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EMERGENCY GUIDANCE

Surveillance strategy during Phase 3 of the Ebola response

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Background

The incidence of Ebola virus disease (EVD) in the three most affected countries in West Africa has fallen from a peak of 950 cases per week during September 2014 to less than 10 cases per week from August 2015 onwards. The risks presented by EVD are subsiding but not negligible, and changing in character. The continuing transmission of infection in Guinea and Sierra Leone into September 2015, plus the suspected re-emergence of infection resulting from exposure to survivor body fluids in Guinea, Liberia and Sierra Leone, highlight the importance of maintaining surveillance across all three countries. While the risk of re-emergence from survivors is not quantifiable, it is likely relatively low and does decline over time.

Phase 3 of the Ebola response builds upon capacity and knowledge gained during earlier phases, and has 2 objectives:

- Objective 1: To accurately define and rapidly interrupt all remaining chains of Ebola transmission
- Objective 2: To identify, manage and respond to the consequences of residual Ebola risks

Against this background, this document presents an overview of the surveillance strategy required to achieve the above objectives of Phase 3 of the Ebola response.

The document displays a set of recommendations that must be understood as the minimal standard countries must implement. If resources allow and if operationally feasible, criteria to test live and dead individuals can be modified and made more sensitive.

The proposed surveillance strategy needs to be reassessed in June 2016 and the systems in place and testing strategies adapted accordingly. Critical to this review will be the status of implementation and performance of national Infectious Disease Surveillance and Response (IDSR), the epidemiology, new knowledge in particular on the persistence of the virus in survivors and the transmission risk associated with this.

Goals of the Phase 3 surveillance strategy

The goals of EVD surveillance during Phase 3 (as in earlier phases of the Ebola epidemic) are to promptly detect new, suspected EVD cases and deaths so as to trigger an appropriate response, including rapid diagnosis, case isolation and management, contact tracing and safe burial, and the identification of transmission chains.

The activities carried out to achieve both objectives cover four distinct periods in each country. Periods A-C covers Phase 3. In period D the approach to surveillance is essentially given by IDSR.

A. From October 2015 until the last known opportunity for transmission (following discharge of the last patient from an Ebola treatment centre, or after burial of the last Ebola death), and for 42 days (end of the outbreak) (Objective 1)
B. After the end of the outbreak, a further 90-day period of heightened surveillance (Objective 2)
C. From 90 days up to one year (Objective 2)
D. After one year (after Phase 3)

General considerations for surveillance during Phase 3

In pursuing these objectives, the following considerations underpin the Phase 3 surveillance strategy:

- The strategy observes the practical requirement to balance the intensity and cost of surveillance against acceptable risks. Until the end of the outbreak (as described above), a surveillance with high sensitivity must be maintained i.e. activities that have a high chance of detecting new EVD cases and deaths, especially in areas of recent EVD activity, recognizing that a significant number of suspects will be found to have no EVD on further investigation.
- Once the outbreak has been declared over, and as the risk of EVD subsides, a sensitive surveillance strategy will be replaced by one that is more specific i.e. less labour intensive and less costly, allowing the possibility that a single new case will not be detected immediately, but maintaining a high probability of detecting a cluster of cases or a community death.

- The transition from a strategy that is exclusive to Ebola to a strategy designed to detect Ebola as one of a range of notifiable diseases under the Infectious Diseases Surveillance and Response (IDSR) system.
- As the West African epidemic proceeds, the identification of new cases is being enhanced by the development of new diagnostic tests and other tools for investigating transmission, including nucleic acid amplification tests (NAT), rapid diagnostic tests (RDT) based on antigen detection, real-time full genome sequencing and other laboratory techniques as deemed necessary (e.g. immune fingerprint evaluation).
- The risk of new cases during Phase 3 arises partly from exposure to EVD survivors body fluids (especially through contact with seminal fluid), but the survivors themselves will not be subject to active surveillance. Survivors, however, will be involved in case investigations carried out in response to the discovery of new cases. This process of investigation must respect the rights of survivors and in all ways avoid the risks of stigmatization. Moreover, survivors should be cared for through a comprehensive program that provides access to appropriate clinical, psychosocial and socio-economic services.
- Under a broad surveillance strategy for Phase 3, the details of implementation will vary among the three most-affected countries.
- The Phase 3 surveillance strategy must be tightly linked to the mechanisms for response (this document does not describe the responses in detail).
- Surveillance is organized by the health services in each country, but success depends on community engagement and participation (e.g. via alerts from citizens, community leaders and traditional healers to local health workers).
- The effectiveness of the Phase 3 surveillance system needs to be monitored and regularly evaluated.
- The key elements of the surveillance strategy for Phase 3 are presented in Tables 1 and 2.

Table 1. Overview of surveillance strategy during Phase 3 of the EVD response

	Phase 3			After Phase 3
	Objective 1: Interrupt all chains of transmission	***Objective 2: Manage residual risk***		
	Period A *From now to end of outbreak**	**Period B** *90-day enhanced surveillance*	**Period C** *> 90 days to 1 year*	**Period D** *> 1 year*
Live patients†	More sensitive testing criteria for detecting suspects (applies the EVD case definition during outbreaks). See Table 3 (left panel), Figure 1.	Change to more specific criteria for detecting suspects (as for routine IDSR). See Table 3 (right panel), Figure 1.		
Dead individuals† *Communities and local authorities should always report all deaths.*	Swab only bodies meeting the criteria: ≥5y, and dying within 14 days of symptom onset, with undetermined cause of death, OR still birth. See Figures 2 and 3.		Swab only bodies meeting the IDSR criteria: illness with fever and no response to treatment for usual causes of fever in the area and any haemorrhagic sign, OR clinical suspicion of EVD.	

* End of outbreak defined as 42 days after last possible transmission
† For diagnosis, use NAT assays alone until RDTs are available and have been validated for combination testing with NAT. Annex 1.

Table 2. Surveillance system to detect EVD among live and dead individuals

	Period A *From now to end of outbreak**	**Period B** *90-day enhanced surveillance*	**Period C** *> 90 days to 1 year*	**Period D** *> 1 year*
Community-based surveillance *As for IDSR, continuously*	●	●	●	●
Active case search in the community *In districts with active transmission*	●			
Facility-based surveillance *As for IDSR, continuously*	●	●	●	●
Active case search in health facilities *In districts with active transmission*	●			

* End of outbreak defined as 42 days after last possible transmission

Overview of the Phase 3 surveillance strategy

Alert system

The alert system is a mechanism to detect and report alerts to those responsible for surveillance. An alert is a condition that meets a very broad (sensitive) definition that aims to identify all signals that could potentially be an EVD case or death (or other conditions). Alerts can be generated by the community, at health-facilities, or picked-up in the media. Alerts are reported to those in charge of surveillance through various means, including, but not restricted to, a telephone hotline, texting, emails, etc. Alerts go through a screening and verification process until they are eventually tested for EVD. The alert system underpins various approaches to surveillance and must be closely tied to the response.

The systems and processes currently in place in the 3 countries have been designed and implemented largely to respond to the EVD outbreak. These EVD alert systems must be now expanded to cover the other diseases and conditions requested by the IDSR.

Live alerts and suspect cases *(See figure 1)*

Identification

Live alerts or suspect cases can be identified through several mechanisms:

- the community itself identifies an alert (community-based surveillance)
- the patient seeks health care, is identified as an alert or suspect case and is reported (health-facility based surveillance and routine reporting, including immediate notification and zero reporting)
- surveillance officer actively looks for alerts or suspect cases in health facilities and registers (active case search in health facilities)
- surveillance officers actively look for alerts or suspect cases in the community through follow-up of contacts or door-to-door search (active case search in the community)

Community-based and facility-based surveillance are the backbone of surveillance within the IDSR framework, must be enhanced and pursued indefinitely.

Active case search in the community and health facilities are to complement the above as part of an investigation of a probable or confirmed case or in places with active transmission chains, and should be discontinued once there is no more active transmission chain.

Criteria for testing

Screening criteria to decide which patients to test must evolve over time, be sensitive up to the end of the outbreak and specific thereafter.

Table 3. Screening criteria for EVD testing in live patients

Period A: Up to the end of the outbreak (42 days after last possible exposure) (*More sensitive criteria)*	**Periods B-D: From the end of the outbreak, indefinitely *(More specific criteria)***

• Any person suffering or having suffered from a sudden onset of high fever and having had contact with:
  - a suspected, probable or confirmed case of Ebola
  - a dead or sick animal (for Ebola); OR
• Any person with sudden onset of high fever and at least three of the following symptoms:
  - Headaches, vomiting, anorexia / loss of appetite, diarrhea, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, hiccup; OR
• Any person with inexplicable bleeding; OR
• Any sudden, inexplicable death; OR
• Clinical suspicion of EVD
	• Illness with fever; AND
	  - no response to treatment for usual causes of fever in the area; AND
	  - any hemorrhagic sign
	• OR: clinical suspicion of EVD

Diagnostic tests

NATs, using conventional or automated PCR, are currently the only reference test that can be used for live alerts, especially until the declaration of the end of the epidemic, and current testing algorithm should continue. Capacity for PCR testing has to be maintained.

RDTs will progressively be introduced from now onwards and into the 90-day enhanced surveillance period, during which careful monitoring and evaluation of the operational aspects must be conducted and results communicated. RDT can be used in particular situations, such as initial investigation of a cluster or when turnaround time for PCR exceeds 72 hours. Reactive samples with RDT must be retested by PCR (Figure 1, Annex 1).

Considering the extremely low expected incidence of EVD and the characteristics of the chosen RDT, the negative predictive value will be close to 100% and the few reactive samples will commonly be false-positive.

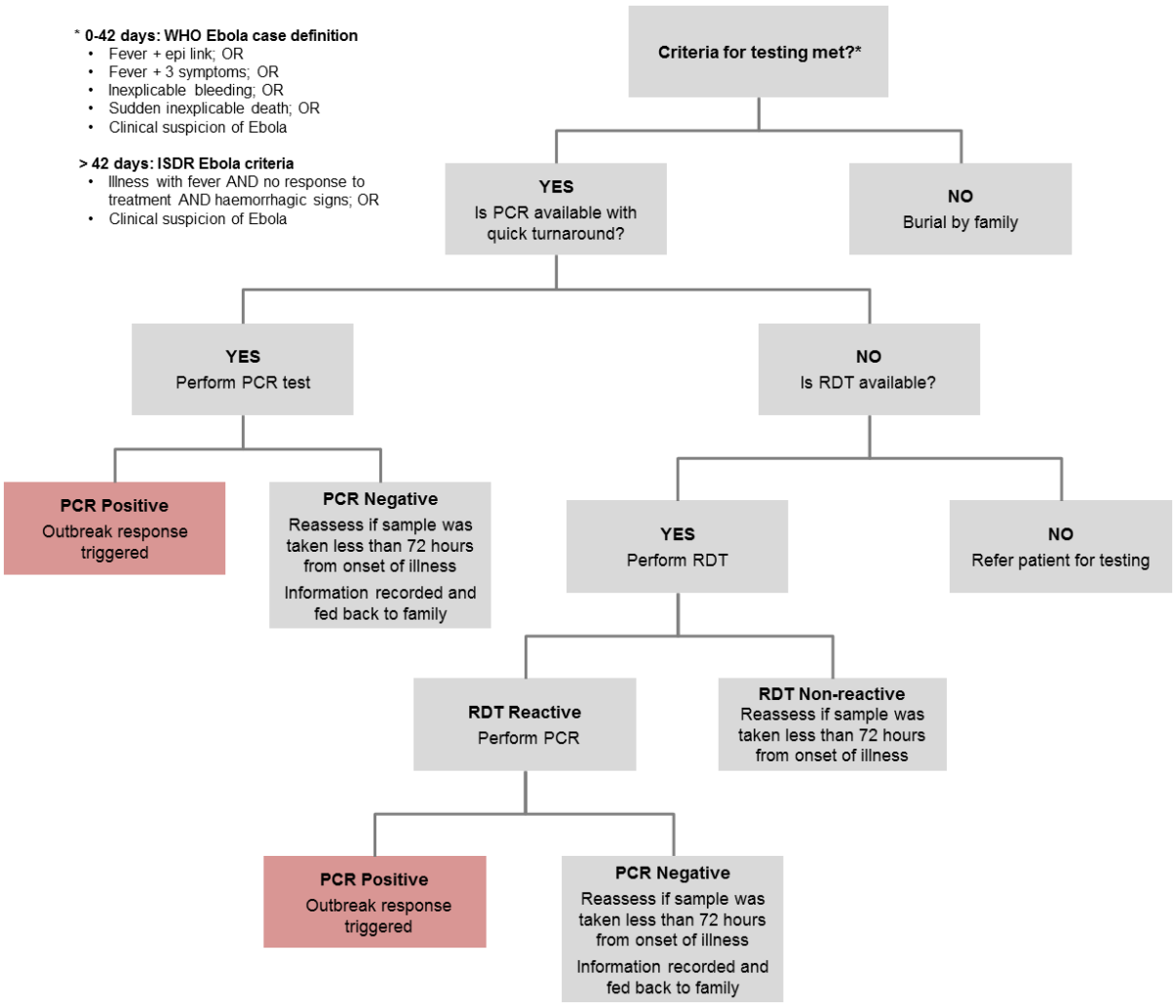

Figure 1. Surveillance and testing of live patients
(Nation-wide coverage, higher index of suspicion in areas with past transmission)

Surveillance for Ebola in dead individuals *(See Figures 2 and 3)*

Identification

Deaths will be identified by the community and the health facilities, acknowledging that the vast majority of deaths occur in the community. All deaths should be reported to the local surveillance officer.

Surveillance for EVD among dead bodies complements the surveillance of live alerts and acts as a safety net to identify initial cases or small clusters at their very beginning.

Death surveillance should be implemented at least until the end of the 90-day enhanced surveillance period and throughout the country, and cover both community and hospital deaths, acknowledging that the majority of hospital-deaths will have an alternative diagnosis.

Criteria for testing

Due to resource constraints and in order to maximise the efficiency of the strategy, it is recommended that only a subset of deaths be tested. The assessment and the decision about who to test is to be made by the local surveillance officer.

Screening criteria for testing dead individuals, for use at least until 90-day enhanced surveillance period:

- any individuals aged 5 years or more, dying within 14 days of symptom onset from an indeterminate cause, OR
- still births.

Following this period, the criteria to test a death will be more specific and be essentially the IDSR case definition i.e.: a death following an illness with fever and no response to treatment for usual causes of fever in the area and any haemorrhagic sign, OR clinical suspicion of EVD.

Diagnostic test

PCR remains the reference test until full validation of RDT on oral swabs (Figure 2). Once validated, RDT should be used according to the algorithm in Figure 3 (see also Annex 1).

Considering the turnaround time of PCR, deaths meeting the above criteria must be swabbed and buried in a safe and dignified manner, regardless of the results. Those not meeting the criteria can be buried according to traditional practices.

Once RDTs become available, only those with reactive results need to undergo safe and dignified burials. All reactive tests will have to be retested by PCR.

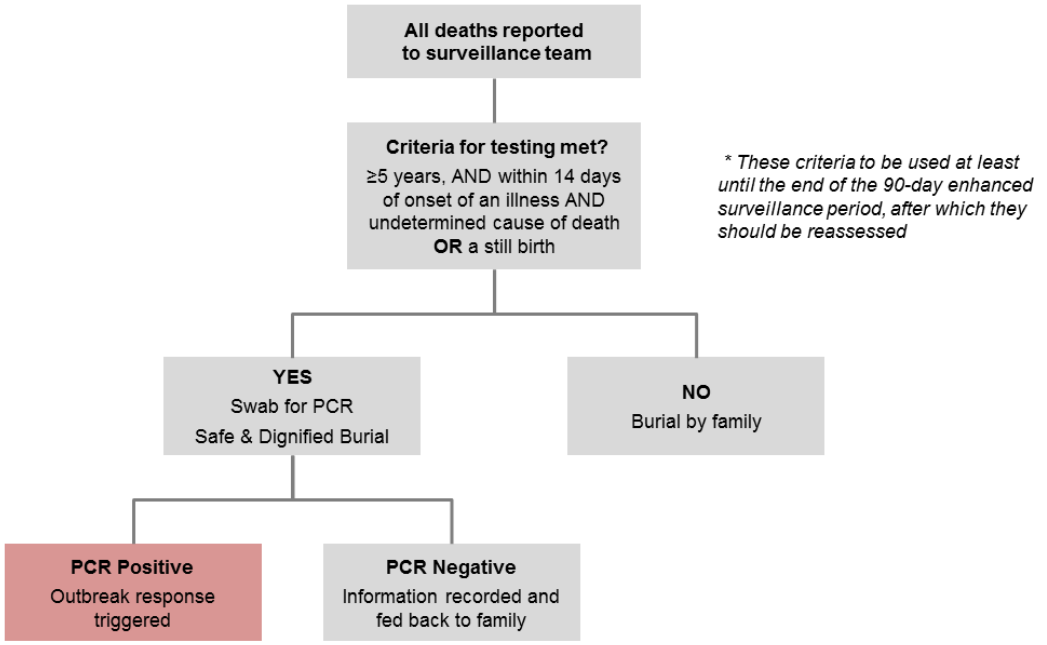

Figure 2. Surveillance and testing of deaths when RDTs are not available

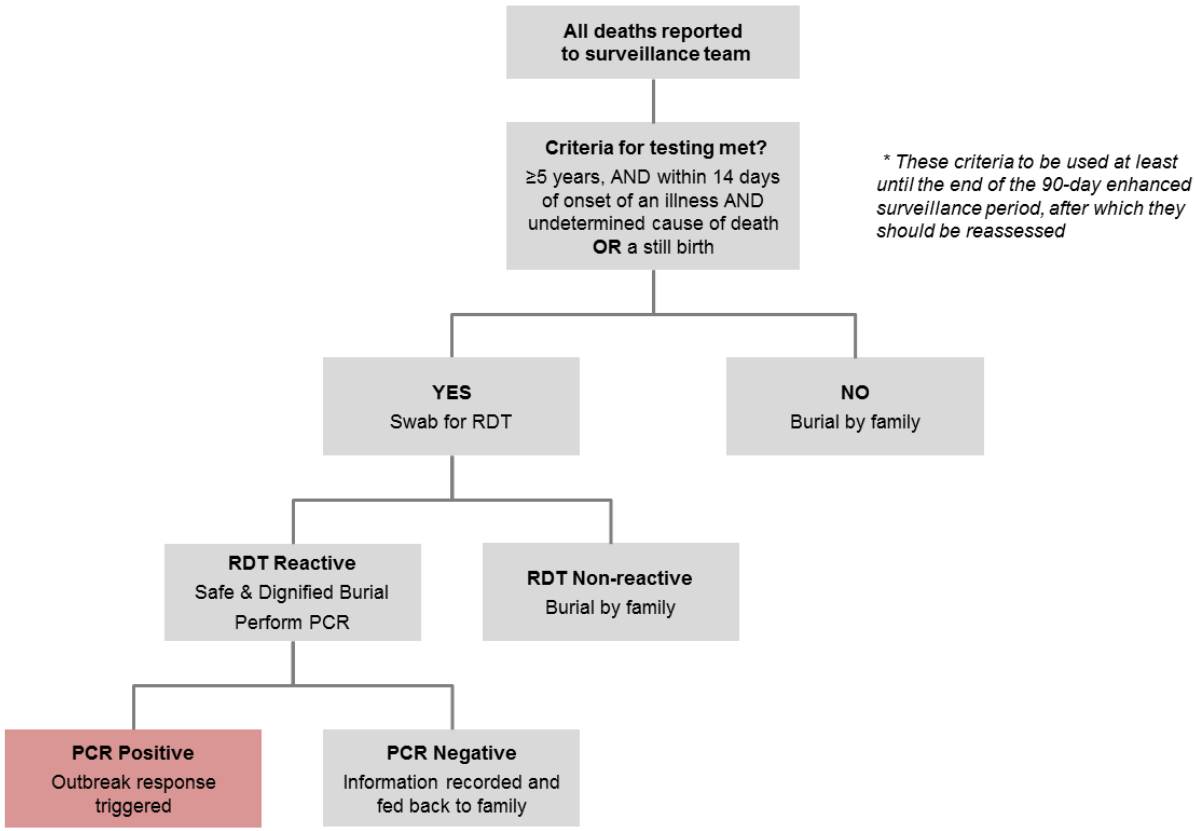

Figure 3. Surveillance and testing of deaths when RDTs are available and validated

Indicators to monitor the Phase 3 response

Key indicators are used to monitor progress towards the end of the outbreak in each country (Objective 1). These are summarized at Annex 2. While these indicators were selected for use during the course of the epidemic they will also be used to report on any new cases and deaths (and surrounding events) arising after the epidemic is declared over, during the 90-day period of heightened surveillance, or at any time thereafter (Objective 2).

In addition, Objective 2 depends on maintaining vigilance across the whole of Guinea, Liberia and Sierra Leone. To this end Phase 3 should also monitor the following surveillance indicators.

1. The number of alerts (live and dead) reported and investigated in each district each week. There is no target for the number of alerts reported per head of population, but a downward trend in alerts, no alerts at all, or silent districts/prefectures should trigger an investigation into the underlying causes.
2. The numbers of samples taken from live and dead individuals (as defined above) in each district and tested for EVD using either RDTs or NATs. Adequate coverage of all districts in the three countries will generate approximately 4000 samples from live suspects and 5000 from dead suspects per month until the end of the 90-day period of heightened surveillance.

Annex 1. The role of in-vitro diagnostic tests in surveillance during Phase 3 of the Ebola response

Two main types of commercially available in-vitro diagnostic (IVD) tests have been listed by WHO and FDA for emergency use in in the current EVD epidemic. They include five nucleic acid tests (NAT) with high sensitivity and specificity (Table 4) and two EVD antigen rapid diagnostic tests (Table 5). Two more RDTs are currently undergoing WHO and FDA assessment for emergency use.

During the Phase 3 surveillance period, the expected number of new EVD infections is very low. The value of RDTs, with high negative predictive value, is rapidly to ascertain (15-20 minutes) that a sample is not reactive. A non-reactive RDT can be considered to be a true negative in the current situation, and no further testing will be required. However, because of the relatively lower specificity than NATs, a sample that is reactive by RDT must be verified by NAT.

Considering the performance characteristics of EVD NAT and RDT assays, there are two main testing strategies for samples taken from live and dead suspects:

1. One test only, using a NAT assay (which is highly sensitive and specific)
2. Two tests, the first of which screens out EVD negatives by RDT, with a second NAT, if necessary, that identifies true EVD positives.

A limiting factor in present use of RDTs is that none apart from one has yet been approved for use by national regulatory authorities. Furthermore, WHO currently recommends only NATs for routine testing of blood (live suspects) and oral secretions (swabs from dead bodies). Under current guidance RDTs should only be used in remote settings when NAT assays are not available (http://www.who.int/csr/resources/publications/ebola/ivd-assays/en/).

In addition, the field performance of RDTs on oral secretions from dead bodies is unknown. An evaluation of four RDTs on oral secretions is ongoing in Sierra Leone and results are expected in January 2016.

General considerations in selecting and using diagnostic tests for EVD

The following aspects should be considered when choosing IVDs that are appropriate for EVD. The order and number of the characteristics do not represent a prioritization listing since priorities will be context-specific.

1. General characteristics of the test
   - Performance characteristics, which include sensitivity, specificity, and positive and negative predictive values for RDTs, and limit of nucleic acid detection of NAT tests.
   - Presence of appropriate test procedure controls supplied with the test kits to ensure that each step of the testing process has been performed correctly.
   - Transport and shelf-life of the specimens and the test reagents.
2. Anticipated use
   - Consideration should be made on the setting of intended use, the minimal technical qualifications of the users, the minimum number of specimens which can be tested per time period and the need for instrument(s) to conduct the testing.
   - Training of all users will be required.
   - Availability of testing quality assurance measures covering the pre-analytical, analytical and post-analytical phases and when applicable use of external Quality Assessment Scheme specimens.
   - Post-market surveillance to monitor the performance of the assays in the field is also critical.
3. Infection prevention and control
   - Specific steps must be taken to minimize chance of acquiring infection during the collection of samples, their transport and the testing process.

- Regardless of the setting in which a test is used, testing should always be performed under strictly applied, universal biosafety precautions, including waste management, by trained and properly equipped personnel.

4. Infrastructure requirements
   - Infrastructure factors should be considered, which include dedicated space for testing with the availability of glove boxes or biosafety cabinets and availability of electricity mainly for NAT assays.
5. Cost
   - Consideration must be given to the cost of reagents, equipment and accessories that are not supplied with the kits. In addition, the cost of PPE, waste disposal and management requirements, and the cost of maintaining instruments, and supply chain management.
6. Regulatory status
   - Manufacturer claims of quality, safety and performance should have been verified by a stringent independent assessment.
   - National registration of the IVD is mandatory before the product can be used in a particular country.

Table 4. Characteristics of commercial EVD NAT assays

	RealStar® Filovirus RT-PCR Kit 1.0 (CE-IVD) (altona Diagnostics GmbH)	**RealStar® Filovirus RT-PCR Kit (altona Diagnostics GmbH)**	**Liferiver™ Ebola virus (EBOV) real time RT-PCR kit Shanghai ZJ Bio-Tech Co., Ltd**	**FilmArray Biothreat-E BioFire, (Biomerieux)**	**Xpert® Ebola Assay (Cepheid)**
Viruses detected	Zaire ebolavirus (ZEBOV) & other	Zaire ebolavirus (ZEBOV) & other	Zaire ebolavirus (ZEBOV) & other	Zaire ebolavirus (ZEBOV)	Zaire ebolavirus (ZEBOV)
Gene Target	L	L	NP	L	NP, GP
Suitable specimen for Testing	Plasma (EDTA, cell free body fluids, swab washes	Plasma collected in EDTA	Venous whole blood or plasma EDTA, serum	Venous whole blood or urine, swabs, stool, csf	Venous whole blood EDTA
Storage conditions for reagents	-20℃ (requires cold chain)	-20℃ (requires cold chain)	-20℃ (requires cold chain)	18-25°C 9 months	2-28℃ (requires cold chain)
Throughput	4-6 hours	4-6 hours	4-6 hours	60 minutes	90 minutes
Specimens per day/instrument	~50	~50	~180	~10	24 - 96

Table 5. Characteristics of commercial EVD RDTs and performance using plasma or whole blood

	ReEBOV™ Antigen assay (Corgenix)	SD Ebola Zaire Ag assay (SD Biosensor)	[3]Oraquick Ebola RDT (Orasure)	[4]DPP Ebola Assay (Chembio)
Viruses detected	Zaire ebolavirus (ZEBOV)	Zaire ebolavirus (ZEBOV)	Zaire ebolavirus (ZEBOV)	Zaire ebolavirus (ZEBOV)
Antigen Target	VP40	VP40, NP and LP	VP40	VP40
[2]Suitable specimen for testing	Fingerstick (capillary) whole blood, collected in EDTA, or plasma collected in EDTA	Fingerstick (capillary) whole blood, collected in EDTA, or plasma collected in EDTA	Fingerstick (capillary) whole blood, collected in EDTA, or plasma collected in EDTA	Fingerstick (capillary) whole blood, collected in EDTA, or plasma collected in EDTA
Storage	2–8℃.	1-40℃	2-30℃	2-30℃
Time to results	15-25 minutes	15-20 minutes	30 minutes	10-15minutes
[1]Sensitivity (95% CI)	93.2 (87.4, 96.8)	84.5 (77.1, 90.3)	84.0 63.9, 95.5	95.0 (75.6, 100)
[2]Specificity (95% CI)	98.0 (93.0, 99.8)	100 (96.3–100.)	100 (97.2, 100)	[5]98.0 (92.6, 99.9)

(1) Sensitivity based mainly on plasma rather than whole blood; (2) Specificity when using whole blood, (3) Oraquick Ebola RDT (Orasure) listed by FDA but not WHO, (4) DPP Ebola Assay (Chembio) are still under assessment and therefore not listed for emergency use by WHO or FDA, (5) Specificity of DPP is based on non- endemic whole blood

Annex 2. Indicators to monitor Phase 3

	Indicator	Numerator	Numerator Source	Denominator	Denominator Source	Target
Alerts, cases and deaths						
1.	Number of alerts	Number of alerts	Guinea: daily WHO and Ministry of Health situation report Sierra Leone & Liberia: daily Ministry of Health situation	N/A	N/A	No numerical target Sudden change in number needs be investigated
2.	Percentage of districts/counties/ prefectures reporting alerts	Number of districts/ prefectures reporting alerts	Guinea: daily WHO and Ministry of Health situation report Sierra Leone & Liberia: daily Ministry of Health situation report	Total number of districts/counties/ prefectures	MoH	100%
3.	Percentage of alerts verified/investigated	Number of alerts verified	Guinea: daily WHO and Ministry of Health situation report Sierra Leone & Liberia: daily Ministry of Health situation report	Total number of alerts	Guinea: daily WHO and Ministry of Health situation report Sierra Leone & Liberia: daily Ministry of Health situation report	100%
4.	Number of reported live patients meeting criteria for an Ebola test	Number of reported live patients meeting criteria for testing	Guinea: daily WHO and Ministry of Health situation report Sierra Leone & Liberia: daily Ministry of Health situation report	N/A	N/A	No target Sudden change in number needs be investigated
5.	Percentage of live patients tested for Ebola	Number of live patients tested	Laboratory database	Number of live patients meeting the criteria for testing	Guinea: daily WHO and Ministry of Health situation report Sierra Leone & Liberia: daily Ministry of Health situation report	100%
6.	Number of confirmed cases	Number of confirmed cases	Guinea: Daily WHO and Ministry of Health situation report Sierra Leone & Liberia: Daily Ministry of Health Ebola situation report	N/A	N/A	0
7.	Number of confirmed deaths	Number of confirmed deaths	Guinea: Daily WHO and Ministry of Health situation report Sierra Leone & Liberia: Daily Ministry of Health Ebola situation report	N/A	N/A	0
8.	Percentage of expected deaths that were reported	Number of reported deaths	Guinea: Daily WHO and Ministry of Health situation report Sierra Leone & Liberia: Daily Ministry of Health Ebola situation report	Number of expected deaths*	Ministry of Health	100%
9.	Percentage of deaths that were swabbed	Number of deaths that were swabbed	Laboratory database	Number of deaths that met the criteria for a swab	Guinea: daily WHO and Ministry of Health situation report Sierra Leone & Liberia: daily Ministry of Health situation report	100% of those meeting criteria

Indicator	Numerator	Numerator Source	Denominator	Denominator Source	Target
10. Proportion of community deaths that tested positive for Ebola	Number of community deaths with positive EVD swab results	Guinea: Weekly WHO and Ministry of Health situation reports Sierra Leone & Liberia: Daily Ministry of Health Ebola situation reports	Number of community deaths for which a sample was taken	Guinea: daily WHO and Ministry of Health situation report Sierra Leone & Liberia: daily Ministry of Health situation report	0%
Diagnostic Services					
11. Number of samples tested and percentage with positive EVD results	Number of new samples tested Number of new samples tested with a positive EVD result	Guinea: Laboratory database Sierra Leone & Liberia: Daily Ministry of Health Ebola situation reports	N/A Number of new samples tested	Guinea: Laboratory database Sierra Leone & Liberia: Daily Ministry of Health Ebola situation reports	0%
12. Percentage of districts/counties/ prefectures providing samples (from live and deaths)	Number of districts/counties/ prefectures providing at least one sample	Laboratory database	Total number of districts/counties/ prefectures	MoH	100%
Contact tracing					
13. Percent of new confirmed cases from registered contacts	Number of new confirmed cases registered as a contact	Case investigation form	Number of new confirmed cases	Guinea: Daily WHO situation reports Sierra Leone & Liberia: Daily Ministry of Health Ebola situation	100%
Hospitalization					
14. Time between symptom onset and hospitalization	Time between symptom onset and hospitalization of confirmed, probable or suspected cases (geometric mean number of days)	Patient database	N/A	N/A	<3 days
Outcome of treatment					
15. Case fatality rate	Number of deaths among hospitalized confirmed cases	Patient database	Number of hospitalized confirmed cases with a definitive survival outcome recorded	Patient database	<60%
Infection Prevention and Control (IPC) and Safety					
16. Number of newly infected health workers	Number of newly infected health workers	Guinea: Daily WHO situation reports Sierra Leone & Liberia: Daily Ministry of Health Ebola situation reports	N/A	N/A	0

Indicator	Numerator	Numerator Source	Denominator	Denominator Source	Target
Safe and dignified burials					
17. Number of unsafe burials reported	Number of reports/alerts of burials that were not known to be safe	Guinea: Daily WHO situation reports Sierra Leone & Liberia: Ministry of Health Ebola situation reports	N/A	N/A	N/A
Social mobilization					
18. Number of samples tested and percentage with positive EVD results	Number of new samples tested Number of new samples tested with a positive EVD result	Guinea: Laboratory database Sierra Leone & Liberia: Daily Ministry of Health Ebola situation reports	N/A Number of new samples tested	Guinea: Laboratory database Sierra Leone & Liberia: Daily Ministry of Health Ebola situation reports	0%
Rapid response teams					
19. Number of functional rapid response teams	Number of multidisciplinary and functional team	Ministry of Health & partners	N/A	N/A	3 (per country)
20. Time between confirmation of an event and deployment of rapid response team	Number of days between confirmation of an event and deployment of the team	Investigation report	N/A	N/A	≤2 days
21. Number of generations of cases after identification of a new index case	Number of generations between index cases and last case	Investigation report	N/A	N/A	≤2 generations

* Number of expected deaths is the total population multiplied by the national crude mortality rate per week