



EBOLA STRATEGY

Global Ebola Vaccine Implementation Team (GEVIT) Practical guidance on the use of Ebola vaccine in an outbreak response

Draft Guidance, May 2016

Draft - Not for Implementation

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Contents

Contents	2
Abbreviations and acronyms	4
Acknowledgements	6
Introduction	8
Purpose of this guide	8
Background	9
Causative agent	10
Clinical signs and symptoms	10
Transmission	10
Diagnosis	11
Laboratory diagnosis	11
Ebola vaccine	11
Ebola vaccine characteristics	13
Ebola virus disease (EVD) vaccine target product profile	13
Ebola vaccination phases	14
1. Pre-epidemic preparedness: minimum requirements	16
1.1 What is required at global/regional level before a possible outbreak	16
1.2 What is required at country level before a possible outbreak	18
2. Alert: action required when there are suspected cases of EVD	23
3. Outbreak response	25
3.1 Case confirmation: immediate action before vaccination	25
3.2 Vaccination response	28
4. Evaluation	30
4.1 Assessment of vaccine delivery	30
4.2 Vaccine effectiveness studies	30
Appendices	31
Appendix A - Ebola vaccines synthesis and documentation	32
Appendix B - Ebola vaccines summary table	33
Appendix C - Overview of proposed roles and responsibilities of constituencies involved in Ebola vaccine outbreak activities	34
Appendix D - Proposed composition and subgroups of Ebola Vaccine Programme Committee	38
Appendix E - Community engagement	41
Appendix F - Community capacity checklist	43
Appendix G - Outline for communications strategy document for Ebola vaccine use	46
Appendix H - Selection of a vaccination strategy	49
Appendix I - Composition and training of vaccination teams	54

Appendix J - Minimum infrastructure of the cold chain and logistics country hub 56

Appendix K - Checklist for vaccination teams and vaccination strategies forecasting tool 61

Appendix L - ICG application template 63

Appendix M - Changes to Ebola surveillance systems to incorporate use of vaccines in outbreak response 64

Appendix N - Monitoring plan during vaccine delivery..... 69

Appendix O - Assessment plan after vaccine delivery 74

Appendix P - Standard practical steps..... 79

Appendix Q - Macro planning template..... 80

Appendix R - Potential study designs for field studies of Ebola vaccine effectiveness 81

draft Ebola strategy

Abbreviations and acronyms

AD	auto disable (syringes)
AEFI	adverse event following immunization
AR	attack rate
C4D	communication for development specialist
CCL	cold chain and logistics
CDC	Centers for Disease Control and Prevention (US)
EBOV-GP	Ebola virus glycoprotein
EHF	Ebola haemorrhagic fever
ELISA	enzyme-linked immunosorbent assay
EVD	Ebola virus disease
EVA	Ebola outbreak response vaccination activities
FLWs	front-line workers
GACVS	WHO Global Advisory Committee on Vaccine Safety
Gavi	Gavi, the Vaccine Alliance
GEVIT	Global Ebola Vaccine Implementation Team
GOARN	Global Outbreak Alert and Response Network
HBR	home-based record
HCW	health-care workers
ICC	Inter-agency Coordination Committee
ICG	International Coordinating Group
ICG EBOV	ICG for the provision of Ebola vaccine
IDSR	Integrated Disease Surveillance and Response
IEC	information, education and communication (materials)
IFRC	International Federation of the Red Cross and Red Crescent Societies
Ig	immunoglobulin
IPC	infection prevention and control
KAP	knowledge, attitudes and practices (surveys)
NGO	non-governmental organization
NIP	National Immunization Programme
NITAG	National Immunization Technical Advisory Group
NRA	National Regulatory Authorities
NVT	national vaccination team
OR	odds ratio
PCR	polymerase chain reaction
PCM	phase change materials
PHD	long-range passive container high-density
PHEIC	Public Health Emergency of International Concern
PPE	personal protective equipment
R&D	research and development
RNA	ribonucleic acid
RR	risk ratio
RRT	rapid response team
RT-PCR	reverse transcriptase-polymerase chain reaction

SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SG	Steering Group (GEVIT)
SOPs	standard operating procedures
SMS	short message service (texts)
TPP	target product profile
ToRs	terms of reference
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VE	vaccine effectiveness
VHF	viral haemorrhagic fever
WG	Working Group (GEVIT)
WHO	World Health Organization

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Acknowledgements

This document is the result of the collaborative efforts of the **Global Ebola Vaccine Implementation Team (GEVIT)** which associates representatives from **countries** most affected by the 2014/2015 Ebola virus disease (EVD) outbreak (**Guinea, Liberia and Sierra Leone**) and from partners including the **Bill & Melinda Gates Foundation (BMGF)**, the **United States Centers for Disease Control and Prevention (CDC)**, **Gavi**, the **Vaccine Alliance (Gavi)**, the **United Nations Children's Fund (UNICEF)**, United States Agency for International Development (**USAID**) and the **World Health Organization (WHO)**.

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This guide was developed and adapted on the basis of existing tools and country experience gained during the 2014/2015 outbreak, and through a series of plenary and working group or subgroup workshops, coordinated by GEVIT and held in Geneva between January and October 2015 with the assistance of international experts.

GEVIT wish to thank the following colleagues for their vital contribution and extensive work during the preparation of this guide.

CDC:

Adam MacNeil, Conchi Estivariz, Danni Daniels, Emily Cloessner, Gavin Grant, Jennifer Harris, John Stevenson and Margaret Watkins.

Gavi:

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WHO in Geneva:

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Special thanks also to all country representatives who reviewed the preliminary drafts, contributed to the workshops and provided invaluable feedback.

WHO extends its gratitude to Gavi, the Vaccine Alliance, for its financial support.

This document has been produced with the financial assistance of Gavi, the Vaccine Alliance. The views expressed herein may in no way be taken to reflect the official opinion of Gavi, the Vaccine Alliance.

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Introduction

Purpose of this guide

The purpose of this guide is to **serve as a resource to governments and partners as they plan for use of Ebola vaccine in an Ebola virus disease (EVD) outbreak response.**

The guide aims to:

- improve understanding of the technical specificities of Ebola vaccines and the possible strategies for outbreak response vaccination;
- guide global partners and countries on preparedness plans to facilitate rapid vaccination response activities in the event of a future Ebola outbreak;
- assist countries in the decision-making process regarding use of Ebola vaccine in the event of an outbreak;
- guide countries on the steps that will be required to utilize Ebola vaccine during an Ebola outbreak.

The guide is not intended to be a prescriptive methodology. This current version focuses specifically on areas where Ebola vaccination activities differ from other outbreak response vaccination activities and should be read alongside the WHO Ebola Strategy, Ebola and Marburg virus disease epidemics: preparedness, alert, control and evaluation, August 2014.¹ It is based on the following assumptions.

- The vaccine will be primarily used in two complementary approaches: protection of high-risk individuals (primarily health-care workers and front-line workers) and specific groups of the general population in the outbreak setting.
- The presentation, as well as instructions for storage, handling and administration of the licensed vaccine to be distributed will be identical to that used in clinical trials at the time this version of the guide was issued.
- The guide will be updated periodically to include additional information on clinical trials and licensing decisions, as well as international guidance on use.

As of April 2016, there is no Ebola vaccine registered for use outside the context of clinical trials or expanded use of an investigational vaccine under exceptional circumstances. Therefore, recommendations for use of vaccine that have governed the development of this version of the guide, will only apply once regulatory authorization for use outside such settings has been obtained.²

¹ Ebola and Marburg virus disease epidemics: preparedness, alert, control, and evaluation. Geneva: World Health Organization; 2014 (WHO/HSE/PED/CED/2014.05; http://www.who.int/csr/resources/publications/ebola/manual_EVD/en/).

² World Health Organization Strategic Advisory Group of Experts (SAGE) on Immunization. Report of the meeting of October 2015 (<http://www.who.int/wer/2015/wer9050.pdf?ua=1>).

Background

The **Ebola virus** causes an acute, serious illness that is often fatal if untreated. Ebola virus disease (EVD) first appeared in **1976** in two simultaneous outbreaks, one in Nzara, the Sudan, and the other in Yambuku, **Democratic Republic of the Congo**. The latter occurred in a village near the Ebola River, from which the disease takes its name.^{3 4}

The **2014/2015 outbreak in West Africa** (first cases notified in March 2014), was the largest and most complex Ebola outbreak since the Ebola virus was first discovered. There have been more cases and deaths in this outbreak than in all others combined.⁵ From the beginning of the outbreak, to 25 November 2015, 28 637 confirmed, probable and suspected cases of EVD have been reported in Guinea, Liberia and Sierra Leone, with 11 314 deaths.⁶ The majority of these cases and deaths were reported between August and December 2014, after which case incidence has begun to decline as a result of the rapid scale-up of treatment, isolation and safe burial capacity in the three countries. Males and females were equally affected. Most cases, 58.6%, were seen in 15–44 year olds, with 18.8% cases in children less than 15 years old and 22.5% cases aged over 45 years. From 1 January 2014 to 31 March 2015, 815 confirmed and probable health-care worker (HCW)/front-line worker (FLW) EVD cases have been recorded, with a case fatality of 66%.⁷ EVD spread from Guinea across land borders to Sierra Leone and Liberia and then subsequently to Senegal and Mali. The outbreak has also spread via passengers on air travel to Nigeria and the United States of America. In total, 54 cases so far have been reported outside the three most affected countries, and have been controlled, in part, due to rapid implementation of public-health control measures.

On 8 August 2014, the WHO Director-General declared the West Africa outbreak a **Public Health Emergency of International Concern (PHEIC)** under the International Health Regulations (2005).⁸

As part of a comprehensive Ebola research and development effort, which included an accelerated vaccine research and development (R&D) component, a multi-partner **Global Ebola Vaccine Implementation Team (GEVIT)** was created, under WHO leadership, in order to facilitate the collaborative planning for the potential use of Ebola vaccines.⁹ GEVIT has incorporated knowledge from the countries most affected by the current EVD outbreak and key partners who will be involved in procuring and introducing an Ebola vaccine: the Bill & Melinda Gates Foundation; US Centers for Disease Control and Prevention (CDC); Gavi UNICEF, USAID and WHO.

GEVIT is led by a Steering Group (SG) with a structure consisting of three Working Groups (WGs): Vaccine Supply, Allocation and Procurement; Country Implementation, and Monitoring, Surveillance and Impact Evaluation. The scope of work of GEVIT is to support affected countries in their efforts to plan for the potential deployment of Ebola vaccines, in accordance with WHO recommendations, and with the following two main objectives.

- 1) To support development and dissemination of tools and guidelines, synthesis of evidence to inform strategies and policies, including community engagement strategies.
- 2) To provide capacity and work with countries and partners to develop and implement their country plans, and to enable and facilitate in-country planning, management and coordination mechanisms.

³ Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ. 1978;56(2):271–293. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2395567/>

⁴ Ebola virus disease. Geneva: World Health Organization; 2015 (WHO Fact Sheet, No. 103); <http://www.who.int/mediacentre/factsheets/fs103/en/>, accessed August 2015).

⁵ Outbreaks chronology: Ebola virus disease. Atlanta: Centers for Disease Control and Prevention (US); (<http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html>, last updated April 2016).

⁶ Ebola situation report, 25 November 2015. Geneva: World Health Organization; 2015 (<http://apps.who.int/ebola/current-situation/ebola-situation-report-25-november-2015>, accessed November 2015).

⁷ Health worker Ebola infections in Guinea, Liberia and Sierra Leone. Preliminary report. Geneva: World Health Organization; 2015 (WHO/EVD/SDS/REPORT/2015.1; <http://www.who.int/csr/resources/publications/ebola/health-worker-infections/en/>).

⁸ WHO Statement on the First Meeting of the IHR Emergency Committee on the 2014 Ebola outbreak in West Africa, 8 August 2014 (<http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/>, accessed August 2014).

⁹ First workshop of the partners group on Ebola vaccines deployment., 24–26 February 2015. Summary report. Geneva: World Health Organization; 2015 (<http://www.who.int/csr/resources/publications/ebola/vaccines-deployment-workshop/en/>).

It has been clear from the 2014/2015, and previous outbreaks, that a rapid response is necessary to minimize the impact of the outbreak. In order to achieve this, significant planning and development of in-country systems for surveillance and response are required before an outbreak occurs. Mathematical modelling data also strongly support the necessity of rapid vaccination response activities to ensure optimal impact. The scope of work and objectives of GEVIT are to support affected countries in their efforts to prepare for potential vaccine use outside the context of clinical trials or expanded use of a licensed product, and as per WHO recommendations. To this end, GEVIT and partners (see “Acknowledgements” section of this document) have developed this practical guidance for use of Ebola vaccine.

Causative agent

Ebola haemorrhagic fever is caused by the Filoviridae family of viruses, of which Marburg virus is also a member.¹⁰ The Filoviridae are characterized as enveloped, non-segmented, negative stranded ribonucleic acid (RNA) viruses. Ebola virus was first identified in 1976 in the Republic of Zaire, now known as the Democratic Republic of the Congo. There are five known subtypes of Ebola viruses: Bundibugyo, Côte d’Ivoire, Reston, Sudan and Zaire, named after the location where they were first identified. Ebola Zaire, Sudan and Bundibugyo subtypes have been associated with large viral haemorrhagic fever (VHF) outbreaks characterized by high person-to-person transmission and a case-fatality rate ranging from 25%–90%, whereas Côte d’Ivoire and Reston subspecies have not been associated, to date, with VHF outbreaks in humans.¹ Zaire strain has been associated with the highest case-fatality rates.¹¹ For the past 38 years, confirmed EVD outbreaks were small, ranging in size from as few as one person, to as many as 425 individuals, until the latest outbreak in West Africa, which began in 2014.¹²

Clinical signs and symptoms

Ebola virus causes an acute and serious illness, which is usually fatal if untreated. The first symptoms are the sudden onset of fever, fatigue, muscle pain, headache, sore throat and impaired kidneys and liver function, which can, in some cases, lead to internal and external bleeding. In 15% to 20% of cases, vomiting, delirium, hiccups and bleeding will occur. These last symptoms are signals of severe electrolyte (potassium, calcium and magnesium) imbalances, and are indicators of serious illness and possible prediction of death.¹³

Transmission

Although not all reservoirs have been identified, Ebola virus has been identified in several animal species, including bats, chimpanzees and forest antelopes.¹⁴ In the 2014/2015 outbreak, infection of human cases with EVD is thought to have occurred from an unidentified animal source.

Person-to-person transmission of Ebola virus occurs through direct contact with the blood, secretions, organs or other body fluids of infected persons, putting HCWs and communities at risk. The incubation period, that is, the time interval from infection with the virus to onset of symptoms is two to 21 days. The latent period (the period from infection to infectiousness) of EVD typically ranges between nine and 15 days (mean 11.8) with serial intervals (the time between disease onsets in one patient and subsequently infected persons) mean 15.3 days.¹⁵

Although “dry” signs and symptoms, such as fever, headache and muscle pains may start earlier, infected persons are not considered to be infectious until “wet” signs and symptoms, i.e. vomiting, diarrhoea, coughing and haemorrhage are present. Persistence of Ebola virus in the semen of recovered men has been

¹⁰ Feldmann, H, Geisbert TW. Ebola haemorrhagic fever. *Lancet*. 2011 ; 377(9768):849–862. (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3406178/>).

¹¹ Townner J, Sealy TK, Khristova ML, Albarino CG, Conlan S et al. Newly discovered Ebola virus associated with hemorrhagic fever outbreak in Uganda. *PLoS Pathog*, 2008;4(11):e1000212 (<http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1000212>).

¹² Outbreaks chronology: Ebola virus disease. Atlanta: Centers for Disease Control and Prevention (US); (<http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html>).

¹³ Ansari AA. Clinical features and pathobiology of Ebolavirus infection. *J Autoimmun*, 2014;55(0):1–9 (<http://www.sciencedirect.com/science/article/pii/S0896841114001309>).

¹⁴ Heaney JL. Ebola: hidden reservoirs. *Nature*. 2015;527:453–455 (<http://www.nature.com/nature/journal/v527/n7579/full/527453a.html>).

¹⁵ Velásquez GE, Aibana O, Ling EJ, Diakite I, Mooring EQ, Murray MB. Time from infection to disease and infectiousness for Ebola virus disease, a systematic review. *Clinical Infectious Diseases*. 2015;61(7):1135–1140 (<http://cid.oxfordjournals.org/content/61/7/1135>).

reported and, although rare, cases of suspected sexual transmission of Ebola have occurred.¹⁶ More surveillance data and research are needed on the risks of sexual transmission, and particularly on the infectivity of virus in semen over time.

The Ebola virus can also be transmitted indirectly, by contact with previously contaminated surfaces and objects. The risk of transmission from these surfaces is low and can be reduced even further by appropriate cleaning and disinfection procedures.

Ebola virus disease is transmitted through contact, and epidemiologic evidence does not indicate the occurrence of airborne transmission of the virus between humans.^{17 18} During prior EVD outbreaks, strict compliance with biosafety guidelines (i.e. appropriate laboratory practices, infection-control precautions, barrier nursing procedures, use of safe and effective personal protective equipment by HCWs caring for patients, disinfection of contaminated objects and areas, safe burials, etc.) has been the main method of protection of health workers.

Diagnosis

Diagnosing EVD in a recently infected person is difficult due to the non-specific early symptoms (such as fever) that are often seen in patients with more common diseases, such as malaria and typhoid fever, in addition to the difficulties of conducting laboratory testing in resource-limited areas. Ebola virus can only be detected in blood after onset of symptoms, most notably fever, which accompany the rise in circulating virus within the body.¹⁹ It may take up to three days after symptoms start for the virus to reach levels detectable by available laboratory tests. Laboratory tests used in diagnosis include polymerase chain reaction (PCR), virus isolation by cell culture, antibody capture enzyme-linked immunosorbent assay (ELISA), serum neutralization and electron microscopy.²⁰

Laboratory diagnosis²¹

The confirmation of cases and deaths by a laboratory using validated diagnostic assays is essential to monitor an outbreak and inform strategic decisions. The symptoms of Ebola are not specific and therefore it is important to confirm a diagnosis, by laboratory test, to identify Ebola patients from non-Ebola patients.²² Where laboratory confirmation is not immediately available, all suspected cases should be considered as Ebola cases and isolated to prevent further transmission until a laboratory diagnosis can be made.

For collection and shipment of specimens, follow-up and interpretation of results, please refer to WHO Ebola Strategy, *Ebola and Marburg virus disease epidemics: preparedness, alert, control and evaluation*, August 2014 (specifically pp. 27–29 and Annexes 6,7 and 8) and WHO Ebola Strategy, *Laboratory diagnosis of Ebola virus disease*, September 2014.²³

Ebola vaccine

Research and development of an Ebola vaccine was accelerated soon after the 2014/2015 outbreak was declared a PHEIC (8 August 2014) and has resulted in many candidates being brought to clinical trials (refer to **Appendix B**).^{24 25} Along with other prevention and control measures detailed elsewhere,¹ it is hoped that an effective vaccine will help to stop future EVD transmission and contribute to the control of an outbreak.

¹⁶ Deen GF, Knust B, Broutet N, Sesay FR, Formenty P, Ross C et al. Ebola RNA persistence in semen of Ebola virus disease survivors - preliminary report. *N Engl J Med*. 2015 (<http://www.nejm.org/doi/full/10.1056/NEJMoa1511410>).

¹⁷ Mahanty S, Bray M. Pathogenesis of filoviral haemorrhagic fevers. *Lancet Infect Dis*. 2004;4(8):487–98.

¹⁸ Baron RC, McCormick JB, Zubeir OA. Ebola virus disease in southern Sudan: hospital dissemination and intrafamilial spread. *Bull World Health Organ*. 1983;61(6):997–1003.

¹⁹ Diagnosis. Atlanta: Centers for Disease Control and Prevention (US) (<http://www.cdc.gov/vhf/ebola/diagnosis/>).

²⁰ Sarwar UN, Costner P, Enama ME, et al. Safety and immunogenicity of DNA vaccines encoding Ebolavirus and Marburg virus wild-type glycoproteins in a phase I clinical trial. *J Infect Dis*. 2015;211:549–57 (<http://www.ncbi.nlm.nih.gov/pubmed/25225676>).

²¹ Ebola response: package and approaches in areas of intense transmission of Ebola virus. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/145724/1/WHO_EVD_Guidance_Strategy_14.2_eng.pdf?ua=1, accessed September 2014).

²² MacNeil A, Farnon EC, Morgan OW et al. Filovirus outbreak detection and surveillance: lessons from Bundibugyo. *J Infect Dis*. 2011;204:S761–S767 (http://www.cdc.gov/vhf/ebola/pdf/Ref26_MacNeil_et_al_Filovirus_outbreak_detection_and_surveillance%20JInfectDis2011-204-S761.pdf).

²³ Interim guidance, laboratory diagnosis of Ebola virus disease. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/134009/1/WHO_EVD_GUIDANCE_LAB_14.1_eng.pdf, accessed September 2014).

²⁴ Ebola vaccines, therapies, and diagnostics - questions and answers. Geneva: World Health Organization; 2015 (http://www.who.int/medicines/emp Ebola_q_as/en/).

Table 1 below outlines some of the differences between vaccination activities with Ebola vaccine and other injectable vaccines frequently utilized for outbreak responses.

Table 1. Differences between Ebola vaccination activities and other outbreak response immunization activities

	Ebola vaccination	Vaccination in other outbreak responses
Target population and indication for use		
Target group	Several options: <ol style="list-style-type: none"> 1. Populations within a specific geographic area OR case contacts and contacts of contacts 2. Populations at increased risk (e.g. HCWs, FLWs) 	Population within a specific geographic area based on outbreak and risk. Occasionally, high-risk individuals will also be targeted
Vaccination activities		
Reaching target population	Combination of fixed site and house-to-house with high levels of infection control needed Tightly linked to Ebola outbreak response activities (especially HCW training and contact tracing)	Primarily fixed/mobile vaccination posts
Infection control	Stringent infection control measures to standard precautions	Standard precautions
Vaccine availability	Limited	Generally available
Vaccine temperature for deployment	Often beyond normal cold-chain temperature: -80°C to -70°C (Non NIP infrastructure)	Usually within the normal cold-chain temperatures 2°C to 8°C or -20°C (NIP infrastructure)
Community engagement	Integrated with the larger EVD response, including other control measures such as safe burial, handwashing, etc. Multiple messages may target specific groups	Focused messaging to the target population (health- and front-line workers, contacts and/or community). Usually, a community has knowledge and experience of disease (e.g. measles, meningitis, cholera)
AEFI	Additional capacity, new forms and closer follow-up	Regular AEFI reporting systems reinforced by a daily follow up for the 48 hours following the vaccination

²⁵ World Health Organization - Immunization, Vaccines and Biologicals, Strategic Advisory Group of Experts (SAGE) on Immunization. Report of the meeting of October 2015 (<http://www.who.int/immunization/sage/meetings/2015/october/en/>).

Ebola vaccine characteristics

A synthesis and documentation of Ebola vaccines, complemented with a table of Ebola vaccine trials, are provided in **Appendices A** and **B**. The documentation will be revised as more data become available and, when relevant, will include a list of all regulatory approved vaccines.

Ebola virus disease (EVD) vaccine target product profile

The WHO has recently published an EVD vaccine target product profile²⁶ that provides target product profiles for two scenarios for use of an EVD vaccine; (a) **reactive/emergency use** in an outbreak (b) **prophylactic use** to protect front-line workers (FLW) and health-care workers (HCW). (**Appendix H** provides a definition of FLW and HCW).

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²⁶ Ebola virus disease (EVD) vaccine target product profile. Geneva: World Health Organization; 2015 (available at www.who.int/entity/immunization/research/target-product-profile/ebolavaccine/en/index.html).

Ebola vaccination phases

This guide outlines a **multidisciplinary, coordinated approach to support rapid implementation of vaccination activities**. This approach describes the measures that need to be implemented during the following four phases.

1. **Pre-epidemic preparedness:** minimum requirements
 - global/regional level
 - country level.
2. **Alert:** additional actions when suspected case of EVD.
3. **Epidemic response:**
 - case confirmation: immediate action before vaccination
 - vaccine response.
4. **Evaluation**

Since this guide takes a timeline approach, there are different parts of the document and appendices that are relevant to different stakeholders.

1. International partners doing preparedness activities and implementation support.
2. Decision-makers deciding on approaches for vaccination and general planning.
3. Implementers who ensure vaccination activities happen on the ground, including:
 - coordination (**Appendices C and D**)
 - planning (**Appendices H, I and J**)
 - team deployment (**Appendix I**)
 - communication (**Appendices E, F and G**)
 - CCL (**Appendix J**)
 - Monitoring and evaluation (**Appendices N and O**)

Figure 1 below outlines the main phases for Ebola vaccine epidemic activities.

Figure 1. Timeline for Ebola vaccine outbreak activities

Timeline for Ebola Vaccine Outbreak Activities



1. Pre-epidemic preparedness: minimum requirements

In April 2015 GEVIT requested that the International Coordinating Group (ICG), an entity coordinating a mechanism for the management and deployment of a stockpile for outbreak vaccines, take responsibility for the allocation of Ebola vaccine (EBOV). The international community, including the WHO Strategic Advisory Group of Experts on Immunization (SAGE), also requested that a similar mechanism for the management and deployment of Ebola vaccine be set up.

The decision-making body of the **ICG for the provision of Ebola Vaccine (ICG EBOV)** is composed of representatives from the four organizations already constituting the ICG Executive Group for other stockpiled vaccines: Médecins Sans Frontières (MSF), International Federation of the Red Cross and Red Crescent Societies (IFRC), UNICEF and WHO.

As is the case with other vaccines, additional expertise and technical advice will be provided, upon request, by a range of partners, experts and research institutions. Vaccine manufacturers, vaccine equipment providers and financial donor institutions will also be consulted.

The mandate of the ICG EBOV is to ensure the rapid, appropriate provision of vaccines and supplies from the stockpile to countries experiencing an Ebola virus disease (EVD) outbreak following a request for vaccine provision by a Ministry of Health or an organization, including any of the partner organizations.

1.1 What is required at global/regional level before a possible outbreak

- An **International Coordinating Group (ICG)** to allocate Ebola vaccines for deployment and to assist with vaccine access.
- **Vaccine to be stockpiled and be ready to be transported to the affected area(s)** as soon as the first EVD case is laboratory confirmed.
- **Initial supplies of bundle vaccines and supplies for vaccination teams to be available and ready for rapid deployment to the field** (please refer to **Appendix K** for further details).
- A **catalogue of the status of the necessary cold-chain equipment for vaccine storage** available at the country level, in addition to a supply of 'stockpiled' cold-chain equipment at the global level to be deployed with the vaccine.
- A **list of technical experts** trained to assist with vaccine delivery (*the list should include existing staff members of global partners and consultants who can be rapidly deployed for longer durations of time*) and possibly linked to the Global Outbreak Alert and Response Network (GOARN): a collaboration of existing institutions and networks, constantly alert and ready to respond. The network pools human and technical resources for rapid identification, confirmation and response to outbreaks of international importance. These experts must be familiar with all aspects of Ebola vaccine deployment, and should be competent to lead vaccination teams in the field with minimal training.
- **Training materials for rapid response teams** to include Ebola vaccine response at regional and national levels.
- **Orientation of teams** at the global, regional and national level, who would likely respond to Ebola outbreaks on the mechanisms and process for rapid vaccine deployment.
- Evaluation and an up-to-date **repository of the VHF** surveillance systems, with focus on their ability to establish surveillance to support Ebola vaccination activities.
- Desktop exercises in countries on how to respond to an Ebola outbreak, including Ebola vaccine response activities.

A shortlist of global readiness objectives, their associated activities and indicators are listed in Table 2.

Table 2. Global readiness objectives activities and indicators for monitoring readiness status of countries to be able to rapidly deploy Ebola vaccine as part of the outbreak response

Domains	Objectives	Activities	Indicators
Cold chain and logistics	Ensure the rapid delivery of cold-chain equipment and supplies	Safely store equipment and supplies at global hub (global hubs are currently located in Accra, Copenhagen and Dubai) that is ready to be rapidly shipped to countries whenever needed	Global hub (e.g. the UN Humanitarian Response Depot in Abu Dhabi, Ghana or Uganda) ready to deploy cold-chain equipment and supplies Hub has an established mechanism to rapidly ship items to countries as needed
Cold chain and logistics	Ensure the rapid delivery of vaccine and associated supplies	Establish vaccine stockpile. Establish the mechanism for immediate shipment of vaccines to countries for rapid response. Ensure that vaccines reach the correct areas	Vaccine stockpile established. Mechanism that estimates and ships immediate needs and subsequent needs is defined and shipment timeline is established
Human resources	Provide technical support for rapid vaccine implementation (available long-term)	Establish a roster of experienced consultants who can be quickly mobilized to support vaccine implementation in affected countries when needed	Experienced individuals identified and roster updated every six months
Human resources	Provide technical support for immediate vaccine implementation (immediate/short-term)	Train and establish roster of staff in partner agencies available for Ebola vaccine deployment	Updated list of staff reviewed every six months
Funding	Ensure funds to support EV deployment are available	Establish a fund for a minimum requirement support	Provision of minimum support funding established and mechanism to get the fund defined
AEFI and safety	Support the establishment of a functioning AEFI surveillance system	Establish an AEFI surveillance system, and vaccine safety monitoring mechanism	Establishment of a well-functioning AEFI surveillance and vaccine safety monitoring systems
Communications	Ensure that countries most likely to be affected by a future	Develop and implement a communications plan at global and country	Communication plans finalized. Competent and experienced

	<p>outbreak are kept informed of developments relating to Ebola vaccines</p> <p>Provide technical support for monitoring and assessing EBV effectiveness</p> <p>Ensure participants in vaccination are monitored for AEFI early management</p>	<p>levels</p> <p>Train and support staff to monitor and assess the vaccine impact (individual effect and population level)</p> <p>Temperature check, telephone call, routine follow-up after vaccination</p>	<p>individuals identified to monitor and assess vaccine impact. 100% of participants monitored after vaccination</p> <p>100% of AEFI cases managed</p>
Strategy, assessment and planning	<p>Integrate Ebola vaccine into Ebola outbreak response plans</p> <p>Ensure mechanisms for Ebola vaccine allocation are available to be rapidly requested</p>	<p>Orient Ebola response teams on the potential role of Ebola vaccine in the setting of an Ebola outbreak</p> <p>Orient technical partners on the ICG-Ebola mechanism and how to submit requests to the ICG</p>	<p>Countries with IDSR training including Ebola vaccine response (at least five staff have completed 30 minute orientation)</p> <p>Countries with at least three staff trained on ICG mechanisms, including application</p>
Monitoring and evaluation	<p>Provide technical support for monitoring and evaluating</p> <p>Reporting after vaccination activities</p>	<p>Strengthen existing capacity and train staff for monitoring activities reporting</p>	<p>Elaboration of a relevant monitoring and evaluation system. Report available</p>

1.2 What is required at country level before a possible outbreak

EVD outbreak responses require robust, rapid and well-coordinated activities. These activities may include Ebola vaccination and are most effective when countries have instituted preparedness for Ebola response, as well as for Ebola vaccination activities. A basic level of readiness to respond before any suspected case is investigated is crucial.

Prior to any outbreak, countries should have a multi-disciplinary team that is well-prepared to handle potential/future outbreaks. To this end, the **National Immunization Programme (NIP)** should be in charge of basic preparedness activities that begin with the identification of potential members for the eventual formation of an **Ebola Vaccine Programme Committee**, which would conduct Ebola vaccine-related programmatic activities under the leadership of the NIP in the case of Ebola vaccine use. Additionally, the **National Immunization Technical Advisory Group (NITAG)**, or similar entity, should consider expanding its membership to include Ebola experts, to be able to eventually provide well-informed technical recommendations to the Ebola Vaccine Programme Committee (see **Appendix C** - Overview of proposed roles and responsibilities of constituencies involved in Ebola vaccine outbreak activities).

During the pre-epidemic phase, the WHO Ebola Strategy, *Ebola and Marburg virus disease epidemics: preparedness, alert, control and evaluation*, August 2014¹ recommends that a **surveillance** system is in place to identify **viral haemorrhagic fever (VHF)** cases and **standard infection control precautions are promoted and reinforced** in all health-care settings. In addition to the ones mentioned, other preparations are required for vaccination activities. These include:

- information such as the location of national and international diagnostic laboratories,²⁷ an inventory/list of social mobilization and community engagement structures and personnel and communication plans

²⁷ For further details on diagnostic laboratories, please refer to WHO Ebola strategy, *Ebola and Marburg virus disease epidemics: preparedness, alert, control and evaluation*. Geneva: World Health Organization;2014:(8):73–73 (WHO/HSE/PED/CED/2014.05, http://www.who.int/csr/resources/publications/ebola/manual_EVD/en/).

that can be rapidly updated and implemented depending on the vaccine strategy decided upon. An up-to-date list of technical experts and HCW who may be called upon and should be available as part of EVD preparedness.

- In the case of countries with an Emergency Operations Centre, a decision should be made in advance as to whether vaccine activities will operate within or outside the Emergency Operations Centre.
- The VHF surveillance system should be evaluated with respect to its ability to support a vaccination campaign.²⁸

The surveillance system for VHF will be crucial for Ebola vaccination activities to:

- provide epidemiologic data to guide the vaccination teams in planning and monitoring the outbreak response;
- lead and assist in contact tracing (including contacts of contacts) if ring vaccination is the chosen strategy;
- support assessments of vaccine effectiveness (**Appendix R**) and safety.³⁰

- A trained rapid response team (RRT) should be ready to become active in the event of suspected cases (see “Alert” section).
- The status of the necessary cold-chain equipment for vaccine storage available at the country level (national and sub-national, as relevant) should be evaluated.
- Identify possible locations for placement of cold-chain hubs in the country. A checklist of what is required for these potential sites is found in **Appendix J**.
- An **Adverse Events Following Immunization (AEFI) surveillance system** should be established if it is not already in place (for further details please refer to the present guide companion tool *Guidance for establishing AEFI surveillance systems in countries planning to use Ebola vaccines*, WHO 2015).³⁰
- A repository of **Knowledge, Attitudes and Practices (KAP) surveys**, focus group discussions, documented community feedback on messaging and communications materials used during clinical trials should be established by WHO and shared with countries who are most at risk of a future outbreak, to help inform and speed up the development of communication materials for a future outbreak. Materials used in a new outbreak will need to be adapted to the new context. Additional perception studies should be conducted as necessary.
- A communications strategy and plan for communicating about Ebola vaccine prior to, and during, an Ebola outbreak should be prepared.
- Messaging on practices that prevent Ebola infection in an outbreak should be integrated into health-promotion activities in country – see Table 3 below. Dissemination of information, at both global and country level, about key developments in testing and licensure of Ebola vaccines should be planned for and implemented.

Adverse event following immunization is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. If not rapidly and effectively dealt with, it can undermine confidence in a vaccine and ultimately could have dramatic consequences for immunization coverage and disease incidence.²⁹

²⁸ Consolidated Ebola virus disease preparedness checklist. Geneva: World Health Organization; 2015 (<http://www.who.int/csr/resources/publications/ebola/ebola-preparedness-checklist/en/>, accessed January 2015).

²⁹ Global vaccine safety. Adverse events following immunization (AEFI). Geneva: World Health Organization (http://www.who.int/vaccine_safety/initiative/detection/AEFI/en/).

³⁰ Guidance for establishing AEFI surveillance systems in countries planning to use Ebola vaccines. Geneva: World Health Organization; 2015 (link to be provided).

Table 3. Country readiness objectives, activities and indicators for monitoring readiness status of countries to be able to rapidly deploy Ebola vaccine as part of the outbreak response

Domains	Objectives	Activities	Indicators
<i>Cold chain and logistics*</i>	Ensure availability of the necessary cold-chain equipment for vaccine storage at the country level	Evaluate the presence and status of the necessary cold-chain equipment for vaccine storage available in country	Report produced and readily available
	Secure power supply for uninterrupted Ebola vaccine cold chain	Ensure backup power systems for uninterrupted running of the cold chain necessary for the Ebola vaccine to be installed	Installation/testing report completed and passed
	Ensure presence of active cold-chain hubs in the country/area	Identify possible locations for placement of cold-chain hubs in the country	Updated list of hubs readily available
	Ensure country readiness to store the vaccine	Establish an updated list of sites where the infrastructure (space and power supply) is available to establish a -80°C cold room	Updated list of sites available every six months.
	Establish a satisfactory cold-chain capacity for rapid deployment in the country	Ensure the transportation of deployment teams and material	Transportation means identified and operational instruction displayed
		Ensure that there is enough room space available for the installation of the active cold-chain equipment	Building/installation completed
		Ensure the cold-chain equipment is installed and functional at the final location	Installation/testing report completed and passed
		Identify waste-disposal sites and purchase disposal equipment	Waste-disposal sites identified and operational functions displayed. Equipment necessary for waste disposal readily available
	Ensure country readiness to include vaccination activities in Ebola outbreak response	Trained rapid response team (RRT) in country should be ready to become active in the event of suspected	Updated lists (within the past six months) of individuals trained in Ebola vaccine rapid response strategies in Ministry (UN agencies by country)

		cases	
<i>Human resources</i>	Develop a strong Ebola vaccine cold-chain management capacity	Organize in-country workshop to train national staff on EV cold chain	Workshop report with lists of participants
		Develop/revise existing national CCL SOPs for the management of EV cold chain	SOP documents developed and/or revised and readily available
	Ensure the institutions in charge are aware of how to facilitate/accelerate the logistics process	Clearly designate in-country institutions that will support the logistics for the Ebola vaccine deployment, with established roles and ready to go	Clearance agencies informed and operational functions simplified
	Ensure that technical experts and HCW will be easily identified and called upon as part of EVD preparedness	Develop and maintain a list of technical experts and HCW	Updated list of technical experts and HCW available every six months
<i>Funding</i>	Ensure funds exist for minimum CCL requirements and human resource needs	Establish a fund for a minimum requirement support	Budget for establishing minimum support funding and mechanism to get the fund defined
<i>AEFI and safety</i>	Ensure a functioning AEFI surveillance system is in place	Establish an AEFI surveillance system, and vaccine safety monitoring mechanism	Well-functioning AEFI surveillance and vaccine safety monitoring systems
	Ensure standard infection control precautions are promoted and reinforced	Ensure standard infection control precautions are in place	Infection control precautions in place
<i>Communications</i>	Ensure that countries have a list of social mobilization and community engagement structures and personnel	Establish a list of social mobilization and community engagement structures and personnel	Updated list available every six months
	Ensure a communications plan is in place	Develop and implement a communications plan	Communication plans finalized
	Ensure dissemination of information, messages and integration with health-promotion activities	Develop a plan to disseminate information about key development in vaccine (testing and licensure)	Information on vaccine testing and licensure and messages are shared with relevant stakeholders and integrated into health-promotion activities

<i>Strategy, assessment and planning</i>	<p>Integrate Ebola vaccine into Ebola outbreak response plans</p> <p>Ensure mechanisms for Ebola vaccine allocation are available to be rapidly requested</p>	<p>Orient Ebola response teams on the potential role of Ebola vaccine in the setting of an Ebola outbreak</p> <p>Orient technical partners on the ICG-Ebola mechanism and how to submit requests to the ICG</p>	<p>Countries with IDSR training, including Ebola vaccine response (at least five staff have completed 30-minute orientation)</p> <p>Countries with at least three staff trained on ICG mechanisms, including application</p>
<i>Monitoring and evaluation</i>	<p>Provide technical support for monitoring and evaluating</p> <p>Reporting after vaccination activities</p>	<p>Strengthen existing capacity and train staff for monitoring activities reporting</p>	<p>Elaboration of a relevant monitoring and evaluation system</p> <p>Report available</p>

*Italics denote activities that are common at global/regional level and country level.

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2. Alert: action required when there are suspected cases of EVD

SUSPECTED CASE: illness with onset of fever, no response to treatment for usual causes of fever in the area and at least one of the following signs: bloody diarrhoea; bleeding from gums, bleeding into skin (purpura) or bleeding into eyes and urine.³¹

When the surveillance system detects/reports **suspected human cases of EVD** (please refer to **Appendix C** - Overview of proposed roles and responsibilities of constituencies involved in Ebola vaccine outbreak activities):

a **rapid response team** (RRT) is sent to the site without delay to investigate, confirm or not and take initial control measures as required.

Recommended actions for alert activities (in order of priority) – see Fig. 2 below

- Collecting specimens URGENTLY from suspected case(s) and sending to a national or international reference laboratory, while notifying the district and local authorities about the suspected case.
- Notifying **WHO** of the suspected EVD case(s) and deploying the RRT.
- Evaluating the risk of an outbreak.
- Evaluating local resources, including cold chain and logistics requirements.
- Initiating a communication plan.

For more specific detail on the above, please refer to Chapter 4 of the WHO Ebola Strategy, *Ebola and Marburg virus disease epidemics: preparedness, alert, control, and evaluation*, August 2014.¹

Additional action to prepare for vaccination

The **NIP** should be alerted to:

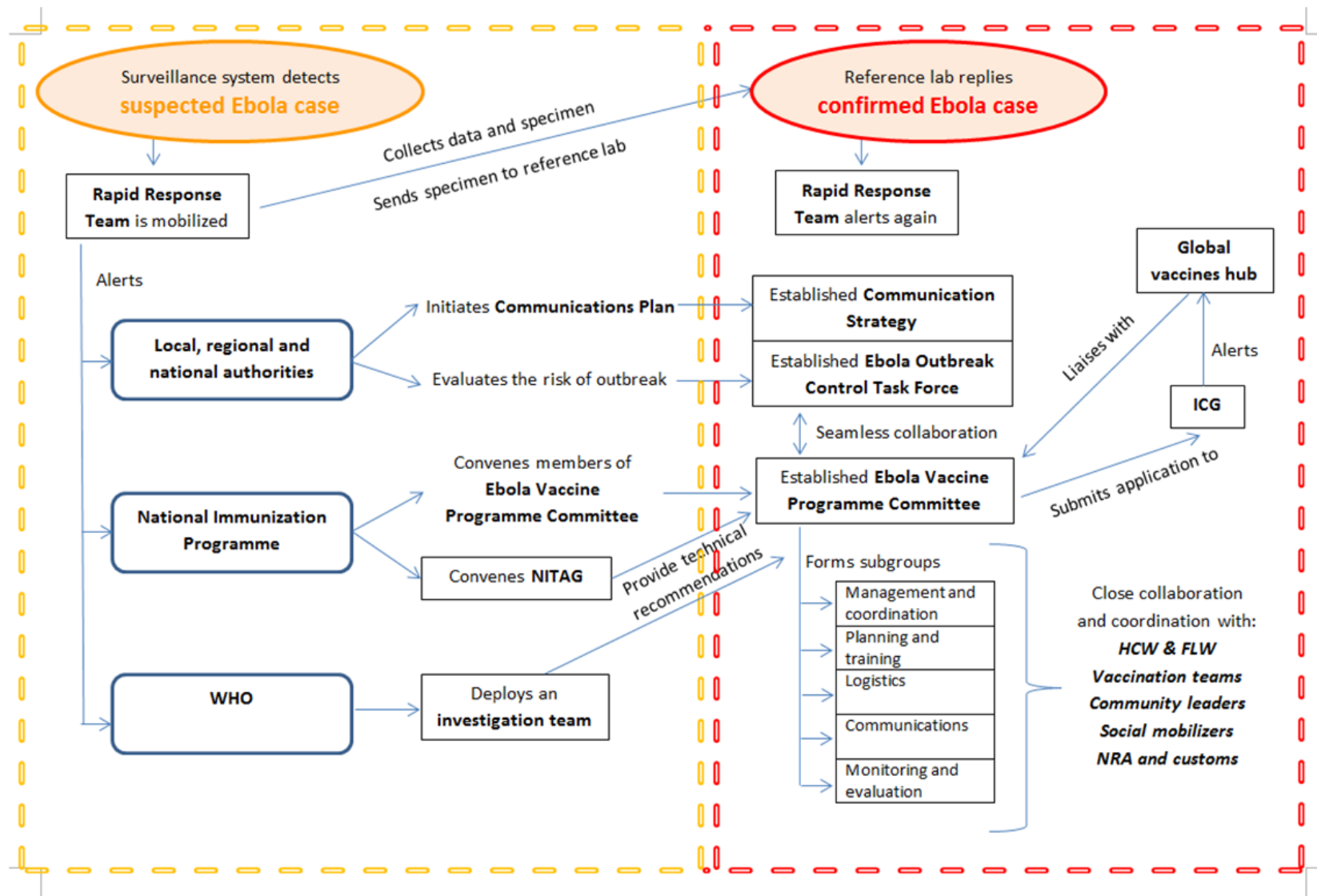
- review vaccine preparedness, including cold chain and logistics requirements and communication strategy;
- establish the **Ebola Vaccine Programme Committee**;
- inform ICG of the situation.

The **NITAG** (including an Ebola expert if at all possible) should be alerted to:

- review the information available;
- be ready to provide technical recommendations if and when the case is confirmed.

³¹ Case definition recommendations for Ebola or Marburg virus diseases. Geneva: World Health Organization; 2014 (<http://www.who.int/csr/resources/publications/ebola/case-definition/en/>).

Figure 2. Main activities to be conducted in the alert phase (suspected cases) and in the immediate vaccine response phase (confirmed case)



3. Outbreak response

3.1 Case confirmation: immediate action before vaccination

The purpose of the **immediate vaccination response** is:

- to rapidly interrupt transmission, targeting the community around the initial case(s);
- to protect uninfected individuals at high risk for infection in the community (including HCW/FLW).

Initial preparations

Once a **case is confirmed** (i.e. the approved reference laboratory has demonstrated a recent infection with Ebola virus)³² the **national RRT** will notify the local, regional and national authorities immediately, as well as **WHO** and partners (WHO Ebola Strategy, *Ebola and Marburg virus disease epidemics: preparedness, alert, control, and evaluation*, August 2014).¹

If there is an available vaccine that could potentially provide protection against the Ebola virus strain, the National Immunization Programme (NIP) should immediately alert the ICG Secretariat and establish an Ebola Vaccine Programme Committee to decide on the likelihood of vaccine efficacy and the choice of the most suitable vaccine, and to take responsibility for a vaccination campaign.

Additionally, the NITAG should develop technical recommendations regarding vaccine-related activities for the Ebola Vaccine Programme Committee to consider and act upon. In those contexts where NITAGs have not yet been established, Inter-agency Coordination Committees (ICCs) may advise.³³

The Ebola Vaccine Programme Committee is ultimately responsible for the management of the vaccine use in country and for making sure that all activities are linked into the greater EVD response. To this effect, the Ebola Vaccine Programme Committee should work in very close collaboration with the **national Ebola Coordination and Resource Mobilization Committee**,¹ also called the national Ebola Outbreak Task Force, which is established by national authorities (usually the Ministry of Health) and meets on a daily basis during an outbreak to give updates on progress made and challenges and opportunities in prevention and control of the disease.

Regular and close communication is of paramount importance to prevent duplication of response efforts between teams, and to ensure that teams use the same communications messages, while strengthening the overall response effort. This communication may be facilitated if a coordinator with sufficient level of authority is identified and stationed within the headquarters of the EVD response, and if meetings are scheduled as needed with principal team actors (refer to **Appendix C** - Overview of proposed roles and responsibilities of constituencies involved in Ebola vaccine outbreak activities).

Once a case has been confirmed, the **Ebola Vaccine Programme Committee should:**

- **select vaccine strategy.** The vaccine strategy should be selected after considering the results of epidemiological and operational assessments, in discussion with global and regional partners.

³² Laboratory diagnosis of Ebola virus disease. Geneva: World Health Organization; 2014 (<http://www.who.int/csr/resources/publications/ebola/laboratory-guidance/en/>, accessed September 2014).

³³ Duclos P. National Immunization Technical Advisory Groups (NITAGs): guidance for their establishment and strengthening. Vaccine. 2010;28S:A18–A25 (<http://www.nitag-resource.org/uploads/media/default/0001/01/223c46c59b1fc5115fbfab56d9687e4ead0790ac.pdf>).

Key points (refer to **Appendix H** - Selection of a vaccination strategy).

- Vaccination of HCWs and FLWs is a priority as they are often among the first cases identified. They are at high risk of contracting EVD and constitute a risk to others.
- Vaccination of HCWs and FLWs should normally be combined with a community vaccination programme through **ring** and/or **geographically targeted** vaccination.
- In ring vaccination, contacts and contacts of contacts are offered vaccination.
- In geographically targeted vaccination, individuals are offered vaccination within a given geographic area.
- Choosing between ring vaccination and geographic vaccination may be challenging.
- Ring vaccination is the preferred approach.
- Targeted geographic vaccination may best be restricted for specific circumstances, for example, when contact tracing is ineffective and incidence is rising rapidly.
- Vaccine strategy should be decided after: (i) a full epidemiological assessment of the outbreak; (ii) an operational assessment of contact tracing effectiveness, availability of vaccines, supplies and trained vaccination teams and cold-chain and waste-management capacity.

- **Set up sub-groups** of the Ebola Vaccine Programme Committee (**Appendix D**).
- **Engage experts:** engage pre-identified and trained local and global EVD and Ebola vaccine experts to facilitate planning and assist with vaccine use.
- **Organize training:** ensure that vaccination teams are trained and ready for deployment (**Appendix I**).
- **Assess cold chain:** assess minimum cold-chain requirements (**Appendix J**). Minimum cold-chain and logistics requirement consists of a central hub and the safe handling and protective gear needed to manage the equipment in this hub. A hub in close proximity to the outbreak area may be sufficient, even if that hub is in another country. When moving to the **comprehensive vaccine response**, the preparation time may be longer: in this second phase a functioning cold chain for deployment and other logistic components needs to be activated and sustainable.
- **Evaluate local resources:** for example, logistical and human resources with the community; missing items; available stock of equipment; means and routes of communication; maps of affected areas, financial need assessments and assessment of health-care settings, etc.
- **Review logistics and develop microplan:** ensure logistics required for implementation (e.g. vaccination teams, transportation) are in place and on standby, and develop microplan/mobilize resources (refer to **Appendices I,J,K**).
- **Coordinate with the ICG** regarding availability of vaccines in the stockpile (based on information shared by the RRT).
 - The **Ebola Vaccine Programme Committee** will **immediately estimate** doses of vaccine and equipment (injection supplies, cold-chain equipment, personal protective equipment (PPE)) needed for an **immediate vaccine response** using the Macroplan Tool (which includes rapid response costing, see **Appendix K**), and **complete** and **submit a first ICG EBOV vaccine request form** (**Appendix L**).

To activate the ICG process it is essential to include the following, as set out in the vaccine request form (incomplete requests will not be considered).

- Epidemiological information.
- Laboratory information.
- Outline of Ebola vaccination strategy (including maps).
- Estimation of vaccines, vaccination kit/ancillary materials needs.

- Estimation of operational costs.

If there is significant concern that the outbreak may not be rapidly contained, the Ebola Vaccine Programme Committee should review plans for a more comprehensive vaccination response and, if needed, complete and submit a **second** EBOV ICG application (using the planning template in **Appendix L**) and using the same vaccine request form.

The ICG will then:

- alert the global hub of potential need for vaccines, associated vaccine supplies and cold-chain equipment (which are stored at the global hub) and request to send them in country.

Once vaccination supplies are approved and the ICG has notified the global hub, the **Ebola Vaccine Programme Committee** will:

- **liaise with the global hub** (please refer to Section 1.1 Table 2 for examples of global hub) to arrange shipping, storage and transport and link with appropriate units (customs, national regulatory authorities (NRA)).
- Ensure that:
 - local **Ebola outbreak response** team in the affected area is notified;
 - **community leaders** are notified of vaccination plan;
 - **HCWs and FLWs** are notified of the upcoming vaccination activities;
 - **vaccination teams** are immediately alerted and ready to:
 - receive the vaccine → **vaccine should be shipped within 3–7 days following the ICG decision** (the ICG has two working days to decide and the time for decision depends on the quality and completeness of the request);
 - determine additional needs for cold chain and waste management for Ebola vaccines; → **the cold chain for Ebola vaccines may require equipment not commonly used in other vaccination activities**;
 - implement vaccination activities the moment the vaccine arrives in country.
- Ensure that communications and social mobilization teams are available and prepared with messages around the need for a vaccine (**Appendices E and G**).
- Ensure that surveillance for EVD and Ebola vaccination campaigns is integrated into the wider outbreak response (**Appendix M**).
- Ensure that AEFI monitoring, response and management systems are in place. For detailed information on how AEFI monitoring should be conducted, along with the relevant forms for monitoring, please see the companion to this guide, *WHO - Guidelines for establishing AEFI surveillance systems in countries planning to use Ebola vaccines*.³⁰
- Ensure that monitoring and evaluation is in place. Monitoring will be necessary for the forms developed for listing eligible individuals, vaccination registers and home-based records, as well as tally sheet and vaccine stock management.³⁴ (**Appendices N and O**).

Final preparations for arrival of the vaccine in country

Before vaccine is shipped from the global hub, several criteria need to be met, especially for a vaccination activity that does not access freezing of phase change materials (PCMs) and vaccine storage. These activities are:

- regulatory approval to use vaccine;

³⁴ For further details on tally sheet, please refer to Monitoring the immunization system – Training for mid-level managers (MLM). Geneva: World Health Organization; 2008 (WHO/IVB/08.05; http://www.who.int/immunization/documents/MLM_module5.pdf). Also, Module 7: Monitoring and using your data – Immunization in Practice: a practical guide for health staff. Geneva: World Health Organization; 2004 (WHO/IVB/04/06; http://www.who.int/immunization/monitoring_surveillance/resources/IIP_Module7.pdf).

- customs clearances pre-arranged ("green light");
- community informed of possible vaccination as part of Ebola case-finding activities;
- vaccination teams assembled AND trained to administer vaccine (includes supplies ready except those travelling with the vaccine);
- plan to deploy vaccine from airport directly to vaccination site, with standby vehicles available

A fast-acting logistics subgroup (as defined in **Appendix D**) is critical to the early stages of the response. A checklist should be considered to ensure that all the required materials are in place and available to the vaccination teams at least 24 hours prior to the vaccination (**Appendix K**). The vaccination teams need to be ready and well prepared, as the vaccine will be available only from a few central locations.

Trained consultants should assist with these activities, and once a country cold-chain hub is established, and the ICG has approved the plan, vaccine may be received at the hub for vaccination activities.

As the cold chain may require several days of preparation, careful timing is required to ensure that there is sufficient cold-chain storage capacity for the vaccine as it moves into the field. It is the responsibility of the logistics team to make sure that the cold chain is activated and ready for deployment on the first day of vaccine use during the comprehensive phase. Once the cold-chain hub, and remaining aspects of the vaccination kits and other logistic components are activated, vaccine is ready to be received (refer to **Appendices K and P**).

3.2 Vaccination response³⁵

Implement vaccination strategy

Typical vaccination campaigns (e.g. oral polio vaccine, measles vaccine) have only an age requirement for vaccination. Ebola outbreak response vaccination is different. For all strategies (ring vaccination, geographic vaccination and HCW/FLW), more detailed information will be needed from individuals to determine vaccination eligibility and, therefore, for individuals who consent to be vaccinated, the amount of data to be recorded in the vaccination register, on the vaccination card and in the vaccine log book may be more extensive.

For each of the proposed vaccination strategies, a complete list of the target population should be available before the vaccination team is sent to the field (unless enumeration and vaccination are jointly conducted as part of a ring vaccination approach) or at the time of consent or refusal. More details about the initial target population lists are given in the Assessment plan after vaccine delivery, **Appendix O**.

For **HCW/FLW vaccination**, the definitions in **Appendix H** will help deployment managers decide who is included in the vaccination deployment target denominator. When the definition of the denominator is established, numerical data is collected from the health facility that should have records on the size of the target population. Vaccination of HCW and FLW may occur within those health centres at highest risk (e.g. closest to recent cases) being prioritized.

For **ring vaccination**, contacts of cases and contacts of contacts should be identified by the contact tracing team in liaison with the vaccination team. The vaccination team should provide vaccination to the contact and their contacts in a single visit, so that enumeration and vaccination are occurring within the first two to three days of confirmation of a case.

For **targeted geographic vaccination**, individuals will be identified by their place of residence and their age. The community should be informed of the time and place of the vaccination. Timing and location should be based upon regional guidelines for vaccination activities in the setting of Ebola, to minimize the vaccination site being a site for transmission. A single village may require several fixed vaccination posts, depending on the state of the epidemic.

³⁵ Guidance for immunization programmes in the African Region in the context of Ebola - WHO information note. Geneva: World Health Organization; 2015 (<http://www.who.int/csr/resources/publications/ebola/ebola-immunization-afro/en/>).

Practical guidance on steps in vaccine delivery of vaccine

Refer to **Appendix P** Standard practical steps, for practical guidance on:

- vaccine storage and handling
- organizing a vaccination post
- screening for eligibility
- vaccine preparation and administration
- documentation of doses
- waste management
- engaging the community
- defining a ring for vaccination
- managing fever after vaccination.

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4. Evaluation

4.1 Assessment of vaccine delivery

For each proposed Ebola vaccine delivery strategy (geographic, ring, HCW and/or FLW), an assessment of vaccine delivery is needed following completion of the activity. The assessment plan should include components for vaccination coverage, data quality, reasons for vaccine refusals or acceptance, wastage, AEFI, human resource adequacy and defaulter tracing.

Of particular note is the key indicator of vaccination coverage. Ebola vaccination coverage assessment will involve a different methodology than coverage estimates that use a probability sample (i.e. post-polio or measles campaign household surveys). Ebola vaccination coverage may be directly calculated for ring vaccination and HCW/FLW vaccination activities, because the target eligible population (denominator) is known and the vaccination status of every individual in the target population (numerator) is known. This is possible because there will be a complete list of all eligible persons and their vaccination status (whether or not they received the Ebola vaccine). For community vaccination activities, it may be necessary to estimate coverage if community population is uncertain. The value of the calculated vaccination coverage is dependent on maintaining a detailed and complete Ebola vaccine register that includes eligibility, refusal or consent and vaccination date.

See **Appendix O** for more detailed discussion of coverage and other post-vaccination assessment components.

4.2 Vaccine effectiveness studies

Vaccine effectiveness under real-world implementation conditions often differs somewhat from the efficacy observed in clinical trials. Hence, the implementation of Ebola vaccine effectiveness studies when the new Ebola vaccine(s) are used for outbreak response would provide important information on the effectiveness of these vaccines under real-world conditions.

Appendix R discusses potential study design options for assessing the effectiveness of a vaccine distributed in response to an EVD outbreak.

Appendices

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Appendix A - Ebola vaccines synthesis and documentation

[hyperlink to Appendix A will be provided at a later stage]

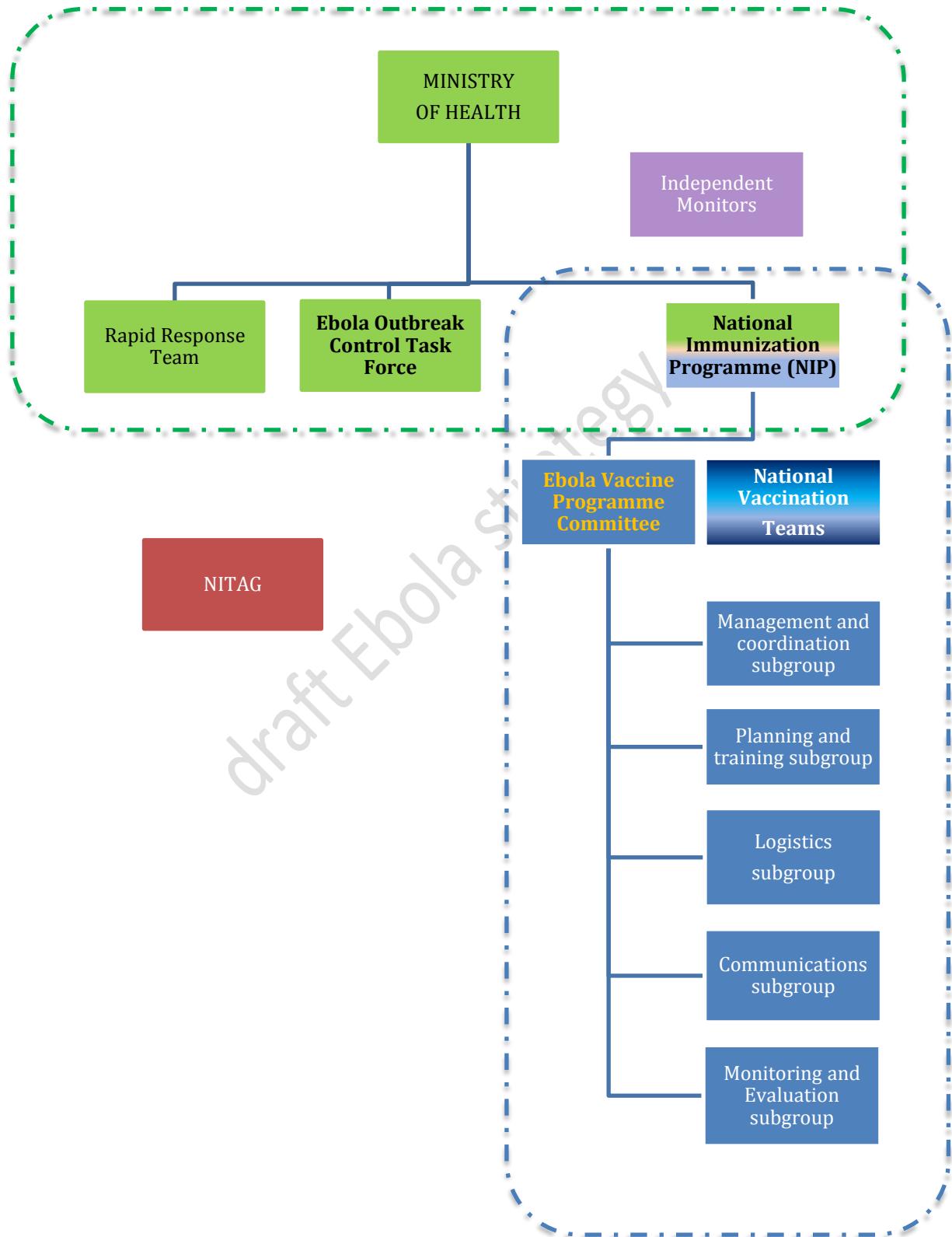
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Appendix B - Ebola vaccines summary table

[hyperlink to Appendix B will be provided at a later stage]

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Appendix C - Overview of proposed roles and responsibilities of constituencies involved in Ebola vaccine outbreak activities



Team	Role	Responsibilities	Timeline
National Immunization Programme (NIP)	Governmental entity under the Ministry of Health in charge of national-level immunization activities	<p>To identify members of an Ebola Vaccine Programme Committee (see below) and to identify members of subgroups:</p> <ul style="list-style-type: none"> - management and coordination - planning and training - logistics - communications - monitoring and evaluation <p>To produce up-to-date information on:</p> <ul style="list-style-type: none"> - national and international laboratory facilities - national HCW/FLW <p>To establish an EVD vaccine communications plan</p> <p>Inform ICG of the situation</p> <p>To review vaccine preparedness and communication strategy and ensure it is part of the Ebola response plan</p> <p>To prepare to set up the Ebola Vaccine Programme Committee</p>	<p>As soon as possible</p> <p>As soon as possible</p> <p>As soon as possible with regular reviews to keep information up-to-date</p> <p>As soon as possible</p> <p>As soon as possible</p> <p>Upon suspected EVD case</p> <p>Upon EVD case confirmation</p> <p>Upon decision to vaccinate</p>
Ebola Vaccine Programme Committee (under the NIP)	<p>To coordinate all Ebola vaccine activities and subgroups</p> <p>To manage vaccine use in country</p> <p>To provide regular communication between Ebola Outbreak Control Task Force and ICG</p>	<p>To activate ICG process should a case be confirmed</p> <p>To rapidly share investigation findings with appropriate parties</p> <p>To establish and train national vaccination teams</p> <p>To form Ebola Vaccine Programme Committee subgroups</p> <p>To develop macroplan</p>	<p>Upon suspected EVD case</p> <p>Upon case confirmation</p> <p>Upon diagnostic result</p> <p>Upon EVD case confirmation</p> <p>Upon decision to vaccinate</p> <p>Upon decision to vaccinate</p>
Subgroups of the Ebola Vaccine Programme Committee – To be activated upon decision to vaccinate. See Appendix D - Proposed composition and sub-groups of Ebola Vaccine Programme Committee for more details.			

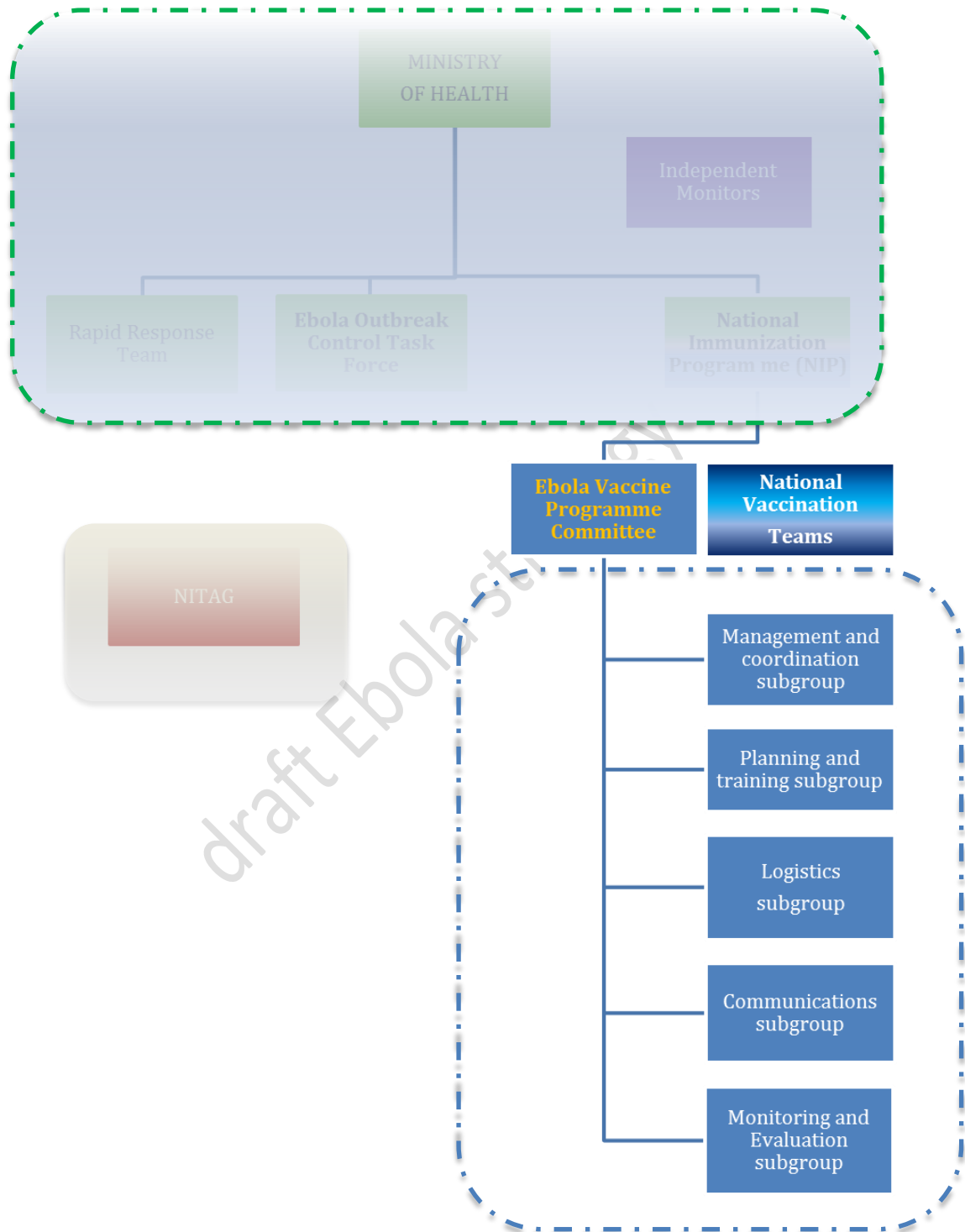
Management and coordination subgroup	To effectively support vaccine roll-out and coordinate other subgroups		
Planning and training subgroup	To develop and roll-out productive training for EVD vaccination deployment		
Logistics subgroup	To support operational aspects of EVD vaccine delivery		
Communications subgroup	Coordinate communications resources and activities, including social mobilization and community engagement during vaccination campaign		
Monitoring and evaluation subgroup	To provide monitoring and evaluation tools and advice		
National vaccination teams (under the NIP)	To carry out vaccination activities	<p>To dispatch to appropriate location</p> <p>To carry out contact tracing</p> <p>To deal with appropriate cold-chain requirements</p> <p>To inform local community about vaccination programme</p> <p>To administer vaccine</p> <p>To record vaccine campaign information</p>	<p>Upon decision to vaccinate Work jointly with RRT</p> <p>Upon arrival of vaccine at location</p> <p>As soon in advance of the vaccination campaign as possible</p> <p>Upon initiation of vaccine campaign</p>
NITAG ^{33 36}	Technical resource providing guidance to national policy-makers and programme managers to enable them to make evidence-based immunization-related policy and programme decisions	<p>To provide technical recommendations around:</p> <ul style="list-style-type: none"> - strategy for eventual Ebola vaccine use in country - surveillance system strengthening needs to be able to provide informed recommendations 	Should be in place already
RRT	To rapidly investigate a suspected EVD case and provide preliminary epidemiological data	<p>To dispatch immediately to the site of a suspected EVD case</p> <p>To send clinical sample to national or international diagnostic laboratory</p> <p>To notify appropriate authorities</p>	<p>Upon suspected EVD case</p> <p>Upon arrival at suspected EVD case site</p> <p>Upon arrival at</p>

³⁶ National advisory committees on immunization. Geneva: World Health Organization (http://www.who.int/immunization/sage/national_advisory_committees/en/, accessed August 2015).

		<p>about suspected case</p> <p>To compile epidemiological information and initiate active case finding and contact tracing</p> <p>To evaluate risk of outbreak and local resources</p>	<p>suspected EVD case site</p> <p>Upon arrival at suspected EVD case site</p> <p>Upon arrival at suspected EVD case site</p>
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Appendix D - Proposed composition and subgroups of Ebola Vaccine Programme Committee



Management and coordination subgroup

- Adopts Ebola epidemic control strategies as recommended by the WHO.
- Formulates a detailed vaccine-related programmatic activities action plan.
- Defines information pathways for vaccine-related programmatic activities.
- Ensures the overall coordination of operations (including convening meetings and monitoring operations).
- Defines responsibilities of the different subgroups.
- Arranges for coordination and regular communications among subgroups, partners and national and international authorities.

Planning and training subgroup

- Coordinates with Ebola outbreak response teams/pillars depending on the strategy selected (including infection prevention and control (IPC) and contact tracing teams).
- Coordinates the development of a training plan for Ebola vaccination deployment activities.
- Prepares the training materials, including the coordination of inputs and materials from other teams.
- Oversees the implementation of the training plan and modifies as required.

Logistics subgroup

- Develops the cold-chain plan for the entire deployment and supervises cold chain and Ebola vaccine management from customs to delivery.
- Identifies and establishes national and sub-national storage areas.
- Coordinates customs clearance.
- Assemble an up-to-date list and map of all health facilities and their catchment areas.
- Maintains accurate inventory management systems and ensures Ebola vaccine and vaccination supplies will reach vaccination teams in a timely manner.
- Supports cold-chain assessment and micro-planning activities.
- Supports the operational aspects of vaccine delivery at all levels.
- Continually assesses logistical needs, including transport, cold chain, staffing, etc.
- Monitors the location and stock of Ebola vaccine and related supplies, to ensure that sufficient stocks are always available to meet the needs outlined in the deployment strategy.
- Develops and maintains the waste-management system.

Communications subgroup (this would be part of the communications pillar)

- Assesses communication needs to gain community and/or HCW/FLW acceptance of vaccination activities.
- Develops communication strategies and plans for Ebola vaccine deployment, including, but not necessarily limited to, plans for media, communities and external partners.
- Liaises regularly with communications teams working on other Ebola outbreak response activities.
- Reports on activities to central level.
- Drafts core materials such as fact sheets, frequently asked questions and press releases.
- Handles media enquiries.
- Monitors implementation and adjusts the communication plans as needed as the deployment progresses.
- Coordinates community engagement.
- Ensures consistent messaging between the overall outbreak response and the vaccination teams.

Monitoring and evaluation subgroup

- Adapts existing supervision and monitoring plans for Ebola vaccine deployment.
- Works with epidemiologists to identify hotspots for ring vaccination (if the ring vaccination strategy is being used).
- Collects, consolidates and analyses all data relevant to the Ebola vaccine as it progresses, and any data on EVD.
- Adapts existing campaign monitoring tools so that Ebola vaccine coverage can be determined.
- Adapts existing mechanisms for post-marketing surveillance of AEFI to include Ebola vaccine.
- Develops national AEFI guidelines for Ebola vaccine.
- Selects and trains team of AEFI response officers who can work with the communications team to rapidly address concerns relating to AEFI, or other concerns about the vaccine (in conjunction with the communications sub-committee).

The Ebola Vaccine Programme Committee selects and trains teams of AEFI response officers who can work with them to rapidly address concerns relating to AEFI, or other concerns about the vaccine (in conjunction with the communications team).

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Appendix E - Community engagement

The importance of well thought-out and sustained community engagement has been clearly illustrated during the 2014/2015 Ebola outbreak. As in any Ebola outbreak, effective community engagement before, during, and after Ebola vaccine deployment will be critical to the overall success of deployment.

From the 2014 West Africa Ebola outbreak, we learnt that community engagement is more the shifting from the individual to the collective empowerment, and ownership of action by community stakeholders themselves. It is also a planned process that invests in the reinforcement of community development platforms to build internal accountability mechanisms.

Community engagement is, however, just one element of **risk communication**, which refers to the real-time exchange of information, advice and opinions between experts, or between officials and people who face a threat to their well-being. Its ultimate purpose in the context of public health is that everyone at risk is able to take informed decisions to protect the health of themselves and their families.

The communications function should be integral to overall planning for deployment, with regular information exchange with the other teams involved in deployment.

Communications about vaccine use should be led and coordinated by the Ministry of Health, with the support of WHO, UNICEF and other partners involved in immunization, taking into account lessons learned during the Ebola outbreak response and other new vaccination introductions and making use, where possible, of existing infrastructure for social mobilization and community engagement.

The checklist (**Appendix F**) should be used to assess whether structural elements required for communications relating to Ebola vaccine deployment are in place, both in the pre-outbreak and outbreak periods.

Research into the perceptions of target audiences (using, for example, surveys or focus groups) will be essential to help inform communications plans. Use should be made of research already conducted, with additional information gathering in a format appropriate to the time available, conducted as needed. Agreed goals and objectives of the communication effort will help focus activities. A mix of strategies and tactics, such as public communications, social mobilization and community engagement, will likely be required (see Table E-1).

Table E-1. Key communication strategies for Ebola vaccine deployment

Strategy	Channels
Public communications	Media, social media, websites, press conferences
Social mobilization	Community radio, IEC materials
Community engagement	Direct or through community influencers and representatives

- **Target audiences** for different types of communications (including members of the government and parliament, health professionals, community leaders, non-governmental organizations (NGOs) and journalists) should be identified early in the planning process. (Please refer to Standard Practical Steps in **Appendix P** for supporting instructions.
- **Messaging and channels of communication** will be dependent on the target audiences. Messaging will need to be context specific, using language, materials and channels appropriate to the target audiences. Influential members of communities, such as community and religious leaders, will be key to effective community engagement. Similarly, as HCW and vaccinators will be on the front line of combating Ebola outbreaks, it will be critical to provide these local representatives with information that will reinforce their ability to provide correct and timely information to the public.
- **Journalists** can play an important role in rapid dissemination about deployment and the content and tone of their articles and broadcasts can significantly influence support for, or resistance to, vaccination. Keeping key national and local journalists updated on developments relating to Ebola vaccine (such as use in other countries and licensure) in the pre-outbreak period, can facilitate a quicker acceptance of an Ebola vaccine in the event of an outbreak. Regular liaison with the media will be needed throughout the course of deployment.

- **Media spokespersons** should be agreed upon before the deployment starts. These spokespersons should be trained, as needed, and regularly briefed so that they have the most up-to-date information about the deployment.
- **Media monitoring** should be conducted continually, with follow-up action taken as appropriate when articles are published that risk negatively impacting deployment or that contain inaccurate information.

If appropriate to the country context, social media and text messaging can also be effective for dissemination of information, and to respond to questions from target audiences. In all cases, however, timely and well-coordinated community engagement will be required. Monitoring of concerns and questions from all sectors of society should be conducted regularly, with follow-up communication addressing questions that are raised. Plans should be adapted according to feedback during deployment.

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Appendix F - Community capacity checklist

To be completed by the Ministry of Health

Name of person completing the form:

Position of person completing the form:

Date:

Checklist for communications planning for Ebola vaccine use
--

1) Has a communications professional been assigned to lead communications on Ebola vaccine work use?

Yes No

If Yes, provide name:

2) Is there a unit with official responsibility for coordination among stakeholders of communication efforts on Ebola vaccine use?

Yes No

If Yes, give details:

3) Is there an inventory of all organizations (government, non-government, public or private) who can/will support communications for Ebola vaccine use, with indication of the roles that they can fulfil?

Yes No

Comments:

4) Is there a written policy/guideline on the verification (for technical accuracy) and release of information on Ebola vaccines?

Yes No

If Yes, give details:

Has the policy/guideline been disseminated to relevant staff?

Yes No

Is the policy/guideline followed in practice?

Yes No

Comments:

5) Are there designated spokespersons (principal and at least one back up) for speaking publicly about Ebola vaccine use?

Yes No

If Yes, give details:

6) Is there a mechanism in place for preparing spokespersons for interview, and providing feedback on performance?

Yes No

7) Are there procedures in place for the dissemination of information about Ebola vaccines?

Yes No

8) What channels of communication are used (indicate all that apply)?

- Media interviews
- Press releases
- Press conferences
- Radio
- Television
- SMS: text messaging
- Social media
- Community meetings
- Websites
- Telephone hotlines
- Listservs (i.e. email)
- Emergency alert systems

9) Is there a website/page available and accessible to media and the public for information dissemination?

Yes No

If Yes, is there a mechanism for regular updating?

Yes No

10) Is there a mechanism in place for listening to the questions and concerns of communities where an Ebola vaccine may be used?

Yes No

Comments:

11) Is there a mechanism for ensuring that such concerns and questions are taken into account when developing and revising communications strategies and plans?

Yes No

12) Do processes exist for the development, testing and dissemination of information, education and communication materials?

Yes No

13) Is there a process in place for monitoring and analysing media (both online and traditional)?

Yes No

If Yes, how often is this done?

If Yes, are findings used to inform communications strategies and plans?

14) Are there established processes for managing rumours relating to new vaccine use?

Yes No

15) Is there a communications strategy and plan for the Ebola response?

Yes No

16) Is there a communications strategy and plan (including budget) for use, routine immunization/new vaccine introduction?

Yes No

17) Is there a communications strategy and plan for Ebola vaccine trials undertaken?

Yes No

Comments:

18) Is the effectiveness of communications efforts evaluated (and documented) in any way?

Yes No

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Appendix G - Outline for communications strategy document for Ebola vaccine use

Background

Country information: geographical situation (including map); population; life expectancy; socio-economic status of population; education level; structure of health system; accessibility of health-care services; primary causes of morbidity and mortality, health and sanitation issues.

Immunization: immunization coverage levels; trends in coverage; new vaccination use or introduction (dates, vaccines, geographic areas, specific issues); issues of relevance relating to existing NIP programme that could impact uptake of a new vaccine; what is known about vaccine hesitancy in the country; information of relevance from clinical trials of Ebola vaccines, information from assessments of perceptions about Ebola and, more specifically, Ebola vaccines.

Objectives

Note 1: all objectives should be SMART, i.e. specific, measurable, achievable, relevant, timely.

Note 2: when formulating objectives, think about what changes you want to see as a result of your activities.

Programme objectives

Relates to the immunization programme.

Example: end transmission of Ebola virus through vaccination of

- primary and secondary contacts of confirmed cases

and

- health-care and front-line workers working in the geographic areas where communities are to be vaccinated.

Communication objectives

Examples

- Community leaders in communities targeted for vaccination accept vaccination activities in their communities.
- All persons identified for vaccination come to vaccination post for vaccination.
- Media reports provide accurate reports of immunization activities.

Audience analysis

Audience analysis and segmentation: a crucial component for all communications efforts.

Primary audiences

People coming to be vaccinated and their parents (for minors). Provide information about the characteristics of these groups, including belief systems, literacy levels, socio-economic status and types of employment.

Secondary audiences

Influencers of primary audiences: depending on the context, can include family members, friends, colleagues, traditional healers, healthworkers, etc.

Tertiary audiences

Individuals and groups who influence the primary and secondary audiences include: district health management teams, district councils, NGOs and other civil society actors. They also include decision-makers in government ministries, UN agencies, donors and other international partners.

Communication and media analysis

Provide information on common forms of communication e.g. community health-care workers, general medical practitioners, radio, TV (specifying most popular channels), community and groups, folk media and social media.

Communications approach

Define key strategic approaches to be taken.

Examples:

- **Targeted advocacy**
Engagement of president, ministers, political influencers and/or parliamentarians to secure political support and funding. The health education division at the Ministry of Health and NIP Programme will need to be directly involved in targeted activities. Types of activities could include: one-on-one consultations with relevant government staff; parliamentary briefings, national and district launching events.
- **Alliance-building for behavioural and social change**
Identify groups that can amplify your messages e.g. civil society organizations, religious and traditional leaders, youth groups and students and, in some cases, the private sector.
- **Meetings with community members**
Subsequent to meetings with community leaders and with their agreement, hold meetings with the wider community.

Messaging

Messaging should be context specific, using language that is appropriate to the audience.

Prepare key messages and supporting facts, and field test them with a sample of the intended audience to ensure that they are understood and accepted, and that they would result in the desired behaviours.

Ensure that approved messages are consistently used by all partners involved in communication about vaccine use.

Channels and materials

Consider the mix of channels and materials that will help you achieve your communications objectives.

For each audience identified, list the channels and products that will be used to reach them.

Channels can include television, radio, telephones, websites or social media channels. Face-to-face meetings with stakeholders, such as partner and community members, are particularly important, given that they allow for two-way dialogue. Creation of a telephone hotline to respond to questions from the general public should be considered.

Journalists can play an important role in rapid dissemination about deployment; the content and tone of their articles and broadcasts can significantly influence support for, or resistance to, vaccination. Relationships with national and local journalists should be established and/or strengthened prior to vaccine deployment, by providing them with correct messaging about the deployment appropriate for general audiences. Regular liaison with the media will be needed throughout the course of deployment.

Materials required will likely include press releases, frequently asked questions, posters and other graphic materials, and possibly material for radio and television. Materials will need to be in languages that are appropriate for the target audiences. Materials should be pre-tested on a sample of the target audience/s before widely distributing.

Workplan

Create a detailed workplan of activities, including the projected cost of each activity. Include responsible persons, target groups and timeframes.

Monitoring and evaluation

Progress of implementation of the workplan would be monitored regularly by ongoing review of problematic issues and is critical to ensure rapid resolution. Adjustments to the initial workplan may be required to ensure achievement of the planned results and outcomes.

Media monitoring should be conducted continually with follow-up action taken as appropriate when articles are published that risk negatively impacting deployment, or contain inaccurate information.

If appropriate to the country context, social media and text messaging can be effective channels for receiving concerns and questions from target audiences. Monitoring of concerns and questions from all sectors of society should be conducted regularly, with follow-up communication addressing questions that are raised. Plans should be adapted according to feedback during deployment.

Indicators

Examples:

- Percentage of required funds mobilized.
- Funds spent as planned.
- Each vaccination team includes a communications specialist.
- List of individuals and organizations, updated with contact details, who can be mobilized to support social mobilization and community engagement.
- Key media identified are briefed on the plan for vaccine use.
- High-level advocates take an active role in the campaign, in line with the plans.
- Sufficient quantities of communication materials are available.
- Communication on vaccine use integrated into Ebola response communication activities.

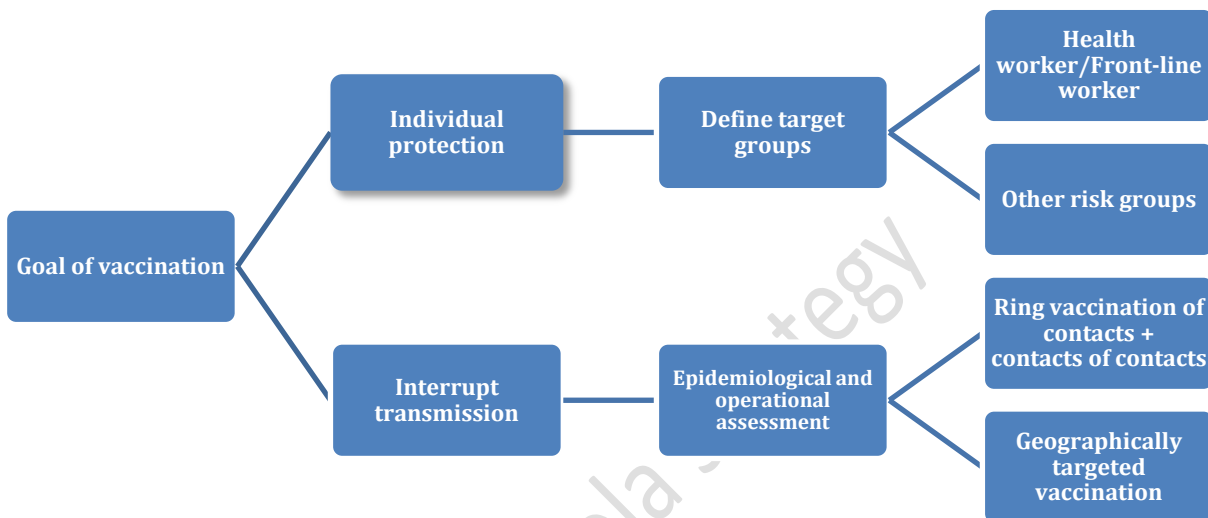
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Appendix H - Selection of a vaccination strategy

Vaccination objectives

The Strategic Advisory Group of Experts (SAGE), a body of experts that makes global vaccine recommendations to WHO, has proposed the following two objectives for Ebola reactive vaccination (i.e. in response to an outbreak): individual protection of those at high risk of infection and interruption of transmission (Fig. H-1 below).

Figure H-1. Ebola vaccination strategies path



Vaccination of health-care workers and front-line workers

Vaccination activities to provide protection to high-risk individuals should primarily target HCWs and FLWs, but other at-risk groups may also be targeted. These activities may take place in conjunction with, or instead of, community vaccination activities.

High-risk individuals include HCW and FLW, which include, but are not limited to, medical doctors, nurses, midwives, cleaners, laboratory workers, ambulance drivers and other staff working in hospitals and other health facilities. Physicians, nurses, midwives and laboratory workers have historically been 20-40 times more likely to become infected than non-HCW and FLW,⁷ especially in the early stages of an outbreak.

Front-line workers, such as contact tracers and safe burial teams, are similar to HCWs in their involvement in the Ebola response and their risk, but would not be considered HCWs as they work outside of health facilities (e.g. ambulance drivers, contact tracers and safe burial teams).

Since HCWs and FLWs provide ongoing care of other affected individuals, while exposing themselves to increased risk of acquiring EVD, the principle of reciprocity provides unambiguous ethical support to prioritizing HCWs and FLWs in Ebola vaccine campaigns.

Vaccination of HCWs and FLWs in affected areas is likely to be a priority for the country. They are often among the first cases identified. They are at high risk of contracting EVD and, if infected, they constitute a risk to others. HCWs and FLWs including other high-risk groups (see Table H-1 below) are generally identifiable and can be vaccinated using selected vaccination points.

Table H-1. Individuals at high-risk of infection who may be considered for vaccination during Ebola vaccine deployment

Category*	Definition	Comment
Health-care workers and front-line workers		
Health-care workers and front-line workers in areas with active community transmission	Individuals working inside or at reception health facilities, including doctors, nurses, cleaners, caregivers, reception/administrative staff, ambulance drivers, vaccination teams and laboratory workers	Lower levels of infection control are employed for routine treatment activities, increasing risk of infection
Health-care workers and front-line workers at Ebola treatment units	Individuals working inside or at reception of Ebola treatment facilities, including doctors, nurses, cleaners, caregivers, reception/administrative staff and ambulance drivers	These health-care and front-line workers have PPE and a high level of other interventions protecting them from infection
Front-line workers		
Community Ebola responders who may come in contact with corpses	Individuals handling corpses of potential Ebola victims. These include burial teams and religious or community members who prepare bodies for burial or at a hospital morgue	Handling dead bodies is a high-risk activity. Even when wearing PPE, burial teams work in conditions which may decrease the PPE's effectiveness
Community Ebola responders who have minimal physical contact with community	Contact tracers and community health educators	Appropriately-trained contact tracers should have low risk of physical contact with bodily fluids of sick individuals
Other high-risk groups	Other individuals with high likelihood of exposure to infectious body fluids, including informal health-care providers (e.g. traditional healers, herbalists, etc.), those involved in funeral rites (e.g. elders, religious leaders, senior members of secret societies and traditional washers) and animal health-care workers and/or veterinarians are at higher risk for infection than the general population	Categories of front-line workers and other risk groups may vary from one community to another and should be defined locally

* The categories of **front-line workers** and other risk groups may vary from one community to another and may need to be defined locally.

Initial implementation should focus on vaccination of HCWs and FLWs in areas of active transmission. Differentiating who is at highest risk in a facility may cause contention, especially during an outbreak, so that targeting all individuals working at selected health facilities is a preferred approach.

Vaccination of HCWs and FLWs should normally be combined with a community vaccination programme to interrupt transmission.

Community vaccination

Vaccination to interrupt transmission, leading to outbreak control, is suggested through geographically targeted and/or ring vaccination.

In geographically targeted vaccination, all eligible individuals (no contraindications to vaccination and within the appropriate age range) are offered vaccination within a given geographic area. The targeted area could be a village, a cluster of villages, a sub-district or a district.

In ring vaccination, contacts and contacts of contacts, identified through surveillance, are targeted for vaccination. This approach targets those individuals at highest risk for EVD, vaccinating a 'ring' of individuals around the case in order to limit transmission.

Table H-2. Comparison of ring vaccination for contacts and geographically targeted vaccination

	Geographically targeted vaccination	Ring vaccination
Target population	Individuals living in the geographical area surrounding a case or, more likely, a cluster of cases	Contacts of the identified EVD case and these contacts' contacts. Contacts may include household contacts, neighbours, health-care and front-line workers, shopkeepers, work colleagues and others
Assumptions	A definable geographic area contains the majority of contacts	Contact tracing is of sufficiently high quality to identify most contacts (measured by proportion of new cases that are known contacts)
Strategies to reach the target population	Can use stationary, temporary vaccination site to vaccinate the targeted population	Requires vaccinating only identified individuals
Logistical issues	The potentially large size of the target population requires more resources	Depending upon the cold-chain requirements of the vaccine, thermostability may limit the effectiveness of the deployment
Community engagement and social mobilization	Target geographical area	Target geographical area of strategy, inform contacts of vaccination and inform larger community of why only certain persons are targeted for vaccination
Benefit	Not dependent on contact tracing	All contacts (even if moved) should be vaccinated Efficient use of vaccine (and resources) May enhance community engagement and contact tracing ("placing their hope in the vaccine")
Risks	May miss individuals who are travelling at time of vaccination Requires vaccination of large population	May not identify all contacts, may miss individuals at high risk (e.g. future drivers of "satellite rings")

Ring vaccination is considered to be more efficient (more cases prevented for a given number of vaccine doses). Instituting a ring vaccination strategy may be sufficient along with other public-health measures to interrupt transmission.

However, effectiveness of ring vaccination in controlling an outbreak will depend, among other factors, on the quality of contact tracing (the proportion of new cases arising outside identified vaccination rings) and the

reproduction number (the number of additional cases arising from a case).³⁷ Contact tracing is likely to be less efficient and the reproduction number higher at the beginning of an outbreak.

Choosing between ring vaccination and geographic vaccination, especially in the initial stages of an outbreak, may be challenging.

Ring vaccination is the preferred approach, especially when most new cases are within identified chains of transmission and the outbreak is not expanding rapidly.

Targeted geographic vaccination may best be restricted for specific circumstances: when contact tracing is inadequate e.g. the majority of new cases falling outside known contact rings, and when incidence is rising rapidly, for example, doubling weekly incidence in a densely populated urban area.

In such circumstances, an initial strategy could be to vaccinate the population in a sub-district/district of high/rapidly increasing incidence, as well as HCWs and FLWs serving that district. If small numbers of cases are occurring outside the area of vaccination, ring vaccination could be used in areas outside the vaccinated district, allowing a combination of strategies. Similarly, ring vaccination could be used for all subsequent cases after the initial targeted vaccination.

Epidemiological and operational assessment

Epidemiological assessment should be used to inform and identify an appropriate vaccination strategy in conjunction with an operational assessment of: contact tracing effectiveness; availability of vaccines and injection materials; availability of trained vaccination teams; cold-chain capacity, waste-management capacity and other operational considerations (see Table H-3).

Table H-3. Issues for consideration when selecting the appropriate vaccination strategy to be used in Ebola outbreaks

Vaccine availability	The number of doses available and the time it will take to deliver the vaccine available to the outbreak area. Quickly obtaining this information from the ICG is critical to all decision-making.
Vaccine safety and efficacy	Preliminary analysis of one vaccine (rVSV-ZEBOV) shows a high level of efficacy (70%–100%). ³⁸ Safety studies have shown that the vaccine is safe. The duration of immunity is currently unknown.
Potential impact	The impact of the Ebola vaccine response is enhanced depending upon how fast and how efficiently the vaccine is deployed to the entire targeted population, as well as the quality of other control measures. What proportion of new cases are in known transmission chains? Realistic expectations of what is needed for the strategy to succeed should be conveyed to decision-makers (by NIP), including the Ebola Vaccine Programme Committee and Ebola rapid response team. The Ebola Vaccine Programme Committee should evaluate the priorities of the outbreak response, the desired impact of vaccination and the feasibility of carrying out a targeted vaccination campaign when attempting to determine what the impact of using Ebola vaccines would be in a given outbreak scenario.
Feasibility	For a strategy to be feasible, adequate vaccine supplies must be available, and there must be sufficient resources to support the campaign's monitoring and evaluation and communications activities. Additionally, feasibility of utilizing Ebola vaccines is dependent upon community and health-care worker and front-line worker cooperation. Most importantly, Ebola vaccination campaigns are feasible when integrated with the Ebola outbreak response and do not disrupt or

³⁷ Kucharski AJ, Edmunds WJ. Case fatality rate for Ebola virus disease in west Africa. *Lancet*. 2014;384(9950):1260 (<http://www.ncbi.nlm.nih.gov/pubmed/25260235>).

³⁸ Henao-Restrepo AM, Longini IM et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet*. 2015;386(9996):857–866 ([http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(15\)61117-5/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)61117-5/abstract)).

	<p>detract from other response activities, such as case-finding, isolation, treatment, and infection prevention and control activities (e.g. surveillance, contact tracing and infection control activities). Briefly, the following questions will be considered: are there sufficient human and financial resources to carry out the proposed strategy? Are there sufficient surveillance officers, health-care workers and communications experts, particularly to lead the substantial community engagement that will be required? Are there sufficient funds to purchase the vaccines and run the programme? Can the cold-chain infrastructure be operational quickly enough?</p>
Epidemiological assessment	<p>The epidemiological situation should be described in person, place and time. This includes an analysis of the existing data on who is affected (age, gender, occupation), where cases are occurring geographically and the weekly incidence trend (increasing, stable or decreasing).</p>

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Appendix I - Composition and training of vaccination teams

Ebola vaccination should be conducted in teams (see Table I-1 below) with a **supervisor** responsible for between **four and six vaccination teams**, depending on local conditions and distances between planned sites.

- **All supervisors should be adequately trained** on all forms, cards and procedures (including infection control measures).
- Vaccine team/supervisor structure should be agreed upon and approved by the Ebola Vaccine Programme Committee.

Training for Ebola vaccine deployments requires more time and resources than training for other, more established vaccine deployments. The Ebola Vaccine Programme Committee should ensure that modules for training are complete and address the country's need for a safe, effective deployment. While standard training modules for vaccine deployments should be used whenever possible, staff involved in Ebola vaccine deployment will need: additional training on specific PPE; AEFI and communication around AEFI (e.g. **media spokespersons** and **community engagement officers** will need special training around AEFI and goals of emergency vaccination deployments), and special vaccine logistics and cold-chain handling.

Wherever possible, the global and country lists of Ebola experts should be used to identify those people who are able to assist in training efforts.

Table I-1. Technical staff needed for vaccination activities at the national and sub-national levels

Technical team	Function	Number/unit	Profile
Vaccine store and distribution (one store is expected to be required)	Cold-chain manager	1	Cold-chain expert (engineer or other trained technical profile)
	Cold-chain assistant	2	Cold-chain technician
	Driver	1	Driver
Vaccination team (per team)	Vaccinator	1	Health-care worker (nurse)
	Pharmacist/maintain cold chain	1	Pharmacist/logistician (a pharmacist may be required to ensure that vaccine is appropriately diluted and filled into syringes for each working day)
	Recorder	1	Volunteer
	Community engagement/social mobilization	1	Communication specialist
	Contact tracer	2	Community member
	Driver	1	Driver

- ✓ **National vaccination teams (NVTs)** should be trained in:
 - **Communication and community engagement.** Communications materials for the public will be required for Ebola vaccines, especially materials addressing why specific populations are targeted at the exclusion of others, and what AEFI mean for the community.
 - **Cold chain.** The Ebola vaccine has cold-chain requirements that require more infrastructure, support and care than other vaccines. Extensive cold-chain training will be required for all persons involved with the deployment.
 - **Personal protective equipment (PPE).** Working in a setting where there is active EVD requires the use of special PPE not routinely used in other health-care settings. Special training on the safe use and disposal of proper PPE is needed for those who will potentially come in contact with individuals who are infected with EVD.
 - **Adverse events following immunization (AEFI)** and how to deal with any resulting community concerns.

- ✓ **NVTs** should be trained to receive and implement vaccination activities within 5–7 days of the vaccine's

arrival in country. It should be provided with **vaccination kits** assembled during the training phase (for further details on vaccination kits please refer to **Appendix K**).

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Appendix J - Minimum infrastructure of the cold chain and logistics country hub

The following section describes the minimum infrastructure of the cold chain and logistics country hub designed to allow for the simultaneous deployment of five vaccination teams.

Active refrigeration/freezing cold-chain equipment capacity: a central hub

Active refrigeration/freezing cold-chain equipment will be installed for storing the vaccines and freezing coolant packs at the required temperature. The selected freezers should have flexibility for temperature range from -80°C to -20°C to anticipate any potential switch in the vaccine characteristics from the current -80°C to higher temperatures. Small to medium size (70 to 100 litres) ultra-cold -86°C freezers should be installed with a vaccine storage capacity of approximately 2500 vials (based on the size of the current single-dose vial).

A total of seven (7) ultra-cold freezers will be installed per cold-chain hub, as follows:

- two units for storing vaccine, i.e. a total storage capacity of 5000 vaccine vials (20 000 doses);
- two units for pre-freezing PCM packs;
- three units for completing the freezing of the PCM packs.
- Each ultra-cold freezer is equipped with a built-in temperature recorder. In addition to the built-in temperature recorder, a remote control device with short message service (SMS) text alerts of temperature limits and power outages will be installed on each freezer to provide redundant temperature tracking.

Safe handling and protection gear

Protective equipment (gloves) should be provided for safe working under the ultra-cold temperatures.

In addition to the ultra-cold freezers, one standard freezer and one refrigerator will be installed. The freezer will be used for the production of water/ice packs required for maintaining the cold chain during the vaccination session, while the refrigerator will be used for cooling the diluents prior to transport to the vaccination session.

LIST OF EQUIPMENT AND ENERGY REQUIREMENT PER HUB

Equipment	Picture (<i>pictures are for illustrative purposes only</i>)	Utilization
Ultra cooler 70 L Storage temperature: -80°C Storage capacity: 70 litres Temperature display alarm: high/low temperatures; door open; power off		Storage of vaccine at -80°C at the central store (2500 vials) production of PCM packs at -80°C for the transportation and emergency storage of vaccines

Secure power supply for the cold chain: a backup power supply

Cold-chain equipment requires a continuous and stable power supply. A backup power system with appropriate size may be required to secure electricity supply in the case of failure of the national/city grid. The following options should be considered for establishing the autonomous power supply:

- a standby generator with appropriate power size to back up the main energy source that is in place (grid or a prime generator);

- a battery bank with adequate power size and autonomy to back up the existing main energy source. The battery bank is charged through the main source of electricity (grid or existing standby generator).
- A hybrid solution that combines an appropriately sized generator and a battery bank connected to the freezer through an inverter-charger (however, a rather difficult solution to sustain).
- An appropriately sized solar generator with a large autonomy battery bank and inverter (a rather easier solution to sustain, although a heavy investment and less flexible to move from one location to another).

Equipment	Picture <i>(pictures are for illustrative purposes only)</i>	Utilization
Power supply Fuel: Diesel Liquid cooling system 15k VA/ 230 V/50 Hz Auto start & voltage regulation Power back up stable 230 V/50 Hz autonomy: 24h power rate: 5–10 kVA		Power supply/back up
		Power supply back up

Buildings and other infrastructure

The cold chain and logistics hub should be located in an easy to access site with sufficient facility space in the building. The following minimum building infrastructure is required to ensure adequate functionality.

- A room space of 40m² for the installation of the active cold-chain equipment (ultra-cold freezers, standard freezer, refrigerator and loaded Arktek™). The store room should be air conditioned to maintain temperature and humidity at the level required for the ultra-cold freezers (25°C and 50% RH).
- A covered space of 20m² for the autonomous power system (standby generator and battery bank). The battery bank should be located in the immediate proximity of the store room.
- A 7.5m² office space for the staff managing the cold chain. The office should provide visual access to the cold store.
- A dry storage space of 100m² for packing the vaccination kits and storing reserve cold boxes and vaccine carriers.

Distribution of the vaccine: passive long-term storage device.


Passive cold-chain equipment will be procured for transporting and maintaining the vaccines at the required temperature during vaccination sessions. The following equipment options should be considered.

Long-term passive cold-storage device

Long-term passive cold-storage device (e.g. Arktek™-like devices) adapted for keeping the temperature at different ranges with sufficient holdover time and equipped with a built-in temperature recorder (e.g. Hobo-like devices).

The storage devices should be provided with an adequate number of coolant packs to operate within three temperature ranges (-70°C, -20°C and +5°C) to anticipate any temperature requirements for the vaccines that may apply. For each temperature range, two sets of coolant packs should be provided. The PCMs for coolant packs should be selected for each temperature range, with adequate thermal characteristics to provide the maximum holdover time of maintaining the

temperature in the field. Each set of coolant packs will be marked clearly for the intended temperature range and filled with the relevant PCM.

Equipment	Picture <i>(pictures are for illustrative purpose only)</i>	Utilization
Passive containers for long range storage Storage temperature: -70°C, -20°C, +5°C Storage capacity: ~ 7 litres Cold life at -70°C: 5–10 days With built-in temperature monitoring device		Used for the temporary storage or transportation of the vaccine at -70°C, -20°C or +5°C, depending on the packs used PCM packs cooled at -80°C are used to keep the storage container at -70°C

Active refrigeration device (to maintain 2–8 degrees)

Portable active refrigeration devices will be used to maintain the vaccine and diluents under +2°C to +8°C cold chain during vaccination sessions. This will be essential when the vaccination teams have to stay longer in the field without access to production of +2°C to +8°C coolant packs. Each portable active refrigeration device will be equipped with a continuous temperature recording system and SMS alert. Two (2) devices are required per vaccination team.

Equipment	Picture <i>(pictures are for illustrative purposes only)</i>	Utilization
Active refrigeration device Type: portable Storage temperature: +2°C to +8°C Storage capacity: 10 litres Temperature recorder		Used to transport and keep vaccine and diluent at the vaccination site and to keep the vaccine temperature between +2°C and +8°C during the vaccination session

Passive long-range vaccine carriers (to maintain 2–8 degrees)

Long-range passive container high-density (PHD-9-type) to be used with water/ice packs to maintain the vaccine under +2°C to +8°C cold chain during vaccination sessions. Each vaccine carrier is supplied with three (3) sets of four (4) coolant packs, type 4 (0.6 litres). Four (4) vaccine carriers are required per vaccination team.

Equipment	Picture <i>(pictures are for illustrative purposes only)</i>	Utilization
Passive containers PHD9: Storage temperature: -70°C Temperature recorder		Used to transport the vaccine to the vaccination site and to keep the vaccine temperature between +2°C and +8°C during the vaccination session

Human resources staffing

Technical staff with appropriate skills for the management of the Ebola cold chain should be available.

Duty station	Function/function	Number	Profile
Vaccine store and distribution	Cold-chain manager Cold-chain assistant Driver	1 /store 2 /store 1/ distribution vehicle	Cold-chain engineer Cold-chain technician Driver
Vaccination team	Vaccination Logistic assistant Pharmacist Vaccinators Social mobilizer Driver	1/team 1/team (dilution) 2/team (1 vaccinator +1 for recording) 1/team 1/team	Cold-chain technician Health-care worker (nurse) Pharmacist Nurses C4D Driver

NB. The staffing should consider a backup person.

Capacity building

Building capacity of human resources by developing appropriate Standard Operating Procedures (SOPs) and in-country training workshops should be considered, to strengthen national competencies for managing the equipment and the vaccine at all levels.

The SOPs should describe “What”, “How”, “By whom”, and “When”.

	Vaccine store	Transportation	Vaccination site
Stock monitoring	What, How, by Whom, When?	What, How, by Whom, When?	What, How, by Whom, When?
Vaccine temperature monitoring	What, How, by Whom, When?	What, How, by Whom, When?	What, How, by Whom, When?
Packaging	What, How, by Whom, When?	What, How, by Whom, When?	What, How, by Whom, When?
Waste management	What, How, by Whom, When?	What, How, by Whom, When?	What, How, by Whom, When?

Examples of SOPs to be developed (list not exhaustive)

- ✓ Operation of a -70°C Ebola vaccine storage device
- ✓ Preparation of vaccine containers to ship the vaccine to the field
- ✓ Preparation of vaccine and supplies to be shipped to the field
- ✓ Temperature monitoring of vaccine during storage
- ✓ Temperature monitoring of vaccine during transportation
- ✓ Temperature monitoring of vaccine at the vaccination site
- ✓ Stock management at the vaccine storage site
- ✓ Transport of vaccine from the store to vaccination site
- ✓ Management of the vaccine stock returning to the store from the field
- ✓ Inventory and accountability of supplies
- ✓ Safe collection and disposal of waste
- ✓ Safe handling of PCMs

Vaccination kits (please refer to **Appendix K** for further details)

Rapid deployment of the vaccination teams on the field requires good organization and supplies prepared in advance. A comprehensive list of all supplies required for vaccination sessions is established as follows.

- ✓ Office furniture, including:
- ✓ tents (two per team)
- ✓ tables and chairs.
- ✓ Vaccination supplies, including:
- ✓ kit for paperwork (tally sheets, etc.)
- ✓ syringes
- ✓ safety boxes
- ✓ bags for waste collection.
- ✓ Minimum safety and personal protective equipment, including:
 - raincoats
 - boots
 - aprons
 - masks/goggles
 - gloves
 - hand sanitizer
 - chlorine sprayer, 1.0 litre (with 5% Na-Hypochlorite).

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Appendix K - Checklist for vaccination teams and vaccination strategies forecasting tool

Supply of bundle vaccine
Items
Front Line Workers (50workers per 50HF per 20districts)
Vaccine for FLW (vials)
No. of rings
No. of contacts per ring
Total No. of contacts to be vaccinated
Vaccine for ring vaccinations (vials)
Anticipated vaccine wastage rate
Total Vaccine needed, including wastage (vials)
Diluent
Mix Syringe
Injection Syringe
Safety boxes
Cotton Swab
Total for bundle vaccine
Supplies for Teams (contents of kit)
Item
No. of vaccination teams to be mobilized
No. of vaccination staff to be mobilized
Apron
Masks
Gloves (2,000,000)
Kit of paperwork (tally sheet, temperature monitoring form, stock management form)
Bags for waste collection
Hand sanitizer
Chlorine spray, 1.0 litres (we used 5% Na-Hypochlorite)
Kleenex
Chairs
Tent
Table
Vaccination teams Per diem
Cold chain & logistics support teams Per diem
Coordination staff
Vehicles rent
Fuel costs
Total supplies for vaccination kits
Cold Chain Package Contents for 5 teams
Item
Ultra cold -85°C freezers (Arctiko freezers):
capacity of one Arctiko (2,500 vials) or 24 PCM packs
2 (vaccine), 2 (pre-freezing PCM packs), 3 (ultra-freezing PCM packs)
Remote temperature tracking devices (-80°C) with:
sms alerts of temp limits and power outages
Standard -20°C freezer
Vaccine ice lined refrigerator
Long Term Storage Device (Arktek), each device with:
6 x 8units of coolant packs (2 sets for each temp range)
built-in temperature recorder (Hobo)
Special vaccine carrier for dry ice (Cryo-Q), each supplied with:
vaccine and dry ice loading racks
Long range vaccine carrier (PHD-9), each supplied with:

3 x 4units of coolant packs type4 (0.6litre)
Remote temperature tracking devices (-80°C) with sms alerts
Backup power supply, including:
standby generator (15 kVA)
battery bank
invertor-charger
Computer laptop for managing cold chain, each supplied with:
Hobo software (pre-installed or to be downloaded)
printer
Air conditioning for freezer room
Total cold chain unit for 5 teams
No. of cold chain units required to be established
Total cost for cold chain units
Office supplies and rent
Item
Laptop & printer
Cell phones
Communication
Office rent
Medical kits WHO
Technical Assistance (Consultants)

[hyperlink to Appendix K → Vaccination Strategies Forecasting Tool available on the website]

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Appendix L - ICG application template

[hyperlink to Appendix L will be provided at a later stage]

IMPORTANT:

Appendix not yet available.

Work is still in progress and additional inputs are awaited.

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Appendix M - Changes to Ebola surveillance systems to incorporate use of vaccines in outbreak response

Characteristics of Ebola virus disease (EVD) surveillance systems

In response to the 2014 West African outbreak, and following WHO guidelines, Guinea, Liberia and Sierra Leone implemented surveillance systems for active case finding of EVD.¹ The major objectives of EVD surveillance in these countries was: 1) immediate reporting of suspected viral haemorrhagic fever (VHF) cases and deaths to initiate control measures; 2) confirmation that Ebola virus was causing the suspected cases and deaths to continue or stop control measures; 3) monitoring the elimination of virus circulation following implementation of control measures.

Post-outbreak, the surveillance systems will be downsized, but essential elements need to be maintained to ensure that the systems quickly detect new cases, and that detection is coordinated with an adequate response to prevent further transmission. Other countries potentially at risk of VHF outbreaks, such as the Democratic Republic of the Congo and Uganda, may also update their surveillance systems to enhance their sensitivity. Recent WHO guidelines for EVD and other VHF recommend the following elements for a surveillance system between outbreaks:

- a. Maintain a network of focal persons in health facilities who are trained in identifying and reporting cases of VHF using standard case definitions. Complement with periodic active searches of potential cases during supervisory visits.
- b. Maintain a network of resource persons who could be trained in the use of a simplified case definition to report potential cases in the community.
- c. Ensure the presence of supplies, personal protective equipment and instructions for collection, packaging storage and shipment of specimens from suspected VHF cases in districts/facilities at risk for receiving a patient with suspected VHF.
- d. Establish national reference laboratories with staff, resources and supplies to conduct diagnostic testing for Ebola and Marburg viruses.
- e. Establish and strengthen epidemic management committees and rapid response teams that meet regularly to be updated on the epidemiological situation. These teams should also develop a system to supervise stockpiles of equipment needed for epidemiological investigation and to ensure proper maintenance of cold-chain equipment, telecommunications systems and vehicles.
- f. Ensure adequate systems to conduct entry of information and bi-directional flow between health facilities/communities, laboratory and response teams, that allow timely reporting of new cases, as well as timely confirmation and response (isolation, contact tracing and case management). The systems used to capture data should minimize errors in case and contact identification.

However, if vaccines are used to control EVD outbreaks in the future, the EVD/VHF surveillance systems will need to include new data elements to capture vaccine use and assess vaccine impact on the response. This document suggests changes in several areas to address those needs.

General considerations for an EVD surveillance system that supports the use of Ebola vaccine in outbreak response

In contrast to vaccines for more common vaccine-preventable diseases, Ebola vaccine deployment is unlikely to be conducted through mass campaigns for the whole population. Because of the patterns of transmission of Ebola virus and the limited vaccine availability, the most likely scenario is that Ebola vaccine will be delivered to individuals considered at high-risk for EVD. The targeted individuals will likely be:

- HCW and FLW expected to be at high-risk for direct contact with EVD cases during an EVD outbreak;
- direct contacts and contacts of contacts of confirmed EVD cases (ring vaccination);
- limited geographically-defined areas at high risk (village, community, neighbourhood).

Specific elements to facilitate integration of vaccination and surveillance for EVD

Case investigation

1. Establish a case-based surveillance system with a unique identification number.
 - a. **A unique identification number should be a standard component of any EVD surveillance system.** A unique identification number is essential to several activities: (a) to match laboratory results that confirm or discard the diagnosis; (b) to manage contacts, especially those linked to multiple cases; (c) to match patients with vaccination records: both those targeted for vaccination and those who were actually vaccinated.
2. Ensure case investigation forms collect all necessary information.
 - a. Ensure that there is an option for identifying FLWs even if they are not HCWs.
 - It is important to ascertain whether the patient is in a group targeted for vaccination before or after EVD exposure. Although FLWs may also be health-care workers, many FLWs are not health-care workers (e.g. burial workers) and may be inadequately characterized if only health-care workers are considered. On the other hand, if a nurse/laboratory technician is working on the Ebola response, both options could be checked.
 - To allow tracking of HCWs and comparison with vaccination lists, the following variables should also be completed when HCW are selected:
 - health-facility name
 - occupation.
 - To allow tracking of FLWs and comparisons with vaccination lists, the following variables should also be completed when Ebola responder is selected:
 - district name and geographical coordinates (as district and village names can be written in different ways);
 - role in Ebola response (e.g. contact tracer, burial team);
 - organization they work for (e.g. Red Cross, District Health Office, WHO).
 - To minimize typographic errors and errors in interpretation of health-care and front-line worker occupations, consider listing the major categories of HCW/FLW. An example of such listing could be:

HCW: doctor / nurse or nurse aid / midwife / community-health nurse / pharmacist / cleaner / porter / security / ambulance driver / administrative / laboratory technician / other.

FLW: surveillance officer / contact tracer / case manager / supervisor / ambulance driver / sprayer / burial team / quarantine / nutrition / security / administrative / other.

Include a question about receipt of any Ebola vaccine prior to becoming ill.

- Potential text for the question:
 1. Has the patient ever received any Ebola vaccine?
 2. If yes, specify the name/type of vaccine, date of vaccination and vaccination identification number (if available).
 3. Reason/source of vaccination e.g. study (specify which study), deployment of vaccine to Ebola workers, or vaccination of contacts.
- As the patient may have received more than one vaccine dose (of the same or different vaccines), consider including two or three fields for type of vaccines and date of receipt.
- If the patient does not know the name of the vaccine, including the name of the study or other source of vaccination (e.g. vaccination of all health-care workers and front-line workers in District XXXX), vaccination of contacts that delivered the vaccine would provide useful information.
- If the patient received vaccine as part of a study or a vaccine deployment, it is likely that he/she received a vaccination number and this ID number will allow matching records with the

database, that includes individuals vaccinated, to ascertain the date and type of vaccination received.

- (Note. There are currently 2-dose 'prime/booster' vaccines in development. Should a multi-dose vaccine schedule be eventually deployed, further modifications should be considered to accommodate this.)

3. Identify both contacts and contacts of contacts rapidly.
 - a. While identification of contacts is a standard part of EVD case investigation, the use of ring vaccination requires that contacts of contacts also be identified.
 - b. All contacts and contacts of contacts should be vaccinated as soon as possible, thus contact identification needs to happen very quickly.
4. Monitor effectiveness of contact tracing in relation to new cases.
 - a. An indicator for effective contact tracing is the **percent of new cases arising from known or monitored contacts**. Surveillance tools should document whether or not a case is related to a previously identified case or contact.
 - b. For example, if all new cases arise from known contacts that were identified through contact tracing, then contact tracing is likely to be very complete. In contrast, if new cases arise in individuals who have not been previously identified as known contacts through contact tracing, then the contact tracing is not adequate to follow transmission of the disease.

Case reporting and management

1. Ensure timely reporting of new EVD cases to the vaccination team in order to prepare an effective vaccination response, including ring vaccination of contacts and contacts of contacts as well as vaccination of exposed or at-risk HCW/FLW.
 - To achieve this objective, the flow of notification of a new suspect case should include a focal person belonging to the vaccination team.
 - Following notification, the vaccine team should stay in close communication and coordination with the surveillance team conducting the case investigation until the case is confirmed.
 - As vaccination will often occur after exposure to EVD, it is essential to minimize the time between confirming a case and administration of vaccine to contacts.
2. Establish strong channels of communication that allow coordination of the vaccination teams with the teams conducting the other components of the outbreak response, such as quarantine, transportation to treatment facilities, etc. Good coordination among teams will increase the effectiveness of vaccination as part of the response. Similarly, note the crucial role that unique identification numbers will play in facilitating communication and collaboration between all teams in the field.
3. Consider the use of modified EVD case definitions for individuals who have been vaccinated after exposure to an EVD case or to infected material, e.g. exposed HCW/FLW or contact of a case. (Information from the ongoing trials in Guinea and Sierra Leone on the most common adverse effects observed and the time of appearance and duration of these effects will be useful to guide the modification of the standard case definitions for these situations). An optimal strategy for finalizing modified EVD case definitions among vaccinees should be completed following documentation of successful strategies from current clinical trials.
 - For example, during the CDC-sponsored vesicular stomatitis virus (VSV) vaccine clinical trial in Sierra Leone, surveillance officers used a modified EVD case definition for vaccinees presenting with symptoms during the first 48 hours following vaccination. The case definition required the presence of at least one symptom expected with EVD but not vaccine (e.g. diarrhoea, bleeding) to reduce the likelihood that vaccinees with fever and other common side-effects (myalgia, headache, arthralgia) were placed in isolation units where they could be exposed to EVD cases. Similar situations are to be expected during the deployment of Ebola vaccine in future outbreaks.

4. Consider the use of alternative isolation procedures for the presence of fever or other post-vaccination symptoms that appear shortly after vaccination of individuals at risk for EVD.
 - During the CDC-sponsored VSV vaccine clinical trial in Sierra Leone, vaccinees that met the modified case definition described above were immediately isolated and tested, as routinely practiced, for suspected Ebola cases. However, if vaccinees did not meet the modified case definition, they were placed on self-isolation with close follow-up. If symptoms resolved within 24–48 hours, symptoms were attributed to vaccination; if they persisted or worsened, vaccinees were isolated and tested for EVD following standard EVD outbreak procedures. This approach was meant to reduce risks of unnecessary exposure to EVD among vaccinees, during blood collection and during internment in isolation units with EVD cases.

Case confirmation

1. Use laboratory tests from an accredited laboratory that distinguish wild Ebola virus from the vaccine.

There are several diagnostic tests to confirm EVD: 1) antigen detection using the enzyme-linked immunosorbent assay (ELISA); 2) detection of IgM antibodies directed against Marburg or Ebola; 3) seroconversion or increasing IgG antibody titres in two subsequent specimens collected within a week of each other; 4) detection of virus RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) and sequencing; 5) detection of virus by immunohistochemical staining of the patients' tissue or blood; 6) viral isolation.^{1 39}

In recent years, RT-PCR tests have become the preferred method for diagnosis in outbreak settings. The advantage of RT-PCR is that it can provide diagnosis early in the course of the disease and in patients with severe disease who may not develop antibodies at levels enough to be detected,^{40 41} and is logistically easier to perform than serologic tests. Seroconversion or increasing IgG antibodies are usually reserved for follow-up of patients with confirmed disease or for assessment of population immunity. In response to the outbreak, several antigen-based and RT-PCR tests were developed by different laboratories and manufacturers and were pre-qualified by WHO for emergency use in the 2014 West African outbreak.⁴² New assays continue to be developed and will become available in the future. Confirmatory laboratory testing should be performed by an accredited laboratory using current validated diagnostic assays. The sensitivity and specificity of assays may be affected by the time of collection, with regard to onset of symptoms, and by improper sample collection, shipping or storage, or inadequate PCR technique.⁴¹ If vaccine is deployed in response to an outbreak, the ideal assay for use would be able to distinguish the presence of Ebola virus versus the presence of Ebola virus proteins contained in vaccines.

There are currently several vaccines in development and it is unknown whether one or several vaccines will be deployed in the future.^{43 44 45} All the vaccines undergoing trials are viral-vectored vaccines that express the Ebola virus glycoprotein (EBOV-GP).^{43 44 45 46 47} Following intramuscular administration, the vaccine

³⁹ Wong G, Kobinger GP, Qiu X. Characterization of host immune responses in Ebola virus infections. *Expert Rev Clin Immunol.* 2014;10:781–790 (<http://www.tandfonline.com/doi/pdf/10.1586/1744666X.2014.908705>).

⁴⁰ Leroy EM, Baize S, Lu CY et al. Diagnosis of Ebola haemorrhagic fever by RT-PCR in an epidemic setting. *J Med Virol.* 2000; 60:463–467 (<http://www.ncbi.nlm.nih.gov/pubmed/10686031>).

⁴¹ Martin P, Laupland KB, Frost EH, Valiquette L. Laboratory diagnosis of Ebola virus disease. *Intensive Care Med.* 2015;41:895–898 (<http://link.springer.com/article/10.1007%2Fs00134-015-3671-y>).

⁴² Emergency use assessment and listing (EUAL) procedure for Ebola virus disease (IVDs). Geneva: World Health Organization (http://www.who.int/diagnostics_laboratory/procurement/purchasing/en/).

⁴³ Ledgerwood JE, DeZure AD, Stanley DA et al. Chimpanzee adenovirus vector Ebola vaccine - preliminary report. *N Engl J Med.* 2014 (<http://www.nejm.org/doi/full/10.1056/NEJMoa1410863>).

⁴⁴ Regules JA, Beigel JH, Paolino KM et al. A recombinant vesicular stomatitis virus Ebola vaccine - preliminary report. *N Engl J Med.* 2015 (<http://www.ncbi.nlm.nih.gov/pubmed/25830322>).

⁴⁵ Sarwar UN, Costner P, Enama ME et al. Safety and immunogenicity of DNA vaccines encoding Ebolavirus and Marburgvirus wild-type glycoproteins in a phase I clinical trial. *J Infect Dis.* 2015;211:549–557.

⁴⁶ Sullivan NJ, Fausther-Bovendo HF, Nabel GJ. Ebola vaccine. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccine*, 6th ed. Philadelphia: Elsevier; 2013:1060–1067.

vector virus and/or the EBOV-GP will be detectable in blood for several days until eliminated by antibodies and other immune responses. Tests (ELISA or RT-PCR) that target a single antigen of the Ebola virus, especially if the target is the EBOV-GP, may result in a false-positive in a recently vaccinated individual.^{20 43}

⁴⁴ This situation was reported in a health-care worker who received a high dose of Ebola vaccine following needle prick with a needle potentially contaminated with Ebola virus. An in-house RT-PCR targeting EBOV-GP was positive one day and up to five days after vaccine receipt. Testing conducted with an alternative test which targeted the large polymerase gene, was negative in all samples. The patient did not develop EVD.⁴⁸ For optimal rule-out of vaccine-associated symptoms, an RT-PCR assay targeting a non-GP Ebola virus target should be deployed in outbreak settings involving active use of vaccine, or the results of two or more RT-PCR tests that target different gene sequences in the diagnosis of EVD should be considered.

With ring vaccination, considered one of the likely vaccine deployment strategies, some individuals will not be vaccinated until several days after exposure to Ebola virus and thus may already be incubating EVD at the time of vaccination. Therefore, a laboratory that will process samples in a population receiving vaccine must be identified and have the resources, capacity, and SOPs to run appropriate tests to confirm the presence of wild Ebola virus in symptomatic vaccinated individuals.

Update laboratory SOPs, training materials and supplies to ensure that sample collection, shipment and testing follows the specifications for required assays.

If new assays and procedures are being established in the designated laboratory that will carry out diagnosis of EVD incorporating differential diagnosis from vaccine virus, it is crucial that forms, SOPs and training materials are updated accordingly. The designated laboratory should be accredited to run these tests. Laboratory assays are only reliable if they are complemented with accurate dates of vaccination and symptom onset, and if specimen collection, transport and manipulation is conducted according to product specifications.

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⁴⁷ Tsuda Y, Parkins CJ, Caposio P et al. A cytomegalovirus-based vaccine provides long-lasting protection against lethal Ebola virus challenge after a single dose. *Vaccine*. 2015;33:2261–2266 (<http://www.ncbi.nlm.nih.gov/pubmed/25820063>).

⁴⁸ Cnops L, Gerard M, Vandenberg O et al. Risk of misinterpretation of Ebola virus PCR results after rVSV ZEBOV-GP vaccination. *Clin Infect Dis*. 2015;60:1725–1726 (<http://www.ncbi.nlm.nih.gov/pubmed/25694650>).

Appendix N - Monitoring plan during vaccine delivery

Guidelines

The following vaccination strategies will be discussed:

- a. ring vaccination strategy;
- b. geographic vaccination strategy;
- c. HCW/FLW vaccination strategy.

More than one of these vaccination strategies may be used in a country.

The detailed information needed from an individual to determine eligibility for vaccine receipt will require close supervision. In addition, for individuals who consent to be vaccinated, the amount of data to be recorded in the vaccination register, on the vaccination card and in the vaccine log book is extensive and detailed.

In typical vaccine campaigns, the aggregate number of persons receiving the vaccine and the number of vaccine vials opened are tallied. Collection and recording of data for Ebola vaccination will be different from typical campaigns, with increased emphasis on accurate, complete and individual-level data collection. This is not so-called 'business as usual'. More data must be collected and the data quality must be high. This will require a higher level of supervision from both campaign supervisors and international monitors.

The guidelines below represent crucial components of campaign monitoring. These should be adapted to relevant observations from effective campaign monitoring processes during Ebola virus vaccine clinical trials.

The vaccination post must be organized to screen people for fever and/or a constellation of symptoms. Information on age eligibility, prior receipt of Ebola vaccine, pregnancy status and breastfeeding status, for women of childbearing age, must be collected. *[Country to update document based on eligibility requirements for the current vaccine candidate under consideration for use.]* If a person is not eligible to receive the Ebola vaccine, the reason must be recorded in the Ebola vaccine register. Consent must be obtained from every individual.

Since it is anticipated that Ebola vaccine will be distributed shortly after case detection, the number of HCW/FLW, the number of contacts or contacts of contacts, or the geographic area should be small (i.e. not country wide). Given the need for detailed data for determination of eligibility status for the Ebola vaccine register, and for the Ebola vaccine log book, all Ebola vaccine vaccination sites must be supervised.

Any problem detected during supervision must be corrected immediately. If a solution cannot be determined, the supervisor at the next level up must be contacted immediately. A supervisory checklist is provided below.

Checklist for supervisors and independent monitors

Screening/eligibility *[Update with eligibility requirements for the current vaccine candidate to be used]*

- | | | |
|--|-----|----|
| • Are individuals being screened for fever? | Yes | No |
| • Are individuals being screened for a constellation of symptoms? | Yes | No |
| • Are women of childbearing age being screened for pregnancy? | Yes | No |
| • Are women of childbearing age being screened for breastfeeding? | Yes | No |
| • Is age eligibility being checked? | Yes | No |
| • Is prior receipt of Ebola vaccine being asked about and checked? | Yes | No |
| • Is prior history of Ebola disease being asked about and checked? | Yes | No |
| • Are individuals cross-checked with the original list of contacts/eligible worker list to verify that they are eligible (i.e. contact or contact of contact for ring strategy; eligible worker for HCW/FLW strategy)? | Yes | No |

Vaccination supplies *[Update in each country using their vaccination supply list]*

For the number of people on the initial target population list, is there an adequate supply of:

- | | | |
|---|-----|----|
| • ebola vaccine | Yes | No |
| • cold-chain components | Yes | No |
| • mixing syringes | Yes | No |
| • AD syringes | Yes | No |
| • safety boxes | Yes | No |
| • gloves | Yes | No |
| • buckets of water with spigot and soap | Yes | No |
| • thermoflashes | Yes | No |
| • vaccination forms and cards. | Yes | No |

Vaccination session [Update in each country with any additional fields in the existing vaccination monitoring log]

- | | | |
|--|-----|----|
| • Was there adequate number of staff to screen for fever? | Yes | No |
| • Was there adequate number of staff to vaccinate? | Yes | No |
| • Was there adequate number of staff to record data in the register? | Yes | No |
| • Was there adequate number of staff to record data on HBR? | Yes | No |
| • Was there adequate number of staff to record data on tally sheet? | Yes | No |
| • Was there adequate number of staff to track vaccine in logbook? | Yes | No |
| • Was the flow of the vaccination session optimal? | Yes | No |
| • Were staff following infection control guidelines? | Yes | No |
| • Were anaphylaxis kits available? | Yes | No |
| • Was wait time post-vaccination implemented for vaccinees? | Yes | No |
| • Was a written vaccine information sheet and verbal key messages given to each vaccine recipient? | Yes | No |
| • Were safety boxes used? | Yes | No |

Ebola vaccine register [Update in each country with any additional fields in the vaccine register]

For all people on the initial target population list, are the following fields being completed?

- | | | |
|--|-----|----|
| • Demographics | | |
| ○ Name | Yes | No |
| ○ Address | Yes | No |
| ○ Cell-phone number for self and for next-of-kin/other | Yes | No |
| ○ Date-of-birth | Yes | No |
| ○ Gender | Yes | No |
| ○ For HCW/FLW: work location and supervisor contact info | Yes | No |
| • Prior history of Ebola disease | Yes | No |
| • Eligibility status | Yes | No |
| ○ For women of childbearing age, are the following recorded? | | |
| ▪ Pregnancy status | Yes | No |
| ▪ Breastfeeding status | Yes | No |
| ○ If the person is ineligible, reason is recorded | Yes | No |
| • Consent status | Yes | No |
| • If vaccinated: | | |
| ○ date of vaccination | Yes | No |
| ○ vaccine manufacturer and lot number (barcode desired) | Yes | No |
| ○ adverse event following immunization (AEFI). | Yes | No |

Home-based record [Update in each country with any additional fields on the home-based record]

- | | | |
|--|-----|----|
| • Demographics | | |
| ○ Name | Yes | No |
| ○ Date-of-birth | Yes | No |
| ○ Gender | Yes | No |
| • Prior history of Ebola disease | Yes | No |
| • Prior history of Ebola vaccination and the name of vaccine | Yes | No |
| • If vaccinated: | | |

- | | | |
|--|-----|----|
| ○ date of vaccination | Yes | No |
| ○ vaccine manufacturer and lot number (barcode desired) | Yes | No |
| ○ adverse event following immunization (AEFI) | Yes | No |
| ○ local and national number to call if AEFI experienced. | Yes | No |

Tally sheet [Update in each country with any additional fields on the tally sheet]

- | | | |
|---|-----|----|
| • Date of vaccination session | Yes | No |
| • Location of vaccination session | Yes | No |
| • Number of doses of vaccine administered | Yes | No |
| • Number of vaccine vials opened | Yes | No |

Ebola vaccine log [Update in each country with fields in the Ebola vaccine log]

- | | | |
|---|-----|----|
| • Number of doses of vaccine at start of session recorded | Yes | No |
| ○ Vaccine manufacturer and lot number recorded | Yes | No |
| • If additional doses received during the session: | | |
| ○ number of doses recorded | Yes | No |
| ○ vaccine manufacturer and lot number recorded. | Yes | No |
| • Number of doses discarded unopened | Yes | No |
| ○ The reason is recorded | Yes | No |
| • Number of doses of vaccine opened for use is recorded | Yes | No |
| • Number of doses of vaccine at end of session recorded | Yes | No |
| • Are vaccine vials (used and unused) kept and returned to the capital? | Yes | No |

Data quality checks

- | | | |
|---|-----|----|
| • Number of Ebola vaccine doses given match between: | | |
| ○ Ebola vaccine register and the tally sheet. | Yes | No |
| • Number of Ebola vaccine doses given make sense between: | | |
| ○ Ebola vaccine register and vaccine log book. | Yes | No |
| • Vaccine lot numbers match between: | | |
| ○ Ebola vaccine register and the vaccine log book. | Yes | No |

Training

- | | | |
|--|-----|----|
| All vaccination session workers were trained regarding their function? | Yes | No |
|--|-----|----|

Supervisor/independent monitor plan

The supervisor supervises the actual implementation. The independent monitor will assess the functioning of the implementation that includes the adequacy of supervision.

1. At least one supervisor/monitor should be present for the duration of each vaccination session. The supervisor should be onsite at least 1–2 hours prior to the session start to ensure adequate last-minute preparations.
2. A supervisory visit to the vaccination site should occur at least one day prior to the session to ensure that all forms and supplies are available.
3. The supervisor/monitor should ensure that all vaccination session workers have been trained.
4. The supervisor/monitor should ensure that all contact tracer workers have been trained on what to inform contacts (i.e. persons who are potentially eligible).
5. Supervision of the contact tracers is a separate function. There should be at least one supervisor/monitor for four or fewer teams of contact tracers. Additional supervision may be needed depending on the outbreak setting.
6. The supervisor/monitor should observe the flow of all vaccination activities to perform quality control during each step of the process.
7. For HCW/FLW settings, the supervisor/monitor should identify the health-facility leadership contact with whom to work to verify employment of potential age-eligible persons for vaccination and to assist in contacting employees as needed, etc.
8. Following the vaccination session:
 - a) supervisor/independent monitor should ensure that all forms are complete and legible. Corrective measures (additional training, etc.) should be undertaken in the event of errors.
 - b) Supervisor/independent monitor should ensure that all forms with personal identifiable information are kept secure and accessible only to those with a 'need-to-know'.

Vaccination activities spanning more than one day

Some vaccination activities could span more than one day. In areas where vaccination activities take longer than one day, monitoring vaccination activities, as well as progress with coverage, is necessary.

Examples of vaccination activities taking more than one day include vaccination at a large health facility or vaccination in a large geographic area. People targeted for vaccination may also have initial reluctance about being vaccinated so vaccination of all targeted individuals may take longer than expected. For employers with a large number of HCWs or FLWs, the employing agency may decide to stagger vaccine receipt of their employees into two or more groups. By staggering vaccine receipt, services delivered by HCW/FLW can continue to be offered, because not all employees will be post-vaccination at the same time. For large geographic areas, the number of days needed to complete vaccination activities is a function of how many people can be screened, vaccinated and recorded per day by the team.

For each of the proposed vaccination strategies, a complete list of the target population is available before the vaccination team is sent to the field, or at the time of consent or refusal. The initial target population list for the

- ring vaccination strategy is the contact tracing list (comprising all the contacts of a confirmed case plus the contacts of those contacts. The ring is not necessarily confined to a single geographical site. For further details please refer to **Appendix P**, Step 2).
- Geographic vaccination strategy is a list of all individuals in the geographic area who are age-eligible to receive the Ebola vaccine.
- HCW/FLW vaccination strategy is a list of individuals working as health-care workers or front-line workers.

(More details about the initial target population lists are given in **Appendix O** - Assessment plan after vaccine delivery.

Progress with vaccination coverage can be monitored using the initial target population list and the administrative data on the daily tally sheet. Based on the result it can be determined how many days will be necessary in order to complete vaccination activities with the current staffing, or if additional staff need to be sent to the area so that vaccination activities can be completed sooner.

Example: Geographic area A has 10 000 age-eligible residents. It was assumed that the team sent to geographic area A could screen, vaccinate and record 5000 residents per day and that vaccination activities would span two days.

At the end of the first day of vaccination activities, 3333 residents were vaccinated. Calculating vaccination coverage at the end of day 1, 33% of the age-eligible residents were vaccinated. This information needs to be communicated to the supervisor at the next level up by the supervisor and/or independent monitor. A plan of action needs to be implemented.

- If no additional vaccination staff can be sent to geographic area A, vaccination activities will be completed in two additional days instead of one additional day. The leaders of the geographic area must be informed of the progress to date and that an additional day of vaccination activities will be necessary. Funds to pay vaccination staff for an additional day of vaccination activities must be secured. The cold-chain logistician must be informed of the need to have vaccine delivered an additional day.
- If additional vaccination staff can be sent to geographic area A, vaccination activities can be completed in a day. The leaders of the geographic area must be informed of the progress to date and the anticipated day of completion of vaccination activities.

Appendix O - Assessment plan after vaccine delivery

Vaccination coverage

After conducting an Ebola vaccination activity, it is important to be able to measure vaccine coverage. For a large population, vaccine coverage is estimated from a vaccine coverage survey using a probability sample design. Often, coverage surveys are conducted because (a) a list of all of the people in the target population is unavailable, and (b) if such a list is available, ascertaining whether every individual on the list has been vaccinated is cost prohibitive when the target population is large. It should be noted that the sampling frame for a coverage survey for Ebola vaccine is a listing of persons eligible for Ebola vaccine and it is dependent on the delivery strategy of the vaccine.

If there is a complete list of all persons eligible to receive Ebola vaccine and the data quality for the number of doses of Ebola vaccine administered is high, there is no need to draw a probability sample to estimate vaccine coverage because vaccine coverage can be directly calculated.

For the proposed delivery strategies for the Ebola vaccine, it will likely be possible to obtain a list of all Ebola vaccine-eligible persons and whether these persons received the Ebola vaccine. Vaccine coverage can be directly calculated instead of being estimated. The target population is known (i.e. the denominator for coverage) and the vaccination status of every individual in the target population is known (i.e. the numerator for coverage). The data quality for the number of doses of Ebola vaccine administered must be high.

The proposed delivery strategies for Ebola vaccine are ring vaccination, geographic vaccination or HCW and/or FLW. For each of these strategies, a complete list of the target population will likely be available before the vaccination team is sent to the field, or at the time of consent or refusal, and will be updated as new information becomes available.

The initial target population list, depending on vaccination strategy.

- Ring vaccination: contact-tracing list (comprising all the contacts of a confirmed case plus the contacts of those contacts. The ring is not necessarily confined to a single geographical site. For further details refer to **Appendix P**, Step 2). This list is available before a vaccination team is dispatched.
- Geographic vaccination: a list of all individuals in the geographic area who are age-eligible to receive the Ebola vaccine. With assistance from community leaders (e.g. village leader, urban ward leaders), this list may be available before a vaccination team is dispatched or can be collected at the time of consent or refusal.
- HCW/FLW vaccination: a list of individuals working as HCWs or FLWs. This list is created by the employing organization ahead of time so that vaccination of employees can be staggered into two or more groups. Staggering vaccination allows continuation of services delivered by HCW/FLW since not all employees will be post-vaccination at the same time.

A detailed and complete Ebola vaccine register is necessary to record prior history of Ebola disease, eligibility, consent or refusal, the date of vaccination, vaccine manufacturer and lot number. Reasons for ineligibility may include being pregnant, previously vaccinated with Ebola vaccine or having a fever/constellation of symptoms.

Using the information in the Ebola vaccine register, vaccine coverage can be directly calculated. The denominator for vaccine coverage is the total number of eligible persons recorded in the Ebola vaccine register. The numerator for vaccine coverage is the total number of eligible persons who received the Ebola vaccine recorded in the Ebola vaccine register.

The data in the Ebola vaccine register can be summarized to provide the following information:

- Ebola vaccine coverage;
- a list of vaccine refusers for interviews on reasons for vaccine refusal. See the reasons for vaccine refusal sub-section for more details.
- A list of vaccine acceptors for interviews on reasons for vaccine acceptors. See the reasons for vaccine acceptors sub-section for more details.

- A list of adverse events following immunization by vaccine manufacturer and lot number. See the AEFI sub-section for more details.
- A list of vaccine defaulters. This information can be used to find these individuals and offer them vaccine. See the vaccine defaulters sub-section for more details.

Data from the target population will be used for the vaccine efficacy portion of surveillance work and AEFI work.

The components below represent optimal practices based on immunization vaccine campaign strategies. Due to the unique nature of Ebola vaccine in outbreak settings, if appropriate these strategies can be adjusted based on observations of best practices from Ebola vaccine clinical trials.

Data quality

A check of data quality includes:

- a visual check of the Ebola vaccine register to make sure that all fields are being completed correctly and a comparison of the number of doses of Ebola vaccine given on the tally sheet with the number of persons listed in the Ebola vaccine register as having received the vaccine;
- a comparison of the number of doses of Ebola vaccine given on the tally sheet with the number of doses used in the vaccine log book;
- a comparison of the vaccine lot numbers in the Ebola vaccine register and the vaccine lot numbers in the vaccine log book.

The data-quality check should occur a minimum of three separate times.

- (a) During vaccination delivery by the vaccination team, the supervisor and/or the independent monitor.
- (b) At the end of vaccination delivery for the site before data are sent to the next administrative level.
- (c) By data-quality monitors at the site after vaccination delivery.

Supportive supervision should occur with the vaccination team to remediate the problem:

- if the fields in the Ebola vaccine register are not being properly completed;
- if there is a discrepancy between the data in the Ebola vaccine register, the tally sheet or the vaccine log book.

Reasons for vaccine refusal

To determine the reasons for non-vaccination, and to address concerns and questions, it is essential that contact be established with people who are targeted for vaccination but do not come forward for vaccination at a vaccination post, or who decline vaccination during a house-to-house or health-facility visit. Contact with these individuals, must be conducted, with sensitivity and respect, by community engagement officers who are known and trusted. Community engagement officers should be fully briefed on questions relating to Ebola vaccination and should request clarification from members of the vaccination team on questions to which they do not know the response.

The primary objectives of these community engagement activities are:

- to answer the concerns and questions of those declining vaccination, such that they have accurate information on which to base their decision to be vaccinated or not. The opportunity should NOT be used to exert pressure on the individual to be vaccinated.
- To inform future communication messages about Ebola vaccine.

A secondary objective is to reinforce infection prevention messages.

If the individual declining vaccination decides, following the community engagement, to be vaccinated, he/she should be informed of where to go and when.

Reasons for vaccine acceptance

When people come to be vaccinated, the opportunity should be taken by the vaccinating team to ask what factors influenced their decision to be vaccinated. Information gathered should be fed back to the community engagement team as it can help inform communication messages going forward.

Vaccination wastage

To calculate vial-specific wastage rates, the vaccine log book should include, at a minimum, the following elements:

- the number of doses of vaccine at the beginning of the vaccination session including the vaccine manufacturer and lot number;
- the number of any additional doses of vaccine received during the vaccination session including the vaccine manufacturer and lot number;
- the number of doses discarded unopened plus the reasons the unopened doses were discarded;
- the number of doses of vaccine opened for use;
- the number of doses of vaccine at the end of the vaccination session.

Vial-specific wastage rates reveal the reasons behind overall wastage. In order to calculate the opened-vial-specific and unopened-vial-specific vaccine wastage rates, the number of persons vaccinated at the vaccination session must be recorded. This information can be obtained from the tally sheet or from the Ebola vaccine register.

Formulas for the vial-specific wastage rates can be found in Annex 2 of the WHO publication *Monitoring vaccine wastage at country level: guidelines for programme managers*.⁴⁹

Adverse events following immunization (AEFI)

Please refer to the companion publication *Guidance for establishing AEFI surveillance systems in countries planning to use Ebola vaccines*, WHO 2015.³⁰

Data from the target population will be used for the AEFI work.

Human resources

Ask the vaccination coverage team whether there is an adequate number of persons to:

- calculate coverage (i.e. using the Ebola vaccine register, calculate the total number of persons eligible to receive the Ebola vaccine and the total number of eligible persons who received the Ebola vaccine);
- summarize the reasons for being ineligible to receive Ebola vaccine;
- check on the data quality of the tally sheets, Ebola vaccine register and Ebola vaccine log;
- interview and summarize the reasons for being a vaccine refuser or accepter;
- create a list of vaccine defaulters.

If there were an inadequate number of persons for any of the activities listed above, seek clarification on what the difficulty was and whether additional persons or tools were needed. Feed this information back immediately to the higher level so that changes can be made.

Defaulter tracing

Using the initial target population list, create a list of vaccine defaulters. The definition of a vaccine defaulter varies by whether a one-dose or two-dose vaccine is used. The definition for a vaccine defaulter can be found in the appropriate sub-section.

⁴⁹ *Monitoring vaccine wastage at country level: guidelines for programme managers*. Geneva: World Health Organization; 2005 (<https://extranet.who.int/iris/restricted/handle/10665/68463>).

At the end of vaccine delivery, all persons in the Ebola vaccination register can be categorized as (a) not on the defaulter tracing list, or (b) on the defaulter tracing list. The vaccine defaulters identified should be located and, if eligible, offered the Ebola vaccine.

One-dose vaccine setting

In the one-dose vaccine setting, vaccine defaulters are defined as people who neither received nor refused Ebola vaccine and whose eligibility for vaccine receipt has not been determined.

At the end of vaccine delivery in the one-dose vaccine setting, all persons in the Ebola vaccination register must be categorized as (a) not on the defaulter tracing list, or (b) on the defaulter tracing list.

- Persons not on the defaulter tracing list include those who received Ebola vaccine, who refused Ebola vaccine, or who were ineligible to receive Ebola vaccine.
- Persons on the defaulter-tracing list include those who neither received nor refused Ebola vaccine and whose eligibility for vaccine receipt has not been determined.

In this setting, vaccine defaulters are persons who were not available when Ebola vaccine was offered. Vaccine defaulters should be located and, if eligible, offered the Ebola vaccine.

Two-dose vaccine setting

In this sub-section we are using two-dose vaccine settings to refer to the following scenarios.

- The setting where an individual receives two doses of the same Ebola vaccine with a minimum interval between the two doses of the same vaccine.
- The setting where an individual receives one dose of an Ebola vaccine and a subsequent dose of another Ebola vaccine with a minimum interval between the receipt of the first and second Ebola vaccine.

For the purposes of the creation of a defaulter-tracing list, these two scenarios are similar, since a person can default on vaccine receipt at two different times. In the defaulter tracing sub-section, we will refer to this as defaulting on the first dose or second dose of the Ebola vaccine without differentiating between the vaccination scenarios.

In the two-dose vaccine setting, a person can default on the first dose or the second dose of Ebola vaccine.

- For the first dose of Ebola vaccine, vaccine defaulters are defined as people who neither received nor refused Ebola vaccine and whose eligibility for vaccine receipt has not been determined.
- For the second dose of Ebola vaccine, vaccine defaulters are defined as people who received the first dose of Ebola vaccine but who did not receive the second dose of Ebola vaccine and the appropriate time interval between the first and second dose has elapsed.

All persons in the Ebola vaccination register must be categorized as (a) not on the defaulter tracing list, or (b) on the defaulter tracing list.

- Persons not on the defaulter tracing list include those who:
 - received both the first and second dose of Ebola vaccine;
 - received the first dose of Ebola vaccine but have not received the second dose of Ebola vaccine because the appropriate time interval between Ebola vaccine doses has not been met;
 - refused the first dose of Ebola vaccine;
 - were ineligible to receive the first dose of Ebola vaccine.
- Persons on the defaulter tracing list include:
 - vaccine defaulters for the first dose of Ebola vaccine. This type of vaccine defaulter is a person who neither received nor refused Ebola vaccine and whose eligibility for vaccine receipt has not been determined. A person on this list was not available when the first dose of Ebola vaccine was offered.
 - Vaccine defaulters for the second dose of Ebola vaccine. This type of vaccine defaulter is a person who received the first dose of Ebola vaccine but who did not receive the second dose of Ebola vaccine and the appropriate time interval between the first and second dose

has elapsed. A person on this list received the first dose of Ebola vaccine but not the second dose of Ebola vaccine.

Vaccine defaulters should be located and, if eligible, offered the Ebola vaccine.

Ring vaccination strategy

The initial target population list for the ring vaccination strategy is the contact-tracing list. The contact tracers have this list; it is available before a vaccination team is dispatched. The vaccination team should work closely with the contact tracers. Prior to vaccination activities, the contact-tracing list is used to complete the name, household address and primary contact in the Ebola vaccination register. Because ring vaccination additionally involves identification of contacts of contacts, their details should also be included (Annex A). Further components of this process should be adapted based on SOPs from Ebola vaccine clinical trials.

At the end of vaccine delivery, create a list of the vaccine defaulters. All persons on this list should be located and if eligible offered Ebola vaccine.

Geographic vaccination strategy

The initial target population list for the geographic vaccination strategy is a list of all individuals in the geographic area who are age-eligible to receive the Ebola vaccine. With assistance from the community leaders (e.g. village leader, urban ward leader), this list may be available before a vaccination team is dispatched, or can be collected at the time of consent or refusal. If the list is available prior to vaccination activities, the contact-tracing list is used to complete the name, household address and primary contact in the Ebola vaccination register.

At the end of vaccine delivery, create a list of the vaccine defaulters. All persons on this list should be located and, if eligible, offered Ebola vaccine.

Health-care worker (HCW)/Front-line worker (FLW) vaccination strategy

The optimal approach for vaccination will involve creation of the initial target population list ahead of time so that vaccine receipt of their employees can be staggered into two or more groups. By staggering vaccine receipt, services delivered by HCW/FLW can continue to be offered because not all employees will be post-vaccination at the same time. Prior to vaccination activities, this list is used to complete the name, household address and primary contact in the Ebola vaccination register.

A number of different strategies can be used to create the groups included, but are not limited to the following.

- Stratify people according to whether their age is an even or odd number. Odd numbers are vaccinated in the first wave and even numbers are vaccinated in the second wave.
- For each shift, half of the people are vaccinated in the first wave. The remaining half of people in each shift will be vaccinated in the second wave.

At the end of vaccine delivery for each wave, create a list of the vaccine defaulters. All persons on this list should be located and, if eligible, offered Ebola vaccine.

A mechanism must be in place to request Ebola vaccine for all new hires during the outbreak.

Appendix P - Standard practical steps

[[hyperlink to Appendix P available on the website](#)]

draft Ebola strategy

Appendix Q - Macro planning template

[[hyperlink to Appendix Q available on the website](#)]

draft Ebola strategy

Appendix R - Potential study designs for field studies of Ebola vaccine effectiveness

Introduction

The purpose of this annex is to discuss potential options for assessing the effectiveness of a vaccine distributed in response to an Ebola virus outbreak. It is assumed that widespread vaccination will not take place until after an outbreak is identified. While it is possible that a small number of national or international first responders may be vaccinated in the absence of an outbreak, it is anticipated that this will represent too small a set of individuals to inform vaccine effectiveness calculations. Thus, early contacts will not have had the opportunity to be vaccinated prior to exposure, and will not be vaccinated immediately afterwards due to the inherent delay in identifying an outbreak and implementing the vaccine deployment strategy. This document assumes that one or both of two vaccine delivery strategies will be used: (1) pre-emptive vaccination of HCW and potentially FLW; (2) vaccinating high-risk persons in the community after an Ebola case has been identified through ring vaccination of epidemiologically-linked contacts and contacts of contacts (including HCW) or targeted geographic vaccination. These delivery strategies and target populations have been the most commonly identified delivery strategies, among various strategic workgroups, based upon the epidemiology of the 2014 outbreak, and historic data, the limited availability of vaccines and limited knowledge about Ebola vaccines.

Considerations for all study designs

Study design: This document focuses on two common study designs for measuring vaccine effectiveness: cohort and case-control studies. Vaccine efficacy and effectiveness are typically calculated as a measure of 1 minus a measure of relative risk comparing the vaccinated group to the unvaccinated group ($VE = 1 - RR$).⁵⁰

- Cohort studies most closely resemble randomized controlled trials and allow for direct calculation of attack rates (AR) in the vaccinated and unvaccinated cohorts. VE is calculated as $1 - AR_{vac}/AR_{unvac}$.^{50 51 52} However, identification and follow-up of vaccinated and unvaccinated cohorts is resource-intensive and frequently not feasible.
- Case-control studies identify persons with the disease of interest and compare their vaccination history to selected persons, without the disease, to get an odds ratio. When a disease is rare, the odds ratio approximates the risk ratio and VE can be calculated as $1 - OR$.⁵¹

Similarity of comparison groups regarding risk of exposure to EVD: Bias may occur if the two comparison groups of an effectiveness study (vaccinated and unvaccinated cohorts in a cohort study, or cases and controls in a case-control study) do not have a similar risk of exposure to EVD.^{51 52} Unlike many vaccine-preventable diseases for which vaccine effectiveness studies have been conducted (e.g. measles, cholera and rotavirus), EVD infection requires direct contact with sick EVD patients or their body fluids. Thus, while large groups of people are considered “contacts” or “high-risk” (e.g. health-care workers), there is huge variation in true risk of exposure within these groups. Finding comparison groups with similar risks of exposure will be very difficult. Furthermore, changes in exposure risk over time, due to other aspects of outbreak response (i.e. infection control, rapid isolation of cases), need to be considered in assessing the comparability of EVD exposure from cohorts defined early in the outbreak and those defined later in the outbreak. This is especially true for unvaccinated cohorts created retrospectively from persons considered to have a high risk of EVD exposure prior to vaccine deployment.

Timing of vaccination and incident EVD: Under the ring vaccination strategy, some persons will be vaccinated after they have been infected with Ebola virus and are in the incubation phase of disease progression. As a result, they may still develop EVD, but this does not mean the vaccine failed. To address this issue, the WHO ring vaccination trial in Guinea defined their outcome of interest as EVD occurring more than 10 days post-vaccination (or 10 days post-randomization in the delayed vaccination group).³⁸ Any

⁵⁰ Halloran, ME, Longini Jr IM, Struchiner, CJ. Case-control studies. In: Halloran ME, Longini Jr IM, Struchiner CJ., eds. Design and analysis of vaccine studies. Chapter 8. New York: Springer; [isbn=0387686363](https://doi.org/10.1007/978-1-4939-9836-3_8).

⁵¹ Nelson KE, Masters Williams CF. Infectious disease epidemiology theory and practice. Sudbury: Jones and Bartlett Publishers; 2007.

⁵² Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field. *Epidemiol Rev.* 1988;10:212–240 (<http://www.ncbi.nlm.nih.gov/pubmed/3066628>).

studies of vaccine effectiveness in which persons may be vaccinated post-EVD exposure will have to consider this issue and develop an appropriate definition for incident EVD.

Sample size considerations: Based on the history of EVD outbreaks prior to the 2014 West Africa outbreak, and considering the lessons learned by the global health community during the 2014 outbreak, future EVD outbreaks may be significantly smaller than the 2014 outbreak. This may be a limitation of any strategy to assess vaccine effectiveness or efficacy, due to limited sample size.

Potential designs for cohort studies

Several potential cohort study designs to measure vaccine effectiveness are outlined below. For each design, there is a discussion of the populations that should comprise the vaccinated and unvaccinated cohorts, as well as the strengths and limitations of each design.

All cohort study designs require the following:

- (1) Individual-level identification of persons comprising the vaccinated and unvaccinated cohorts so that they can be followed for incident EVD, either through study procedures or national EVD surveillance.
- (2) If national EVD surveillance is used to ascertain incident EVD among the study cohorts, the surveillance system must be strong enough to ensure that incident EVD cases in both the vaccinated and unvaccinated cohorts are identified.
- (3) Availability of vaccination dates for persons in the vaccinated cohort.
- (4) A measurement/classification of EVD exposure risk to ensure that the vaccinated and unvaccinated cohorts have similar risk.

Potential study designs assuming a presumptive vaccination of HCW/FLW strategy.

- (1) Overall cohorts of vaccinated and unvaccinated HCW/FLW in a district/region/country:
 - a. The vaccinated cohort consists of all vaccinated HCW/FLW.
 - b. The unvaccinated cohort consists of (a) all unvaccinated HCW/FLW from lists of HCW/FLW targeted for vaccination, or (b) HCW/FLW from areas of the district/region/country affected by EVD before vaccine was available.
 - c. Potential strengths: larger numbers of persons in the vaccinated and unvaccinated cohorts increase the chance of having an adequate number of incident EVD cases to assess effectiveness.
 - d. Potential limitations: with a licensed vaccine, it is likely that very few HCW/FLW will refuse vaccination. This will limit the size of the unvaccinated cohort. Retrospective unvaccinated cohorts may be possible, such as HCW/FLW from areas affected by EVD before vaccine was available, but it may be very difficult to define these cohorts and their follow-up time. If all targeted HCW/FLW are included, it is likely that the majority will not actually be exposed to EVD, thus, large cohorts may not necessarily result in many incident EVD cases.
- (2) Smaller cohorts of HCW with more specific eligibility criteria.
 - a. The vaccinated cohort consists of HCW at facilities that had EVD cases.
 - b. The unvaccinated cohort consists of either (a) non-vaccinated HCW at the same facility, or (b) HCW at facilities that had EVD cases before vaccination was deployed.
 - c. Potential strengths: with smaller cohorts from health-care facilities that had EVD cases, better data on EVD exposure and other risk factors can be collected. In addition, more restrictive eligibility criteria will ensure that the highest risk persons are included in the study and reduce the resources required to follow low-risk persons who are unlikely to develop incident EVD.
 - d. Potential limitations: this design may have similar limitations to the previous design. It is likely that few people in affected health centres will refuse vaccination and identifying appropriate cohorts retrospectively may be challenging. Furthermore, there may be substantial differences in exposure risk between vaccinated and unvaccinated persons within a health facility, as staff with a high risk of exposure may be more likely to accept vaccination than those with a low risk of exposure. Finally, if HCW from different facilities are used as the comparison group, there may be substantial differences in exposure risk based

on the characteristics of the index cases and infection-control practices of the health facilities.

Potential study designs, assuming epidemiologic ring or targeted geographic vaccination strategies.

- (1) Targeted geographic vaccination.
 - a. The vaccinated cohort consists of geographic areas that were vaccinated.
 - b. The unvaccinated cohort consists of retrospective geographic areas that had EVD cases during the same outbreak, but prior to vaccine deployment.
 - c. Potential strengths: geographic areas should allow for easier definition and follow-up of retrospective cohorts than some of the other options.
 - d. Potential limitations: analysis will need to account for post-exposure vaccination and clustering of geographic areas.

- (2) Epidemiologic ring vaccination (vaccinating contacts and contacts of contacts). This could also include staff at health-care facilities if they were not vaccinated until after exposure to an initial EVD case.
 - a. The vaccinated cohort consists of vaccinated contacts and contacts of contacts.
 - b. The unvaccinated cohort consists of epidemiologic rings (contacts and contacts of contacts) around EVD cases from early in the epidemic, prior to vaccine deployment.
 - c. Potential strengths: contact tracing with individual identification and follow-up (for a limited period of time, typically 21 days) is a standard EVD outbreak response measure; this study design builds upon the established contact tracing system. Retrospective, non-vaccinated cohorts of contacts (but not necessarily contacts of contacts) from the entire outbreak should be identifiable from contact-tracing lists/databases.
 - d. Potential limitations: contacts of contacts are not typically identified as part of EVD contact tracing but must be included in the unvaccinated rings if vaccinated and unvaccinated rings are to be compared. Thus, contact-tracing activities throughout the entire outbreak (even prior to vaccine deployment) would have to identify contacts of contacts using a standard definition that remains the same for unvaccinated and vaccinated cohorts. As with geographic rings, analysis must account for post-exposure vaccination and clustering of rings. In addition, each new case potentially creates a new ring, but new rings will have a lot of overlap with the ring of the source-case. Thus, careful identification and classification of individuals in rings is important.

Potential case-control study design

Additional considerations for case-control studies:

Controls should be selected from the same population as cases. They should be similar in both their probability of vaccination and exposure to infection.⁵¹ Given that EVD transmission is only through direct contact with a person who is sick with EVD, or their body fluids, and that outbreak response vaccination will likely be targeted to very specific populations, ensuring similar probabilities of vaccination and exposure to infection may be more difficult with EVD than with other vaccine-preventable diseases.

*Selection of cases and controls must be independent of vaccination status.*⁵³ In case-control studies, selection of cases and controls must be independent of vaccination status.

Case-control studies will require:

- (1) vaccination records to determine whether cases and controls have been vaccinated (and date of vaccination). These could be found either with the individual or at a centralized location.
- (2) Data on timing of exposure to EVD patients.
- (3) Definitions to classify participants' vaccination status in situations where they were vaccinated after EVD exposure.

⁵³ Comstock GW. Evaluating vaccination effectiveness and vaccine efficacy by means of case-control studies. *Epidemiol Rev.* 1994;16:77–89 (<http://www.ncbi.nlm.nih.gov/pubmed/7925730>).

Potential study design for any vaccination strategy:

- (a) Selection of cases. Cases should be persons with laboratory-confirmed EVD that are diagnosed after vaccination has been introduced so that they had a possibility of being vaccinated.
- (b) Selection of controls. Controls should be EVD-negative persons who arise from the same population as the case, with a similar risk of EVD exposure and probability of vaccination. Potential controls for a case that was a contact of an earlier EVD patient would be other contacts from the same contact list. Matching on type of exposure to the incident case should be considered. Potential controls for HCW/FLW would be HCW/FLW with similar types of exposure to the index case. For example, if the index case was a nurse who provided direct care for a particular EVD patient, potential controls would be other HCW that provided direct care for that patient.
- (c) Potential strengths: case-control studies are typically smaller than cohort studies, hence it may be possible to collect more detailed exposure data on each participant. In addition, case-control studies do not require identification and follow-up of the entire vaccinated and unvaccinated cohorts.
- (d) Potential limitations: if the Ebola vaccines are efficacious and there is high acceptance of them among persons targeted for vaccination, there will be very few cases in vaccine-eligible populations, resulting in a very small sample size for a study. If controls are carefully matched for exposure risk, there may be few appropriate controls for some cases.

Choice of study design

The choice of study design will depend on the resources available and the vaccination strategy used, as well as the availability and quality of vaccination and outbreak response tools, such as the EVD surveillance system and lists of vaccinated and unvaccinated individuals. Any vaccine effectiveness (VE) study design will require significant funding as well as expertise in study design and implementation. Furthermore, they will require time to plan and implement. Thus, if a country is interested in conducting a VE study, planning should begin prior to an Ebola outbreak. Potential resources for funding and technical expertise include the vaccine manufacturers and academic organizations. Cohort studies typically require more resources and time than case-control studies, due to the follow-up of large numbers of people. If resources are adequate, it is possible to define vaccinated and unvaccinated groups and the surveillance system for follow-up is strong, a cohort design is preferable because it allows all available data to be used and direct calculation of attack rates. If a cohort study is not feasible, a case-control study is an alternative. Regardless of the design selected, these studies will be challenging to conduct and will require sophisticated epidemiologic and statistical support.