WHO);
- the fact that the vaccine quantity supplied by WHO to the Government:
 - a. may have been manufactured many years ago and may be past its original expiry date;
 - b. may have been manufactured from old bulk suspension which was produced many years ago and may not, therefore, meet current standards;
 - c. may have been manufactured through the use of techniques which do not reflect current standards and/or current state of the art, or techniques which have not, or not yet, been accepted by any regulatory authority;
 - d. may not have been shown to be clinically effective in the prevention of smallpox (even if the vaccine may have satisfied the safety requirements of regulatory bodies);
 - e. may possibly give rise to adverse events (i.e. over and above those described in the literature referred to above), including serious, life-threatening or fatal adverse reactions.

The Government confirms that it has read the information package provided by WHO, including literature on the risks of using the vaccines in the WHO SVES and their adverse events, and including a flyer describing WHO’s recommendations for their administration. The Government acknowledges and agrees that this information has been provided to the Government to assist it in gaining knowledge about the vaccines in the SVES, but is by no means exhaustive, and does not relieve the Government of its undertaking to have obtained full knowledge.

The Government further acknowledges that it has been duly informed about the vaccine's regulatory approval status (e.g. that the vaccine is approved by national authorities in the country of manufacture or authorized for emergency use by national authorities in the donor country or is not, may no longer be, or may never have been licensed for use in any country of the world). Even if the vaccine may have been approved by national authorities in the country of manufacture or may have been authorized for emergency use by national authorities in the donor country, the vaccine may not fulfil the requirements for licensing in other countries.

The vaccine quantity provided hereunder is being supplied "as is", without any warranties or representations whatsoever, whether express or implied, including, but expressly not limited to, any implied warranties as to the vaccine's fitness for a particular purpose or use, or as to its safety, efficacy, or quality in any respect. Similarly, neither WHO nor any (direct or indirect) supplier of the vaccine to WHO or to the Government (including but not limited to any donor country, manufacturer or distributor of the vaccine) warrants or represents that the vaccine quantity has been manufactured to meet its specifications and/or Good Manufacturing Practices (GMP), nor that it has been stored, handled and/or transported under appropriate conditions.

Although WHO shall require that its forwarding agent, and/or any other party delivering the vaccine quantity to the Government, ensures that adequate procedures are followed to protect the physical security of the vaccine, and to follow the WHO guidelines on international packaging and shipping of vaccines²² in respect of the storage, handling and transportation of this vaccine quantity by this forwarding agent or other party, the Government agrees that neither WHO nor any (direct or indirect) supplier of the vaccine quantity to WHO or to the Government (including but not limited to any donor country, manufacturer or distributor of the vaccine) shall be responsible for any damage to, or loss of, vaccine during its storage, handling or transportation up to the delivery of the vaccine quantity to the Government at the agreed delivery destination.

The Government confirms that it will weigh the risks associated with a virologically and epidemiologically confirmed outbreak of smallpox in the Country against the risks associated with the use of the aforesaid vaccine quantity, including the possible occurrence of serious, life threatening or fatal adverse reactions in a potentially high number of cases. In deciding to use this vaccine quantity, the Government shall come to its own conclusion that such use is justified under the circumstances.

The Government shall thus be solely responsible for, and accepts, any and all liability for the use of the vaccine. Specifically, the Government agrees to indemnify and hold harmless WHO and any (direct or indirect) supplier of the vaccine to WHO or to the Government (including but not limited to any donor country, manufacturer and/or distributor of the vaccine) as well as their officers, employees, contractors and agents, for any and all claims and liabilities (including reasonable costs and expenses) of any kind arising from, as a result of, or in connection with the supply, distribution and/or use of the vaccine in the Country, by or on behalf of the Government or otherwise.

By signing this request form and returning the signed request form to WHO, the Government unconditionally agrees to be bound by the terms and conditions set forth in this request form. Moreover, to the extent these terms and conditions limit potential liabilities associated with the supplies of smallpox vaccine by or on behalf of WHO, the Government expressly acknowledges that these terms and conditions are for the benefit

²² http://apps.who.int/iris/bitstream/10665/69368/1/WHO_IVB_05.23_eng.pdf (accessed 14 November 2017).

of WHO and for the benefit of any (direct or indirect) supplier of the vaccine to WHO or to the Government (including but not limited to any donor country, manufacturer and/or distributor of the vaccine) and, therefore, that these terms and conditions create benefits and rights which are not only directly enforceable by WHO, but also any such (direct or indirect) supplier of the vaccine on its own behalf (as third party beneficiary to the terms of this request form).

Ownership of the vaccine will transfer to the Government upon delivery at the agreed delivery destination. The Government will be responsible for handling the rapid importation and customs clearance of the vaccine into the Country. The Government will then be responsible for arranging for any subsequent storage and transportation of the vaccine (under appropriate conditions, including compliance with cold chain requirements²³ and ensure its rapid delivery and administration to patients.

The Government agrees and will ensure that the vaccine supplied hereunder will:

- not be used for any purpose other than as provided in this request form;
- only be provided to persons in the Country who have been targeted in accordance with the Country's smallpox outbreak response measures;
- not be exported or otherwise made available for use outside the Country; and
- be used and distributed in accordance with any requirements under which the vaccine has been authorized in the Country.

In addition, bearing in mind that the aforesaid quantity is being provided to the Government free of charge, the Government will ensure that the vaccine supplied by WHO will not be sold, but will only be provided to patients in the Country free of charge or at nominal cost to recuperate reasonable expenses incurred in connection with its delivery to patients.

The labelling and inner packaging of the smallpox vaccine, as well as leaflets and outer packaging may be in English and/or other languages. By signing this request form, the Government explicitly accepts and agrees to the use of packaging, labelling and leaflets as described above. The Government will distribute the leaflets to health-care professionals who administer the vaccine, together with the attached information package (including literature on the risks of using the vaccine and the possible adverse events, and including a flyer describing WHO's recommendations on the administration of the vaccine).

By signing this request form, the Government confirms that it shall ensure that all health-care practitioners and others administering smallpox vaccine to the population of the Country:

- are fully aware of, understand and will ensure adherence to all recommendations for the proper handling, administration and use of the vaccine as contained in the above mentioned leaflets; and
- will inform all persons to whom the vaccine may be administered, of all possible safety concerns to which the vaccine may give rise, including its possible side effects and known adverse events.

The Government furthermore confirms that it will implement surveillance of adverse events following immunization as contained in "Surveillance of adverse events following immunization: field guide for

²³ http://apps.who.int/iris/bitstream/10665/67824/1/WHO_V-B_02.16_eng.pdf (accessed 14 November 2017).

managers of immunization programmes,²⁴ and have a recall procedure in place as described in the *WHO Expert Committee on Specification for Pharmaceutical Preparations*.²⁵

Neither WHO nor any (direct or indirect) supplier of the vaccine to WHO or to the Government (including but not limited to any donor country, manufacturer and/or distributor of the vaccine) will be liable or held responsible for any delay or failure in the supply of smallpox vaccine as a result of force majeure or act by any governmental or other authorities that may prevent or restrict WHO and/or any (direct or indirect) supplier of the vaccine to WHO or to the Government (including but not limited to any donor country, manufacturer and/or distributor of the vaccine) in supplying and delivering the vaccine, or that may preclude or restrict the free movement of the vaccine to the agreed site of delivery. In addition, neither WHO nor any (direct or indirect) supplier of the vaccine to WHO or to the Government (including but not limited to any donor country, manufacturer and/or distributor of the vaccine) will be liable or held responsible for closure of airlines, airports, borders or other elements of the transportation system which may limit the free movement of goods within or between countries.

Any matter relating to the interpretation and application of this request form, which is not covered by its terms, will be resolved by reference to the laws of France, excluding the conflict of law rules.

All disputes relating to the interpretation or application of this request form that cannot be resolved amicably will be finally settled by arbitration to be conducted in accordance with the Rules of Arbitration of the International Chamber of Commerce by one or more arbitrators appointed in accordance with said Rules. The language of arbitration shall be English. The place of arbitration shall be agreed by mutual consent of the parties, or in the absence thereof, shall be Paris, France. The parties shall accept the arbitral award as the final and binding adjudication of their dispute.

It is understood and agreed that except for the enforcement of any arbitral award as aforesaid, nothing contained in this request form will be deemed to submit the Government to any national court jurisdiction.

It is further agreed and understood that:

- the terms and conditions contained in this request form are not aimed at establishing an international treaty, are not subject to international law and are not intended to give rise to any rights or obligations in international law; and
- nothing in this request form shall be deemed to constitute a waiver of any privileges or immunities enjoyed by WHO and/or the donor countries, and/or as submitting WHO and/or the donor countries to any national court jurisdiction.

The Government agrees that any supply of vaccines and other materials, as well as any other support and assistance which may be provided by WHO to the Country in furtherance of this request form, will be provided in accordance with the terms of the Agreement for technical advisory cooperation or assistance concluded with the Government.

The terms and conditions contained in this request form are irrevocable and cannot be amended or changed, except by mutual agreement of the Government, WHO and any (direct or indirect) supplier of the vaccine to

²⁴ http://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf (accessed 14 November 2017).

²⁵ <http://www.who.int/medicines/publications/pharmprep/en/> (accessed 14 November 2017).

WHO or the Country, including in so far as the benefits and rights of any (direct or indirect) supplier of the vaccine to WHO or the Country in this request form are concerned.

1.1.4 Epidemiological situation in the country

Please provide a line listing of the first smallpox cases in the country sorted by date of onset of symptoms according to the following table.

Table 1. Epidemiological information per location and per week

Description of the first smallpox cases						Location of the cases		
Age	Sex M / F	DOS* dd/mm/ yr	Alive yes/ no	Smallpox vaccination yes/no	Laboratory confirmation status**	Province and district	Sub-district	Locality of infection

* Date of onset of symptoms.

** Laboratory confirmation status: 0 = not smallpox; 1 = smallpox confirmed; 2 = result pending.

Total number of cases, including deaths (both suspected and confirmed cases):

Total number of WHO reference laboratory confirmed cases:

Total number of deaths:

Date of onset of the first case related to this outbreak (dd/mm/yyyy):

Date of onset of the last reported case related to this outbreak (dd/mm/yyyy):

1.1.5 Laboratory confirmation form

Table 2. Laboratory confirmation form

Sample No.	Type of test performed	Where performed	Results

1.1.6 Affected population in the country

Please indicate the total population in the affected area, as well as the target population for vaccination.

Note that the total vaccine requirement is calculated by the following formula:

Total vaccine doses required = number of targeted subjects x 1.11 wastage factor

Table 3. Target population for vaccination and total vaccine requirement

Name of location	Type of location *	Total population in affected area	Target population for vaccination (number)	Target population for vaccination (type) **	Total vaccine requirement
Total vaccines required within the country:					

* Example: rural (Ru); city (C); sub-district (SD); district (D); province (P); region (R).
** Example: contacts of contacts (CC), health-care workers (HCWs), first responders (FR).

1.1.7 Organization of the response in the requesting country

Has an epidemic coordination committee been established to plan and monitor outbreak response activities in the Country? Yes ☐ No ☐

If yes, Please describe **briefly** the composition of the committee and recommendations/actions taken

Please specify the current plan or considerations for vaccination (e.g. ring vaccination or other vaccination strategies)

1.1.8 National vaccine stockpiles in the requesting country

Is there a national stock of smallpox vaccine that can be used to control the outbreak in the country?

Yes ☐ No ☐

If yes, please indicate the vaccine type(s), number of doses and expiry date(s):

Vaccine type(s):

Number of doses of each vaccine type:

Expiry date(s) per vaccine type (dd/mm/yyyy):

1.1.9 Vaccine request for use by the requesting country

Table 4. Estimation of vaccines and injection material needed

Type of material	Total estimated needs (total vaccine requirement) ^a	Stock available (non-expired doses) in the country	Quantity needed for emergency use ^b
Vaccines			
Diluent to reconstitute vaccine			
Sterile bifurcated needles ^c			
Safety boxes (container 15 L)			

^a The estimated quantity of vaccines needs to correspond to the quantity calculated in table 3 – last column.

^b The quantity needed should correspond to the total vaccine requirement minus any stock of non-expired vaccine available to the country. This quantity should include both the quantity requested from WHO and the quantity requested from other sources.

^c Most vaccines are administered using bifurcated needles.

❖ Requested from WHO

- Total number of doses requested from WHO:
- Total number of bifurcated needles requested from WHO: *
- Total number of syringes requested from WHO: *
- Requested date of delivery:

* The needles used for smallpox vaccination differ by type of vaccine. Please indicate the quantity of both bifurcated needles and syringes.

Note: The vaccine doses supplied by WHO are bundled with reconstitution diluent. Safety boxes may be provided by WHO or by the requesting country.

❖ Requested from other sources (bilateral agreement/donation)

- Vaccine requested from – indicate source(s):
- Total number of requested doses:
- Total number of requested bifurcated needles: *
- Total number of requested syringes: *
- Specifications of the vaccine requested from other sources:
- Total number of doses pledged by other sources:
- Expected delivery date(s) of doses from other sources:
- Total number of doses already received from other sources:
- Total number of safety boxes requested:

* The needles used for smallpox vaccination differ by type of vaccine. Please indicate the quantity of both bifurcated needles and syringes.

Planned date for the start of the vaccination campaign in the Country (dd/mm/yyyy):.....

Estimated duration of the campaign:.....

1.1.10 Outline of smallpox vaccination plan

The smallpox vaccination plan should include the following information:

1. Introduction, rationale and objectives

- * Brief description/analysis of country's smallpox situation
- * Regional and district context

2. Profile of affected area and target population group

- * Affected population profile: characteristics (e.g. size, concentration, displaced or refugee populations) and risk factors (e.g. latest vaccination, population movements, border regions)
- * Considerations for vulnerable populations, e.g. HIV+ or other immunosuppressed populations
- * Targeted area and population

3. Vaccine needs

- * Target vaccine coverage
- * Buffer stock and justification/rationale
- * Calculation of vaccine needs

A. Organization and coordination

- * National and local epidemic committee: composition, organization, role and involvement
- * Partners involved, their roles and capacities at local or international level

B. Selection of vaccination sites and priority areas

- * Vaccination site (in accordance with section 2)
- * Fixed sites vs. mobile posts
- * Expected number of vaccinations per day and per team (fixed and mobile sites)

C. Social mobilization

- * National, regional, local information campaign in national and local languages

D. Micro-plan

1) Organization of the campaign

- * Composition and number of vaccination teams (according to estimated vaccination performance)
- * Vaccination campaign timeline per sub-district (including start date and duration per sub-district)
- * Supervision (including composition of the team and organization)
- * Training of vaccination and supervisors' teams

2) Logistics

- * Cold chain at regional, district and vaccination post level
- * Local purchases, if any, needs identified (cotton, plastic bags, stationery, vaccination cards, etc.)
- * Local transportation (national, regional and partners)
- * Waste management: strategy, means, human resources

1.1.11 Request for technical and operational costs support

WHO may provide logistical and technical support for the vaccination campaign when delivering the vaccines and auxiliary supplies. Please specify if you need additional technical support and what type (surveillance, laboratory, strategy, evaluation, etc.). WHO does not undertake to actually provide such support.

Please indicate if you need to receive support for operational costs. If yes, please provide a detailed budget of operational costs for the implementation of the vaccination campaign (per diem for staff, local transportation of vaccines and materials, training of health staff, social mobilization, cold chain, waste management, evaluation of vaccination coverage, etc.) by filling out the table below. WHO does not undertake to actually provide such support.

Table 5. Estimation of operational costs

Human resources	
Training	
Local transport for vaccines and injection supplies	
Cold chain	
Waste management	
Safety boxes	
Vaccination cards	
Evaluation of response/vaccine coverage	
Other	
Total costs	

1.1.12 Shipment information

Please provide the name and details of the consignee to whom the vaccine is to be shipped.

Consignee in the recipient country	
Consignee organization	
Contact name	
Phone	
Fax	
Email	
Address	
P.O. Box	
Town	
Country	

Please provide any information regarding packing material and labelling and/or standards for packing infectious material and non-infectious material that are in effect in the country:

--

1.1.13 Information package

Annex 1.1, sections 1.1.1–1.1.14, (“request form”) is accompanied by information that the recipient country agrees to read and/or complete and includes:

Annex 1.2 A feedback report on the vaccination campaign to be completed by the recipient country and submitted to WHO after the vaccination campaign is completed

Annex 4. An information package about smallpox vaccine types, including literature on the risks of using the vaccine and the possible side effects. This information is being provided to assist governments to become more knowledgeable about the vaccines in the WHO SVES, but is by no means exhaustive, and does not relieve the government of its obligation to gain full knowledge as provided above.

1.1.14 Signature

On behalf of the Government of [Country]:

1. I acknowledge that I have read all the information provided above and that to the extent of my knowledge all the information provided by the Government to WHO is truthful and accurate;
2. I request vaccine from the WHO SVES, as described in this request form, and confirm that such vaccine has been authorized by the Government of [Country] for use in the control of a confirmed outbreak of smallpox in [Country];
3. I confirm that the Government of [Country] will provide the vaccine received from the WHO SVES only to persons in the Country who have been targeted in accordance with the Country's smallpox outbreak response plan; and
4. I irrevocably and unconditionally accept and agree to the above terms and conditions.

Signed:

Name:

Title:

Date:

1.2 Feedback report on vaccination campaign

1. Administrative vaccination coverage per district/locality – please refer to the table below

Region name	District name	No. of cases confirmed by WHO reference laboratory	Date of laboratory confirmation	Week of vaccination	Target population	Total target population vaccinated	Wastage

2. Main challenges encountered during the campaign (e.g. wastage, transportation, supervision, training, micro-planning, financing, buildings, cold chain, stock management, social mobilization)

--

3. Date of vaccine arrival

District	Date of arrival in district	Date of start of vaccination	Number of doses of vaccine remaining

4. Use of vaccination cards in case of vaccination coverage survey plan (please tick box)

Yes ☐

No ☐

5. Availability of independent coverage survey results (please tick box)

Yes ☐

No ☐

Not Planned ☐

If answer is yes, please specify the method used to measure coverage and results by district in the table below:

Region name	District name	Target population	Number of vaccinated	Coverage rate by cards	Card retention (%)

2. Standard operating procedure for the release and delivery of smallpox vaccine from the donor to WHO

1. Purpose

Several WHO Member States have pledged donations to the WHO of smallpox vaccine from their respective national stockpiles. This document provides a SOP for current or potential donors²⁶ and the WHO for the release, transportation and delivery of the smallpox vaccine and other ancillary items that have been pledged or may be pledged to WHO.

This is intended to align with the operational framework for the WHO SVES for emergency response to an outbreak of smallpox. It is not intended to be, to imply, or to be construed as a legally binding agreement between the donor country and WHO. The document is intended to provide step-by-step guidance for the logistics involved in the release and delivery of pledged smallpox vaccine. Any release and delivery decisions will be made on a case-by-case basis. Deviations from the steps stated in the document may be warranted in any particular case.

2. Introduction

Smallpox, a highly transmissible and infectious disease caused by the variola virus, was eradicated as a human disease in the late 1970s through a successful WHO global vaccination campaign. Since then, WHO Member States have expressed concerns about the potential hazard of smallpox outbreaks, either from the use of variola virus as a biological weapon or from an accidental laboratory release. In fact, the IHR (2005)²⁷ state that one single case of smallpox is unusual or unexpected and may have a serious public-health impact and thus shall be notified to the World Health Organization (WHO) as a potential PHEIC.

In 1979, the World Health Assembly formally recognized the need to maintain an emergency reserve of smallpox vaccine and accepted a set of formal responsibilities for maintaining capacity and expertise to respond to a re-emergence of smallpox in the post-eradication era. The WHO SVES permits the immediate, initial control of outbreaks, while allowing time for the distribution of vaccine from alternative sources.

The WHO SVES has two components:

1. WHO physical smallpox stockpile:
 - a. WHO maintains this smallpox vaccine stockpile under its immediate control and management;
 - b. If needed, it is available for immediate use;
2. smallpox vaccine stocks held by donors that have been pledged to the WHO:
 - a. donors maintain their pledged smallpox vaccine, either in their national stockpiles or at the smallpox manufacturer;
 - b. if needed, Member States will release the pledged vaccines to WHO, upon request.

²⁶ Donors may include WHO Member States or other entities that pledge vaccine to the WHO.

²⁷ http://apps.who.int/iris/bitstream/10665/43883/1/9789241580410_eng.pdf (accessed 5 October 2017).

This SOP provides guidance for the request, release, logistics, transport and delivery of the smallpox vaccine stocks held by donors that have been pledged to WHO. The steps outlined in this document are subject to change according to ongoing multilateral efforts to address logistical, regulatory and legal barriers to the international deployment of medical countermeasures during emergencies and may also be adjusted on a case-by-case basis depending on the situation during which it is applied.

3. Standard operating procedure

WHO's request for the release of the pledged smallpox vaccine

1. The WHO Director-General²⁸ [requests] that the donor(s) release(s) pledged smallpox vaccine by contacting each through the following communication channels:
 - a. Their International Health Regulations (IHR) (2005) National Focal Point (NFP); and/or
 - b. Other agreed points of contacts (see Annex 2.1).
2. The Director-General [requests] assistance in the form of a letter asking for release of the vaccine. This request [specifies]:
 - a. the intended recipient Member State(s) of the requested vaccine;
 - b. the quantity of doses of smallpox vaccine²⁹ requested (the amount of ancillary supplies required will be calculated based upon the number of vaccine doses).

The request also [states] intentions that:

- c. the Director-General and the donor mutually [agree] upon and confirm the following AFTER the Director-General receives signed request form(s) from the recipient Member State(s):
 - i. date and the time that the vaccine would be delivered;
 - ii. point of delivery (see Annex 2.1);
 - iii. entity that would accept the vaccine at the point of delivery – the accepting entity could be WHO or a mutually agreed upon organization acting on behalf of WHO.

Donor reply to WHO request

3. After receiving the request for release of the pledged smallpox vaccine, the donor:
 - a. immediately [acknowledges] receipt of the request to the Director-General through the communications channels noted under 1 above;
 - b. within 48 hours, [advises] the Director-General of the donor's intention to supply the vaccine.

Preparations for the release of the vaccine

4. Upon positive reply from the donor, the Director General:

²⁸ From this point forward, "the Director-General of the WHO" will be referred to as "the Director-General" which would include any individual delegated by the Director-General of WHO.

²⁹ From this point forward, "vaccine" will refer to the smallpox vaccine and any ancillary items that WHO shall be providing.

- a. [Acknowledges] receipt of the donor's intention to proceed with the donation and requests that the donor begins preparations to pack and deliver the vaccine BUT does not actually ship the vaccine until notified by the Director-General to do so;
- b. provides the donor the point of contact information for:
 - i. a WHO staff member (or designee) to coordinate logistics with the donor;
 - ii. a WHO staff member or WHO-designated representative (forwarding agent) to be onsite at the point of delivery (see Annex 2.1) to accept delivery and transfer ownership of the vaccine;
- c. sends the official request form to the recipient country(ies) for signature if the form has not already been returned to the WHO.

Request for dispatch of the vaccine

- 5. After the recipient country(ies) [sign(s) and return(s)] the request form to WHO, the Director-General:
 - a. [Informs] the donor that the recipient country(ies) has/have signed the request form;
 - b. if the donor has chosen to use the optional Smallpox Vaccine Donation and Transfer of Title Agreement (see Annex 2.1),³⁰ the Director-General [sends] a counter-signed copy of that document to the donor at this time;
 - c. [Reconfirms] with the donor the (see Annex 2.1):
 - i. delivery date and time;
 - ii. point of delivery;
 - iii. entity to accept the vaccine at the point of delivery, including contact details.
 - d. [Retains] the original request form(s) signed by the recipient country(ies) and sends two copies of the request form(s) to the donor – one copy is retained by the donor, the other sent with the vaccine;
 - e. [Requests] that the donor packs, releases and delivers the vaccine to the agreed point of delivery on the date and the time of day agreed.

Packing the vaccine

- 6. The donor:
 - a. [Packs] the vaccine for transit using material that maintains and controls the appropriate temperature for transit and other environmental conditions set by the manufacturer and/or the donor;

³⁰ If a donor country decides not to use the template agreement in Annex 2.1, the donation and transfer of title of smallpox vaccine and ancillary supplies shall exclusively be subject to the operational framework, including the terms and conditions contained in the vaccine request form and the pledge letter from the donor country to WHO for the WHO virtual stockpile.

- b. [Adheres] to International Civil Aviation Organization Regulations (ICAO), International Air Transport Association (IATA) and “WHO Guidelines on the International Packaging and Shipping of Vaccines”;³¹
- c. [Ensures] that any necessary licenses required by the donor in order to export vaccine are met prior to deployment;
- d. [Ensures] that necessary documentation is included with the shipment, as advised by WHO. This includes a copy of the request form with the vaccine for each recipient country (see Annex 2.5 for a list of potential documents to accompany the delivery).

Delivery and transfer of title

7. The donor [dispatches] the vaccine in close coordination with the WHO staff member (or designee) as referred to under point 4 b.i. coordinating deployment logistics. In the case of a delay in shipment, parties must inform each other as soon as possible.

8. The vaccine [transfers] to the WHO at the time of delivery at the agreed delivery destination, as evidenced by the airway bill signed for WHO by its designated forwarding agent or the smallpox vaccine delivery document (see Annex 2.7) signed by a duly authorized representative of WHO or WHO’s designated forwarding agent in the recipient country as referred to under point 4 b.ii.

9. The WHO staff member, or a WHO-designated representative, [is] on site at the mutually agreed upon point of delivery to:

- a. accept delivery of the vaccine after the amount and condition of the vaccine is verified;
- b. at the point of delivery, retrieve the temperature monitoring device from the consignment and return the vaccine arrival form (VAR) to the donor country, as necessary.

10. Immediately upon receipt, the WHO representative [informs] the Director-General and the donor that the material has been successfully delivered (see Annex 2.7).

11. WHO and the donor, as available and feasible, [share] information about the smallpox outbreak and any vaccination results on a routine basis, including:

- a. information about the outbreak, including case counts, as per the IHR (2005);³²
- b. uptake and results of the use of the vaccine, including the incidence of adverse events in the recipient country.

³¹ http://apps.who.int/iris/bitstream/10665/69368/1/WHO_IVB_05.23_eng.pdf (accessed 1 October 2017).

³² <http://www.who.int/ihr/9789241596664/en/> (accessed 5 October 2017).

2.1 Lines of communication/point of delivery

(Completed by [name of donor])

Please delete non-relevant categories as necessary:

1. **International Health Regulations (IHR) (2005) (1) National Focal Point (NFP) – To be completed by WHO Member States; IHR (2005) NFP must be available 24/7 in accordance with the IHR (2005)**

IHR (2005) National Focal Point	[NFP name]
P.O. Box	[Please add]
Street address	[Please add]
City	[Please add]
State / province	[Please add]
Postal code	[Please add]
Country	[Please add]
Fax	[Please add]
Telephone	[Please add]
Mobile telephone	[Please add]
Email address	[Please add]
Other contact information	[Please add]

2. **Emergency contact for other donors – contact must be available 24/7**

Name	[Name]
P.O. Box	[Please add]
Street address	[Please add]
City	[Please add]
State / province	[Please add]
Postal code	[Please add]
Country	[Please add]
Fax	[Please add]
Telephone	[Please add]
Mobile telephone	[Please add]
Email address	[Please add]
Other contact information	[Please add]

3. **Emergency contacts for the World Health Organization**

The World Health Organization maintains the Strategic Health Operations Centre (SHOC) within the Headquarters in Geneva. The SHOC provides a single point of coordination for response to acute public health crises including infectious disease outbreaks, natural disasters and chemical emergencies. It is the hub of alert and response operations, combining the latest information and communications technologies to support field operations and facilitate collaboration with Member States and technical partners in external networks such as the Global Outbreak Alert and Response Network (GOARN).

Name	Strategic Health Operations Centre, Outbreak Duty Officer
Address	Avenue Appia 20, 1211 Geneva 27, Switzerland
Fax	+ 41 22 791 44 88
Telephone	+41 22 791 5533
Mobile telephone	+41 791 5533 (mobile)
Email addresses	smallpox@who.int outbreak@who.int

4. **Point of delivery**

[Please add the name and address of the international airport in the donor's country to which the vaccine will be delivered for pick-up by the WHO.]

2.2 Pledged smallpox vaccine

(Completed by [name of donor])

[Name of donor] has pledged [number of doses] doses of smallpox vaccine to the WHO Virtual Smallpox Vaccine Emergency Stockpile.

Description of the pledged smallpox vaccine(s)

[Please add]

Description of diluent³³ for smallpox vaccine (for each vaccine type)

[Please add]

Smallpox vaccine details

Vaccine manufacturing company	[Please add the name and, if necessary, the successor in title]
Product name	[Please add]
Licensure status in [donor country]	[Licensed/unlicensed]
Storage conditions for the vaccine	[Please add]
Special instructions for each type of vaccine (i.e. unfrozen vaccine; reconstituted vaccine, etc.)	[Please add]
Number of doses in each vaccine ampoule	[Please add]
Vaccination technique	[Please add]
Packaging composition (one pallet)	<ul style="list-style-type: none">• [Number of cartons per pallet]• [Number of boxes per carton]
Cold chain packaging	<p>Cool box:</p> <ul style="list-style-type: none">• [Volume]• [Total weight]• [Number of ice packs per cool box]• [Number of vaccines] <p>Thermal pallet shipper:</p> <ul style="list-style-type: none">• [Volume]• [Weight]• [Number of vaccines]
Transport storage temperature	[Please add]

Diluent details (if necessary)

Storage conditions for the diluent	[Please add]
Volume of diluent per ampoule	[Please add]
Capacity of syringe needed to reconstitute the vaccine	[Please add]
Packaging composition (one pallet)	<ul style="list-style-type: none">• [Number of cartons per pallet]• [Number of box per carton]

³³ Many documents refer to diluent for reconstitution. In this document, the words "solvent" and "diluent" refer to the liquid that is necessary to reconstitute the freeze-dried smallpox vaccine.

	<ul style="list-style-type: none"> • [Weight (pallet, carton)] • [Volume (pallet, carton)]
Transport and storage temperature	[Please add]

Date of manufacture and expiration date for the pledged smallpox vaccine

[Donor name] has pledged the smallpox vaccine [please add the name of the vaccine], which has the lot numbers [please add the lot numbers]. The vaccine ampoules [have/do not have] a label that provides the date of manufacture or the expiration dates.

Lot	Date of manufacture (spell out month)	Expiration date (spell out month)
[Please add]	[Please add]	[Please add]

Certificate of analysis for the pledged smallpox vaccine – Please provide the details below OR attach the certification of analysis to this document

Lot	Certificate of Analysis (spell out month)			
	Original analysis	Reanalysis	Reanalysis	Reanalysis

The last testing of the vaccine was in [please add] and the date of the report was [please add]. The titre of all tested charges was higher than [please add].

Copies of certificates of analysis for the pledged smallpox vaccine

[Please add]

Copies of certificates of origin for the pledged smallpox vaccine

[Please add]

Certificate of release for the pledged smallpox vaccine - please provide the details below OR attach the certification of release to this document

[Please add]

Lot	Date of certificate of release (spell out month)

Copies of certificates of release for the pledged smallpox vaccine

[Please add]

Copy of product information (package insert) for the pledged smallpox vaccine, if available

[Please add]

2.3 Ancillary items

(Completed by [name of donor])

Ancillary items include all the material needed to conduct a successful vaccination of the pledged vaccine. Donors may provide none, some or all of the ancillary items noted below:

- sterile auto-disable syringes with attached sterile needle to transfer the solvent liquid from the solvent ampoule to the smallpox vaccine ampoule or for vaccination by injection;
- sterile bifurcated needles for vaccination;
- files to cut vaccine ampoules;
- stands to hold the vaccine ampoules and the diluent ampoules; and/or
- materials for medical waste disposal.

[Donor name] has stated that as of [add date] they plan to include the following ancillary items along with the vaccine:

[Please add included ancillary items and quantities]

Please note that needles (either bifurcated or AD syringes) form part of the pledge

Sterile auto-disable syringe with attached needle

[If pledged, please add relevant instructions or information]

Sterile bifurcated needles

[If pledged, please add relevant instructions or information. This may include packaging information and certification/ marketing authorization.]

Files to cut vaccine ampoules

[If pledged, please add relevant instructions or information]

Stands to hold the vaccine ampoules and the diluent ampoule

[If pledged, please add relevant instructions or information]

Medical waste sacs, safety boxes, or other like sharps containers

2.4 Packing the vaccine

(Completed by [name of donor])

[Donor name] would pack the vaccine and ancillary supplies using appropriate packing materials and labelling and standards for packing infectious material and non-infectious material as specified in the current acceptable international guidelines and any specifications of [Please add the WHO Member State].

Since the delivered smallpox vaccine is “infectious material”³⁴ and considered according to the ICAO regulations and IATA guidelines “biological substance”,³⁵ it is necessary to pack smallpox vaccine following the standards for packing infectious material. (s. IATA 3.6.2.3 or ADR 2.2.62.1.3 and 2.2.62.1.9)

For further information regarding smallpox vaccine, packing, and transport of infectious substances, please consult:

- World Health Organization, Epidemic and Pandemic Alert and Response “Guidance on regulations for the Transport of Infectious Substances”, applicable as from 1 January 2009, WHO/HSE/EPR/2008.10
- United States Centers for Disease Control and Prevention, Atlanta, Georgia, “Guidelines for Smallpox Vaccine, packing and shipping”
<http://www.bt.cdc.gov/agent/smallpox/vaccination/pdf/packing-shipping.pdf>

Packing pledged smallpox vaccine

[Please add]

Packing diluent for pledged smallpox vaccine

[Please add]

Details regarding packing of pledged smallpox vaccine, diluent for pledged smallpox vaccine, bifurcated needles, etc.

[Please add details or attach packaging configuration]

Article	Basic information	Smallest carton	Total transport data

³⁴ For the purposes of transport, infectious substances are defined as substances that are known or are reasonably expected to contain pathogens. Pathogens are defined as microorganisms (including bacteria, viruses, rickettsia, parasites, fungi) and other agents such as prions, which can cause disease in humans or animals.

³⁵ Biological products are those products derived from living organisms that are manufactured and distributed in accordance with the requirements of appropriate national authorities, which may have special licensing requirements, and are used either for prevention, treatment, or diagnosis of disease in humans or animals, or for development, experimental or investigational purposes related thereto. They include, but are not limited to, finished or unfinished products such as vaccines.

Article	Basic information	Smallest carton	Total transport data

2.5 Accompanying documents

(Completed by [name of donor])

[Donor name] intends to supply all the documents that are required for the international shipment of vaccines and ancillary supplies.

It is expected that the delivery will include the following:

No.	Item	Comments	Source
1	Air waybill (3 pages)	<p>Serves as a receipt of cargo and contract of carriage.</p> <p>Serves as a receipt of cargo and contract of carriage, handling, dispatch, and delivery of the shipment to the consignee</p> <p>The original pages 1 and 2 are handed over to the recipient authorities upon arrival. Page 1 is kept by the recipient and page 2 is signed by the consignee and returned to the consignor</p> <p>Page 3, signed by the transport company stays with the donor to be matched against returned copy (page 2) to confirm delivery</p>	Source: Air carrier or authorized agent
2	Packing list	<p>This list should be very detailed:</p> <ol style="list-style-type: none">1. total weight of shipment2. total volume of shipment3. detailed list of contents4. number of cold boxes with detailed instructions about the temperature that is maintained in order to preserve the cold chain.5. number of cartons that can be kept at room temperature, 20°C to 30° C (if not this range, please specify the required range)6. For the donating country: the name, address and other necessary contact details of the person or agency responsible for sending the shipment7. For the recipient country(ies): the name of the consignee, address and other necessary contact details of the person or agency responsible for receiving the shipment.	Donor/freight forwarder

No.	Item	Comments	Source
3	Proforma invoice	<p>The invoice should contain:</p> <ol style="list-style-type: none"> 1. for the donor: the name, address, contact details; 2. for the recipient country(ies): the name of the consignee, address, contact details; 3. the statement, “[not for commercial purposes/donation not for resale]” or another statement normally used in the donor country; 4. a replacement value for the donated vaccine. 	Freight forwarder
4	Product information for the smallpox vaccine	<ol style="list-style-type: none"> 1. Name, address and contact information of the pharmaceutical company that manufactured the vaccine 2. Requested storage conditions 3. Special precaution or handling instructions 4. Vaccine vial volume 5. Number of doses in a vial 6. Vaccination technique 7. Date of manufacture expiration date and batch number(s) 	Manufacturer (if in existence)
5	Photocopy of the original certificate of release for each lot of smallpox vaccine, if available	<p>This certificate of release should be the original certificate.</p> <p>Each lot of vaccine should have a separate certificate of release</p> <p>The certificate may be issued by the government (the national regulatory authority) or another acceptable agency</p>	Manufacturer (if in existence)
6	Photocopy of the original certificate of analysis for each lot of smallpox vaccine, if available	<p>The certificate of analysis should be the original certificate</p> <p>Each lot of vaccine should have a separate certificate of analysis</p> <p>Normally, the manufacturer issues the certificate of analysis</p>	Manufacturer (if in existence)

No.	Item	Comments	Source
7	Certificate of analysis for each lot of smallpox vaccine	This certificate of analysis should have been issued within the past five years Each lot of vaccine should have a separate certificate of analysis	Manufacturer (if in existence)
8	Photocopy of the certificate of origin issued by the manufacturer or another acceptable agency (i.e. Chamber of Commerce)	This may or may not be necessary, depending on the donor country and the recipient country(ies)	Manufacturer (if in existence)
9	Photocopy of the export permit or declaration for each lot of vaccine	This may or may not be necessary, depending on the donor country	Donor
10	Photocopy of certificate of donation	Required for importation into country and to assist with import tax issues, needs to state that vaccines are a donation with US\$ 0 (zero) value	WHO
11	Photocopy of the import permit or declaration for each lot of vaccine	If required, WHO will supply this document so that it can be included with the documents that accompany the pledged vaccine during transit	WHO/recipient country
12	One copy of the signed request form including the smallpox disclaimer for the donated smallpox vaccine	The recipient country will be required to complete and sign the request form including the terms and conditions before the vaccine leaves the stockpile One copy of the signed request form, including the terms and conditions, should accompany the vaccine from the time the vaccine leaves the stockpile to the time that the vaccine arrives in the receiving country	WHO
13	WHO donation letter	Issued by WHO headquarters to facilitate customs clearance	WHO
14	Any other document that is normally required for transporting vaccine within the donor country or is normally required for transporting vaccine internationally	ND	ND

ND: not determined.

2.6 Smallpox donation and transfer of title document

* Donor countries may choose not to utilize this template agreement. If a donor country decides not to use this template agreement, the donation and transfer of title of smallpox vaccine and ancillary supplies shall exclusively be subject to the operational framework, including the terms and conditions contained in the vaccine request form and the pledge letter from the donor country to WHO for the WHO virtual stockpile.

The donor country and WHO will execute this agreement, upon election by the donor, to govern the transfer of title of any smallpox vaccine and ancillary supplies described in Appendix I ("the vaccine") AFTER an identified recipient has submitted a signed vaccine request form (see Annex 1.1) to WHO and WHO has made a formal request to the donor to release pledged vaccine under the procedures described in document 1.

Smallpox Vaccine (Donation and) Transfer of Title Agreement

Donation and transfer of title will be made effective by and between [Donor] and the World Health Organization ("WHO") or its designated representative (collectively, "the parties") for further distribution in accordance with: (1) the terms of this Agreement; (2) [version, date of the operational framework for the deployment of WHO's Smallpox Vaccine Emergency Stockpile in response to a smallpox event, including the terms and conditions contained in the signed Request Form for Member States to Obtain Emergency Smallpox Vaccine from the WHO Stockpile ("the Vaccine Request Form")]; and (3) the [date] [pledge/letter] from [Donor] to WHO for the WHO virtual stockpile. The following terms and conditions apply to the donation and transfer of title of smallpox vaccine and ancillary supplies described in (Appendix I) ("the vaccine") from [Donor] to WHO. This document is a contract and does not give rise to obligations under international law.

[Donor] agrees to donate and transfer title to the above-referenced vaccine to WHO, and WHO agrees to accept title to the vaccine for the sole purpose of responding to a smallpox outbreak in _____ [Country/Countries] in accordance with the terms of this Agreement. [Donor] will – at its cost – ship the vaccine in accordance with directions from WHO to a delivery destination and at a date and time, so designated by WHO and accepted by [Donor] (acceptance not to be unreasonably withheld). Unless otherwise agreed by WHO and [Donor], the delivery destination will be [an international airport in the country of Donor or another international airport requiring further air transport by WHO's designated forwarding agent]³⁶ [an international airport in the Recipient Country]³⁷. Title to the vaccine will transfer from [Donor] to WHO at the time of delivery at the agreed delivery destination, as evidenced by [the airway bill signed for WHO by its designated forwarding agent] or [the Smallpox Vaccine Delivery Document signed by a duly authorized representative of WHO or WHO's designated forwarding agent in the recipient

³⁶ If the vaccine quantity is delivered at an international airport in the country of the donor (FCA Incoterms 2010) or another international airport requiring further air transport by WHO's designated forwarding agent (FCA Incoterms 2010), delivery to WHO will be evidenced by the airway bill dated and signed for WHO by its designated forwarding agent.

³⁷ If on the other hand, the vaccine quantity is delivered at an international airport in the recipient country (CIP Incoterms 2010), delivery to WHO will be evidenced by the Smallpox Vaccine Delivery Document.

country]³⁸ as further described in the SOP for the Release and Delivery of Smallpox Vaccine from the Donor to the World Health Organization.

In consideration of the promised donation, delivery, and transfer of title, WHO agrees, upon signature of this document, as described below.

1. Once title to the vaccine has transferred to WHO, WHO will require its forwarding agent and/or any other party delivering the vaccine for WHO to the designated recipient (if any):
 - (a) to ensure that adequate procedures are followed to protect the physical security of the vaccine, and that the WHO *Guidelines on international packaging and shipping of vaccines*³⁹ are followed, in respect of the storage, handling and transportation of the vaccine by this forwarding agent or other party;
 - (b) to comply with all applicable laws, regulations, and orders related to the storage and shipment of the vaccine, up to its delivery to the designated recipient.
2. Prior to shipment of the vaccine by [Donor], WHO will require the recipient to complete and sign the Vaccine Request Form. Pursuant to this Vaccine Request Form, the recipient will agree that neither WHO nor any (direct or indirect) supplier of the vaccine quantity to WHO or to the Government (including but not limited to any donor country, manufacturer or distributor of the vaccine) shall be responsible for any damage to or loss of vaccine during its storage, handling or transportation up to the delivery of the vaccine quantity to the Government at the agreed delivery destination.
3. In accordance with the terms and conditions contained in the Vaccine Request Form, the vaccine will be supplied “as is”, without any warranties or representations whatsoever, whether expressed or implied, including, but expressly not limited to, any implied warranties as to the vaccine’s fitness for a particular purpose or use, or as to its safety, efficacy, or quality in any respect.
4. Pursuant to the Vaccine Request Form, the recipient shall be solely responsible for any and all liability arising from the use of the vaccine. Specifically, the recipient shall be held to indemnify and hold harmless [Donor] and WHO, as well as their officers, employees and agents, for any and all claims and liabilities, including reasonable costs and expenses, of any kind arising from, as a result of, or in connection with the supply, distribution and/or use of the vaccine in the recipient’s country. Neither [Donor] nor WHO agrees to release, hold harmless, or indemnify the other party from liability that may arise from or relate to this transaction.

The undersigned represents and warrants that he/she has the right, power, legal capacity, and appropriate authority to execute this donation and title transfer on behalf of the party for which he/she signs.

³⁸ WHO will inform the donor of the identity of its designated forwarding agent.

³⁹ http://apps.who.int/iris/bitstream/10665/69368/1/WHO_IVB_05.23_eng.pdf (accessed 14 November 2017).

[Agreed and accepted for Donor]

[Name, signature, and title]
[Date]

Agreed and accepted for WHO

[Name, signature, and title]
[Date]

2.7 Smallpox vaccine delivery document

* Donor countries may choose not to utilize such an agreement.

*If the vaccine quantity is delivered at an international airport in the recipient country, the **donor** and **WHO** will, upon election by the donor, **execute this document** to evidence the delivery of (and transfer of title to and risk of loss of and damage to) smallpox vaccine and ancillary supplies described in Appendix I (“the vaccine”) from the donor to WHO. This will occur **AFTER** an identified recipient has submitted a signed Vaccine Request Form (see Annex 1.1) to WHO, WHO has made a formal request to the donor to release pledged vaccine under the procedures described in title, version, date of this SOP, and the donor and WHO have executed a Smallpox Vaccine Donation and Transfer of Title Agreement.*

Smallpox Vaccine Delivery Document

Upon signature below, WHO accepts delivery of smallpox vaccine and ancillary supplies described in Appendix I (“the vaccine”) in accordance with the terms of the Smallpox Vaccine Donation and Transfer of Title Agreement between donor and WHO of ...[date].

The undersigned represents and warrants that he/she is a duly authorized representative of WHO or WHO’s designated forwarding agent in the recipient country and as such, has the right and appropriate authority to accept delivery of the vaccine on behalf of the party for which he/she signs.

Agreed and accepted for the World Health Organization

[Name, signature, and title]

[Date]

2.8 Logistical requirements

Information to be requested from donors

Vaccines:

- packaging composition for one non-breakable box. This refers to the minimum unit packing (i.e. carton box of 50 vials of 20 doses) then similar information per pallet:
 - number of boxes per carton
 - number of cartons per pallet
 - specify if pallets are of European or United States origin
 - plastic or wooden; if wooden, need the fumigation certificate;
- cold chain packaging:
 - cool box:
 - volume
 - total weight
 - number of ice packs per cool box
 - number of vaccines;
 - thermal pallet shipper:
 - volume
 - weight
 - number of vaccines;
- transport storage temperature required:
 - specify temperature range.

Diluents:

- packaging composition for one pallet:
 - number of boxes per carton
 - weight (pallet, carton)
 - volume (pallet, carton)
 - number of cartons per pallet;
- transport and storage temperature.

Ancillary items (proportional):

- bifurcated needles and/or auto-disable syringes
- safety boxes or other waste containers
- other related material if applicable (cap openers, container support, anti-tumbling devices etc.).

Location where donation will be handed over to WHO:

- airport(s)
- other.

Donor country other logistics issues:

- name and contacts of logistics focal point
- list of countries under embargo, if any.

3. Communication challenges with international donation and deployment of smallpox vaccine

Introduction

Extensive risk communication research data show that being transparent with the public about difficult situations and unknown factors actually strengthens their trust in an organization and enhances its public credibility, especially if further uncertainty or bad news is expected. To this end, transparency in the actions and words of authorities regarding the importance and use of medical interventions, throughout the duration of the health emergency is absolutely critical to public confidence and national cohesion. Only when such trust is established will the public follow the advice they need regarding the smallpox vaccine.

Purpose

The communication challenges surrounding the international sharing of medical interventions (vaccines, pharmaceuticals, etc.) are broad and complex and can vary in their degree and impact based on an entity's role (e.g. donor, recipient, third party) in the sharing process. The purpose of this communication plan template is to serve as a guidance document, upon which more specific, tailored plans may be developed that will support an entity's communication strategy regarding the donation to and/or receipt from others of medical interventions during a public health emergency of international concern.

Background

Smallpox vaccines are grouped into "categories" based on when they were first developed and their methods of production. The WHO Smallpox Vaccine Emergency Stockpile currently contains a diverse mix of smallpox vaccines, including vaccines of different generations, which comprise different formulations and may exhibit different sets of side effects. Furthermore, smallpox vaccine stockpiles maintained by selected countries for domestic use may also vary in generation and formulation.

Given these variations in smallpox vaccines, significant communications challenges may emerge when deploying vaccines internationally. What follows is a summary of the most salient issues that should be considered when developing a successful communications response.

Key considerations

1. "Good" vs. "bad" vaccine comparisons

It is likely that, given the multiple vaccine formulations, some will be unlicensed in some countries. This is likely to lead to the notion that vaccine A, which is licensed, is better tolerated than vaccine B, which is unlicensed. As such, the public and the media will probably perceive and label vaccine A as the "better" or "good" vaccine, and vaccine B may be characterized as the "bad" or "ineffective" vaccine.

2. Emergency use of unlicensed vaccine

It is likely that, in some countries, the emergency approval of an unlicensed vaccine will require the word(s) “unlicensed” and/or “experimental” to be included on package labelling. The public will not understand the principles behind emergency use authorization, thus vaccine B could potentially be characterized as dangerous and those given vaccine B might be considered experimental guinea pigs.

3. Scientific vs. political decision-making

When making their decisions, national governments face the challenge of balancing the scientific/technical risks and benefits of various vaccines against the political risks of which vaccine(s) to donate or accept, and how much. Donating vaccine A (“good” vaccine) could be more scientifically sound, with greater potential for reducing illness and death in the outbreak location than by donating vaccine B (“bad” or “experimental” vaccine). There will also be political risks when deciding which vaccine to donate. Similarly, nations seeking vaccine will face similar dilemmas if accepting vaccines that may be different from those donated elsewhere.

4. Additional preventative/containment measures

National governments will face the reality that other available response measures (such as border closures, vaccinia immunoglobulin, antivirals, quarantine, isolation, cancellation of large-scale public events, masks, etc.) may be employed in some capacity, and may affect decisions about the quantities of vaccine being considered for donation or receipt.

5. Vaccination refusal

Vaccine refusal, vaccine hesitancy, along with other cultural and societal beliefs and myths, may emerge in an international donation scenario, leading to significant challenges for vaccination campaigns.

6. National government decision to donate

The fundamental question of whether or not to donate also brings many communication challenges.

If the decision to donate is **yes**

The national population may be critical of the decision to give away some of their protection. Effectively explaining the principles around prevention and containment, along with how the vaccine works will be critical to this argument.

Even if vaccine is donated, the amount donated could also raise challenges. The international community may say that it is not enough while the donor country population could say it is too much – “we want to help, but not with that much vaccine.”

If the decision to donate is **no**

The international reaction may generate criticism that the “privileged” countries are being selfish and that they consider the affected populations expendable. It is also quite possible that a sizeable segment of the donor country population would be critical of their own government for refusing to help out those who are less fortunate.

If there is **no decision**

One possible course of action would be inaction – a decision to make no decision. If the outbreak then expands beyond the point of potential containment, there would be significant criticism that the rich countries of the world stood by and let the outbreak happen, refusing to help others in the world.

7 . Listing to concerns

In addition to having these potential situations and issues in mind, risk communication plans must also involve actively listening to public concerns and misinformation. Depending on the context of the country, social media and medimedia monitoring, feedback from key stakeholders, community representation and focus groups, as well as mini knowledge, attitude and practice surveys can be used to listen actively. The findings of any mix of the methods should be routinely integrated in a response plan for risk communication.

4. Summary table of vaccines physically stockpiled or pledged to the WHO Smallpox Vaccine Emergency Stockpile (SVES)

Information on smallpox vaccines is crucial to enable donor countries and WHO to communicate decisions and information on which types of vaccines will be deployed to international partners. It is equally essential to enable potential recipients to address the challenges of communicating their decision to vaccinate their populations with any of the smallpox vaccines.

First-generation vaccines are the most abundantly available/stockpiled smallpox vaccines and form the bulk of vaccine available to respond to a smallpox outbreak, should it occur. Limited quantities of second- and third-generation vaccines are currently available, with some third-generation vaccines still undergoing clinical testing for efficacy and safety.

A comparison of the general characteristics of first-, second- and third-generation vaccines is provided in Table 1. A detailed summary of the characteristics of specific first-, second- and third- generation vaccines is given in tables 1–4. This information is provided to aid WHO and WHO Member States with decision-making and risk communications about the administration of smallpox vaccines.

The smallpox vaccines described are those that are part of, or intended to be donated to, the (physical and virtual) WHO stockpile. Of note, smallpox vaccines donated for the virtual WHO stockpile are also intended for use in the donor countries in case of an outbreak. All smallpox vaccines forming the WHO stockpile (physical and virtual) will be subject to prequalification by WHO to confirm acceptability for use in an emergency situation.

Information on smallpox and/or smallpox vaccines is available at:

<http://www.who.int/topics/smallpox/en/>

Table 6. General characteristics of first-, second-, and third-generation vaccines, by category

Category	First generation	Second generation	Third generation
Vaccine characteristics	Live smallpox vaccines made from replicating vaccinia virus strains	Live smallpox vaccines made from replicating vaccinia virus strains	Live smallpox vaccines made from replicating more attenuated vaccinia virus strains (LC16m8) or made from replication-deficient more attenuated vaccinia virus strains (MVA ^a -based)
Vaccine strains	Vaccinia virus strains with proven pre- and post-exposure field effectiveness against smallpox.	Vaccinia virus strains with proven pre- and post-exposure field effectiveness against smallpox or monoclonal isolates derived thereof (ACAM2000)	Further attenuated vaccinia virus strains, no proven pre- or post-exposure field effectiveness
Production system	Produced on skin or lymph of live animals (e.g. calf, sheep, buffalo)	Tissue or cell culture derived (e.g. primary rabbit kidney cells, CAM ^b , chicken embryo cells, Vero cells)	Cell-culture derived (primary rabbit kidney cells or chicken embryo cells)
	Produced according to good manufacturing practices in place at the time of production	Produced according to good manufacturing practices in place at the time of production	Produced according to good manufacturing practices in place at the time of production
Pharmaceutical form	All vaccines are freeze-dried vaccine preparations to be reconstituted with a diluent before use, except WetVax. WetVax is a liquid, ready-to-use preparation.	All vaccines are freeze-dried vaccines to be reconstituted with a diluent before use, except VV Lister CEP VV-Lister CEP is a liquid, ready-to-use preparation	LC16m8: Freeze-dried vaccine to be reconstituted with a diluent before use MVA ^a (Imvanex/Imvamune) is a liquid, ready-to-use preparation
Number of doses per container	Multidose (20, 25, 100 and/or 200 doses per container)	Multidose (100 and 200 doses per container)	LC16m8: Multidose (50 doses per container)
			MVA ^a (Imvanex/Imvamune; single dose in a prefilled syringe)

Vaccination regimen and method of administration	One dose administered by scarification using a bifurcated needle	One dose administered by scarification using a bifurcated needle	<p>LC16m8: One dose administered by scarification using a bifurcated needle</p> <p>MVA-BN^c (Imvanex/Imvamune): two doses given 4 weeks apart by intramuscular injection. Additional doses might be considered in immunocompromised patients</p>
Efficacy/effectiveness	Historically confirmed vaccine pre- and post-exposure effectiveness. Vaccine ‘take’ (major reactions) rates indicate successful vaccination.	<p>Some vaccines (e.g. manufactured on CAM cells) have been used in smallpox outbreak settings. Most vaccines were tested in recent clinical trials. Capability to elicit vaccine ‘take’ (major reactions) rates was demonstrated</p> <p>High likelihood that these vaccines are as efficacious as first generation vaccines</p>	<p>Field effectiveness in preventing human variola virus infections was <u>not</u> demonstrated. Immunogenicity of LC16m8 was confirmed in adults by neutralizing antibody response rates to vaccinia virus and through animal challenge studies</p> <p>LC16m8: elicited high vaccine ‘take’ (major reactions) rates in clinical trials</p> <p>MVA-BN^c (Imvanex/Imvamune): Immunogenicity confirmed in adults by neutralizing antibody response rates and through animal challenge studies</p>
Safety	<p>May cause blisters, scarring, or spread infection by touching the vaccination site. May cause serious adverse reactions, including high fever, bacterial superinfections, myopericarditis, encephalitis, permanent neurological sequelae and death</p> <p>May not be safe for immunocompromised, or pregnant patients</p>	<p>May cause blisters, scarring, or spread infection by touching the vaccination site</p> <p>May cause serious adverse reactions, including high fever, myopericarditis, encephalitis, permanent neurological sequelae and death</p> <p>May not be safe for immunocompromised, or pregnant patients</p>	<p>LC16m8 may cause blisters, scarring, or spread infection by touching the vaccination site</p> <p>MVA-BN^c (Imvanex/Imvamune) may be safely used in persons who have an increased risk of adverse reactions to traditional smallpox vaccination, e.g. immunocompromised patients, patients with atopic dermatitis</p>

Logistics of transportation in the event of an outbreak	Transport and storage at 2–8°C	Transport and storage at 2–8°C	LC16m8: Transport and storage at 2–8°C
Regulatory status	<p>All vaccines available in WHO and national stockpiles were originally produced during, or previous to, the WHO smallpox eradication campaign in the 1970s</p> <p>First-generation vaccines are currently licensed in Russia only</p>	<p>All vaccines available in WHO (virtual and physical) and national stockpiles were produced after 2001</p> <p>Some nationally stockpiled vaccines are licensed for emergency use</p>	<p>LC16m8 is currently licensed in Japan and an approved vaccine production facility is maintained</p> <p>MVA^a is currently licensed in Canada and Europe</p>
Availability for rapid deployment by WHO	<p>Vaccines stockpiled by WHO (physical stockpile) are available for immediate distribution by WHO</p> <p>Vaccines that are part of the national stockpile but donated to WHO (virtual stockpile) are available through WHO following agreement on the conditions of deployment with the recipient country</p>	<p>Vaccines stockpiled by WHO (physical stockpile) are available for immediate distribution by WHO</p> <p>Vaccines that are part of the national stockpile but donated to WHO (virtual stockpile) are available through WHO following agreement on the conditions of deployment with the recipient country</p>	<p>LC16m8 will be stockpiled for immediate distribution by WHO (physical stockpile)</p> <p>The MVA-BN^c vaccine is part of the national stockpile of some countries. It case it is donated to WHO (virtual stockpile), it is available through WHO following agreement on the conditions of deployment with the recipient country</p>

^a Modified vaccinia Ankara.

^b Chorioallantoic membrane.

^c Modified vaccinia Ankara - Bavarian Nordic.

Table 7. Overview of stockpiled first-generation smallpox vaccines

Vaccine characteristic	Wetvax/APSV (1, 2)	Lancy-Vaxina (3, 4, 5)	Lister/Elstree-RVIM (6)	FCP	Pourquier vaccine (7)
Description	Liquid-frozen preparation of live vaccine containing the NYCBH ^a strain; manufactured from calf lymph	Freeze-dried live vaccine containing the Lister-Elstree strain; manufactured on sheep skin	Freeze-dried live vaccine containing the Lister-Elstree strain; manufactured from calf lymph	Freeze-dried live vaccine containing the Lister-L-IVP strain; manufactured on calf skin	Freeze-dried live vaccine containing the Lister strain; manufactured from calf lymph
Manufacturer	Aventis-Pasteur, USA	Berna Biotech (now Johnson & Johnson), Switzerland	RVIM, ^b The Netherlands	National Institute of Russia	Pourquier Institute laboratories, France
Production	Production discontinued in the 1950s	Originally produced before 1970s	Originally produced before 1970s	Originally produced before 1970s	Originally produced before 1970s
Route of administration	Percutaneous route (scarification)	Percutaneous route (scarification)	Percutaneous route (scarification)	Percutaneous route (scarification)	Percutaneous route (scarification)
Number of doses per container	Multidose (100 doses per container)	Multidose (100 and/or 200 doses per container)	Multidose (25 doses per container)	Multidose (20 doses per container)	Multidose (100 doses per container)
Shelf-life	Subject to extensions Potency tested annually to support use, if needed	Subject to extensions Potency tested regularly to support use, if needed	Subject to extensions	Subject to extensions	Subject to extensions Potency tested regularly to support use, if needed

Efficacy	Vaccine was effective in preventing smallpox infection in 95% of patients vaccinated during the eradication campaign	Used in the UK, Africa, Asia and Oceania eradication campaign In clinical trials vaccine take rates of 99–100% were reported with undiluted vaccine (3, 4, 5)	Used in the UK, Africa, Asia and Oceania eradication campaign In a field trial conducted in 1973 approx. 97% of primary vaccinees (total of 2992 children aged 0–14 years) had vaccine ‘take’ reactions (6)	Used in the USSR, Africa and Asia eradication campaign	Used in France and in the worldwide eradication campaign In a clinical trial in 226 healthy volunteers aged 27–63 years, 95.6% of revaccinees had ‘take’ reactions (7)
Potential side effects	<p>The listed adverse reactions were documented for first-generation vaccines in the pre-eradication era and may occur following vaccination. The frequency of occurrence of the adverse reactions listed may vary depending on the vaccination status and age of the vaccinee, and the vaccine strain used (8, 9, 10).</p> <p>Common adverse reactions include: injection site reactions (e.g. erythema pruritus, pain, swelling and secondary infections at the vaccination site) and systemic reactions (e.g. fever, fatigue, malaise, rigours, generalized rash, headache, lymphadenopathy).</p> <p>Transmission of live vaccinia virus by inadvertent inoculation of other body sites including the face can occur. These infections are usually self-limited. However, accidental infections of the eye may result in ocular complications including keratitis, corneal scarring and blindness.</p> <p>Rare serious adverse reactions include post-vaccinial encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia and eczema vaccinatum, which may result in severe disability, permanent neurological sequelae, or death.</p> <p>In recent vaccination campaign cases of myocarditis and/or pericarditis were observed (11).</p>				
Regulatory status (as of 2014)	Unlicensed	Unlicensed	Unlicensed	Licensed in Russia	Licensed in France

^a New York City Board of Health.

^b The Netherlands National Institute for Public Health and the Environment.

Table 8. Overview of stockpiled second-generation smallpox vaccines

Vaccine characteristic	ACAM2000 (12, 13)	Elstree-BN (14)	VV Lister CEP	Lister/Elstree-RVIM^a (6)
Description	Freeze-dried live smallpox vaccine made from a clonal isolate derived from the NYCBH strain; produced in Vero cells	Freeze-dried live smallpox vaccines made from the Lister/Elstree strain; produced in chicken embryo cells (specific pathogen free)	Frozen liquid live smallpox vaccines made from the Lister/Elstree strain; produced in chicken embryo cells (specific pathogen free)	Freeze-dried live smallpox vaccine made from the Lister-Elstree strain; produced in rabbit kidney cells
Manufacturer	Sanofi Pasteur Biologics Co., USA	Bavarian Nordic, Denmark	Sanofi Pasteur, France	RVIM, The Netherlands
Route of administration	percutaneous route (scarification)	percutaneous route (scarification)	percutaneous route (scarification)	percutaneous route (scarification)
Number of doses per container	Multidose (100 doses per container)	Multidose (100 doses per container)	Multidose (100 doses per container)	Multidose
Shelf-life	15 years After reconstitution, vaccine may be stored at 2–8°C for 30 days	Subject to extensions Potency tested regularly to support use if needed	Subject to extensions Potency tested regularly to support use if needed	Subject to extensions
Efficacy	Efficacy demonstrated in human clinical trials Vaccine "take" rates were comparable to that of Dryvax (12)	Only limited information available that points to an efficacy (vaccine take rates) comparable with traditional vaccine (14)	No data from clinical trials in humans are available	In a field trial conducted in 1973 approx. 97% of primary vaccinees (total of 15 390 children aged 0–14 years) had vaccine 'take' reactions (4)

Potential side effects	Safety data available from clinical trials involving 2983 subjects (<i>13</i>) It is to be expected that the safety profile is comparable with first-generation vaccines made from the NYCBH ^b strain except that the frequency of some adverse reactions might be lower (e.g. myo/pericarditis)	Very limited safety information from clinical trials available It is to be expected that the safety profile is comparable with first-generation vaccines made from the Lister-Elstree strain	No safety information from clinical trials available It is to be expected that the safety profile is comparable with first-generation vaccines made from the Lister-Elstree strain	Safety information from a field trial indicates a comparable safety profile to a first-generation Lister vaccine
Risks	Has never been tested during a human smallpox outbreak. Vaccine has not been tested in subjects younger than 18 years of age Risk of rare serious and/or life-threatening adverse reactions	Has never been tested during a human smallpox outbreak. Vaccine has not been tested in subjects younger than 18 years of age Risk of rare serious and/or life-threatening adverse reactions.	Has never been tested during a human smallpox outbreak or in clinical trials in humans Risk of rare serious and/or life-threatening adverse reactions	Has never been tested during a human smallpox outbreak Risk of rare serious and/or life-threatening adverse reactions
Regulatory status (as of 2014)	Stockpiled and licensed in the USA for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection	Stockpiled in various European Union countries, currently not licensed	Licensed in France and the UK	Stockpiled in the Netherlands

^a The Netherlands National Institute for Public Health and the Environment.

^b New York City Board of Health.

Table 9. Overview of stockpiled third-generation smallpox vaccines

Vaccine characteristic	LC16m8 (8, 15, 16, 17, 26, 27, 28)	MVA Imvanex/Imvamune (18, 19, 20, 21, 22, 23, 24, 25)
Description	Freeze-dried live smallpox vaccine made from the more attenuated replicating Lister-derived strain LC16m8 Produced in primary rabbit kidney cells	Live virus smallpox vaccines made from the replication-deficient more attenuated MVA ^a strains Produced in chicken embryo cells (specific pathogen free)
Manufacturer	KAKETSUKEN, Japan	Bavarian Nordic, Denmark
Route of administration	Percutaneous route (scarification)	Subcutaneous injection
Number of doses per container	Multidose	Single dose pre-filled syringe
Shelf-life	4 years at -20°C; 2-years at 2–8°C	2 years at 2–8°C
Efficacy/immunogenicity	In vaccinia-naïve subjects, vaccine “take” rates were reported from field trials in children and clinical trials in adult conducted in Japan of 95% and 94%, respectively In a phase I clinical trial conducted in vaccinia-naïve adults in the USA, a take rate of 100% was observed In a study conducted in healthy adults in Japan, take rates were 94.4% (n=198) for vaccinia-naïve adults and 81.7% (n=71) for re-vaccinated adults	No vaccine “take” reactions due to the nature of the vaccine Two doses required to achieve seroconversion rates of 80–90% in vaccinia-naïve subjects as measured by PRNT ^b Less immunogenic in HIV patients with seroconversion rates of approx. 60% after two vaccinations
Potential side effects	During the 1973–1974 field study in approx. 10 000 children, lower fever rates and reduced local induration at the vaccination site were reported compared to parenteral Lister strain vaccine One case of eczema vaccinatum, three cases of temporary febrile convulsions and eight cases of post-vaccinal exanthem, all of which were mild, were recorded No case of encephalitis occurred In two recent studies in vaccinia-naïve and vaccinia-experienced adults conducted in Japan and in the	No reports of known post-vaccinial adverse reactions observed through phase 2 and 3 clinical trials (approx. 3000 subjects) The most frequently reported adverse reactions were injection site and mild to moderate systemic reactions (e.g. headache, myalgia, nausea) Generally well-tolerated in HIV patients and patients with atopic dermatitis Inadvertant vaccination of pregnant women (13 cases) revealed no untoward findings

	<p>USA, no cases of myo/pericarditis, generalized vaccinia, progressive vaccinia, eczema vaccinatum have been observed</p> <p>No viraemia as confirmed by PCR^c analyses of blood samples tested at different time points (day 0 through to day 22 post-vaccination)</p> <p>Inadvertent inoculation from vaccine site is possible. No serious adverse events were observed in a study conducted in healthy adults (n=268) in Japan</p>	<p>For more information refer to currently approved European product information (18)</p>
Risks	<p>Has never been tested during an outbreak of smallpox in humans. Unknown efficacy/field effectiveness</p> <p>Rare serious adverse events</p>	<p>Has never been tested during a human outbreak of smallpox. Unknown efficacy/field effectiveness</p> <p>Not tested in subjects younger than 18 years of age.</p> <p>Rare serious adverse events</p>
Regulatory Status (as of 2014)	<p>Licensed in Japan</p> <p>Under IND^d in the USA</p>	<p>Licensed in Europe – Imvanex, for active immunization against smallpox in adults (18), and in Canada – Imvamune, for active immunization against smallpox in adults with immune deficiencies or skin disorders (19)</p> <p>Under IND^d status in the USA, may be authorized for use in a smallpox emergency under EUA^e in the USA in HIV+ or atopic dermatitis patients, phase three clinical trials are ongoing</p>

^a Modified vaccinia Ankara.

^b Plaque reduction neutralization test.

^c Polymerase chain reaction.

^d Investigational New Drug program of the Food and Drug Administration (FDA).

^e Emergency Use Authorization of the FDA.

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World Health Organization
Avenue Appia 20,
CH 1211 Geneva 27
Switzerland

