



ACCESS TO MEDICINES, VACCINES AND PHARMACEUTICALS

Identifying & responding to serious Adverse Events Following Immunization, following use of smallpox vaccine during a Public Health Emergency

A guidance document for smallpox vaccine safety surveillance



World Health
Organization

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Identifying and responding to serious Adverse Events Following Events following use of smallpox vaccine during a Public Health Emergency: A guidance document for smallpox vaccine safety surveillance.

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About this guidance

This guidance document has been developed from the principles contained in *WHO's Global Manual on Surveillance of Adverse Events Following Immunization*,² the *CIOMS guide to active vaccine safety surveillance*³ and from available literature on smallpox vaccines.

² Global manual on surveillance of adverse events following immunization. WHO 2014 (revised 2016)
http://www.who.int/vaccine_safety/publications/aeft_surveillance/en/

³ CIOMS Guide to active vaccine safety surveillance: report of CIOMS Working Group on Vaccine Safety. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2017
<https://cioms.ch/shop/product/cioms-guide-to-active-vaccine-safety-surveillance/>

Intended Audience

This document provides information to National Immunization Programmes, health care workers and immunization staff of WHO Member States and other stakeholders on how to rapidly establish vaccine monitoring and safety surveillance systems in countries introducing smallpox vaccination in a public health emergency situation following an outbreak of smallpox.

In addition, the guide may be of use for the National Crisis Management Committee as part of the overall response to a smallpox outbreak; and may also help countries to establish minimum capacity for safety monitoring when introducing new vaccines during an emergency.

Abbreviations

ADEM	Acute Disseminated Encephalitis/ Encephalomyelitis
AEFI	Adverse Events Following Immunization
AIDS	Acquired Immunodeficiency Syndrome
CDC	Centre for Disease Control
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DCM	Dilated Cardiomyopathy
EDPLN	WHO Emerging and Dangerous Pathogens Laboratory Network
EV	Eczema Vaccinatum
FLW	Front Line Workers
GV	Generalised Vaccinia
HBV	Hepatitis B virus
HCW	Health care workers
MVA	Modified Vaccinia Ankara
NIP	National Immunization Programme
NITAG	National Immunization Technical Advisory Group
NRA	National Regulatory Authority
NYCBH	New York City Board of Health
PHEIC	Public Health Emergency of International Concern
PV	Progressive Vaccinia
PVE	Post vaccinal encephalitis
PVEM	Post vaccinal encephalomyelitis
RIVM	Dutch National Institute for Public Health and the Environment
SAGE	Strategic advisory group of experts
SVES	Smallpox Vaccine Emergency Stockpile
VIG	Vaccinia Immune Globin
WHA	World Health Assembly
WHO	World Health Organization

Glossary

Active Surveillance

Surveillance is continuing, systematic collection of data that are analysed and disseminated for decision-making and action to protect the health of the population. Active surveillance involves outreach by the public authority such as regular telephone calls or visits to laboratories, hospitals and providers on a regular or episodic basis to stimulate reporting of specific diseases.

Adventitious agent

Adventitious agents are microorganisms that may have been unintentionally introduced into manufacture of a biological medicinal product. These include bacteria, mycobacteria, rickettsia, protozoa, parasites, transmissible spongiform encephalopathy (TSE) agents and viruses. They could be inadvertently introduced into a vaccine through starting materials used for production such as cell substrates, porcine trypsin, bovine serum or any other source of human or animal origin.

Adverse event following immunization (AEFI)

Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Cluster

Two or more cases of the same or similar events related in time, geography (place), and/or vaccine administered.

AEFI clusters are usually associated with a particular supplier/provider, health facility, and/or a vial of vaccine or a batch of vaccines.

Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
Contraindication	A situation where a particular treatment or procedure, such as vaccination with a particular vaccine, must not be administered for safety reasons. May be relative or absolute.
Immunization safety surveillance	A system for ensuring immunization safety through detecting, reporting, investigating, and responding to AEFI.
Line listing (of AEFI)	A line list is a list of persons suffering an AEFI and investigated during a reporting period. One line of information is written for each case. It includes: the case number; the patient's name and address; date and place of immunization; the vaccine (or vaccines) used; dose number (for multi-dose vaccines), manufacturer, and lot number; the patient's symptoms and date of onset of the event. This information is useful in identifying clusters or other patterns for further investigation and follow-up action.
Non-serious AEFI	An event that is not “serious” and does not pose a potential risk to the health of the vaccinee. Non-serious AEFI should also be carefully monitored because they may signal a potentially larger problem with the vaccine or immunization, or may have an impact on the acceptability of immunization in general.
Public health emergency	An occurrence or imminent threat of an illness or health condition caused by bioterrorism, epidemic or pandemic disease or a novel and highly infectious or biological toxin that poses a

substantial risk of a significant number of human facilities or incidents or permanent or long-term disability

Precautions

A condition in a vaccinee that might increase the chance or severity of a serious adverse reaction, or that might compromise the ability of the vaccine to induce immunity. In general, vaccines are deferred when a precaution condition is present. However, situations may arise when the benefit of protection from vaccine outweighs the risk of an adverse reaction and a provider may decide to give the vaccine.

Ring immunization

Vaccination of all persons (contacts) who were in contact with a case. The objective is to create a barrier of immune persons around the case and their contacts as quickly as possible.

Sentinel Site

Sentinel sites are prearranged sample of health-care providers who agree to report all cases of certain conditions. These sentinel providers are clinics, hospitals, or physicians who are likely to observe cases of the condition of interest.

Sentinel Surveillance

Sentinel surveillance involves the collection of case data from a sample of providers to learn something about the larger population. It may be the best type of surveillance if more intensive investigation of each case is necessary to collect the necessary data.

Serious AEFI

An adverse event following immunization that results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Smallpox vaccine – First generation	Smallpox vaccines produced and successfully used during the intensified eradication program are called first generation vaccines.
Smallpox vaccine – Second Generation	Second generation smallpox vaccines use the same smallpox vaccine strains employed for manufacture of first generation vaccines with improved manufacturing processes, primarily improved consistency between lots and minimization of the risk of contaminations by adventitious agents.
Smallpox vaccine – Third Generation	Third generation smallpox vaccines are more attenuated vaccine strains specifically developed as safer vaccines at the end of the eradication phase by further passage in cell culture or animals, or genetically modified.
Stimulated passive surveillance	Stimulated passive surveillance is when the health department contacts providers/physicians to solicit information on disease under surveillance.
Surveillance	The continuing, systematic collection of data that are analysed and disseminated to enable decision-making and action to protect the health of populations.
Vaccine	A biological preparation that improves immunity to a particular disease. In addition to the antigen, it contains multiple components (excipients) and each component may have unique safety implications.
Vaccine take	For most smallpox vaccines inoculated into the superficial layers of the skin, the virus grows and induces an immune reaction that protects against

smallpox. The reaction that follows is termed “a take” or “primary reaction” from the first vaccination and a “major reaction” from subsequent vaccinations.

A vaccine introduced too deeply into the skin or without sufficient penetration of the external layer of the skin does not result in local reaction or “take” and is known as “no take”.

1. The vaccines used for preventing smallpox in a public health emergency and their known safety profile

This guidance is developed to serve as a resource to governments and partners to identify and respond to serious adverse events following immunization (AEFI) as they plan for use of smallpox vaccine in the event of a smallpox outbreak.

The guide aims to:

- provide information on the smallpox vaccines that are part of WHO's stockpile.
- provide information on the AEFI from smallpox vaccine.
- guide countries on how to rapidly establish a surveillance system and respond if smallpox were to occur, based on the local context.

The guide will assist the National Immunization Programme (NIP), health care workers (HCW) and immunization staff. In addition the guide is of use for the National Crisis Management Committee as part of the overall response to a smallpox outbreak.

1.1 Introduction

Public health emergencies from emerging and re-emerging infections (natural, accidental or deliberate release) are a constant threat to the health of populations worldwide. Public health emergencies may be disease outbreaks (emerging, re-emerging infections or pandemics), natural disasters, biological use or chemical agents or radiation. WHO defines a public health emergency as an occurrence or imminent threat of an illness or health condition caused by bioterrorism, epidemic or pandemic disease or a novel and highly infectious or biological toxin that poses a substantial risk of a significant number of human fatalities or incidents or permanent or long-term disability.⁴

One of the control measures in managing public health emergencies due to vaccine preventable diseases is immunization. Maintaining vaccine stockpiles ensures timely access to life saving interventions during public health emergencies. Currently vaccine stocks are maintained by WHO for five diseases for which there is a need for

⁴ www.who.int/hac/about/definitions/en

emergency use: smallpox, yellow fever, cholera, meningitis and polio.^{5,6,7} The WHO reserve of Smallpox Vaccine Emergency Stockpile (SVES) consists of approximately 33.7 million doses.

Smallpox (*Variola major*, *Variola minor*) was successfully eradicated by a global effort in the 1960s and 1970s using a panel of vaccinia virus vaccines. The last naturally occurring case was reported in 1977 in Somalia and in May 1980 the World Health Assembly (WHA) declared that smallpox had been eradicated.⁸

In the event of a public health emergency due to a smallpox outbreak, immunization with smallpox vaccine is a key intervention for its control in a public health emergency. This guidance document focuses on active surveillance of serious AEFI following use of smallpox vaccine in a public health emergency.

1.2 Smallpox vaccines⁹

To date there have been three generations of smallpox vaccines. The key features of each generation is summarised in Table 1.

Smallpox vaccines produced and used successfully during the eradication program are referred to as first generation vaccines. There were 71 manufacturers who produced smallpox vaccines during the intensified eradication phase. The vaccinia virus strains used were NYCBH, EM 63, Ecuador, Lister, L-IVP, Merieux 37, Nigeria, Patwadanger, B-51, TianTan, Copenhagen, Bern, Ikeda and Tashkent. Of these, the most widely used strains were Lister, NYCBH, EM63 and TianTan.

First generation vaccines were developed before and during the eradication effort and contain live vaccinia virus produced by infecting the abdominal skin or flanks of large animals. The lymph exudate was then collected, purified, stabilized, and lyophilized. Although each virus strain was associated with similar side effects, the adverse events rates differed widely by virus strain. The judicious use of these

⁵ Yen C, Hyde TB, Costa AJ, Fernandez K, Tam JS, Hugonnet S, Huvos AM, Duclos P, Dietz VJ, Burkholder BT. The development of global vaccine stockpiles. *Lancet Infectious Disease* 2015; 15(3):340-347. Doi.10.1016/S1473-3099(14) 70999-5.

⁶ <http://www.who.int/csr/disease/icg/en/>

⁷ http://www.who.int/immunization/sage/meetings/2014/october/presentations_background_docs/en/

⁸ <http://www.who.int/csr/disease/smallpox/en/>

⁹ Summary report on first, second and third generation smallpox vaccines available http://www.who.int/immunization/sage/meetings/2013/november/2_Smallpox_vaccine_review_updated_11_10_13.pdf?ua=1

vaccines, along with surveillance, contact tracing, and isolation of infected individuals successfully eradicated smallpox disease.

Table 1: Summary of the features of each generation of smallpox vaccines

Smallpox Vaccines	
Vaccine generation	Features
First generation	<ul style="list-style-type: none"> • Developed before and during the eradication efforts. • Contain live vaccinia virus. • Produced in large animals - lymph exudate collected, purified, stabilized, and lyophilized. • Common side effects: blisters, scarring, or spread of infection by touching the vaccination site. • Each virus strain associated with similar side effects, adverse events rates differ widely by virus strain.
Second generation	<ul style="list-style-type: none"> • Developed using first generation vaccines strains. • Contain live vaccinia virus. • Production in embryonated eggs or well-characterized mammalian cell lines. • Administered by scarification. • Safety profiles similar to first generation vaccines.
Third generation	<ul style="list-style-type: none"> • Attenuated vaccine strains specifically developed as safer vaccines, by further passage in cell culture or animals or genetically modified. • LC16m8, MVA or MVA-BN. • MVA-BN is a non-replicating vaccine and may have less adverse reactions than 1st and 2nd generation smallpox vaccines. Considered for use in persons with an increased risk of adverse reaction e.g. immunocompromised patients, patients with atopic dermatitis.

In terms of safety, first generation smallpox vaccine may cause blisters, scarring, or spread of infection by touching the vaccination site. They may also cause serious adverse reactions, including high fever, bacterial superinfections, myopericarditis, encephalitis, permanent neurological sequelae and death. These vaccines may not be safe for the immunocompromised or pregnant people because of the greater potential for severe adverse events.



Bifurcated needle used for smallpox vaccination.



Bifurcated needle used for smallpox vaccination.

Second generation vaccines were developed using first generation vaccines strains. They also contain live vaccinia virus; however, production methods have shifted to embryonated eggs or well-characterized mammalian cell lines. This allows for more precise control over vaccine components, lower levels of adventitious agents, and higher purity and product consistency. These vaccines are administered by scarification (applied by percutaneous multiple puncture technique) in an identical manner to first generation vaccines.

Second generation vaccines include: Lister vaccine produced in rabbit kidney cells (RIVM), Elstree-BN (Bavarian Nordic), VV Lister/CEP (Sanofi Pasteur), CJ -50300 (CJ CheilJadang Corporation, South Korea). The safety profiles of the second-generation smallpox vaccines are similar to the first generation.

Third generation vaccines are more attenuated vaccine strains specifically developed to be safer vaccines after the end of the eradication phase, by further passage in cell culture or animals or genetically modified. These are LC16m8 and MVA (Imvanex, Imvamune or MVA-BN). The latter is a non-replicating vaccine and therefore may have less adverse reactions than first and second-generation smallpox vaccines. MVA-BN (Imvanex/Imvamune) may be considered for use in persons who have an increased risk of adverse reactions to traditional smallpox vaccination, e.g. immunocompromised patients, patients with atopic dermatitis.

1.3 Smallpox vaccines for use during a public health emergency

The smallpox vaccines that are part of WHO's stockpile and available for use during public health emergencies are ACAM2000, LC16m8, NYCBH strain and Lister strain,

Table 2: Adverse reactions to smallpox vaccines held in emergency stockpile

Vaccine	Adverse reactions
ACAM 2000^{10,11}	<ul style="list-style-type: none"> Derived from NYCBH strain used for Dryvax, thus safety profile considered similar to Dryvax. Myocarditis, pericarditis, post-vaccinial encephalitis (PVE), encephalomyelitis (PVEM), encephalopathy, progressive vaccinia (PV, vaccinia necrosum), generalised vaccinia (GV), severe vaccinia skin infections, erythema multiforme including Stevens-Johnson syndrome, eczema vaccinatum (EV) resulting in permanent sequelae or death, ocular complications, blindness, fetal death in pregnancy. Death (rare) 1 death per 1 million vaccinations. Possible relationship to ACAM2000 – single reports of atrial fibrillation, chest discomfort and chest pain, new onset seizures. ACAM2000 has not been studied in infants or children.¹² Risk of serious AEFI with live vaccinia virus is higher in infants. ACAM2000 is a pregnancy Category D agent and has not been studied in pregnant women although note that live vaccinia viruses can cause fetal vaccinia and fetal death.
LC16m8	<ul style="list-style-type: none"> No serious adverse events have been reported.
NYCBH strain/ Lister¹³ strain	<ul style="list-style-type: none"> PVE, PVEM, encephalopathy, PV, GV and EV, which may result in severe disability, permanent neurological sequelae, myopericarditis or death.
MVA	<ul style="list-style-type: none"> Currently for prophylaxis of individuals who are immunosuppressed or with atopic dermatitis. In vaccinia naive patients - Extraocular muscle paresis, sarcoidosis. No reported myo/pericarditis with MVA vaccines.
Other: Accidental infection can also occur, most frequently inoculation of the eyelids or conjunctiva, although accidental infection of other body sites is also possible. In most patients this occurred 5-12 days after vaccination.	

¹⁰ <https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm142572.pdf>

¹¹ <https://www.cdc.gov/smallpox/pdfs/revaccination-memo.pdf>, With primary references of

<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5204a1.htm> and

<http://www.nejm.org/doi/full/10.1056/NEJM196911272812201> and

<https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm142572.pdf>

¹² <https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm142572.pdf>

¹³ <https://www.ncbi.nlm.nih.gov/pubmed/16933957>

MVA (Imvanex, Imvamune). Following SAGE recommendations,¹⁴ licensed vaccines ACAM2000 (2nd generation vaccine) and LC16m8 (3rd generation vaccine) are preferred as the vaccines to be used to control an outbreak. If they are not available, 1st generation vaccines used during the eradication campaign can be used. SAGE further recommended that to control an outbreak, countries should use any available vaccine that meets WHO standards of potency, purity and stability.

Table 2 describes adverse reactions to the smallpox vaccines held in the WHO stockpile for use during a public health emergency.

In general, vaccination complications are more common in those receiving primary vaccination than those who are being revaccinated. Those at highest risk are infants under 1 year old.

1.3.1 ACAM2000 and LC16m8 vaccines

ACAM2000, manufactured by Sanofi Pasteur Biologics Colorado, USA, is a second generation freeze-dried live smallpox vaccine produced in Vero cells from a single plaque purified vaccinia strain which originates from the Dryvax vaccine (a first generation vaccine intensively used in campaigns in the US) NYCBH strain. Clinical trials in humans have shown the vaccine take with ACAM2000 is comparable to that of Dryvax. It is administered by percutaneous route (scarification) with a bifurcated needle. The vaccine needs to be transported and stored at 2-8°C.

LC16m8, manufactured by Kaketsuken, Japan, is a third generation vaccine. It is a freeze-dried live smallpox vaccine produced in primary rabbit kidney cells, and made from replicating further attenuated Lister strain. In vaccinia-naïve subjects, vaccine take rates from field trials in children, and clinical trials in adults conducted in Japan were reported as 95% and 94%, respectively. In a phase I/II clinical trial conducted in vaccinia-naïve adults in the US, a take rate of 100% was observed. It is administered by percutaneous route (scarification) with a bifurcated needle. The vaccine needs to be stored at -20°C and can be transported and temporarily stored at 2-8°C.

1.3.2 NYCBH and Lister strain vaccines

Amongst the most widely used of the first generation smallpox vaccines during the intensified eradication phase were those produced using NYCBH and Lister strains, propagated and harvested from skin of calf, sheep or buffalo or calf lymph. Of these,

¹⁴ Meeting of the Strategic Advisory Group of Experts on immunization, November 2013 – conclusions and recommendations. Weekly epidemiological record. 2014, 89 (1):1-20. <http://www.who.int/wer/2014/wer8901/en/>

Dryvax (NYCBH strain), Lancy Vaxina Berna and Porquier vaccine (both from Lister strains) were evaluated clinically post eradication.

The NYCBH strain currently in the WHO stockpile is Wetvax. Wetvax (Wyeth/Aventis Pasteur) is a first generation frozen liquid live vaccine produced by infection of skin of calves using NYCBH strain. Wetvax was effective in preventing smallpox infection in 95% of patients vaccinated during the eradication campaign. This vaccine needs to be stored frozen below 0°C and can be transported and temporarily stored for use below 8°C.

Two vaccines using the Lister strain are currently in the WHO stockpile – Lancy Vaxina Berna (manufactured from Lister strain produced on skin of sheep) and Porquier vaccine (from Lister strain from calf lymph). Both vaccines have shown successful immune response in clinical trials. These are lyophilized live vaccines. These vaccines have to be transported and stored at 2-8°C.

Vaccines derived from both NYCBH and Lister strains are no longer licensed for general use, but regulatory mechanisms are in place in countries holding stockpiles for approval of these vaccines to enable their use in emergency situations. These first generation vaccines from the WHO stockpile are required to meet the standards of purity, potency, and stability detailed in WHO/TRS No 926, 2004.¹⁵ They are administered percutaneous (scarification). SAGE recommends that they be used during a public health emergency if ACAM 2000 or LC16m8 (1st option licensed vaccines) are not available.

1.3.3 MVA vaccines

MVA (Imvanex, Imvamune) vaccine, a third generation liquid vaccine (given intramuscularly or subcutaneously) is manufactured by Bavarian Nordic. The vaccine has received a market authorization in Europe and Canada. Its use may be considered for prophylaxis of individuals at high risk of exposure and for whom standard replicating vaccine is contraindicated because of immunodeficiency, immunosuppression therapies or atopic dermatitis.

¹⁵ <http://www.who.int/biologicals/publications/trs/areas/vaccines/smallpox/en/>

1.4 Response strategies in the event of a smallpox outbreak

Since smallpox was eradicated in the year 1980, several countries, have as part of their national emergency response plans conducted regular training for first responders in order to enable prompt response to outbreaks.

The principles for control in the event of an outbreak include:

- surveillance
- containment (quarantine/isolation)
- ring vaccination of contacts (mass vaccination is not recommended)
- monitoring of vaccine take, if applicable (MVA will not have a vaccine take)
- monitoring of adverse events following immunization (AEFI).

Training of HCWs to confirm diagnosis of smallpox through algorithms for differential diagnosis of smallpox may be required.¹⁶ Based on the SAGE recommendations, WHO advises that if an outbreak of smallpox occurs, smallpox vaccine should be reserved for the following at-risk groups:^{17,18}

1. Immediate contacts of cases e.g. personnel caring for smallpox patients, should be vaccinated immediately after their initial contact.
2. Health-care workers (HCW).
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 in the first instance. However, second ring contacts should be identified, and communications established for tracing, so that they can be vaccinated if a first ring contact actually develops smallpox or symptoms that suggest smallpox infection. SAGE also recommends vaccinating laboratory or other health-care personnel who collect diagnostic specimens from patients, or who handle or process such specimens.

¹⁶ WHO has developed a set of training material for health workers on how to diagnose Smallpox <http://www.who.int/csr/disease/smallpox/clinical-diagnosis/en/>

¹⁷ Meeting of the strategic Advisory Group of Experts on immunization, November 2013 – conclusions and recommendations. Weekly epidemiological record. 2014, 89 (1):1-20.

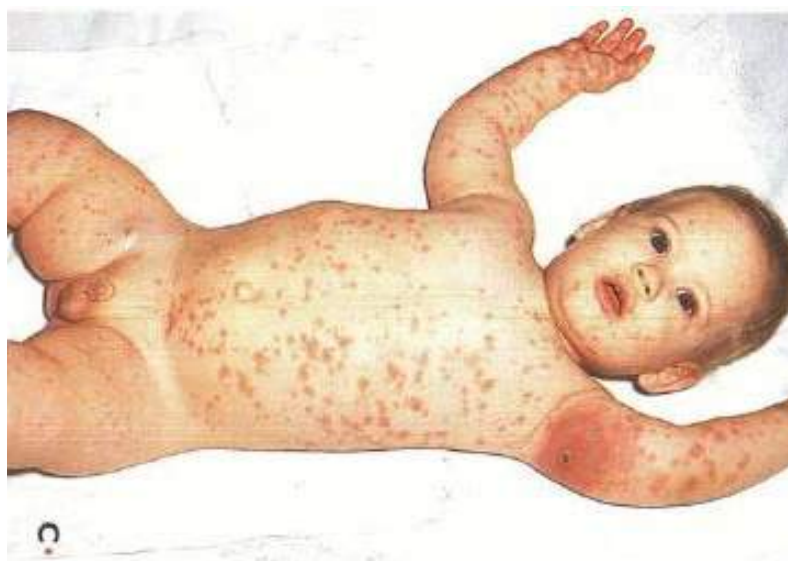
¹⁸ Operational framework for the deployment of the World Health Organization Smallpox Vaccine Emergency Stockpile in response to a smallpox event

It is necessary that HCW and front line workers (FLWs) are vaccinated as soon as the first case is identified. Replicating vaccines administered within 1 week may protect against disease and/or death.¹⁹ This is important as pre-and post-exposure smallpox vaccination is not a policy in most countries.

Once smallpox vaccination is administered, monitoring for adverse events should be an integral part of the immunization strategy for smallpox vaccination in the event of its use in containing an outbreak.

WHO's smallpox vaccine stockpile was established as a mechanism to store, maintain and distribute smallpox vaccine in the event of a smallpox re-emergence, to enable WHO and Member States to rapidly respond to any outbreak.²⁰ Technical expertise and support will be available from WHO and global health partners.

Photos of adverse reactions to smallpox vaccination (1)



Generalized Vaccinia, 10 days after vaccination, benign scarring.
Source: WHO

¹⁹ <http://apps.who.int/iris/bitstream/handle/10665/39485/9241561106.pdf?sequence=1&isAllowed=y>

²⁰ Operational framework for the deployment of the World Health Organization Smallpox vaccine emergency stockpile in response to a smallpox event, WHO 2017, available at <http://www.who.int/csr/disease/icg/smallpox-vaccine-emergency-stockpile/en/>



Progressive vaccinia in a child with an immunodeficiency.
Source: WHO

2. Smallpox vaccination and possible serious adverse events

This chapter describes the procedures related to smallpox vaccination, different AEFI that may follow, clinical management considerations and laboratory considerations.

2.1 Preparing for administration of smallpox vaccine(s)

All HCWs should be trained in administration of smallpox vaccine if smallpox were to re-emerge.²¹ They should be able to identify expected events and adverse events after smallpox vaccination. Details about the administration of smallpox vaccine, the usual progression of the lesion at the site of inoculation and expected events after smallpox vaccination are provided in Annex 1. The family/ caretaker should be informed about the possible expected local and systemic AEFI that might occur following vaccination.

All vaccinees should be registered centrally. Details recorded at the time of vaccination should include:

- Detailed address and contact phone number.
- Details of the vaccine and diluent should also be recorded, with particular attention given to batch numbers.
- The place, date and time of vaccination.

Vaccinees and parents of vaccinated children should be given a vaccination card providing the following:

- details of the vaccine administered
- hotline number
- details of the central AEFI monitoring unit
- advice to report any event that causes concern following immunization.

Vaccinees and parents of vaccinated children should also be advised about the risk of inadvertent autoinoculation. The most common sites involved are the face, nose,

²¹ WHO has developed instructions for smallpox vaccination with bifurcated needle available at <http://apps.who.int/iris/handle/10665/67962>

mouth, lips, genitalia and anus. Accidental infection of the eye (ocular vaccinia) may result in ocular complications such as keratitis, corneal scarring and blindness.²² Vaccinees should be strongly encouraged to report severe events including cardiac events or other unusual events should they occur. They should also be advised to notify any adverse event that causes any concern to the health care provider who vaccinated them.

2.2 Contraindications for smallpox vaccine

Vaccinating people in response to a smallpox event carries a risk for adverse events from the smallpox vaccination. However, this risk is outweighed by the risk of severe smallpox disease and spread of cases. Because of the high case-fatality rate and severity of smallpox during a public health emergency, there are no absolute contraindications for the use of smallpox vaccines for persons exposed to smallpox virus or at high risk for smallpox infection. Relative contraindications for immunocompromised persons, persons with autoimmune conditions, atopic dermatitis or other exfoliative skin conditions, persons with vaccine or vaccine component allergies, pregnant women and children under 1 year of age.²³

2.3 Adverse events following smallpox vaccination

AEFI is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavourable or unintended sign, an abnormal laboratory finding, a symptom or a disease. AEFI are rated by intensity of the event (that is: mild, moderate, severe); the event itself may be of minor medical significance.

An AEFI is considered serious if it results in death, is life threatening, requires in-patient hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or requires intervention to prevent permanent impairment or damage.²⁴ For more information on AEFI please see the WHO Global Manual on Surveillance of Adverse Events Following Immunization.²⁵ Details can also be found in Annexes 1, 2 and 3.

²² <https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142572.pdf>

²³ <https://www.cdc.gov/smallpox/clinicians/vaccination-contraindications1.html>

²⁴ Definition and application of terms for Vaccine Pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance. CIOMS 2012.

www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf

²⁵ http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/

Expected vaccine-related common reactions following smallpox vaccination are usually mild to moderate in severity and include local reactions such as pain, intense erythema and inflammation at the vaccination site; and systemic reactions such as fever, malaise, myalgia, headache, chills, nausea, fatigue, and lymphadenopathy. These reactions usually resolve within 2-3 weeks.²⁶ More details are provided in Annexes 1, 2 and 3.

2.4 Known serious AEFI following smallpox vaccination

While serious AEFI are rare, it is important to be aware of and monitor for the described adverse reactions. The adverse reactions that need to be reported by the health care provider to the central monitoring unit are found in Table 3.

Information on the occurrence of serious AEFI should be kept in a central repository to allow the determination of the frequency of adverse events, and to also determine if there might be other causes for the reported event. All vaccination staff must report any serious AEFIs brought to their notice as per the case definitions described in Annex 3.^{27,28}

2.5 Clinical management of serious AEFI

It is important to note that since smallpox vaccination will be occurring in the setting of a public health emergency, it is important to distinguish if the presenting signs and symptoms (i.e. AEFI) are due to vaccination or due to natural infection (which, at the time of writing this document, has not occurred since 1977)²⁶. It may be useful to identify specific hospitals for referral of cases with complications of smallpox disease and for serious AEFI following smallpox vaccination. Key features for diagnosis and management of the serious AEFI are summarised in Table 3.

Most of the AEFI occur within three weeks of smallpox vaccination, but superinfection of the vaccination site or regional lymph node swelling may occur up to 60 days following vaccination.²⁹ Also, because of uncertainty about association of cardiac

²⁶ http://www.who.int/immunization/sage/meetings/2013/november/2_Smallpox_vaccine_review_updated_11_10_13.pdf

²⁷ Surveillance guidelines for smallpox vaccine (Vaccinia) adverse reaction. MMWR 2006.

²⁸ Fulginits VA, Papier A, Lane JM, Neff JM, Hendersen A. Smallpox vaccination: A review part II: Adverse events. Clinical infectious Diseases 2003; 37:251-271.

²⁹ Surveillance guidelines for smallpox vaccine (Vaccinia) adverse reaction. MMWR 2006; 55 (RR-1)

symptoms (myopericarditis, cardiomyopathy), smallpox vaccinees could be followed up for at least six months.³⁰

Photos of adverse reactions to smallpox vaccination (2)



Eczema vaccinatum in the unvaccinated contact of a vaccinated sibling.

Source: WHO



Accidental autoinoculation with vaccinia virus.

Source: WHO

2.6 Reporting of AEFI following smallpox vaccination

Health care workers (HCW) should document all adverse events using the standard AEFI reporting form (Annex 4). These reports should be sent to the next level of hierarchy for monitoring and surveillance, as defined/recommended by the existing health system. The reports should also be sent to the central AEFI monitoring unit (institution/ district/ province level), and to other reporting levels, as required.

HCW should note that in the event of a smallpox outbreak, a person receiving smallpox vaccine may have received other vaccines (especially children as part of routine immunization activities) within the same time frame. Serious adverse events may occur with any vaccine, and if the cause of the serious adverse event observed is suspected to be due to another vaccine, detailed investigations as per guidelines laid down by WHO need to be conducted.³¹

³⁰ Follow up periods reported in literature for myocarditis/pericarditis vary in different prospective studies/ smallpox vaccine trials (if clinically indicated up to 5-6 years).

³¹Global manual on surveillance for adverse events following immunization World Health Organization, 2014 (revised March 2016) available at http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/

All reported AEFI cases are to be line listed (Annex 5), to help identify any trends in the causes of AEFI (defined in section 2.7). Serious cases need to be investigated using the standard AEFI investigation procedures outlined in the WHO's Global manual on surveillance for adverse events following immunization,³¹ which can be accessed at

http://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf .

A brief outline on the steps of conducting an AEFI investigation for serious AEFI cases is available online at

http://www.who.int/vaccine_safety/initiative/investigation/New_aide-memoire_AEFI.pdf.

It is recommended that the standard AEFI investigation form for serious AEFI cases be used for this purpose, with special emphasis on events of interest as described in italics, can be found in Annex 6 ³² and can be accessed at

http://www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_form_2Dec14.pdf

2.7 Reporting of the causes of AEFI

Identifying causes of AEFI is an important component of surveillance and monitoring. The following are definitions of causes of adverse events following smallpox vaccination that are to be used in line-listing:³¹

- **Vaccine product-related reaction:** An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product. Table 3 summarises vaccine product related adverse reactions to smallpox vaccines in the WHO stockpile for use in a public health emergency.
- **Vaccine quality defect-related reaction:** An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including the administration device, as provided by the manufacturer.
- **Immunization error-related reaction:** An AEFI that is caused by inappropriate vaccine handling, prescribing or administration, and by its nature, is preventable.

³² http://www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_form_2Dec14.pdf

- **Immunization anxiety-related reaction:** An AEFI arising from anxiety about the immunization.
- **Coincidental event:** An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

Table 3: Clinical features, diagnosis, management and prevention of specific serious AEFI following smallpox vaccination¹

A clinical differential diagnosis also exists for skin lesions and includes amongst others herpesviruses such as *Varicella zoster* (chicken pox). These diagnosis and differentials should be reviewed with clinical specialists². Lesions due to suspected smallpox natural infection or secondary AEFI will require specialized expertise and input from infectious diseases and public health physicians for diagnosis and management.

AEFI	Clinical Features and Diagnosis	Management	Prevention
Bacterial infection of the vaccination site with or without associated regional lymph nodes swelling	<ul style="list-style-type: none"> • Most likely causative agents are staphylococci and β-haemolytic streptococci bacteria (Group A streptococci). • More common in infants and young children. • Diagnosis made clinically. • Confirmed by culture by swabbing of purulent lesions, aspirated specimens from vesicular or pustular lesions or blood culture if septic symptoms occur. 	<ul style="list-style-type: none"> • Cleaning and debridement of affected area. • Appropriate empiric antibiotic therapy, which is then modified, based on culture and sensitivity testing. • Applying a loose dressing +/- application of topical antimicrobial to hasten healing. 	<ul style="list-style-type: none"> • Avoid vaccination at site of existing skin infection. • Care of vaccination site to avoid contamination. • Local or systemic antimicrobial use to prevent infection (prophylaxis) is not recommended.
Inadvertent inoculation	<ul style="list-style-type: none"> • Given that vaccination site is frequently pruritic virus is transferred by touch or scratch even with minor breaks to the skin. • The implanted lesions are characteristic of a normal vaccination in healthy 	<ul style="list-style-type: none"> • No specific treatment is required if there is only one or a few implantations. • Administration of vaccinia 	<ul style="list-style-type: none"> • Rule out atopic dermatitis, diseases involving disrupted skin, burns, wounds and inflammatory eye disease in the vaccine or his/her

¹ Source: Surveillance guidelines for smallpox vaccine (Vaccinia) adverse reaction. MMWR 2006; 55 (RR-1).

² <https://www.cdc.gov/smallpox/clinicians/algorithm-protocol.html>

AEFI	Clinical Features and Diagnosis	Management	Prevention
cont.	<p>individuals.</p> <ul style="list-style-type: none"> • In those with cell mediated immunity defects lesions are more extensive, do not heal and may expand. In these individuals immunologic and virologic investigations should be undertaken. • In those with atopic dermatitis or other reasons for skin disruption lesions may be confluent. 	<p>immunoglobulin (VIG) if multiple or confluent lesions in those with atopic dermatitis (where disease can be severe) – see below.</p>	<p>contact prior to vaccination.</p> <ul style="list-style-type: none"> • Vaccination in those patients who have only small areas of skin disruption may be permissible and should be accompanied by counselling on limiting autoinoculation.
Eczema vaccinatum (EV)	<ul style="list-style-type: none"> • Lesions in those with EV are the same as those with primary vaccination and undergo the same evolution. • Large areas of skin may be affected. • Secondary bacterial infection of lesions can also occur. • Untreated patients can present with systemic symptoms and may die of septic shock. • Diagnosis is made in those with history of atopic dermatitis and appearance of lesions. • Contacts can also become infected although the diagnosis is more challenging. Differentiation between 	<ul style="list-style-type: none"> • Urgent VIG to be administered (ideally within 1–2 days). • Usual dose of VIG is 0.6ml/kg body weight, but as much as 1–10ml/kg body weight has been used in life threatening complications.³ • Antibiotic treatment should be based on culture and sensitivity if secondary bacterial or fungal infection present. 	<ul style="list-style-type: none"> • Exercise caution in vaccination in those with atopic dermatitis or other extensive skin disorders.

³ Fulginiti VA, Papier A, Lane JM, Neff JM, Hendersen A. Smallpox vaccination: A review part II: Adverse events. Clinical infectious Diseases 2003; 37:251-271.

AEFI	Clinical Features and Diagnosis	Management	Prevention
cont.	other viruses such as herpes (causing eczema herpeticum – another serious and treatable infection) is also important.	<ul style="list-style-type: none"> • Extensive ICU care if septic shock occurs. 	
Vaccinia keratitis	<ul style="list-style-type: none"> • Lesions on the cornea secondary to implantation of vaccinia virus. • Approximately 7–10 after implantation of the virus into the eye, a central, greying discoform corneal lesion can be seen. • Slit lamp examination by a specialist is necessary. On slit-lamp examination there may be uveal involvement. Corneal lesions can be craterlike, indurated, oedematous and infiltrated. • Diagnosis is made clinically. 	<ul style="list-style-type: none"> • Treatment should be guided by consultation with experienced ophthalmologist (slit lamp examination) is recommended. • Topical antiviral agents and interferon found effective in treating keratitis in experimental investigations. • Controversy over VIG use but it may be considered if keratitis occurs in association with a life threatening complication. 	<ul style="list-style-type: none"> • Instruct vaccinees and contacts of vaccinees to avoid touching, rubbing or performing any manoeuvres that might transfer vaccinia virus to the eye. • Vaccination of those with inflammatory eye disease should be avoided if there are abrasions in the cornea and if steroids are being used to treat the eye disease.

AEFI	Clinical Features and Diagnosis	Management	Prevention
Erythema multiforme (including rare evolution to Stevens-Johnson syndrome)	<ul style="list-style-type: none"> • Diagnosis is made clinically and further investigations are usually not required. • Onset typically 1–2 weeks after vaccination. • Clinical presentation varies but most are benign in nature and require only supportive care. • Mildest form: red irregular patches, which may or may not be extensive. Rash may be symmetric and often involves the palms and soles. • Other forms: urticarial (hives), vesicles (fluid filled) or pustules (rare) can also occur. Rash is often itchy. • Stevens-Johnson syndrome (SJS) (rare) can be life threatening and often involves the whole body as well as conjunctival and corneal inflammation. Extensive skin peeling is seen during this process. 	<ul style="list-style-type: none"> • Most: supportive treatment including antihistamines or antipruritics. • SJS: requires hospitalization and supportive therapy including specialist consultation, including ophthalmology. 	<ul style="list-style-type: none"> • There is no clear method to predict or prevent these reactions. General screening for sensitivities to vaccine or vaccine components may prevent some rashes.
Generalised Vaccinia	<ul style="list-style-type: none"> • This is a specific syndrome resulting from viraemic spread of virus from the vaccination site in presumably healthy individuals. • Typically considered a benign complication of primary vaccination. • Typically appear within a week after vaccination. 	<ul style="list-style-type: none"> • Most cases require no specific treatment. • Extensive or recurrent disease should be treated with VIG. • If there is underlying immunodeficiency, this also requires 	<ul style="list-style-type: none"> • No preventive measures are known. • In those with B-cell immunodeficiency, vaccination risk and benefits must be weighed. In non-emergency setting, live

AEFI	Clinical Features and Diagnosis	Management	Prevention
cont.	<ul style="list-style-type: none"> Lesions (usually similar but smaller than primary vaccination) appear that rapidly evolve to scarring within 5–6 days. Rarely, lesions may recur. Lesions may occur on palms and soles. Important differential diagnosis includes from vesicular or vesiculopapular erythema multiforme, EV, early stages of progressive vaccinia, severe chickenpox and pustular impetigo. 	management.	vaccines are not given to those with immunodeficiencies.
Progressive Vaccinia (PV, Vaccinia necrosum)	<ul style="list-style-type: none"> Most severe complication of smallpox vaccination and is life threatening. Prognosis is poor despite therapy. Occurs because of immune defect (typically a cell-mediated immunity (CMI) defect). The first sign is failure of the primary vaccination site to heal and the patient may not be very ill at this stage. Viraemia ensues and secondary viraemic lesions appear anywhere on the body and are progressive in nature. Enlarged lymph nodes and big spleen can be seen. With progression, toxic or septicaemic shock and disseminated intravascular coagulation appear. 	<ul style="list-style-type: none"> True PV in individuals with profound T cell deficiency is often fatal. No successful cure exists although treatments such as VIG and antivirals should be considered along with expert consultation with infectious diseases specialists. 	<ul style="list-style-type: none"> In the absence of a smallpox outbreak, those with T cell abnormalities should not receive smallpox vaccine.

AEFI	Clinical Features and Diagnosis	Management	Prevention
cont.	<ul style="list-style-type: none"> Patients are susceptible to systemic fungal, parasitic and opportunistic bacterial infections with septicaemia and death. Diagnosis is by clinical appearance and progression of lesions, augmented by identification of immunologic deficit. 		
Congenital vaccinia	<ul style="list-style-type: none"> Infection of fetus in utero may occur rarely. Early fetal death may occur and congenital vaccinia may supervene in third trimester (very rare). Not associated with congenital anomalies. Lesions may be typical of GV or may be progressive in nature, and are often confluent and extensive. Diagnosis, if there is a smallpox outbreak, is by history of vaccination, typical lesions and viral isolation from lesions. Typically results in premature birth and risk of death before or shortly after birth is high. Newborn may have typical GV skin lesions or they may progress. In order to confirm diagnosis, virological studies are needed in the absence of 	<ul style="list-style-type: none"> No known treatment however VIG and antiviral therapy could be used if available although no studies exist on these therapeutics. 	<ul style="list-style-type: none"> Smallpox vaccination of pregnant women should be avoided unless she has been exposed to smallpox, in which case she should be vaccinated as the benefit of vaccination will outweigh the risk of natural disease.

AEFI	Clinical Features and Diagnosis	Management	Prevention
cont.	natural smallpox in the environment or history of maternal vaccination.		
Post vaccinia encephalitis (PVE)/meningoencephalitis (PVEM)	<ul style="list-style-type: none"> • Pathogenesis unknown but is likely to be para- or post-infection. • Mid-brain, cerebral, medullary lesions and spinal lesions have been observed. Myelitis have been observed in one fifth of the cases. • Encephalitis occurs 7–14 days after vaccination – headache, vomiting, drowsiness and fever are the most typical symptoms. • In some severe cases, symptoms progress to include paralysis, incontinence, urinary retention, coma and convulsions. • Death can occur suddenly, usually within a week of onset of symptoms; approximately one quarter of patients die. • Diagnosis is based on temporal association with vaccination (onset within 7–14 days) and meningoencephalitic symptoms. 	<ul style="list-style-type: none"> • Studies should be undertaken to rule out other causes of encephalitis (e.g. herpesviruses) some of which are treatable with antivirals. • No specific therapy for PVE/PVEM. • Supportive care, anticonvulsant and intensive care to be provided as per individual case requirement. • Specialist consultation with neurology and infectious diseases is warranted. 	<ul style="list-style-type: none"> • No specific indicators of susceptibility, although incidence moderately increased in infants.
Myocarditis	<ul style="list-style-type: none"> • Occurs within 6 weeks of vaccination. • Typical clinical presentation of inflammatory heart disease can include 	<ul style="list-style-type: none"> • Supportive. 	

AEFI	Clinical Features and Diagnosis	Management	Prevention
cont.	<p>pain, dyspnoea and palpitations of probable cardiac origin that range from mild to severe.</p> <ul style="list-style-type: none"> Results of specific cardiac diagnostic testing are variable but should include cardiac enzymes and ECG. 		
Pericarditis	<ul style="list-style-type: none"> Occurs within 6 weeks of vaccination. Chest pain typical of pericarditis involves pain made worse when lying down and relieved when sitting up/leaning forward. Pleuritic chest pain. Abnormalities can be seen on ECG. 	<ul style="list-style-type: none"> Supportive. 	
Dilated cardiomyopathy^{4,5} (DCM)	<p>The following criteria must be met in a person who received a smallpox vaccine:</p> <ul style="list-style-type: none"> Cardiac muscle dysfunction characterized by ventricular dilatation and impaired contraction of one or both ventricles. No evidence of DCM or congestive heart failure before vaccination, either by history or by cardiac evaluation, including chest radiography or ECG if available. No other cardiac or non cardiac disease can likely account for the symptoms or abnormalities present; if another cardiac disease co-exists, it is not sufficient to cause the degree of myocardial dysfunction present. 		

⁴ Morgan J, Roper MH, Sperling L, Scheiber RA, Heffelfinger JD, Casey CG et al. Pericarditis and dilated cardiomyopathy after smallpox vaccination among civilians in the United States, Jan – Oct 2013. Clinical Infectious Disease 2008;46:S242-250

⁵ <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0118283>

2.8 Laboratory testing of AEFI specimens

For confirmation and management of AEFI after smallpox vaccination, laboratories with biosafety level BSL3/BSL4 play an important role. The laboratory testing of specimens may include testing of human specimens, vaccines and logistics. WHO has set up the WHO Emerging and Dangerous Pathogens Laboratory Network (EDPLN), made up of global and regional EDPLN networks of high security human and veterinary diagnostic laboratories to assist countries.^{1,2}

Diagnoses of AEFI to smallpox vaccination are mainly carried out on the basis of clinical evaluation and assessment of a careful patient history of recent smallpox vaccination or contact with a recent vaccinee. Laboratory tests for the purpose of AEFI confirmation and management are needed for the clinical diagnosis of the signs and symptoms of the patient. These tests (e.g. blood, urine, radiology, ECG etc.) are based on the provisional clinical diagnosis and recommendations of the treating physician and should be performed in clinical laboratories with BSL4. When evaluating an adverse event from smallpox vaccination, standard laboratory testing should be conducted to rule out other infections, including viral infections (e.g. herpes zoster, varicella, enteroviruses and herpes simplex).

Diagnostic tests for vaccinia are not readily available as these are largely research tools to assist the evaluation, diagnosis and treatment of adverse reactions after smallpox vaccination.³ CDC has prepared guidelines for specific types of specimen to be collected for each serious AEFI following smallpox vaccination.⁴

For further information see:

<https://www.cdc.gov/smallpox/lab-personnel/specimen-collection/vaccinia-specimen.html>

2.8.1 Human specimens

The decision to undertake specific microbiological/virological tests should be made jointly by the treating physician and infectious disease and public health specialists responsible for the management of the smallpox outbreak, based on suspected AEFI as described in Table 3.

¹ <http://www.who.int/csr/bioriskreduction/laboratorynetwork/en/>

² http://www.who.int/csr/disease/OP_EDPLN_FINAL.pdf?ua=1&ua=1

³ Surveillance guidelines for smallpox vaccine (Vaccinia) adverse reaction. MMWR 2006; 55 (RR-1).

⁴ <https://www.cdc.gov/smallpox/lab-personnel/specimen-collection/vaccinia-specimen.html>

There are only a small number of laboratories with specific experience conducting laboratory tests for vaccinia. These include the Dutch National Institute for Public Health and the Environment (RIVM) and Centers for Disease Control (CDC).

For further information see:

https://www.rivm.nl/en/Topics/W/WHO_Collaborating_Centre_Smallpox_Vaccine

<https://www.cdc.gov/smallpox/lab-personnel/specimen-collection/vaccinia-specimen.html>

Diagnostic techniques that can assist in diagnosis of vaccinia are electron microscopy, viral culture and PCR. Positive results should be interpreted with caution, as serologic testing of single serum samples for vaccinia cannot differentiate historical from recent infection. Testing of acute and convalescent sera for antibodies is also difficult, as paired sera samples are seldom available. It is necessary to record the type, date and time of collection of each and every sample. Provision of complete documentation of clinical investigations and medical records related to the incident will assist with correct laboratory investigations.

All smallpox related specimens (including those for biochemical, histopathological and microbiological examination) should be handled in laboratories with biosafety level BSL3/BSL4 that are part of the EDPLN.

If the treating physician suspects a death is due to an AEFI after smallpox vaccination, they may specifically request that an autopsy be performed. Containment measures must be in place when handling the tissues if smallpox or smallpox AEFI are suspected as the cause of death. All post-mortem procedures require standard precautions with use of personal protective equipment, as per CDC guidelines.⁵

2.8.2 Vaccines

Laboratory testing of vaccines would be resource intensive and may not yield useful data. Therefore, the testing of a vaccine lot/batch would be recommended only if the clinical and/or epidemiological information about the AEFI case(s) indicates a potential vaccine quality problem. Samples of vaccines collected, following serious AEFI should be sent to the WHO Collaborating Centre for Smallpox Vaccine,⁶ at RIVM, incorporating also the Centre for Infectious Disease Control and the Centre for Immunology of Infectious Diseases and Vaccines, are equipped specifically for this purpose.

⁵ Surveillance guidelines for smallpox vaccine (Vaccinia) adverse reaction. MMWR 2006; 55 (RR-1).

⁶ http://apps.who.int/whocc/Detail.aspx?cc_ref=NET-86&cc_code=net&institution_full_name=rivm&cc_subject=smallpox&

For further information see:

https://www.rivm.nl/en/Topics/W/WHO_Collaborating_Centre_Smallpox_Vaccine

2.8.3 Logistics

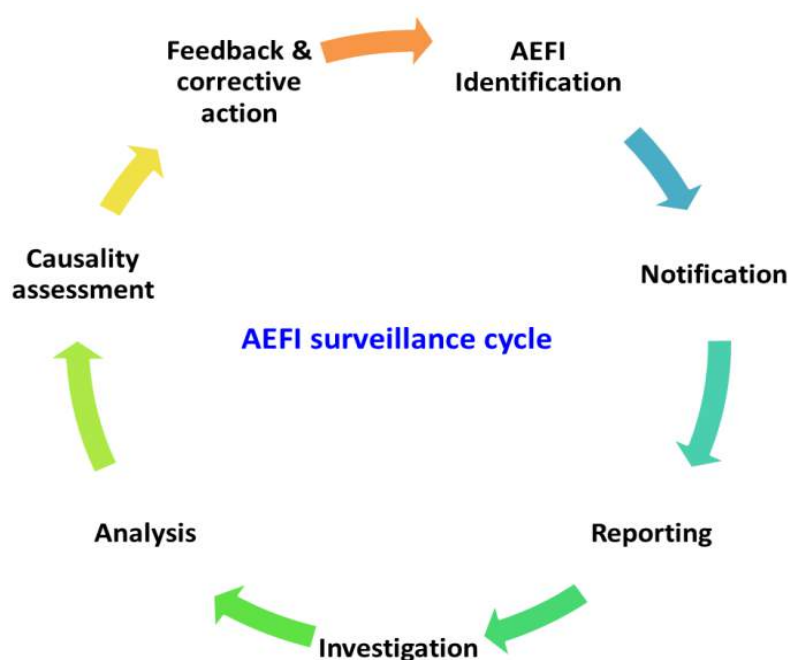
The appropriate specimen in the correct quantity required for the investigation should be collected. Securing samples (vaccine vials, blood etc.), as well as storing and transporting them correctly is important because they may be required later during investigation. The specimens should be stored and transported as recommended and accompanied by clear supporting documents, reasons for specimen collection and any additional information that maybe be required during the outbreak. Where laboratory investigation is required, please use the WHO standard format for a request for laboratory investigation for serious AEFI, provided in Annex 7. The date and time of collection of each sample must be recorded.

For further information see:

<https://www.cdc.gov/smallpox/lab-personnel/specimen-collection/vaccinia-specimen.html>

3. Identifying and responding to serious AEFI after smallpox vaccination in a public health emergency

Figure 2 AEFI surveillance cycle



Identifying and responding to serious AEFI after smallpox vaccination requires the establishment of a surveillance system for serious AEFI (or the enhancement of an existing surveillance system within a country). Such a system reinforces the safe use of all vaccines in the country while also helping to maintain public confidence in vaccination. This is a key component of quality vaccination and should be done systematically. A surveillance system for serious AEFI following smallpox vaccination should be operated in collaboration with all stakeholders, including sharing information and timely updating of the safety profiles of vaccines.

3.1 Objectives of surveillance

The objectives of surveillance if serious AEFI in the context of smallpox vaccine are:¹

- To monitor for known risks of smallpox vaccines, rapidly detect and respond on time to the occurrence of AEFI.
- To identify clustering or unusually high rates of AEFI.

¹ Global manual on surveillance of adverse events following immunization. WHO 2014 (revised 2016)
http://www.who.int/vaccine_safety/publications/aeft_surveillance/en/

- To detect defects in quality of the vaccines.
- To detect, correct and prevent immunization error-related reactions.
- To ensure that co-incidental events are not mistaken with vaccine reactions.
- To maintain public confidence in the immunization programme by appropriate and timely response to their concerns about immunization safety.
- To collaborate and share information with all stakeholders in order to generate additional information on vaccine safety.

3.2 Key components

The key components of an AEFI surveillance system focused on smallpox vaccination are:²

1. **AEFI Identification:** When an adverse event is first identified by the vaccinee, relative or care provider.
2. **AEFI notification:** When an adverse event is brought to the notice of the health care system either by the patient or by his relative.
3. **AEFI reporting:** Follow up for serious adverse events by a health care worker (any person in the health care system) and the information on the event is documented in an AEFI reporting form.
4. **AEFI investigation:** When a detailed enquiry is made for serious AEFI cases and effort taken to collect adequate information so that the underlying cause of the event can be determined.
5. **Analysis:** When the information of the AEFI cases are collated and the data is processed to determine adverse reaction rates and identify epidemiological patterns and signals.
6. **Causality assessment:** When the details of the AEFI is evaluated and it is determined if the event was consistent or inconsistent with vaccination, or is indeterminate.

² Global manual on surveillance of adverse events following immunization. WHO 2014 (revised 2016)
http://www.who.int/vaccine_safety/publications/aeft_surveillance/en/

3.3 Surveillance strategies for monitoring of serious AEFI following smallpox vaccination

Currently, ring vaccination of contacts is recommended following an outbreak of smallpox. However, it is essential that an enhanced AEFI surveillance system is immediately set up prior to the vaccination campaign. The principles of rapidly establishing AEFI surveillance systems for smallpox vaccines are based on the CIOMS guide to active vaccine safety surveillance.³ It is important to remember that these strategies need to be tailor made to the local context.

A serious AEFI surveillance system for smallpox should ideally be undertaken by a National Crisis Management Committee (NCMC). Processes to establish a NCMC and AEFI monitoring are described in Annex 8.

AEFI can be detected, monitored and responded through three types of surveillance systems, each described in detail below.

1. Stimulated passive surveillance.
2. Sentinel surveillance.
3. Active surveillance.

Irrespective of the type of surveillance strategy adopted, when the vaccinee is vaccinated the health care worker should:

- Document the date and time of vaccination on the patient immunization card.
- Provide the details of the vaccine administered, including the batch numbers of the vaccine and diluent.
- Advise potential vaccinees on the likely AEFI that could occur after vaccination.
- Provide contact details of the AEFI focal person or hotline number should an AEFI occur.
- Inform the vaccinee to report ANY other condition that they suspect could be vaccine-related to the hotline at the nearest AEFI monitoring centre (or central AEFI monitoring unit).
- Advise the vaccinee of the need to be referred to the referral health centre for further management.

³ CIOMS Guide to active vaccine safety surveillance: report of CIOMS Working Group on Vaccine Safety. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2017

Reporting of serious AEFI should be carried out using standard case definitions (Annex 3) and in standard formats (Annex 4 and 5). Information on serious AEFI must be sent to the Central Monitoring Unit.

3.3.1 Stimulated passive surveillance

In stimulated passive AEFI surveillance, the staff participating in the immunization activities and other HCWs, are trained in recognising AEFI. Once a serious AEFI is detected, an agreed protocol is used for patient care and management. A channel of communication should be established to transmit AEFI reports and data to the case management team, immunization staff and HCW using these channels. AEFIs that are reported should be followed-up by a central AEFI monitoring unit. Data should be systematically reviewed daily to enable identification of trends in AEFI (signals) and the response team alerted for corrective action. This type of stimulated passive AEFI surveillance provides a sensitive system for the detection and reporting of AEFI.

3.3.2 Sentinel-site based AEFI surveillance and reporting

During ring vaccination using smallpox vaccine, selected health care centres catering to the normal health seeking preferences of populations in the vicinity of the ring vaccination localities need to be identified as smallpox specialist treatment centres i.e. sentinel-sites for AEFI surveillance and reporting.

The following criteria should be considered when selecting a sentinel site:

- It should be willing to participate.
- The population has easy access to it.
- It has staff specially trained to identify and report smallpox cases and smallpox vaccine related AEFI cases.

At the sentinel site, it is necessary to identify a sentinel-site AEFI focal person who is trained specifically in smallpox case detection and management, as well as on smallpox vaccine related AEFI. The sentinel-site AEFI focal person should provide information to the central AEFI monitoring unit.

Sentinel sites need to have well qualified staff that can identify serious AEFI related to smallpox vaccination. In addition, these sentinel sites can provide good quality data on AEFI type and frequency, since currently there is limited data on the safety profile of the new generation smallpox vaccines.

Vaccination strategies should also be adapted to the locations of sentinel sites to assist in the management of AEFI. Sentinel-site based active reporting should also be associated with a stimulated passive surveillance system, and all suspected serious AEFI referred to previously approved health facilities for adequate care.

Sentinel sites should ideally comprise of a limited network of carefully selected reporting sites that can provide comprehensive care for smallpox and also provide smallpox vaccine through their facilities.

It may also be useful to limit the number of sentinel sites. This would allow a more focused effort on reporting through the sentinel sites. An advantage of this approach is that the number of sites can be selected based on available resources; they can be more easily managed and efforts focused on increased reporting may be more effective.

3.3.3 Active surveillance for serious AEFI

In resource limited settings with limited expertise, an event-based active surveillance system may be set up to identify serious AEFI, especially if populations have limited access to formal care.

An AEFI focal team tasked specifically to respond to serious AEFI should be established. The team should be set up before implementing the smallpox vaccination strategy and will be responsible for assessing each reported serious AEFI.

This team should have links to both:

- The local health staff, who will have to be trained and will assist in preliminary investigation of AEFI.
- The designated tertiary care hospital/specialised smallpox treatment centres to promptly provide the requisite treatment for any reported serious AEFI.

The AEFI focal team responding to serious cases should have a designated person to provide information to the central co-ordinating unit. The primary role will be active follow up of vaccinees by telephone, home visit, hospital visits etc. for identification of serious AEFI.

Active surveillance is labour intensive, time consuming and expensive, and is difficult to sustain. Wherever possible, event-based active reporting of serious AEFI should be associated with a stimulated passive surveillance and all suspected serious cases referred to identified hospitals for adequate care.

3.4 Other issues

3.4.1 Organization of the health system to respond to AEFI

Annexes 8 and 9 describe the suggested organization of the health system to best monitor and respond to serious AEFI following smallpox vaccination, and the recommended approaches to reporting, reporting and investigation such AEFI.⁴

3.4.2 Risk Communication

An important aspect of responding to AEFI following smallpox vaccination is risk communication, described in Annex 10. The re-emergence of smallpox would, most likely, cause fear and panic due to the disfiguring effects of the illness and mortality. There might also be increased reporting of AEFI due to heightened public awareness.

3.4.3 Contact details

Contact details for further information and reporting in WHO can be found in Annex 11.

Annex 12 contains links to each of the key documents and forms referred to in this guidance document.

⁴ <https://openwho.org/>

Annex 1 Administration of smallpox vaccine, usual progression of smallpox vaccination and expected events following smallpox vaccination

All health care providers should be trained in administration of smallpox vaccine. All smallpox vaccines currently in the WHO stockpile for use in public health emergency are to be administered by percutaneous injection (scarification) or injectable (MVA is not currently recommended for use in an outbreak situation). This situation might change as newer vaccines get introduced in the stockpile for use in a public health emergency.

1.1 Administration of smallpox vaccines

The vaccine is administered using a bifurcated needle. Each bifurcated needle is sterile and individually wrapped. The needle is designed to hold a minute drop of the vaccine of sufficient size to ensure a vaccine take. The preferred site of vaccination is the deltoid area of the upper arm.

The vaccine is administered giving multiple perpendicular punctures. After vaccination the site should be covered with gauze. The vaccinees should minimize the risk of contact vaccination of the virus by avoiding rubbing or scratching of the vaccination site. The vaccination site must be inspected 6-8 days after vaccination to ensure that a “vaccine take” has occurred.



Vaccinees must be requested to report to the vaccination centre for revaccination if there is no local reaction after 8 days. Gauze used to cover the vaccination site must be put into a plastic bag and safely disposed. Each vaccinee and anyone caring for the vaccination site should wash their hands thoroughly after handling gauze or otherwise touching the site. Vaccinia virus can contaminate the vaccinee's hand or skin and mucosa of others with whom the vaccinee comes into contact. Vaccinees and guardians should be advised that virus can be transmitted from the vaccination site until a scab has formed at the vaccination site.

Vaccination in areas of skin likely to be contaminated by bacteria (buttocks, inner thigh) could result in bacterial infection.

When the smallpox vaccine is inoculated in the skin the reaction that follows is termed as a "vaccine take" or "primary reaction" from first vaccination and a "major reaction" from additional vaccination (there will be no vaccine take if MVA is administered). A vaccine inoculated too deeply in to the skin or without sufficient penetration of the external layer of the skin does not result in infection and is referred to as "no take".

Each vaccine may contain antibiotics and preservatives and specific allergies to these products may occur.

1.2 Usual Progression of small pox vaccination

Following primary vaccination, the usual progression of a vaccine take reaction is as follows: There is no visible skin reaction for the first 3-4 days, after 3-4 days, a papule appears which progresses to a vesicle with surrounding erythema at approximately day 5-6. By day 7-9, the centre of the vesicle umbilicates and pustulates. The pustule crusts, and a dark brown or black scab forms by approximately day 12, which detaches in 2.5- 3 weeks leaving a scar. In some previously unvaccinated persons, vaccination reaction may not occur. In such situations it should be assumed that the individual is not immune and at least 3 attempts (i.e. re-vaccinate) should be made to achieve a primary take, with careful attention to correct technique.

1.3 Expected and normal events in response to vaccination

Health care workers (HCW) involved in smallpox vaccination must be able to identify normal and adverse events after vaccination. An adverse event following immunization is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavourable or unintended sign, an

abnormal laboratory finding, a symptom or a disease. These events may be a vaccine product related reaction, vaccine quality defect related reaction, immunization error related reaction, immunization anxiety related reaction or a coincidental event.

Most of the information on adverse events of first generation vaccines is taken from documentation describing adverse events during the pre-eradication phase; for some of the second generation and third generation vaccines the information is from reports published at the end of the eradication phase, from limited use in military personnel and/or from clinical trials. Below are the expected local and systemic events and adverse events following use of smallpox vaccines. Available evidence on vaccine specific adverse events are given in Annexes 5 and 6.

Expected local events are¹: intense erythema ringing the vaccination site (common); appearance of satellite lesions within ~2.5 cm (1 inch) of the primary vaccination site, local oedema, discomfort and pain and viral cellulitis (intense inflammation surrounding the papule). These events require only symptomatic treatment with anti-inflammatory, antipyretic, antipruritic agents as required.

Robust take (which has to be differentiated from bacterial infection) is a vaccinia cellulitis and is defined as >3 inches (7.5 cm) of redness with swelling, pain and warmth at the vaccination site. In contrast to robust take, superinfections refer to cellulitis caused by agents other than vaccinia. The symptoms peak on days 6-12 post vaccination and regress within the following 24-72 hours. It occurs in 16% of the smallpox vaccinees.

Expected systemic events after vaccination are: soreness at the vaccination site (almost universal); temperature > 37.7°C in the first three weeks after vaccination (2-16%); malaise, myalgia, headache, chills, nausea and fatigue (0.3%- 37%); local lymphadenopathy (25%-50).

¹ Fulginiti VA, Papier A, Lane JM, Neff JM, Hendersen A. Small Pox vaccination: A review Part I. Background, vaccination technique, normal vaccination and revaccination and expected normal reactions. Clinical infectious Diseases 2003; 37:241-250.

Annex 2 Historical data on rates of adverse reactions to smallpox vaccines

Reaction	Rate
Accidental Inoculations	Incidence Rate during eradication campaign (Dryvax) – 24.5 – 529 per million primary vaccination; 1-42 per million re-vaccinations.
Erythema multiforme	Incidence Rate during eradication campaign (Dryvax) – 51.6 -164.6 per million primary vaccinations; 2.1 – 10 per million re-vaccinations.
Generalised Vaccinia (GV)	Incidence Rate during eradication campaign (Dryvax): 23.4- 241.5 per million primary vaccinations; 1.2 – 10.8 per million re-vaccinations.
Erythema Vaccinatum (EV)	Incidence Rate (Dryvax) – 8.1 -80.5 per million primary vaccinations; 0-5.4 per million re-vaccinations.
Progressive Vaccinia (PV)	Incidence Rate during eradication campaign (Dryvax) – 0 - 7 per million primary vaccinations; 0-3 per million re-vaccinations.
Post vaccinal encephalitis (PVE)	Incidence Rate during eradication campaign (Dryvax) – 2.7 – 12.3 per million primary vaccinations, 0-2 per million re-vaccinations. Incidence in Europe during Eradication campaigns – 17- 401 per million vaccinations (primary and re-vaccinations).
Myo/Pericarditis	Initial estimates (Dryvax/ACAM 2000): 17- 160 cases per million vaccinations. 2015- Prospective surveillance study – 4630 symptomatic cases per million vaccinated.
Deaths	PEV, PV, EV are principal causes of death. Historically death rates have been assumed to be 1-2 per million vaccinations.

Annex 3 Case definitions for serious AEFI following smallpox vaccination

Case definitions for reportable serious adverse events following smallpox vaccination

Adverse Reactions	Suspected case	Probable Case	Confirmed case
Superinfection of the vaccination site or regional lymph nodes	<p>A suspected case of superinfection of the vaccination site or regional lymph nodes is defined by the following criteria:</p> <ul style="list-style-type: none"> vaccination site or regional lymph nodes with three or more of the following findings: pain and/or tenderness, warmth, redness, AND other (regional lymphadenopathy; lymphangitic streaking; oedema, induration and/or swelling; fluctuance; and blister with pus or honey-crusted plaque); <p>AND</p> <ul style="list-style-type: none"> Temporal criterion: <ul style="list-style-type: none"> —onset or peak symptoms occur from day of vaccination to day 5 after vaccination and/or day 13–60 after vaccination (excludes days 6–12 after vaccination); <p>AND</p> <ul style="list-style-type: none"> Clinical course: <ul style="list-style-type: none"> —clinical criteria persist or worsen for hours to days after vaccination; patient report is adequate. 		<p>A confirmed case of superinfection of the vaccination site or regional lymph nodes is defined by the following criteria:</p> <ul style="list-style-type: none"> vaccination site or regional lymph nodes with three or more of the following findings: pain and/or tenderness, warmth, redness(regional lymphadenopathy; lymphangitic streaking; oedema, induration and/or swelling; fluctuance; and blister with pus or honey-crusted plaque); <p>AND</p> <ul style="list-style-type: none"> Temporal criterion: <ul style="list-style-type: none"> —symptoms occur from day of vaccination to 60 days after vaccination (inclusive); <p>AND</p> <ul style="list-style-type: none"> Laboratory criteria having one or more of the following findings: <ul style="list-style-type: none"> —positive results of pathogenic culture (e.g., bacterial, fungal, atypical, or nonvaccinal viral culture), —positive microscopy results (e.g., Gram stain, silver stain, acid-fast

			<p>bacillus stain, or dark field) —positive result of bioburden testing of the vaccinia vaccine vial (A positive bioburden test indicates that the accepted limits of bioload have been exceeded and the vaccine is not suitable for use);</p> <p>OR</p> <ul style="list-style-type: none"> • radiographic findings: —findings consistent with superinfection (e.g., lymphadenopathy or abscess) by magnetic resonance imaging (MRI), computed tomography (CT) scan, or ultrasound.
<p>Inadvertent autoinoculation (nonocular)</p>	<p>A suspected case of inadvertent autoinoculation is defined by the following criteria:</p> <ul style="list-style-type: none"> • affected person has been recently vaccinated and had one or more lesions at one or more sites beyond the boundaries of the dressing that was used. Lesions progress morphologically through papule, vesicle, pustule, and scab*; <p>AND</p> <ul style="list-style-type: none"> • lesions appear up to 10 days after the period beginning with initial vaccination or contact through final resolution and scarring of lesions at 	<p>A probable case of inadvertent autoinoculation meets the criteria for a suspected case;</p> <p>AND</p> <ul style="list-style-type: none"> • does not meet the case definition for generalized vaccinia*, eczema vaccinatum, or progressive vaccinia; <p>AND</p> <ul style="list-style-type: none"> • other likely etiologies (e.g., bacterial or viral infection) have been excluded. 	<p>A confirmed case of inadvertent autoinoculation meets the criteria for a suspected or probable case of inadvertent autoinoculation,</p> <p>AND has the following laboratory evidence of vaccinia infection (on the basis of testing skin lesions distant from the vaccination site in a vaccinee):</p> <ul style="list-style-type: none"> • positive test results for vaccinia polymerase chain reaction (PCR) assay or antigen detection techniques (e.g., direct fluorescent assay or direct fluorescent antibody), <p>OR</p> <ul style="list-style-type: none"> • demonstration of vaccinia virus by

	vaccination or contact inoculation site. *Generalized vaccinia should be considered if >20 lesions are present.		culture. See footnote on histopathologic examination ¹
Contact transmission (nonocular)	<p>A suspected case of contact transmission is defined as</p> <ul style="list-style-type: none"> the development of one or more lesions that progress through papule, vesicle, or pustule stages; history of close contact with <ul style="list-style-type: none"> —someone who has received the vaccine <3 weeks before the exposure, <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> —someone who has had autoinoculation GV, EV and PV diagnosed; <p>AND</p> <ul style="list-style-type: none"> lesions appear 3–9 days after vaccinia exposure. 	<p>A probable case of contact transmission meets the case definition for suspected case, and other likely etiologies (e.g., bacterial or viral infection) have been excluded.</p>	<p>For a confirmed case of contact transmission, laboratory evidence of vaccinia infection exists on the basis of testing skin lesions in a close contact of a known vaccinee.</p> <p>Laboratory evidence of vaccinia infection includes:</p> <ul style="list-style-type: none"> positive test results for vaccinia PCR assay or antigen detection techniques (e.g., direct fluorescent antibody) <p>OR</p> <ul style="list-style-type: none"> demonstration of vaccinia virus by culture. <p>See footnote on histopathologic examination¹</p>

¹ Histopathologic examination showing typical orthopox cytopathic changes or electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent PCR or culture.

Ocular vaccinia	<p>A suspected case of ocular vaccinia is defined as the new onset of erythema or oedema of the conjunctiva (conjunctivitis), eyelid (blepharitis), or periocular area or inflammation of the cornea (keratitis) in a recent vaccinee (or close contact of vaccinee) that cannot be ascribed to another ocular diagnosis;</p> <p>AND</p> <ul style="list-style-type: none"> • Temporal criteria: <ul style="list-style-type: none"> —onset after vaccinia exposure but not more than 10 days after the period beginning with initial vaccinia exposure through final resolution and scarring of lesions at vaccination site or exposure site; <p>OR</p> <ul style="list-style-type: none"> —onset during the presence of visible vaccinia lesions before scab separation. 	<p>A probable case of ocular vaccinia is the presentation in or near the eye of lesions consistent with vaccinia infection to include formation of vesicles that progress to pustules that umbilicate and indurate in a manner similar to a normal vaccinia reaction;</p> <p>AND</p> <p>Temporal criteria:</p> <ul style="list-style-type: none"> —onset after vaccinia exposure but not more than 10 days after the period beginning with initial vaccinia exposure through final resolution and scarring of lesions at vaccination site or exposure site; <p>OR</p> <ul style="list-style-type: none"> —onset during the presence of visible vaccinia lesions before scab separation. 	<p>A confirmed case of ocular vaccinia meets the criteria as a probable or suspected case of ocular vaccinia with laboratory evidence of vaccinia infection (testing lesions on or near the eye).</p> <p>Laboratory evidence includes:</p> <ul style="list-style-type: none"> —positive test results for vaccinia PCR assay or antigen detection techniques (e.g., direct fluorescent antibody); <p>OR</p> <ul style="list-style-type: none"> —demonstration of vaccinia virus by culture.
Generalized vaccinia (GV)		<p>A probable case of GV occurs in persons recently vaccinated or in a close contact of a recent vaccinee and meets the following criteria:</p> <ul style="list-style-type: none"> • a vesicular or pustular eruption at one or more body areas distant from the vaccination site or inadvertent inoculation site; <p>AND</p> <ul style="list-style-type: none"> • skin eruption occurring approximately 4–19 days after smallpox vaccination or contact with someone vaccinated against smallpox; 	<p>A confirmed case of GV can occur in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a probable case and no laboratory evidence of vaccinia infection (on the basis of testing skin lesions distal from vaccination site in a vaccinee or distal to likely inoculation site [if identifiable]) exists in a close contact of a known vaccinee or in a patient who is not known to be a close contact.</p>

		<p>AND</p> <ul style="list-style-type: none"> • lesions follow approximately the same morphologic progression as a primary vaccination site (i.e., papule, vesicle, pustule, scab, and scar); <p>AND</p> <ul style="list-style-type: none"> • it is unlikely that autoinoculation accounts for skin eruption; <p>AND</p> <ul style="list-style-type: none"> • other likely etiologies have been excluded. 	<p>Laboratory evidence of vaccinia infection includes:</p> <ul style="list-style-type: none"> —demonstration of vaccinia virus by culture; <p>OR</p> <ul style="list-style-type: none"> —histopathologic examination shows typical orthopox cytopathic changes, and either PCR assay or antigen detection techniques (e.g., direct fluorescent antibody) revealing vaccinia or electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture.
Eczema vaccinatum		<p>A probable case of EV occurs in persons recently vaccinated or in a known close contact of a recent vaccinee and meets the following criteria:</p> <ul style="list-style-type: none"> • a history of, or current, exfoliative skin condition consistent with a diagnosis of eczema/atopic dermatitis or Darier's disease; <p>AND</p> <ul style="list-style-type: none"> • multiple skin lesions that developed <ul style="list-style-type: none"> —in a vaccinated person concurrently or soon after lesion at vaccination site or in a close contact of a recent vaccinee up to 3 weeks after exposure, if time of relevant exposure is known; 	<p>A confirmed case of EV can occur in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a probable case and laboratory evidence of vaccinia infection exists (on the basis of testing skin lesions distal from vaccination site in a vaccinee or distal to likely inoculation site, if identifiable) in a close contact of a known vaccinee or in a patient who is not known to be a close contact.</p> <p>Laboratory evidence of vaccinia infection includes:</p> <ul style="list-style-type: none"> —demonstration of vaccinia virus by culture; <p>OR</p>

		<p>AND</p> <p>—are distant from the vaccination or likely inoculation site (i.e., are unlikely to be satellite lesions);</p> <p>AND</p> <p>—are or have become vesicular/pustular sometime during their evolution (i.e., do not remain macular or papular). Erosive or ulcerative lesions might be observed;</p> <p>AND</p> <ul style="list-style-type: none"> • other likely etiologies have been excluded such as eczema herpeticum (which can be particularly difficult to distinguish), smallpox, chickenpox, disseminated herpes zoster, or pustular (bacterial) impetigo. 	<p>—PCR assay or antigen detection techniques (e.g., direct fluorescent antibody) revealing vaccinia, histopathologic examination showing typical orthopox cytopathic changes, and electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture.</p>
Progressive Vaccinia	<p>A suspected case of PV occurs in persons recently vaccinated or in a known close contact of a recent vaccinee and meets the following criteria:</p> <ul style="list-style-type: none"> • have a known or suspected depressed or defective immune system (suspicion might arise as result of clinical suspicion of PV); <p>AND</p> <ul style="list-style-type: none"> • have a vaccination site lesion or inadvertent inoculation site with one of the following criteria: <ul style="list-style-type: none"> —no or minimal inflammatory response around lesion associated 	<p>A probable case of PV occurs in persons recently vaccinated or in a known close contact of a recent vaccinee and meets the following criteria:</p> <ul style="list-style-type: none"> • a known or suspected depressed or defective immune system; <p>AND</p> <ul style="list-style-type: none"> • a vaccination site lesion or inadvertent inoculation site with one of the following criteria: <ul style="list-style-type: none"> —no or minimal inflammatory response around lesion associated with a non-healing or enlarging vaccination lesion, 	<p>A confirmed case of PV can occur in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a suspected case and laboratory evidence of vaccinia infection exists (on the basis of testing skin lesions at least 15 days after vaccination or likely time of inoculation in a close contact of a recent vaccinee or in persons with no known contact with a vaccinee).</p> <p>Laboratory evidence of vaccinia infection includes:</p> <ul style="list-style-type: none"> • demonstration of vaccinia virus by

	<p>with a non-healing or enlarging vaccination lesion, —progressive expansion at or after 15 days of vaccination, —Failure to heal or failure of lesion to regress at or after 15 days of vaccination;</p> <p>AND</p> <ul style="list-style-type: none"> other likely etiologies (e.g., bacterial superinfection) have been excluded. 	<p>—progressive expansion at or after 21 days of vaccination, —failure to heal or failure of lesion to regress at or after 21 days of vaccination;</p> <p>AND</p> <ul style="list-style-type: none"> other likely etiologies (e.g., bacterial superinfection) have been excluded. 	<p>culture;</p> <p>OR</p> <ul style="list-style-type: none"> histopathologic examination showing typical orthopox cytopathic changes, and either PCR assay or antigen detection techniques (e.g., direct fluorescent antibody) revealing vaccinia or electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture.
Fetal Vaccinia	<p>A suspected case of fetal vaccinia is the presence of any skin lesion in a fetus or newborn exposed to vaccinia virus in utero and no other attributable cause.</p>	<p>A probable case of fetal vaccinia is the presence of multiple skin lesions that might include macules, papules, vesicles, pustules, scars, ulcers, areas of maceration, or epidermolysis (blisters/ bullae) in a fetus or newborn exposed to vaccinia in utero and no other attributable cause.</p>	<p>A confirmed case of fetal vaccinia meets the criteria for a probable case and has laboratory evidence for vaccinia infection.</p> <p>Laboratory criteria for diagnosis includes:</p> <ul style="list-style-type: none"> positive test results for vaccinia virus by PCR assay or antigen detection techniques (e.g., direct fluorescent antibody); <p>OR</p> <ul style="list-style-type: none"> demonstration of vaccinia virus by culture. <p>Vaccinia infection: Fetus, newborn, or product of conception with laboratory evidence of infection and without any clinical symptoms or signs.</p>
Acute encephalitis	<p>A suspected case of encephalitis is defined as the presence of the acute onset of:</p> <ul style="list-style-type: none"> encephalopathy (e.g., depressed or 	<p>A probable case of encephalitis is defined by the acute onset of:</p> <ul style="list-style-type: none"> encephalopathy as outlined for a suspected case; 	<p>A confirmed case of encephalitis is defined as:</p> <ul style="list-style-type: none"> demonstration of acute cerebral inflammation (with or without

	<p>altered level of consciousness, lethargy, or personality change lasting >24 hours);</p> <p>AND</p> <ul style="list-style-type: none"> • clinical evidence suggestive of cerebral inflammation to include one of the following: <ul style="list-style-type: none"> —fever (temperature >100°F [>38°C]) or hypothermia (temperature <95°F [<35°C]), —meningismus (i.e., nuchal rigidity and photo/ phonophobia), —cerebrospinal fluid (CSF) pleocytosis (>5 white blood cells/mm³), —presence of focal neurologic deficit, —electroencephalography findings consistent with encephalitis, —neuroimaging findings on MRI consistent with acute inflammation (with or without meninges) or demyelination of the nervous system, —seizures (either new onset or exacerbation of previously controlled seizures); <p>AND</p> <ul style="list-style-type: none"> • no alternative (investigated) etiologies are found for presenting sign and symptoms. 	<p>AND</p> <ul style="list-style-type: none"> • two or more of the criterion listed for suspected encephalitis as clinical evidence suggestive of cerebral inflammation; <p>AND</p> <ul style="list-style-type: none"> • no alternative (investigated) etiologies are found for presenting sign and symptoms. 	<p>meninges) or demyelination by histopathology;</p> <p>AND</p> <ul style="list-style-type: none"> • no alternative (investigated) etiologies are found for presenting sign and symptoms.
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Acute myelitis	<p>A suspected case of myelitis is defined as presence of the acute onset of:</p> <ul style="list-style-type: none"> myelopathy (development of sensory, motor, or autonomic dysfunction attributable to the spinal cord, including upper- and lower-motor neuron weakness, sensory level, and bowel or bladder dysfunction); <p>AND</p> <ul style="list-style-type: none"> additional evidence suggestive of spinal cord inflammation, to include one of the following: <ul style="list-style-type: none"> —fever (temperature >100°F [>38°C]) or hypothermia (temperature <95°F [<35°C]), —CSF pleocytosis (>5 white blood cells/mm³), —presence of focal neurologic deficit, —electromyographic (EMG) studies suggestive of central (spinal cord) dysfunction, —neuroimaging findings on MRI demonstrating acute inflammation (with or without meninges) or demyelination of the spinal cord; <p>AND</p> <ul style="list-style-type: none"> no alternative (investigated) etiologies are found for presenting sign and symptoms. 	<p>A probable case of myelitis is defined by the acute onset of:</p> <ul style="list-style-type: none"> myelopathy as outlined for a suspected case; <p>AND</p> <ul style="list-style-type: none"> two or more of the criterion listed for suspected myelitis as evidence suggestive of spinal cord inflammation; <p>AND</p> <ul style="list-style-type: none"> no alternative (investigated) etiologies are found for presenting sign and symptoms. 	<p>A confirmed case of myelitis is defined by:</p> <ul style="list-style-type: none"> demonstration of acute spinal cord inflammation (with or without meninges) or demyelination by histopathology; <p>AND</p> <ul style="list-style-type: none"> no alternative (investigated) etiologies are found for presenting sign and symptoms. <p>NOTE: Cases fulfilling the criteria for both encephalitis and myelitis in any category would be classified as encephalomyelitis).</p>
Acute myocarditis	<p>A suspected case of acute myocarditis is defined by the following criteria and</p>	<p>A probable case of acute myocarditis, in addition to the symptoms of a</p>	<p>A case of acute myocarditis is confirmed if histopathologic evidence</p>

	<p>the absence of evidence of any other likely cause of symptoms or findings below:</p> <ul style="list-style-type: none"> • presence of dyspnea, palpitations, or chest pain of probable cardiac origin in a patient with either one of the following: <ul style="list-style-type: none"> —electrocardiogram (ECG) abnormalities beyond normal variants, not documented previously, including: <ul style="list-style-type: none"> – ST-segment or T-wave abnormalities, – paroxysmal or sustained atrial or ventricular arrhythmias, – AV nodal conduction delays or intraventricular conduction defects, – continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy; <p>OR</p> <ul style="list-style-type: none"> —evidence of focal or diffuse depressed left-ventricular (LV) function of indeterminate age identified by an imaging study (e.g., echocardiography or radionuclide ventriculography). 	<p>suspected case and in the absence of evidence of any other likely cause of symptoms, has one of the following:</p> <ul style="list-style-type: none"> • elevated cardiac enzymes, specifically, abnormal levels of cardiac troponin I, troponin T, or creatine kinase myocardial band (a troponin test is preferred), <p>OR</p> <ul style="list-style-type: none"> • evidence of focal or diffuse depressed LV function identified by an imaging study (e.g., echocardiography or radionuclide ventriculography) that is documented to be of new onset or of increased degree of severity (in the absence of a previous study, findings of depressed LV function are considered of new onset if, on follow up studies, these findings resolve, improve, or worsen), <p>OR</p> <ul style="list-style-type: none"> • abnormal result of cardiac radionuclide imaging (e.g., cardiac MRI with gadolinium or gallium-67 imaging) indicating myocardial inflammation. 	<p>of myocardial inflammation is found at endomyocardial biopsy or autopsy.</p>
Acute pericarditis	<p>A suspected case of acute pericarditis is defined by the presence of</p> <ul style="list-style-type: none"> • typical chest pain (i.e., pain made worse by lying down and relieved by 	<p>A probable case of acute pericarditis is a suspected case of pericarditis, or a case in a person with pleuritic or other chest pain not characteristic of any</p>	<p>A case of acute pericarditis is confirmed if histopathologic evidence of pericardial inflammation is evident from pericardial tissue obtained at</p>

	<p>sitting up and/or leaning forward)</p> <p>AND</p> <ul style="list-style-type: none"> • no evidence of any other likely cause of such chest pain. 	<p>other disease, that, in addition, has one or more of the following:</p> <ul style="list-style-type: none"> • pericardial rub, an auscultatory sign with one to three components per beat, • ECG with diffuse ST-segment elevations or PR depressions without reciprocal ST depressions that are not previously documented, • echocardiogram indicating the presence of an abnormal collection of pericardial fluid (e.g., anterior and posterior pericardial effusion or a large posterior pericardial effusion alone). 	<p>surgery or autopsy.</p>
Dilated cardiomyopathy**	<p>The following criteria must be met in a person who received a smallpox vaccine:</p> <p>Cardiac muscle dysfunction characterized by ventricular dilatation and impaired contraction of one or both ventricles.</p> <p>AND</p> <p>No evidence of DCM or congestive heart failure before vaccination, either by history or by cardiac evaluation, including chest radiography or ECG if available.</p> <p>AND</p> <p>No other cardiac or non cardiac disease can likely account for the symptoms or abnormalities present; if another cardiac disease coexists, it is not sufficient to cause the degree of myocardial dysfunction present.</p>		

Source: Surveillance guidelines for smallpox vaccine (Vaccinia) adverse reaction. MMWR 2006; 55 (RR-1).

** Morgan J, Roper MH, Sperling L, Scheiber RA, Heffelfinger JD, Casey CG et al. Pericarditis and dilated cardiomyopathy after smallpox vaccination among civilians in the United States, Jan – Oct 2013. Clinical Infectious Disease 2008;46:S242-250

Annex 4 Reporting form for serious adverse events following immunization (AEFI)

AEFI reporting id number: SP-COU-PR-DIS-YR-001

<p>*Patient name:</p> <p>*Patient's full Address:</p> <p>Telephone:</p> <p>Sex: <input type="checkbox"/> M <input type="checkbox"/> F</p> <p>*Date of birth (DD/MM/YYYY): _ _ / _ _ / _ _ _ _</p> <p>OR Age at onset : <input type="checkbox"/><input type="checkbox"/> Years <input type="checkbox"/><input type="checkbox"/> Months <input type="checkbox"/><input type="checkbox"/><input type="checkbox"/> Days</p> <p>OR Age Group: <input type="checkbox"/> < 1 Year <input type="checkbox"/> 1 to 5 Years <input type="checkbox"/> > 5 Years</p>	<p>*Reporter's Name:</p> <p>Institution :</p> <p>Designation & Department:</p> <p>Address:</p> <p>Telephone & e-mail:</p> <p>Date patient notified event to health system (DD/MM/YYYY): _ _ / _ _ / _ _ _ _</p> <p>Today's date (DD/MM/YYYY): _ _ / _ _ / _ _ _ _</p>
--	--

Health facility (or vaccination centre) name:								
Vaccine						Diluent		
*Name	*Date of vaccination	*Time of vaccination	*Primary/ Re-vaccination	*Batch/ Lot number	Expiry date	*Batch/ Lot number	Expiry date	Time of reconstitution

<p>*Adverse event (s):</p> <p><input type="checkbox"/> Fever > 38 °C</p> <p><input type="checkbox"/> Severe local reaction <input type="checkbox"/> > 3 days <input type="checkbox"/> beyond nearest joint</p> <p><input type="checkbox"/> Seizures <input type="checkbox"/> febrile <input type="checkbox"/> afebrile</p> <p><input type="checkbox"/> Abscess</p> <p><input type="checkbox"/> Sepsis</p> <p><input type="checkbox"/> Encephalopathy</p> <p><input type="checkbox"/> Toxic shock syndrome</p>	<p>Describe AEFI (Signs and symptoms):</p>
--	--

<input type="checkbox"/> Thrombocytopenia <input type="checkbox"/> Anaphylaxis <input type="checkbox"/> Other (specify)..... Date & Time AEFI started (DD/MM/YYYY): ___ / ___ / _____ <input type="checkbox"/> <input type="checkbox"/> Hr <input type="checkbox"/> <input type="checkbox"/> Min	
--	--

Smallpox vaccines' specific	
<input type="checkbox"/> Superinfection of the vaccination site or lymph nodes <input type="checkbox"/> Inadvertent autoinoculation <input type="checkbox"/> Contact transmission <input type="checkbox"/> Contact transmission <input type="checkbox"/> Ocular vaccinia <input type="checkbox"/> Anaphylaxis <input type="checkbox"/> Erythema multiforme	<input type="checkbox"/> Generalised Vaccinia <input type="checkbox"/> Eczema Vaccinatum <input type="checkbox"/> Progressive Vaccinia <input type="checkbox"/> Foetal (congenital vaccinia) <input type="checkbox"/> Post vaccinia encephalitis <input type="checkbox"/> Post vaccinia encephalomyelitis <input type="checkbox"/> Myo/pericarditis

*Serious: Yes / No ; ➔ If Yes <input type="checkbox"/> Death <input type="checkbox"/> Life threatening <input type="checkbox"/> Disability <input type="checkbox"/> Hospitalization <input type="checkbox"/> Congenital anomaly	
*Outcome: <input type="checkbox"/> Recovering <input type="checkbox"/> Recovered <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Not Recovered <input type="checkbox"/> Unknown <input type="checkbox"/> Died If died, date of death (DD/MM/YYYY): ___ / ___ / _____ Autopsy done: <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	

Past medical history (including history of similar reaction or other allergies), suffering from any immunosuppressive diseases, taking any immunosuppressive drugs, concomitant medication and other relevant information (e.g. other cases). Were there any cardiovascular risk factors or conditions (e., ischemic heart diseases, myocardial infarction, angina, congestive heart failure, hypertension, smoking etc.) Use additional sheet if needed :
--

First Decision making level to complete:

Investigation needed: <input type="checkbox"/> Yes <input type="checkbox"/> No	If yes, date investigation planned (DD/MM/YYYY): ___ / ___ / _____
--	---

National level to complete

Date report received at national level (DD/MM/YYYY): ___ / ___ / _____	AEFI worldwide unique ID :

Annex 5 AEFI Line listing – CODING AND FORM

5.1 Codes for the line listing form

Codes should be established for area, reaction type, cause of AEFI, and certainty of cause. These will facilitate data recording, data entry and analysis. Because of the potential for coding errors, the code should be double-checked.

Use the following coding for *Cause of AEFI*:

[A1] Vaccine-related	[A2] Immunization error-related	[A3] Immunization anxiety-related	[B] Indeterminate	[C] Coincidental	[D] Inadequate information to classify
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5.2 AEFI line listing example form

[illegible]

Annex 6 AEFI Investigation Form

AEFI INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization – Death / Disability / Hospitalization / Cluster)

Section A		Basic details			
Province/State	District	Case ID			
Place of vaccination (✓): <input type="checkbox"/> Govt. health facility <input type="checkbox"/> Private health facility <input type="checkbox"/> Other (specify) _____					
Vaccination in (✓): <input type="checkbox"/> Campaign <input type="checkbox"/> Routine <input type="checkbox"/> Other (specify) _____					
Address of vaccination site:					
Name of Reporting Officer:		Date of investigation: ____ / ____ / ____			
Designation / Position:		Date of filling this form: ____ / ____ / ____			
Telephone # landline (with code):		Mobile: e-mail:			
<div style="display: flex; justify-content: space-between;"> Patient Name Sex: <input type="checkbox"/> </div> <div style="display: flex; justify-content: space-between;"> M <input type="checkbox"/> F </div> <p>(use a separate form for each case in a cluster)</p> <p>Date of birth (DD/MM/YYYY): ____ / ____ / ____</p> <p>OR Age at onset: ____ years ____ months ____ days OR Age group: <input type="checkbox"/> < 1 year <input type="checkbox"/> 1–5 years <input type="checkbox"/> > 5 years</p> <p>Patient's full address with landmarks (Street name, house number, locality, phone number etc.):</p>					
Name of vaccines/diluent received by patient	Date of vaccination	Time of vaccination	Dose (e.g. 1st, 2nd, etc.)	Batch/Lot number	Expiry date
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
Type of site (✓) <input type="checkbox"/> Fixed <input type="checkbox"/> Mobile <input type="checkbox"/> Outreach <input type="checkbox"/> Other _____					
Date of first/key symptom (DD/MM/YYYY): ____ / ____ / ____ Time of first symptom (hh/mm): ____ / ____					

Date of hospitalization (DD/MM/YYYY): ____ / ____ / ____

Date first reported to the health authority (DD/MM/YYYY): ____ / ____ / ____

Status on the date of investigation (✓): ☐ Died ☐ Disabled ☐ Recovering ☐ Recovered completely ☐ Unknown

If died, date and time of death (DD/MM/YYYY): ____ / ____ / ____ (hh/mm): ____ / ____

Autopsy done? (✓) ☐ Yes (date) _____ ☐ No ☐ Planned on (date) _____

Time _____

Attach report (if available)

Section B Relevant patient information prior to immunization		
Criteria	Finding	Remarks (If yes provide details)
Past history of similar event	Yes / No / Unkn	
Adverse event after previous vaccination(s)	Yes / No / Unkn	
History of allergy to vaccine, drug or food	Yes / No / Unkn	
Pre-existing illness (30 days) / congenital disorder	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause	Yes / No / Unkn	
Patient currently on concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy	Yes / No / Unkn	
For adult women <ul style="list-style-type: none"> Currently pregnant? Yes (weeks) _____ / No / Unknown Currently breastfeeding? Yes / No 		
For infants <p>The birth was <input type="checkbox"/> full-term <input type="checkbox"/> pre-term <input type="checkbox"/> post-term. Birth weight: _____</p> <p>Delivery procedure was <input type="checkbox"/> Normal <input type="checkbox"/> Caesarean <input type="checkbox"/> Assisted (forceps, vacuum etc.) <input type="checkbox"/> with complication (specify) _____</p>		
Section C Details of first examination** of serious AEFI case		
Source of information (✓ all that apply): <input type="checkbox"/> Examination by the investigator <input type="checkbox"/> Documents <input type="checkbox"/> Verbal autopsy <input type="checkbox"/> Other _____ If from verbal autopsy, please mention source _____		
Name of the person who first examined/treated the patient: _____ Name of other persons treating the patient: _____		

Other sources who provided information (specify): _____		
<p>Signs and symptoms in chronological order from the time of vaccination:</p> <p><i>Smallpox specific signs and symptoms in chronological order</i></p> <p>(Please list if there was <i>Superinfection of the vaccination site or lymph nodes, Inadvertent autoinoculation, Contact transmission, Ocular vaccinia, Anaphylaxis, Erythema multiforme, Generalised Vaccinia (GV), Eczema Vaccinatum (EV), Progressive Vaccinia(PV), Fetal (congenital vaccinia), Post vaccinal encephalitis (PVE), Post vaccinal encephalomyelitis (PVEM) Myo/pericarditis, Dilated Cardimyopathy</i></p>		
Name and contact information of person completing these clinical details:	Designation:	Date/time
<p>**Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e.</p> <ul style="list-style-type: none"> • <i>If patient has received medical care</i> – <u>attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below</u> • <i>If patient has not received medical care</i> – obtain history, examine the patient and write down your findings below (add additional sheets if necessary) <p>Provisional / Final diagnosis:</p>		

Section D Details of vaccines provided at the site linked to AEFI on the corresponding day									
Number immunized for each antigen at session site. Attach record if available.	Vaccine name								
	Number of doses								
a) When was the patient immunized? (✓ the <input type="checkbox"/> below and respond to ALL questions)									
<input type="checkbox"/> Within the first vaccinations of the session <input type="checkbox"/> Within the last vaccinations of the session <input type="checkbox"/> Unknown									
In case of multidose vials, was the vaccine given <input type="checkbox"/> within the first few doses of the vial administered? <input type="checkbox"/> within the last doses of the vial administered? <input type="checkbox"/> unknown?									
b) Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?								Yes / No	
c) Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?								Yes / No / Unable to assess	
d) Based on your investigation, do you feel that the vaccine's physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?								Yes / No / Unable to assess	
e) Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?								Yes / No / Unable to assess	
f) Based on your investigation, do you feel that there was an error in vaccine handling (e.g. break in cold chain during transport, storage and/or immunization session etc.)?								Yes / No / Unable to assess	
g) Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?								Yes / No / Unable to assess	
h) Number immunized from the concerned vaccine vial/ampoule									
i) Number immunized with the concerned vaccine in the same session									
j) Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations: _____									
k) Is this case a part of a cluster?								Yes / No / Unkn	
i. If yes, how many other cases have been detected in the cluster?									
a. Did all the cases in the cluster receive vaccine from the same vial?								Yes / No / Unkn	
b. If no, number of vials used in the cluster (enter details separately)									

It is compulsory for you to provide explanations for these answers separately

Section E Immunization practices at the place(s) where concerned vaccine was used	
(Complete this section by asking and/or observing practice)	
Syringes and needles used:	
Are AD syringes/bifurcated needles used for immunization?	Yes / No / Unkn
If no, specify the type of syringes used: <input type="checkbox"/> Glass <input type="checkbox"/> Disposable <input type="checkbox"/> Recycled disposable <input type="checkbox"/> Other	

<i>Specific key findings/additional observations and comments:</i>			
Reconstitution: (complete only if applicable, ✓ NA if not applicable)			
Reconstitution procedure (✓)		Status	
vaccine?	Same reconstitution syringe used for multiple vials of same	Yes	No
		Yes	No
vaccines?	Same reconstitution syringe used for reconstituting different	Yes	No
		Yes	No
Separate reconstitution syringe for each vaccine vial?		Yes	No
Separate reconstitution syringe for each vaccination?		Yes	No
Are the vaccines and diluents used the same as those recommended by the manufacturer?		Yes	No
<i>Specific key findings/additional observations and comments:</i>			

Section F Cold chain and transport	
<i>(Complete this section by asking and/or observing practice)</i>	
Last vaccine storage point:	
Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
If "yes", was there any deviation outside of 2–8 °C after the vaccine was placed inside?	Yes / No
If "yes", provide details of monitoring separately.	
Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No / Unkn
Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unkn
Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unkn
Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No / Unkn
Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unkn
<i>Specific key findings/additional observations and comments:</i>	
Vaccine transportation:	
Type of vaccine carrier used	
Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No / Unkn
Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No / Unkn
Was a conditioned ice-pack used?	Yes / No / Unkn
<i>Specific key findings/additional observations and comments:</i>	

Section G Community investigation (Please visit locality and interview parents/others)
--

Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality? Yes / No / Unknown If yes, describe:

If yes, how many events/episodes?

Of those effected, how many are

Vaccinated: _____

Not vaccinated: _____

Unknown: _____

Other comments:

Section H Other findings/observations/comments
--

<h1 style="margin: 0;">AEFI – LABORATORY REQUEST FORM (LRF)</h1> <p style="margin: 0;">(To be completed by _____. LRF should be accompanied with specimens)</p>																																																																																	
<p>(For Serious Adverse Events Following Immunization)</p>																																																																																	
<p>AEFI category (Encircle): Death / Hospitalized / Cluster / Disability</p>																																																																																	
Province												Case ID																																																																					
District																																																																																	
Sub District																																																																																	
Name of person sending the specimen:														Date of filling LRF :																																																																			
Designation:																																																																																	
Phone Number :																																																																																	
Case Name																																																																																	
Date of Birth												D	D	M	M	Y	Y	Y	Y	Age (in months)								Sex	Male		Female																																																		
Complete Address of the patient with landmarks (<i>Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.</i>)																																																																																	
P	H	O	N	E	-																																																																												
Date of vaccination												D	D	M	M	Y	Y	Y	Y	Date of Onset								D	D	M	M	Y	Y	Y	Y																																														
Date of collection of specimen												D	D	M	M	Y	Y	Y	Y	Time of collection of specimen								H	H	M	M	(AM	PM)																																														
<p>. Precise description of samples:</p> <p>a) For vaccine/diluents specimens: (to be transported in reverse cold chain)</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 15%;">Mention vaccine/diluent</th> <th style="width: 15%;">Quantity sent</th> <th style="width: 25%;">Name of manufacturer (in BLOCK letters)</th> <th style="width: 15%;">Batch no.</th> <th style="width: 15%;">Manufacturing date</th> <th style="width: 15%;">Expiry date</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table> <p>b) For logistics specimens: (AD, reconstitution, disposable syringes)</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 15%;">Mention logistics</th> <th style="width: 15%;">Quantity sent</th> <th style="width: 25%;">Name of manufacturer (in BLOCK letters)</th> <th style="width: 15%;">Batch no.</th> <th style="width: 15%;">Manufacturing date</th> <th style="width: 15%;">Expiry date</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>																												Mention vaccine/diluent	Quantity sent	Name of manufacturer (in BLOCK letters)	Batch no.	Manufacturing date	Expiry date																															Mention logistics	Quantity sent	Name of manufacturer (in BLOCK letters)	Batch no.	Manufacturing date	Expiry date												
Mention vaccine/diluent	Quantity sent	Name of manufacturer (in BLOCK letters)	Batch no.	Manufacturing date	Expiry date																																																																												
Mention logistics	Quantity sent	Name of manufacturer (in BLOCK letters)	Batch no.	Manufacturing date	Expiry date																																																																												

c) For biological product specimen: (CSF, blood, urine, etc.)

2. Test requested:				
3. Preliminary clinical diagnosis (working hypotheses):				
4. Name and complete address of officials to whom laboratory results should be sent:				
Send to	Complete address	Phone/Fax	Mobile	Email ID
National Level				
Province/ state level				
District level				
Others (specify)				

To be completed by lab officials after receiving the specimen

Date of receipt of specimen at laboratory	D	D	M	M	Y	Y	Y	Y
Name of person receiving specimen(s) at laboratory								
Condition of specimen upon receipt at lab (<i>encircle</i>)	Good	Poor	Unknown					
Comments by pathologist, virologist or bacteriologist:								
Date specimen results sent from this lab	D	D	M	M	Y	Y	Y	Y
Name of laboratory professional								
Signature								
Phone number:					Email ID:			

Annex 8 Organizing health systems to respond to serious AEFI following smallpox vaccination

8.1 National Crisis Management Committee

A National Crisis Management Committee (NCMC) will be the national centre spearheading the smallpox emergency response activities in a country. The committee will coordinate the preventive, promotive, curative and rehabilitative efforts undertaken by the national government. The committee will also be involved in the national communication aspects and media management. The NCMC will be represented by (for example) the national focal points from:

1. Ministry of Health
2. Ministry of Home Affairs
3. National committee for managing disasters
4. National Technical Advisory Group for Immunization
5. Disease surveillance and control
6. National immunization safety expert committee.

When establishing a system, the NCMC should define what is the purpose, what is intended to be monitored (serious adverse events) and define who will identify the AEFI and collect information, who and where to report, the timelines, who and how to process data, and analyse and define the outputs of the system and the periodicity of monitoring.

8.2 The central AEFI monitoring unit

In the context of smallpox vaccine deployment, a central AEFI monitoring unit should be established at the district/ province or regional level depending on the area of jurisdiction decided by the national planners. The unit should have a team for vaccine safety and a focal person to lead the team. The hierarchy and reporting structure should be decided by the local planners.

The central AEFI monitoring unit has a pivotal role to coordinate the activities of the field in responding to AEFI reported after smallpox vaccination. All team members of the unit should be specially trained for the specialized activity they undertake. The central AEFI monitoring Unit has the following roles:

1. Obtain information from the field on the locales of the smallpox vaccine deployment and identify the nearest health facilities, specialized smallpox management Centres and district, province and state focal persons as decided by the planners.
2. Maintain a hotline that is fully functional 24/7 and operated by a team that includes a trained Medical person. The team should have information on all aspects of the above as well as capable of differentiating between a serious and non-serious case.
3. Have provision to complete an AEFI reporting form (Annex 4) – preferably an electronic form- with information obtained over telephone.
4. Provide guidance to the patient and health care worker on receipt of information on the AEFI to differentiate between serious and non-serious AEFI and advise on case management (home care or referral).
5. Directly communicate with relevant levels in the hierarchy such as the referral centre, health care provider, specialized smallpox treatment centre and coordinate case triage and case management.
6. Send the electronic copy of the AEFI reporting form for all serious AEFI cases to all levels to initiate action.
7. Maintain a line list of all reported AEFI cases (Annex 5) and do a data analysis and mapping periodically (daily or weekly) to identify clustering or signals.
8. Coordinate with the field investigation team and provide technical and operational expertise
9. Collate information obtained from the field investigation (dossier) and present the same to the national immunization safety expert committee (within the National Crisis Management Committee) for causality assessment.
10. Manage the vaccine safety training and communication in the local area of jurisdiction in the context of the smallpox vaccine deployment.

Annex 9 Establishing a systematic approach to reporting and investigation of serious AEFI following smallpox vaccination

AEFI surveillance systems should be tailored such that all serious AEFI cases identified by vaccinees themselves and/ or their relatives, health care providers and immunization staff are brought to the notice of the health care provider i.e. notification. ALL serious AEFI cases notified to the health care provider should be informed to the central AEFI monitoring unit. The AEFI monitoring unit should document the same using the standard reporting form (See Annex 4).

The focal person in the central AEFI monitoring unit for vaccine safety should discuss (9.1 – Step A) with the reporter/ health care provider and decide if the reportable AEFI should be classified as non-serious or serious case (death, life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity).

For any serious AEFI, the central AEFI monitoring unit should refer the patient and send the reporting form to the referral centre for case management (9.2 – Step B) and alert the district to initiate AEFI investigation (9.3 – Step C). The central AEFI monitoring unit should also send the reporting form to the Immunization Safety Expert committee (part of the NCMC) and to other levels of the hierarchy for information and alert.

The detailed steps are as follows:

- Step A: Notification, reporting and recording
- Step B: Triage and case management and
- Step C: Field investigation of AEFI.

9.1 Step A: Notification, reporting and recording

Notification is the process where the patient brings the AEFI to the notice of the health care system. Reporting is the process when details of the patient, events, vaccine and reporter are documented and recorded in a standard reporting form (Annex 4). Notification to the central AEFI monitoring unit can be made by a patient, by a vaccinator or other HCW.

On notification, the central AEFI monitoring unit will initiate the reporting process by:

1. Thanking the notifier for reporting the AEFI.
2. Assigning a unique report identifying number (e.g. SP-COU-PRO-DIS-YR-001); Where the acronyms stand for the following: SP represents Smallpox, COU the country, PRO – the province or state, DIS – the district, YR – the year of onset and 001 the sequence of the case in that year).
3. Completing ALL details in the AEFI reporting form (Annex 4) with particular attention to the date and time of reporting.
4. Obtaining a detailed address with landmarks.

For ALL serious AEFI cases, the central AEFI monitoring unit should communicate and electronically transmit the AEFI reporting form to:

- The nearest district health authority for AEFI investigation, to initiate AEFI investigation by contacting the district focal person in the locality where the patient resides so that the focal person and a team can conduct field investigation.
- Referral centre and other levels in the hierarchy, depending on the organizational structure for information, to inform them about the patient.
- National Crisis Management Committee (NCMC), for information.

9.2 Step B: Triage and case management

All serious cases are advised to have a clinical examination at a referral hospital.

The purpose of this is to differentiate if the signs and symptoms are due to:

- Coincidental events such as chicken pox, other pox virus infections, meningitis, cardiac and other diseases.
- Adverse event due to smallpox vaccine.
- Smallpox disease.

Once the patient has been clinically confirmed negative to smallpox, the patient should be managed at the referral centre itself or have treatment at a suitable specialist hospital, if necessary.

9.3 Step C: Field investigation of AEFI

Field investigation is coordinated by the central AEFI monitoring unit and is conducted by: visiting the patient, the care provider(s) and the hospital; interviewing

relevant stakeholders (vaccinees, parents, health care provider, treating doctor, vaccine supply focal person); conducting the investigation of the AEFI case; initiating collection of medical reports and relevant samples as required, completion of the AEFI investigation form (Annex 6).

It is necessary to:

- Collect all documentation on the patient regarding the vaccination and the sequence of events leading to the AEFI (including contact tracing).
- Obtain relevant information on the condition of the patient prior to the vaccination.
- Ascertain the particulars, circumstances and procedures around the vaccine used to immunize the affected vaccinee.
- Examine the operational aspects of the programme, even if an event seems to be vaccine product induced or coincidental.
- Determine whether a reported event was a single incident or part of a cluster, and if it is a cluster, confirm that the suspected immunizations were indeed given and the individual vaccines that were used.
- Determine whether unimmunized people are experiencing similar medical incidents.
- Collect and consolidate all the above details for each patient and prepare a dossier.
- Collect information about the vaccines:
 - lot number
 - expiration date
 - diluent
 - manufacturer etc.

Data on serious AEFI should be compiled and analysed.

Annex 10 Risk communication

Risk communication is critical to any health emergency response, including smallpox events. Proactive, timely and regular exchange of information, advice and opinion with working partners and stakeholders, with the public, and directly with the affected communities can help build and maintain trust and increase the uptake of public health advice. Risk communication, as one of the core capacities identified under the International Health Regulations (IHR 2005), indicates key areas for effective risk communication with institutional structures and competencies for coordination, public communication, community engagement and mechanisms to address perceptions, risk behaviours and misinformation.

In the context of smallpox, risk communication should be addressed in the Country Smallpox Contingency Plan. An agency/organization with a dedicated focal point for risk communication, along with experts for continued community engagement and social science, should be identified. The plan should address mechanisms for effective risk communication, which include coordination mechanisms between different responsible sectors/agencies; mechanisms for proactive and timely release of public information; and mechanisms for gathering evidence about public perceptions and concerns on smallpox virus and the vaccine (in particular its safety and efficacy).

Due attention must be paid to translational communications to transform scientific information and health advice into understandable and easy to use communication materials and messages targeted for priority groups in relevant languages, and use communications channels that people prefer and trust.

The plan should also address the possibility of AEFIs occurring during a smallpox vaccination campaign and define clear protocols or Standard Operating Procedures for handling AEFI events.

In countries that have well established systems for conducting risk communication of AEFIs, it may be appropriate to use these systems for smallpox vaccine AEFIs.

Conducting a smallpox vaccination campaign in a community on a precautionary basis, when there is no overt threat from the smallpox virus, would be likely to be very challenging, even without AEFIs. Community leaders, families and individuals may be sceptical of the need for vaccination, and their concerns would need to be

taken very seriously. Existing community engagement networks and trusted interlocutors should be identified to enable effective community engagement.

Conducting a smallpox vaccination campaign after the re-emergence of smallpox virus would be a very different situation. The re-emergence of smallpox, particularly if linked to a bioterrorism incident, would be likely to cause substantial public alarm. At least in the immediate aftermath of the re-emergence, public perception of the risk from the virus would be high, and demand for smallpox vaccination would also be high and would require a risk communication strategy of its own. If fear of the virus remained high, then one or more AEFIs may have little impact on demand for the vaccine.

It may not be practical to rehearse all the scenarios where smallpox vaccine might be used, or how AEFIs might play out. The key point for planners is that they will need to have capabilities and systems in place to rapidly assess the risk perceptions and concerns of the high-risk populations and the general public about:

- the smallpox virus and the smallpox vaccine **ahead of** a vaccine campaign
- the smallpox virus, the smallpox vaccine and any widely reported AEFI(s) **during a** vaccination campaign.

It will also be necessary to assess vaccine hesitancy data from other countries (where available) and other background information to shape risk communication and the overall response.

Messages should be crafted and adapted in light of:

- the risk perception of the high-risk population
- the risk perception of the general public
- barriers identified to the desired health behaviours and/or practices you want to advocate for
- feedback on the effectiveness of earlier risk communication interventions, health messages and practices related to vaccine uptake among high risk populations
- prior data and intelligence on vaccine hesitancy, education levels, health literacy, language and channel preferences.

Effective mechanisms for reaching stakeholders will also need to be regularly reviewed, and may change over time. Nonetheless, frontline health workers (FHW) will likely play an important role in influencing vaccination decisions throughout the campaign. They can also be an important source of feedback on why people chose to get vaccinated or not. Social media channels, as well as traditional media and mass communication, can also be important influencers in many countries.

When a vaccine safety investigation is under way as a result of an AEFI event, the public should be informed about the investigation, the results, and actions taken or planned regarding the event. The public should also be assured that the vaccine safety issue is being investigated and will be resolved, and that the smallpox immunization programme will continue. At the same time, it is crucial to highlight the benefits of immunization even when communicating about an investigation.

WHO Risk Communication web page

<http://www.who.int/risk-communication/en/>

Evidence based guidance on good practice in *Communicating Risk in Public Health Emergencies* is available from WHO at:

<http://www.who.int/risk-communication/guidance/download/en/>

Advice on managing the communication response to Vaccine Safety Events is available from WHO Europe at:

http://www.euro.who.int/_data/assets/pdf_file/0007/187171/Vaccine-Safety-Events-managing-the-communications-response.pdf

OpenWHO <https://openwho.org>

Annex 11 Contact details at WHO

WHO smallpox

Email: smallpox@who.int

<http://www.who.int/csr/disease/smallpox/en/>

Vaccine assessment Prequalification (PQ)

email: vaccprequalification@who.int

http://www.who.int/immunization_standards/vaccine_quality/vq_index/en/

WHO Global Vaccine Safety

email: vaccsafety@who.int

http://www.who.int/vaccine_safety/en/

WHO Emerging and Dangerous Pathogens Laboratory Network

<http://www.who.int/csr/bioriskreduction/laboratorynetwork/en/>

WHO Collaborating Centre for Smallpox Vaccines - RIVM

http://apps.who.int/whocc/Detail.aspx?cc_ref=NET-86&cc_code=net&cc_subject=smallpox&

<http://www.rivm.nl/en/>

WHO Collaborating Centre for Smallpox and Other Poxvirus Infections - CDC

http://apps.who.int/whocc/Detail.aspx?cc_ref=USA-126&cc_subject=smallpox&

<http://www.cdc.gov>

WHO Collaborating Centre for Orthopoxvirus Diagnosis and Repository for Variola Virus Strains and DNA

http://apps.who.int/whocc/Detail.aspx?cc_ref=RUS-104&cc_subject=smallpox&

<http://www.vector.nsc.ru>

Annex 12 Web addresses of key documents and forms

DOCUMENTS:

Global manual on surveillance of adverse events following immunization. WHO 2014 (revised 2016)

http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/

CIOMS Guide to active vaccine safety surveillance: report of CIOMS Working Group on Vaccine Safety. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2017

<https://cioms.ch/shop/product/cioms-guide-to-active-vaccine-safety-surveillance/>

Mid-Level Management Course for EPI Managers BLOCK III: Logistics
Module 9: Immunization safety

<http://apps.who.int/iris/bitstream/handle/10665/260490/9789290233824-eng.pdf?sequence=1&ua=1>

FORMS:

Reporting form for serious AEFI

http://www.who.int/vaccine_safety/initiative/tools/AEFI_reporting_form_EN_Jan2016.pdf?ua=1&ua=1

AEFI Line Listing Form

Can be found in Annex 4 (p108) of the Global manual on surveillance of adverse events following immunization. WHO 2014 (revised 2016). Link appears above.

AEFI Investigation Form

http://www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_form_2_Dec14.pdf?ua=1

AEFI Laboratory Request Form

Can be found in the *Mid-Level Management Course for EPI Managers BLOCK III: Logistics Module 9: Immunization safety*, Annex 6, p56–57. Link appears above.



Access to Medicines, Vaccines and Pharmaceuticals Cluster

<http://www.who.int/medicines/en/>

empinfo@who.int



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