WHO's response to the Ebola epidemic

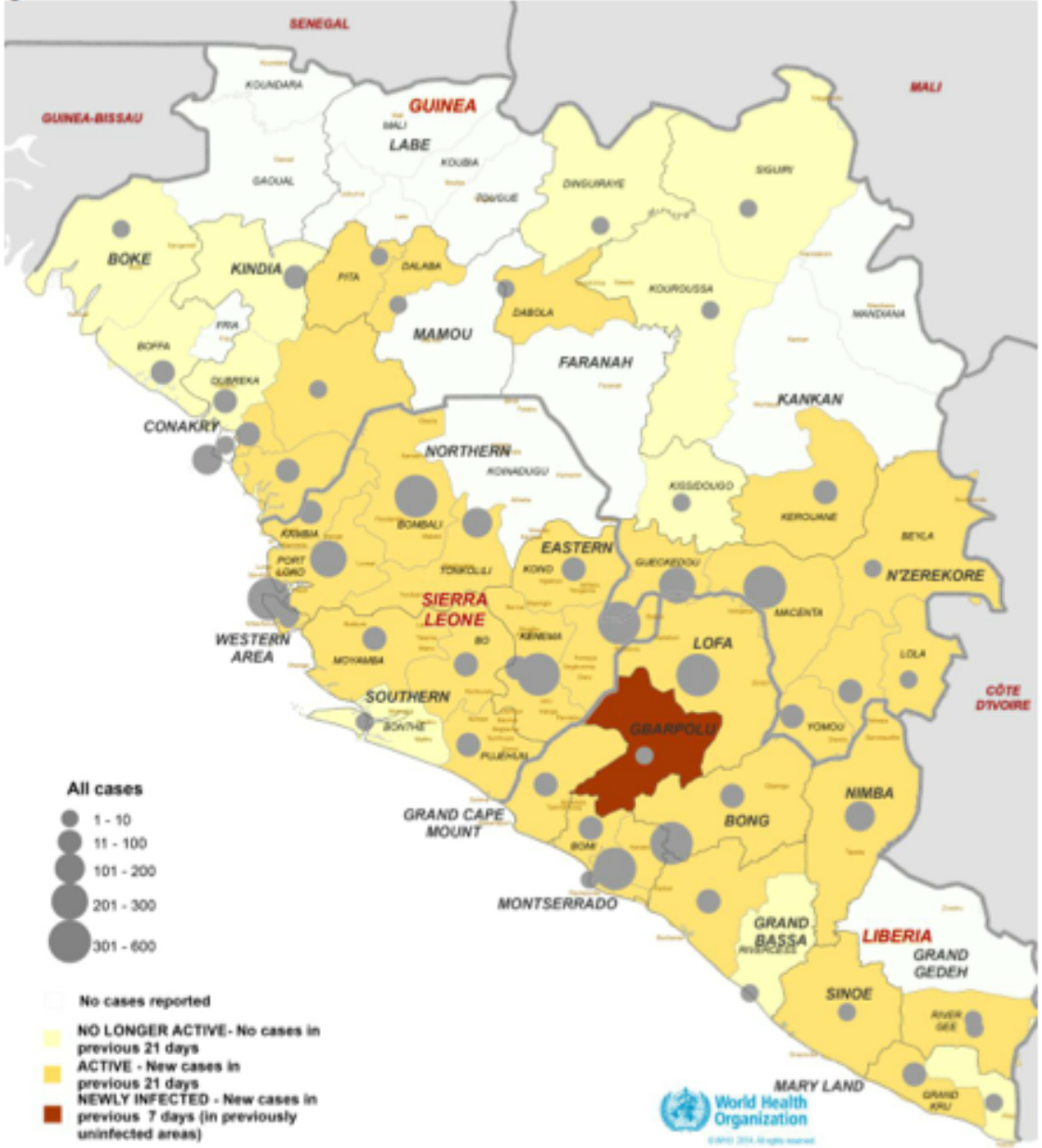
Dr David Wood
Health Systems and Innovation

World Health Organization

October 2014

Distribution of Ebola virus cases in countries with intense transmission

October 10, 2014



Data are based on official information reported by Ministries of Health up to the end of 7 October 2014 for Guinea and Liberia, and 8 October 2014 for Sierra Leone. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

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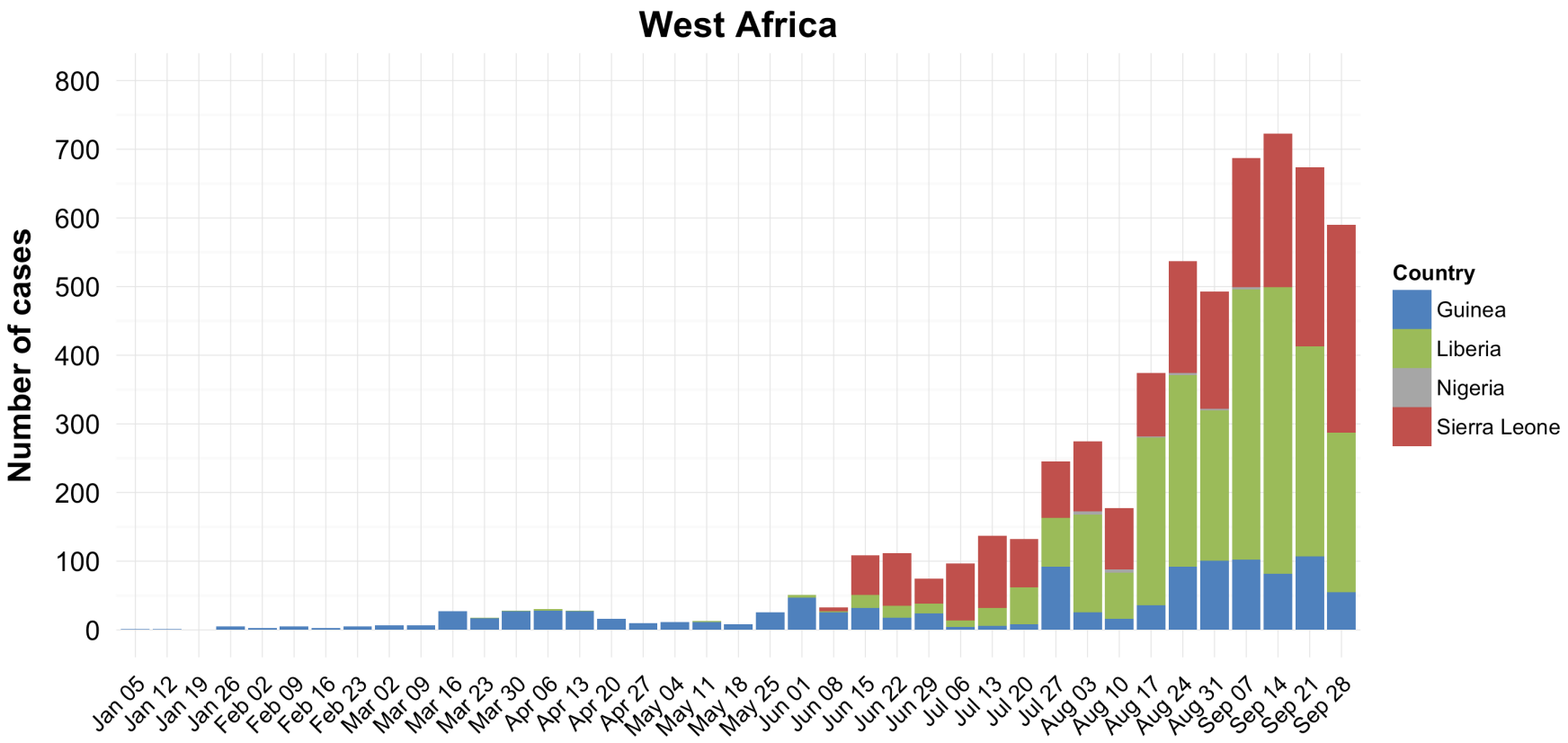
Ebola epidemiological curve,
as of 28 September 2014 *



* In addition, 2 cases have also been reported in the Spain (1 case, 0 deaths) and the United States of America (1 case, 1 death).

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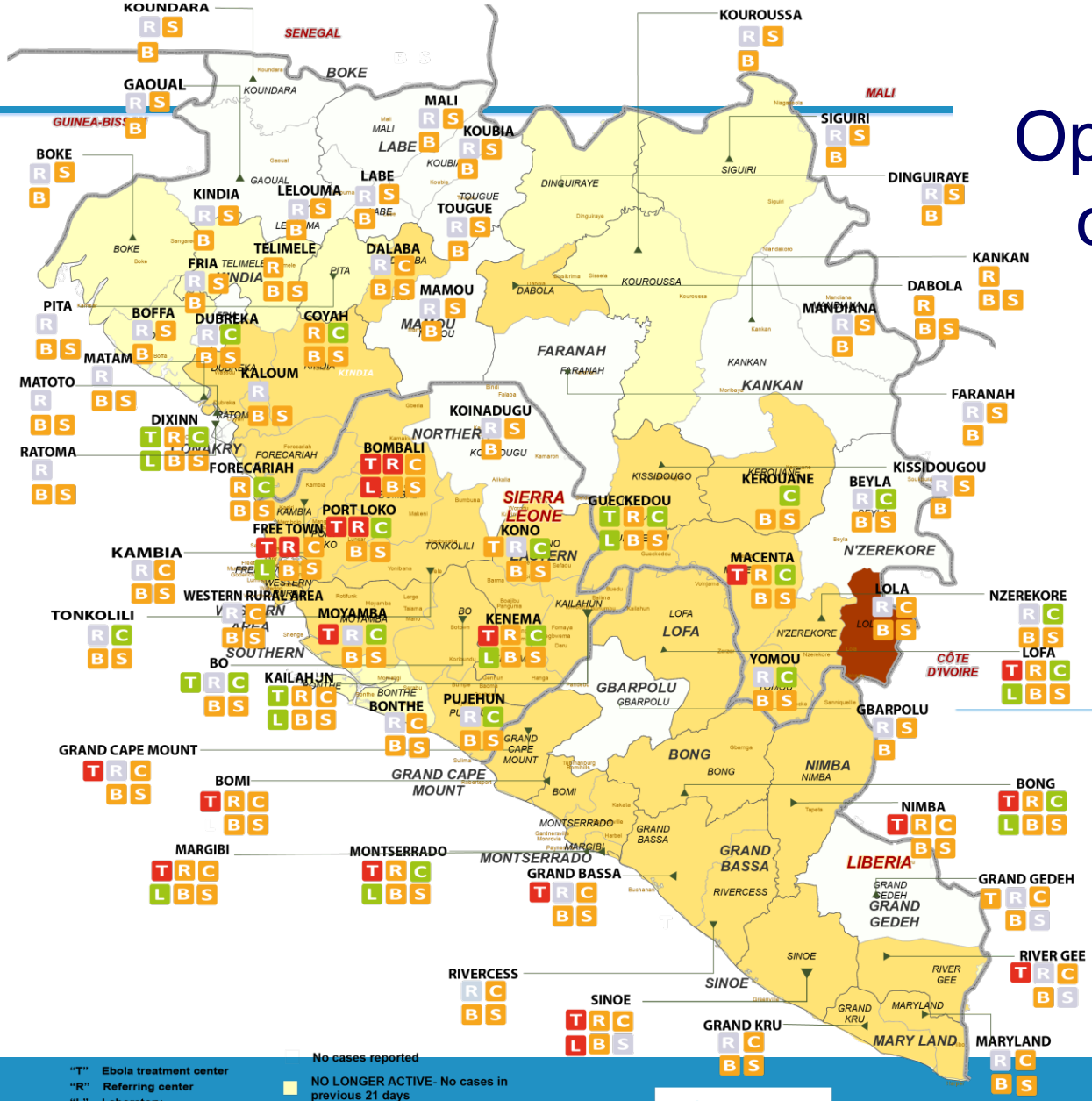
Ebola infections in health-care workers

Table 2: Ebola infections in healthcare workers as at end 14 September 2014

Country	Case definition	Cases			Deaths
		Total	Last 21 days	Last 21 days/total cases (%)	
Guinea	Confirmed	52	9	17%	22
	Probable	8	0	0%	8
	Suspected	1	1	100%	0
	All	**61**	**10**	**16%**	**30**
Liberia	Confirmed	66	3	4%	56
	Probable	85	18	21%	26
	Suspected	21	0	0%	3
	All	**172**	**21**	**12%**	**85**
Nigeria	Confirmed	11	2	18%	5
	Probable	0	0	0%	0
	Suspected	0	0	0%	0
	All	**11**	**2**	**18%**	**5**
Sierra Leone	Confirmed	71	1	1%	30
	Probable	1	0	0%	1
	Suspected	2	0	0%	0
	All	**74**	**1**	**1%**	**31**
Total		**318**	**34**	**11%**	151

Operationalization of the response: Guinea, Liberia, and Sierra Leone



"T" Ebola treatment center
"R" Referring center
"L" Laboratory
"C" Contact tracing
"B" Safe burial
"S" Social mobilization
No information available

No cases reported
NO LONGER ACTIVE- No cases in previous 21 days
ACTIVE - New cases in previous 21 days
NEWLY INFECTED - New cases in previous 7 days (in previously uninfected areas)

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Overview of major WHO actions

July 2014

- **Ministerial meeting** convened in Accra, Ghana, to accelerate actions on Ebola virus disease *(*EVD) in West Africa

- *Strategic Ebola Operations* ***Coordination Centre*** established in Conakry, Guinea

- *Ebola virus disease* ***outbreak response plan*** for Guinea, Liberia, and Sierra Leone and WHO

Overview of major WHO actions

August 2014

Emergency Committee convened by the WHO Director-General under the International Health Regulations (2005)

Ebola outbreak is declared a *Public Health Emergency of International Concern*

Temporary Recommendations to reduce the risk of international spread

Ebola and Marburg disease **guidelines** updated and released

WHO convenes an **Ethics Panel** to consider the use of unregistered interventions for EVD

The Panel reaches consensus that it is ethical, under certain circumstances, to use unregistered products

Ebola Response **Roadmap** is released on 28 August 2014

Overview of major WHO actions

August 2014:

WHO consultation - **Ethical considerations for use of unregistered interventions for Ebola viral disease** (August 11, 2014)

Objective: to consider and assess the ethical implications of the use of investigational and unproven medical interventions

Consensus: *in the current context it is **ethical to offer unproven interventions** (with unknown efficacy and adverse effects) **as potential treatment or prevention***.

Ethical, scientific and pragmatic criteria must guide the provision of such interventions

- Transparency (information) about all aspects of care
- Fairness and promotion of cosmopolitan solidarity
- Informed consent and freedom of choice
- Confidentiality, respect for the person and preservation of dignity
- Risk–benefit assessment

INTERIM version 1.2

Ebola and Marburg virus disease epidemics: preparedness, alert, control, and evaluation

Geneva, Switzerland

August 2014

PANDEMIC AND EPIDEMIC DISEASES

World Health Organization

WHO/HIS/KER/GHE/14.1

Ethical considerations for use of unregistered interventions for Ebola viral disease

Report of an advisory panel to WHO

World Health Organization

World Health Organization

Ebola Response Roadmap

	OBJECTIVES	KEY MILESTONES
1	Full geographic coverage with **complementary Ebola response activities** in countries with widespread & intense transmission	Reverse trend in new cases & areas within 2 months; stop all Ebola within 6-9 months
2	**Emergency application of comprehensive Ebola response** in countries with initial case(s) or localized transmission	Stop all transmission within 6-8 weeks of index case
3	Preparedness of all countries, esp. those sharing **land borders** with intense transmission areas and with international transportation hubs	Surveillance, preparedness, in all bordering areas & int'l transport hubs in 1 month

Overview of major WHO actions

September 2014

WHO **Consultation** on potential Ebola vaccines and therapies (Sept 4-5)

Use of **whole blood therapies and convalescent plasma** considered as a matter of priority.

Safety studies of **two candidate vaccines** – vesicular stomatitis virus (rVSV-ZEBOV) and chimpanzee adenovirus (ChAD3-ZEBOV) – are underway. If proven safe, a vaccine could be available in November 2014.

Use of **novel therapeutic drugs** are being studied. Additional safety and efficacy data are needed. Existing supplies of all experimental medicines are limited.

Investigation of these interventions should NOT detract attention from implementation of effective clinical care, rigorous infection prevention and control, careful contact tracing and follow-up, effective risk communication, and social mobilization.

UN Security Council Emergency Session

September 2014

UN Security Council Emergency Session on Ebola

WHO Director-General addressed the UN Security Council (Sept 18, 2014)

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The first time in history that the UN has created a mission for a public health emergency.

- UNMEER will be headquartered in Accra, Ghana, with a strong operational presence in Guinea, Liberia, and Sierra Leone.
- It will work with the governments and partners to ensure all components of the national plans to stop Ebola are rapidly put in place.

Overview of major WHO actions

September 2014:

WHO consultation – **Consultation on study designs for Ebola vaccines** (Sept 29-30, 2014)

Objective: to assess the efforts under way to evaluate and produce safe and effective Ebola vaccines as soon as possible

Consensus: Phase 1 trials should be expedited and their results shared broadly in order to facilitate rapid progression to phase 2. If the results in phase 1 are favorable, phase 2a studies should be conducted in Africa but outside the current Ebola outbreak zone and should proceed in parallel with phase 2b studies conducted in exposed populations. This approach will provide robust efficacy and safety data as quickly as possible. Results from phase 2a trials in unexposed populations would inform the use of these vaccines in expanded populations, including children and people who are HIV-positive. The phase 2b trials in exposed populations would enroll people who are at the highest risk for Ebola virus disease, including frontline workers at Ebola treatment facilities.

The design of these proposed trials in exposed populations raises many complex questions that pit issues of scientific rigor against feasibility and acceptability.

Even if adequate safety and immunogenicity are demonstrated in the phase 1 studies, vaccines will not be available in substantial quantity until the first quarter of 2015 at the earliest.

Overview of major WHO actions

September 2014:

WHO consultation – **Consultation on study designs for Ebola vaccines** (Sept 29-30, 2014)

If feasible, well-designed randomized, controlled trials would generate the most reliable and robust data regarding vaccine efficacy.

The feasibility of such studies may be affected by the same fear and resistance to interventions that communities have evinced in the West African epidemic to date.

The trials therefore need to be designed with participation from local governments and communities so that they can proceed in a manner that is acceptable to the affected populations.

The consensus at the Geneva meeting (Sept 2014) was that there are reasonable alternatives, if individually randomized, controlled trials are not acceptable in some settings — for example, studies using a stepped-wedge design.

Kanapathipillai R et al. N Engl J Med 2014. DOI: 10.1056/NEJMp1412166

New therapeutic and preventive medicines* to fight the Ebola epidemic

Status report

*drugs, blood products, vaccines

In parallel…

Development

Testing

Licensure

Use

of Ebola experimental interventions is a HIGH PRIORITY

Whole blood and convalescent plasma

There is consensus that the use of whole blood and convalescent blood serums needs to be considered as a matter of priority.

Use of convalescent whole blood or plasma collected from patients who have recovered from Ebola virus disease for transfusion as an empirical treatment during outbreaks

The guideline covers:

- Identification of patients recovered from EVD as potential blood donors
- Informed consent and selection of donors
- Donor's blood grouping and screening for transfusion-transmissible infections
- Blood collection and donor care
- Labelling, storage, and transportation of blood and plasma products to sites where transfusion is given
- Selection of EVD patients for this intervention
- Clinical transfusion process
- Data collection at the transfusion site
- Assessment of effectiveness of this empirical treatment

http://apps.who.int/iris/bitstream/10665/135591/1/WHO_HIS_SDS_2014.8_eng.pdf

Experimental therapies used to treat Ebola

Prioritized for consideration based on the availability of NHP efficacy data with a filovirus challenge and justification for a human dose based on clinical data of the product or comparable products within that class.

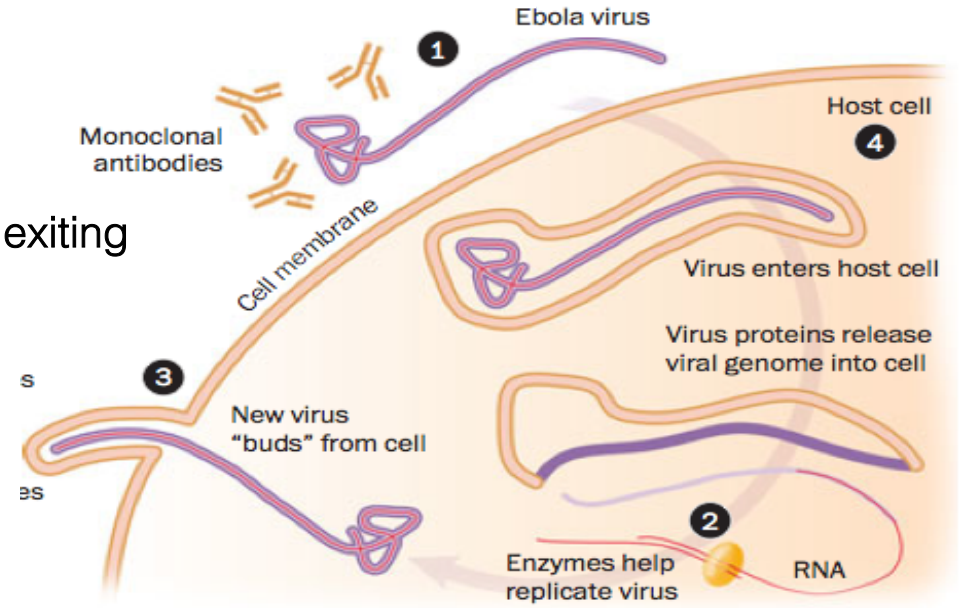
1- Targets the virus before it enters the cell

Zmapp A cocktail of three monoclonal antibodies, which block or neutralises the virus by binding to or coating a different site on the covering or "envelope" of the virus

Hyperimune globulin Antibodies that can neutralize the different EVD strains.

4- Bolsters human cells

Interferons - Induce an antiviral state in exposed cells and regulates the immune system



3- Prevents virus from exiting host cells

5- Testing existing drugs approved for other purposes

All drugs Screening all licensed drugs.

6- Whole blood transfusions and convalescent plasma

2- Interferes with viral production

TKM 100802Ebola Target two essential viral genes to stop the Ebola from replicating.
AVI 7537 Sarepta Molecules that bind viral RNA, blocking gene function.
Favipiravir T705 Disrupts enzymes that the virus uses to make copies of himself.
BCX4430 Biocryst Disrupts enzymes that the virus uses to make copies of himself.
Brincidofovir Disrupts enzymes that the virus uses to make copies of himself.

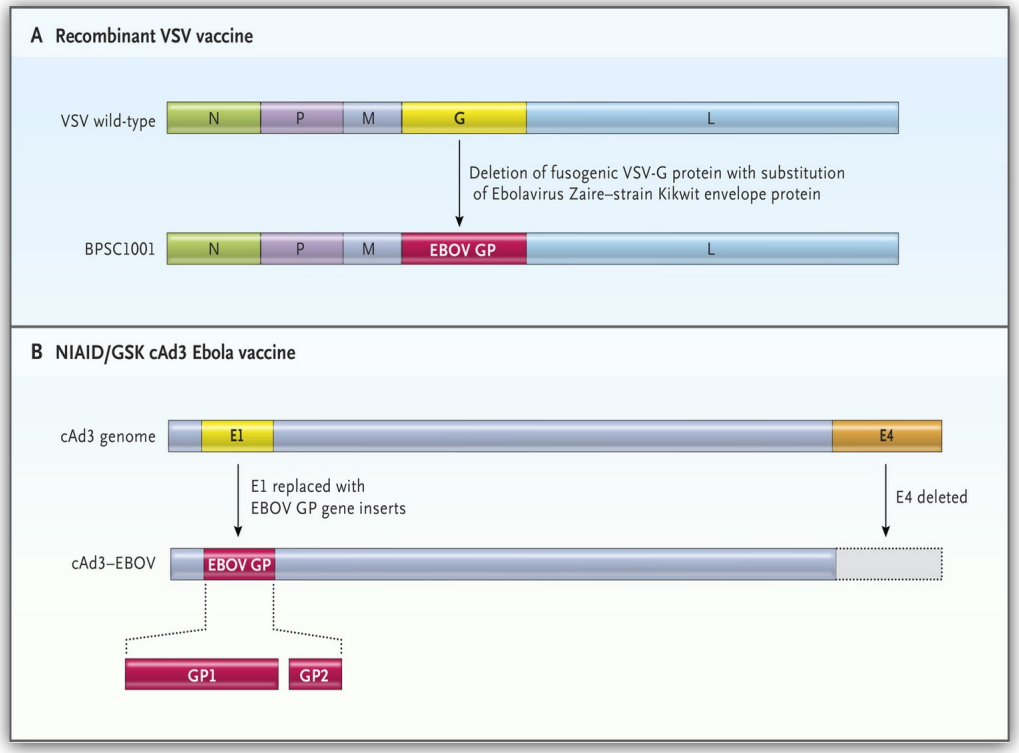
Source: Adapted from the Washington Post, Oct 7, 2014

Type of intervention	Admin. route	No. doses / time	Storage
Convalescent plasma	IM, IV equipment & supplies for sterile injection and/or infusion, & HCW who can administer	1st batches could be available by end 2014	Commercial IVIGs may be stored at room temperature; however these contain stabilizers and are pH-controlled. May require refrigeration and rewarming before transfusion.
ZMapp	IV equipment & supplies for sterile infusion & HCW who can administer	Few hundred doses by end 2014 (tentatitive	Shipping & storage -20°C. MappBio currently gathering stability data to determine stability at 4°C. Antibody preparations should be stored in small aliquots, and thawed once; repeated freezing and thawing may negatively impact antibody – hence frost-free freezers are not appropriate, as they alternate between freezing and thawing.
Hyperimmune globulin from animal plasma	IM or IV depending on volume needed (?) - equipment & supplies for sterile injection and/or infusion & HCW who can administer	Large-scale GMP-compliant equine or transgenic animal batches for human use not before mid-2015	Other hyperimmune globulins (e.g., TIG & RIG) should be stored at 2-8°C and should not be frozen
TKM-100802: **(Lipid nanoparticle siRNAs)**	IV equipment & supplies for sterile infusion & HCW who can administer	Up to 100% survival in rhesus macaques. Survival better with 7 vs 4 PI treatment doses	Lyophilized LNP stable at 40°C
AVI 7537 (phosphorodiamidate siRNA) antisense RNA)	IV equipment & supplies for sterile infusion & HCW who can administer	75% survival in rhesus macaques (40 mg/kg) Mfr. estimates 16 mg/kg, but says this may be an overestimation.	Product is stored in bulk at 2-8°C, for stability, but after fill/finish and lyophylized, stable at room temp for months; vials have been retested for stability at 12-18 months with good results.
Interferons (Type 1 [α,β])	SQ/IM equipment & supplies for sterile infusion & HCW who can administer	Not known – probably 1 injection/day.	Store at 2-8°C. Do not leave out of refrigerator for >24h. Do not freeze or shake. Protect from light (instructions for PEGASYS peginterferon α-2a for subcutaneous use).
Favipiravir/T-705	Oral	14 days bid in mice (Smither). No data in humans against Ebola.	Stable at room temperature
BCX4430	IM equipment & supplies for sterile injection & HCW who can administer	Unknown – studies in macaques showed protection against MARV when given 15 mg/kg IM bid x 14 d beginning 1-48 hours post infection.	Probably stable at room temperature

Two candidate vaccines currently under clinical evaluation

- **A- rVSV-ZEBOV – recombinant vesicular stomatitis virus**
  The rVSV vaccine aims to induce EVD-specific immune responses.
  NewLink Pharmaceuticals/Public Health Agency of Canada

- **B - ChAd3-ZEBOV – chimpanzee adenovirus 3**
  Uses a chimpanzee adenovirus that does not grow, containing the gene for EVD surface protein.
  GSK/NIAID



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Candidate vaccines were selected on the basis of protection in nonhuman primates post-lethal challenge (100%) and availability of GMP-grade vaccine.

Additional candidate vaccines are also in the pipeline, but at a less advanced stage of development.

Ebola vaccines under development

Type of vaccine	State of research	Safety in humans
Chimpanzee adenovirus serotype 3 (ChAd3) vaccine	• In a study of animals given a lethal dose of EVD, all 16 were protected by a single dose of the vaccine.	• More than 1300 people have received these vaccines for other diseases, including over 1000 people (Gambia, Senegal, Burkina Faso, and Kenya). • As yet there is no safety information on an EVD vaccine in humans.
Recombinant vesicular stomatitis virus (rVSV) vaccine	• The vaccine protected all 20 animals from a lethal dose of EVD. • Animals with weakened immunity were not harmed by rVSV-EVD. • The vaccine was safe when injected directly into the brain of animals.	• It is unknown if rVSV-EVD will grow in humans, especially in people with weak immunity. • Too little growth could make a weak vaccine, while too much could cause illness. • The consequences of spreading rVSV-EVD to unvaccinated people or animals are unknown. • One laboratory worker was given rVSV after a needle stick injury, and remained well. This does not prove the vaccine will be safe or protective.

Ebola vaccines under development
Number of doses available

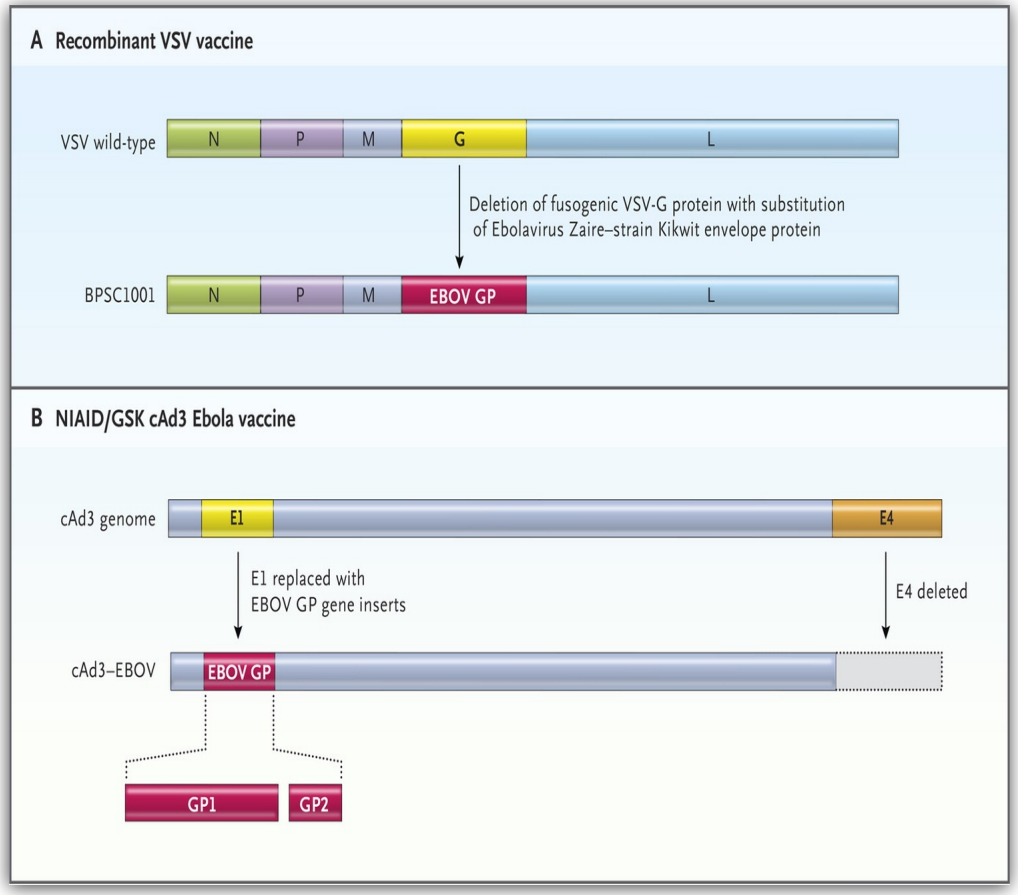
A- rVSV-ZEBOV – recombinant vesicular stomatitis virus

800 vials

Donated to WHO by the Government of Canada

B - ChAd3-ZEBOV – chimpanzee adenovirus 3

20,000 doses by Q1 2015



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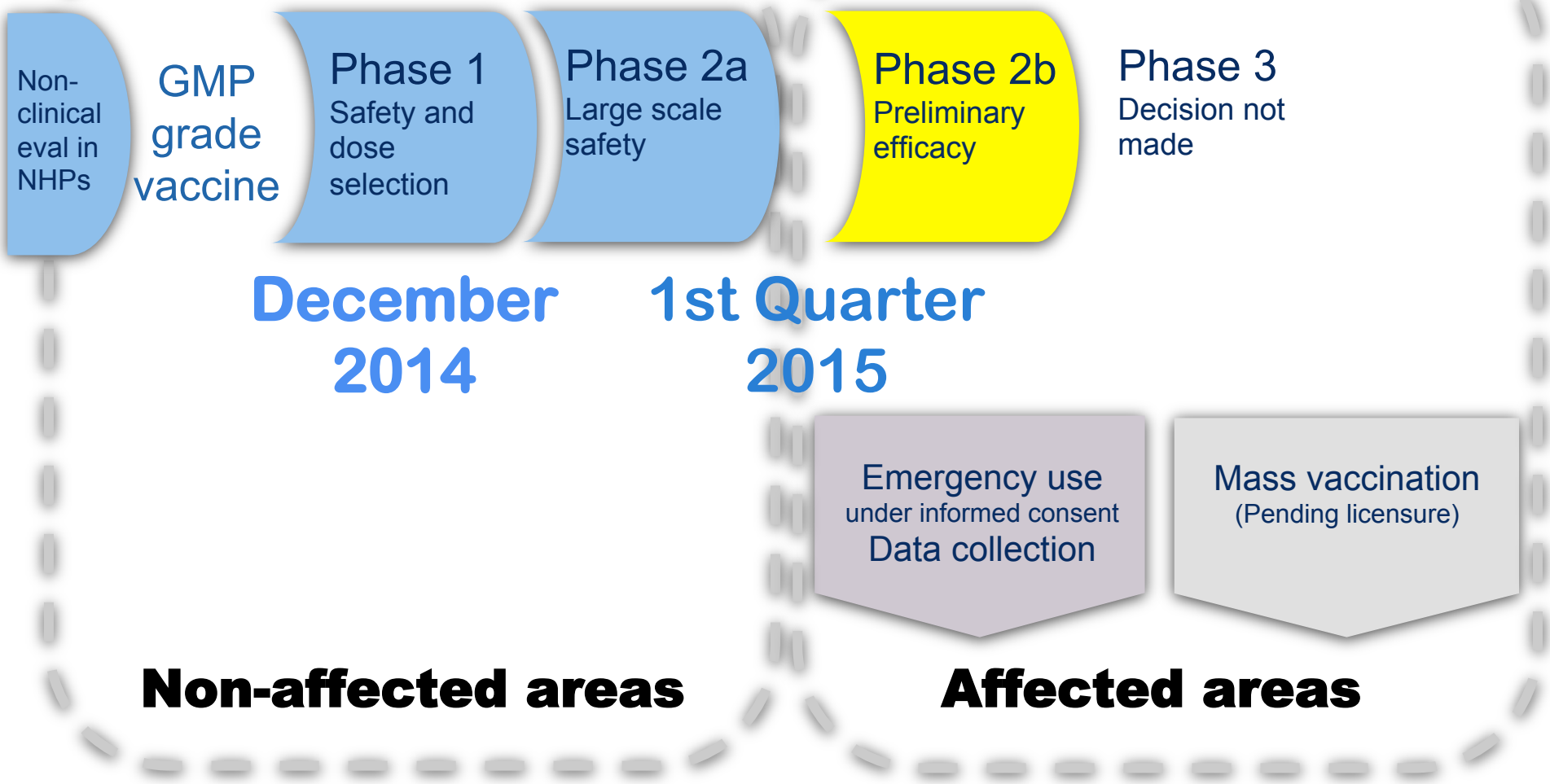
Near-term development plan
Pre-exposure use



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ChAd3 : Overview of Phase 1 trials

Site	*Number vaccinated*	*Trial start (planned dates)*	*Characteristics*
VRC – USA	20	September 2014	Bivalent, healthy adults, dose-escalation, safety
Oxford – UK	60	September 2014	Monovalent, healthy adults, dose-escalation, safety
CVD – Mali	40	October 2014	Monovalent, healthy adults, dose-escalation, safety
Gambia	40	To be confirmed	Monovalent, healthy adults, dose-selection, safety
Lausanne, Switzerland	100	October 2014	Monovalent, healthy adults, dose-selectio0n, safety
Total vaccinated Phase I = 260			

rVSV : Overview of Phase 1 trials

Site	Number vaccinated	Trial start (planned dates)	Characteristics
WRAIR – USA	30	October 2014	Healthy adults, dose-escalation, safety
NIAID – USA	30	October 2014	Healthy adults, safety, two-dose schedule
Hamburg, Germany	20	Oct-Nov 2014	Healthy adults, dose-selection, safety
Africa site 1	60	Oct-Nov 2014	Healthy adults, dose-selection, safety
Africa site 2	40	Oct-Nov 2014	Healthy adults, dose-selection, safety
Geneva, Switzerland	100	Oct 2014	Healthy adults, dose-selection, safety
Total vaccinated Phase I = ≥250			

Phase 2b trials: Highly exposed populations, pre-exposure

Population / Possible designs	Number vaccinated	Trial start (planned dates)	Possible sites
Frontline workers, including health-care workers. Those who agree under informed consent. ***Either RCT with ? 4:1 randomization (20% controls) Crossover vaccination of all OR Stepped wedge***	~4 000	January 2015	• Liberia and Sierra Leone • Possibly Guinea Sites to be chosen based on high incidence and possibility for good data collection without interfering with running of Ebola treatment facilities
Total vaccinated Phase 2b = ~4 000 – 5 000			

Phase 2a trials: Neighbouring countries

Population	Number vaccinated	Trial start (planned dates)	Possible sites
Healthy adults, including health-care workers	~2 500	January 2015	Burkina Faso, Cameroon, Gambia, Ghana, Mali, Nigeria, Senegal, others
Healthy children	~200	January 2015	
Clinically well HIV positives	~30–50	March 2015	
Data collection on those who are subsequently found to be pregnant	TBD	From January 2015	
Total vaccinated in Phase I – 2a = ~3 000			

Stepped-wedge Study Design

If feasible, well-designed randomized, controlled trials would generate the most reliable and robust data regarding vaccine efficacy.

The feasibility of such studies may be affected by the same fear and resistance to interventions that communities have evinced in the West African epidemic to date.

The trials therefore need to be designed with participation from local governments and communities so that they can proceed in a manner that is acceptable to the affected populations.

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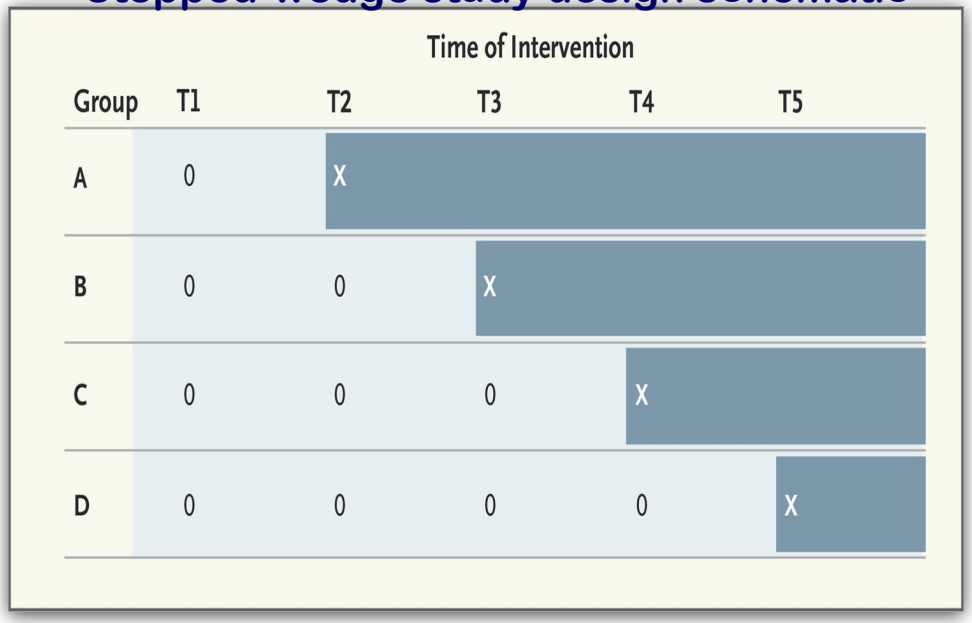
Stepped-wedge study design schematic



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Measuring key milestones - Vaccines

Target date	Milestone
October 2014	Agreed mechanisms for evaluating and sharing data in real time
October – November 2014	Agreed generic protocols (including for Phase 2 trials) across different sites
	Preparation started of sites in affected countries for Phase 2 b studies
November – December 2014	Initial safety data from Phase 1 trials available
January 2015	GMP vaccine available for Phase 2
January – February 2015	Phase 2 studies approved and initiated in affected and non-affected countries

In parallel with acquisition of efficacy data – Planning for large-scale use, including systems for vaccine financing, allocation, and use

Assessing experimental Ebola vaccines and therapies

This will require the following crucial elements:

- Rapid development of **appropriate protocols** for informed consent and safe use
- A mechanism for **evaluating preclinical data** should be put in place in order to recommend which interventions should be evaluated as a first priority
- A platform much be established for **transparent, real-time collection and sharing of data**
- A **scientific technical advisory group** needs to be established to evaluate data from all interventions

All of these will require continual ethical oversight

Assessing experimental Ebola vaccines and therapies

Equity is important, therefore vaccines should be distributed in a fair and consensual manner to the affected countries.

Maximizing the **quality of data collection** during this phase is critical, so coordination among countries receiving vaccine is key.

Ebola vaccine acceleration

Gavi could have a role to play in a vaccine response, at least in the medium-term and perhaps even earlier, depending on how the outbreak unfolds.

The Gavi Secretariat has been tasked by the **Executive Committee of the Board to evaluate potential options for Gavi** involvement in speeding up the availability of a potential Ebola vaccine.

These options will be presented to the Board during its next meeting on 11-12 December.

WHO is contributing in the preparation of the concept and the feasibility of GAVI financing to present to the next GAVI Board meeting.

Thank you

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