Ebola Vaccines and Vaccination

Report of the SAGE Working Group on Ebola Vaccines and Vaccination with provisional recommendations for vaccination

September 30, 2015

SECTION B: VACCINES AND VACCINATION

Introduction

On 8 August 2014, the World Health Organization declared a public health emergency of international concern related to the ebola virus disease outbreak originating in Guinea and causing ongoing transmission in Sierra Leone and Liberia[1]. For Ebola vaccine development what followed was a chain of events leading to accelerated timelines for vaccine development.

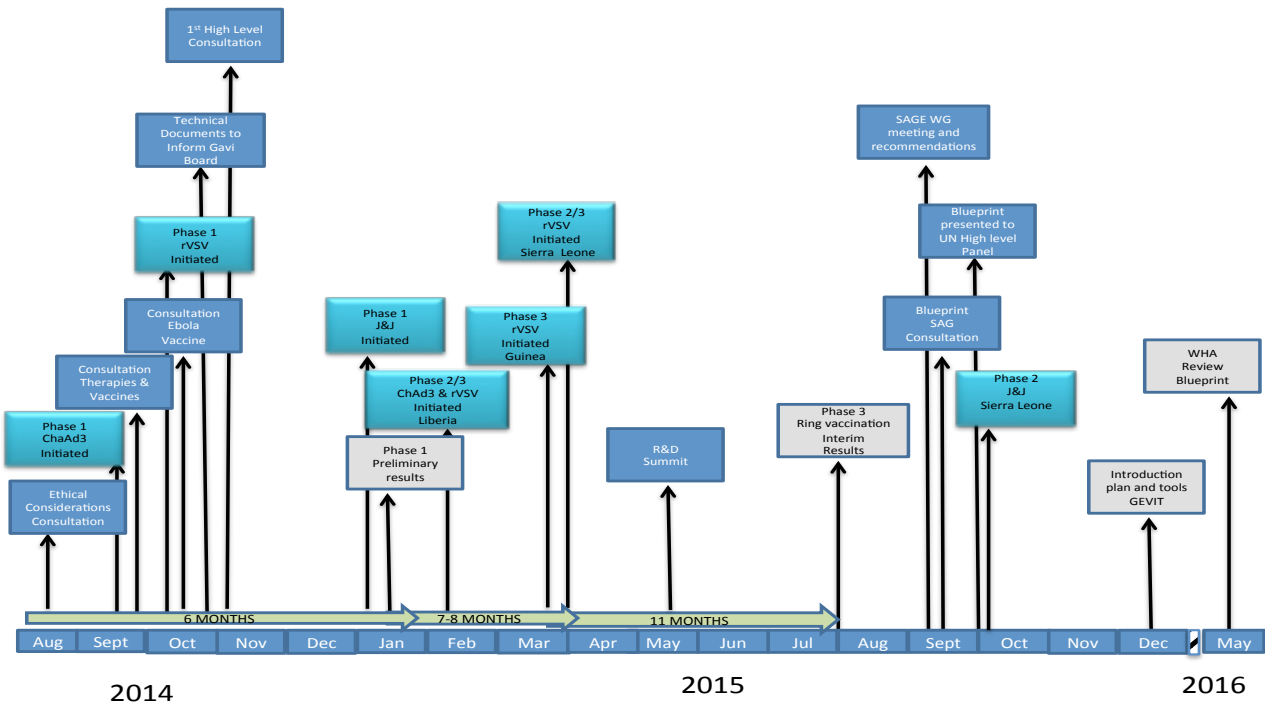
During the several years before the crisis, scientists and, governments had generated promising preclinical data on several Ebola vaccine candidates.

However development stalled in part because public sector investment mechanisms were not in place to support pre-emptive clinical evaluation of these candidates, and there was a perception that regulatory pathways were limited for Ebola vaccines.

Efforts need to be coordinated amongst scientists, international organizations, national governments, industry and major non-governmental organizations.

Table of contents

Figure 1. Overview of selected milestones



[1] http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/

A. OVERVIEW OF MAJOR ACTIVITIES

The Ebola R&D effort has mobilised people, institutions and resources globally in ways never seen before. This is one positive outcome in an otherwise terrible human calamity. New tools have been developed with unprecedented speed, though the window of opportunity for testing some is closing.

This is a contribution to scientific knowledge, but it is also a contribution to better preparedness. Thanks to the work of the entire scientific community, the world will be far better equipped to respond when the next Ebola outbreak inevitably occurs. What we see emerging, over a very short time, is a new model for the accelerated development, testing, and approval of new medical products during emergencies caused by any emerging or re-emerging infectious disease.

The collaborative efforts prove that the traditional R&D model can be adapted, timeframes can be compressed, and partnerships that are otherwise unlikely can be formed.

The task now is to harness the lessons from Ebola to create a new R&D framework that can be used for any epidemic-prone disease, in any infectious disease emergency. In this sense, the R&D response to Ebola marks an historical, ground-breaking event. Public research institutes, private funders, civil society, countries, and industry have collaborated, in unprecedented ways, to defend the world against a deadly and deeply dreaded disease.

This document provides an overview of some major activities and achievements recognizing that many more efforts took place and should also be catalogued and documented in the future.

1. Construction of ad-hoc international forums for global coordination and scientific deliberations

When the emergency was declared WHO consulted widely, and immediately and fostered interactions with the international scientific, ethics, regulatory and funders' communities on key activities to undertake on an emergency basis. The consensus was that even in the emergency setting, clinical trial data would be required on novel vaccine candidates to determine how best they could complement the public health response.

Notably, WHO convened meetings from August 2014 of high-level government representatives and these were from development partners as well as from Ebola-affected countries. In addition, there were scientists, vaccine manufacturers, regulatory authorities, international organizations, funding agencies and civil society.

The purpose was to discuss and agree on how to fast-track the testing and the deployment of promising vaccines in sufficient numbers to use in the field in 2015 to try and impact the Ebola epidemic curve. Three important consensus commitments came from this meeting.

First, that phase 1 clinical trials of the two most advanced vaccines had started. Without waiting for the results of the phase 1 all was to be put in place, by all partners, to start efficacy trials in affected countries as early as December 2014.

Second, the pharmaceutical companies developing vaccines committed to ramping up the production capacity to millions of doses in 2015, with hundreds of thousands ready in the first half of 2015.

Third, community engagement would be key and work should be scaled up urgently in partnership between local communities, national governments, and other stakeholders to have this happen.

All parties called upon WHO to coordinate efforts and ensure effective communication between the various actors.

Table 1. Overview of selected consultations to coordinate vaccine R&D

Meeting title	**Internet link**
Ethical considerations for use of unregistered interventions for Ebola virus disease, 15 August 2014	http://who.int/entity/csr/resources/publications/ebola/ethical-considerations/en/index.html
WHO Consultation on potential Ebola therapies and vaccines, 4–5 September 2014	http://www.who.int/entity/csr/resources/publications/ebola/ebola-therapies/en/index.html
WHO Consultation on Ebola vaccines 29-30 September 2014	http://www.who.int/entity/immunization/diseases/ebola/WHO_consultation_ebola_sep2014/en/index.html
First WHO High-level meeting on Ebola vaccines access and financing, 23 Oct 2014	http://www.who.int/mediacentre/news/ebola/23-october-2014/en/ http://apps.who.int/iris/bitstream/10665/137184/1/WHO_EVD_Meet_EMP_14.2_eng.pdf?ua=1
Development of technical document on Ebola vaccines to inform Gavi Alliance Board decision to commit to purchasing Ebola vaccine for affected countries, Oct 2014	http://www.gavi.org/Library/News/Press-releases/2014/Gavi-commits-to-purchasing-Ebola-vaccine-for-affected-countries/
WHO Meeting of the Scientific and Technical Advisory Committee on Ebola Experimental Interventions, 13 Nov 2014	http://www.who.int/medicines/ebola-treatment/scientific_tech_meeting/en/
First meeting of WHO Ebola Science Committee, 13-14 Nov 2014	http://www.who.int/medicines/ebola-treatment/meetings/ebola_science_committee/en/
WHO Technical Consultation: Heterologous Prime-Boost Immunization in Ebola vaccine development and testing, licensure and use, 21 Nov 2014	http://www.who.int/immunization/research/meetings_workshops/ebola_primeboost_21nov14/en/
The VSV Ebola Consortium (VEBCON)	http://www.ncbi.nlm.nih.gov/pubmed/25289888?dopt=Abstract
Second WHO High-level meeting on Ebola vaccines access and financing, January 8, 2015	http://apps.who.int/iris/bitstream/10665/149045/1/WHO_EVD_Meet_HIS_15.1_eng.pdf
WHO Ebola Science Committee, 3-4 March 2015	http://www.who.int/medicines/ebola-treatment/meetings/science-committee-march/en/
WHO Ebola R&D summit , 11-12 May 2015	http://www.who.int/entity/medicines/ebola-treatment/meetings/Executive-summary-WHO-Ebola-RandD-summit.pdf?ua=1
Developing Global Norms for Sharing Data and Results during Public Health Emergencies , 1-2 September 2015	http://www.who.int/entity/medicines/ebola-treatment/data-sharing_phe/en/index.html
Draft framework for formulating recommendations for the deployment of Ebola vaccines. SAGE Working Group on Ebola Vaccines and Vaccination	http://www.who.int/entity/immunization/sage/meetings/2015/april/Ebola_vaccine_Draft_framework_final.pdf

2. Laying out the regulatory support to guide clinical trials oversight in the context of this emergency

A series of consultations on regulatory approaches for expediting development and availability of Ebola vaccines were held. Overall the regulatory experts debated around the following objectives:

- to review the critical regulatory paths for the lead candidate Ebola vaccines and identify the main regulatory challenges;
- to clarify the timelines for availability of these vaccines for both clinical trials and potential future large-scale deployment;
- to discuss and map out possible avenues to address the regulatory challenges while keeping safety as a main concern.

Table 2. Overview of selected consultations to discuss regulatory pathways and oversight of planned Ebola vaccines trials

Meeting title	Internet link
First teleconference on regulatory approaches for expediting development and availability of Ebola vaccines 30 October 2014	http://www.who.int/medicines/ebola-treatment/meetings/2014-1030_1stT_RegEbola_vaccines_summary.pdf?ua=1
African Vaccine Regulatory Forum (AVAREF), 3-7 November 2014	http://www.who.int/immunization_standards/vaccine_regulation/africa_network/en/
Report of the joint review facilitated by WHO for the GSK ChAd3 Ebola Vaccine clinical trials application, 17 December, 2014	http://www.who.int/immunization_standards/vaccine_regulation/2014-1217_BriefingAfricanNRA_EC.pdf?ua=1
Second teleconference on regulatory approaches for expediting development and availability of Ebola vaccines, 27 January 2015	http://www.who.int/entity/medicines/ebola-treatment/meetings/2015-0127_2ndTC_RegEbola.pdf?ua=1
WHO hosts joint review of Phase II clinical trial application for GSK Ebola vaccine, 15-16 December 2014	http://www.who.int/entity/medicines/ebola-treatment/meetings/phaseII_clinical_trial_meeting/en/index.html
Phase II clinical trial application for ChAd3 Ebola vaccine reviewed by national regulators, 18 December 2014	http://www.who.int/entity/medicines/ebola-treatment/meetings/phaseII_clinical_trial_meeting_outcomes/en/index.html
WHO Informal Consultation on regulatory considerations for evaluation of Ebola Vaccines intended for emergency use, WHO/HQ Geneva, Switzerland , 18-19 March 2015	http://www.who.int/immunization/GIN_March_2015.pdf
The AVAREF joint review process of Ebola clinical trial applications. WHO, Jan 8, 2015	http://www.who.int/mediacentre/events/2015/S3.3_Stahl_AVAREF_joint_review_process.pdf

Regulatory support was provided through AVAREF meetings, whereby regulators from high-income authorities, attended consultations in support of African regulators (North-South collaboration). In addition AVAREF enabled African authorities with experience of pre-licensure vaccine trials to support those in the most affected countries with less experience of clinical trials (South-South collaboration).

3. Promoting scientific debate on trial designs and enabling parallel Phase 1,2 and 3 clinical trials of Ebola vaccines

On 8 August and subsequent days, WHO rapidly assembled consortia linking regulatory authorities, ethics committees, health research funders, the two prioritized manufacturers (GSK, and Newlink later Merck) and clinical and laboratory investigators together with appropriate independent oversight mechanisms including DSMB and GCP monitoring (Figure 1).

Information sharing throughout all of the above required activities was facilitated by regular convenings, and conference calls, including some hosted by WHO DG Margaret Chan. WHO played a critical role in sharing information between all stakeholders in the accelerated vaccine R&D effort.

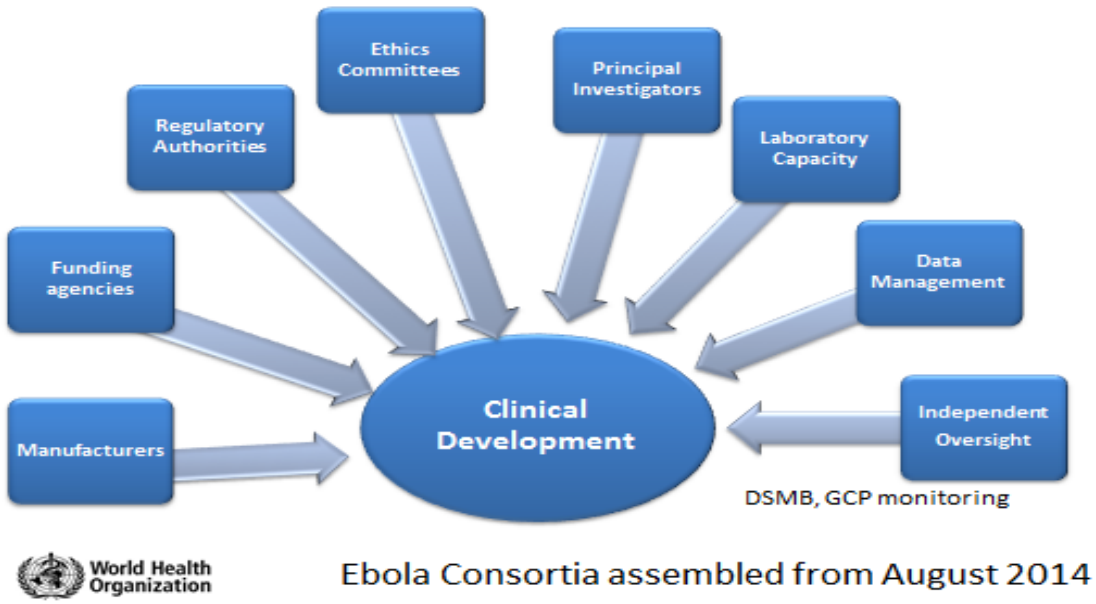


Figure 2: Key elements of the consortia assembled from August 2014

WHO used a set of criteria to objectively assess which vaccine candidates would be proactively fast-tracked for clinical evaluation. The criteria included availability of Good Manufacturing Practice grade vials after lot release for clinical trials, and that 100% efficacy had been documented in non-human primates with acceptable pre-clinical safety.

Both GSK (ChAd3) and Newlink (rVSV) were the two commercial entities with candidate vaccines that met those criteria as of August 2014. J&J (Ad26/MVA) and Novavax (recombinant protein) met the criteria later in the epidemic.

In addition, WHO hosted a series of scientific meetings to discuss trial design options, locations of the studies and timetables towards the initiation and completion of the trials.

Table 3. Overview of selected consultations hosted by WHO to discuss clinical trial design and progress with the conduct of the Ebola vaccines trials

Meeting title	Internet link
WHO consultation on potential Ebola therapies and vaccines, September 2014	http://apps.who.int/iris/bitstream/10665/136103/1/WHO_EVD_Meet_EMP_14.1_eng.pdf
WHO consultation on Ebola Vaccines September 29-30, 2014	http://www.who.int/immunization/diseases/ebola/WHO_consultation_ebola_sep2014/en/
First teleconference on vaccine clinical trial designs in Guinea, Liberia, and Sierra Leone 28 October 2014	http://www.who.int/medicines/ebola-treatment/2014-1028_Minutes-1stTC_on_vaccine_clinical_trials.pdf
Second teleconference on vaccine clinical trials design for Guinea, Liberia, and Sierra Leone , 25 November 2014	http://www.who.int/medicines/ebola-treatment/2014-1125_Minutes-2ndTC_on_vaccine_clinical_trials.pdf?ua=1
Third teleconference on vaccine clinical trials design for Guinea, Liberia, and Sierra Leone. 18 December 2014	http://www.who.int/medicines/ebola-treatment/3rd-teleconference-vaccines.pdf
The rVSV vaccine was selected for the Guinea trial according to a framework developed by the WHO Scientific and Technical Advisory Committee on Ebola Experimental interventions (STAC-EE).	http://www.who.int/medicines/ebola/treatment/guinea_ebola_trial/en/
Fourth teleconference on Ebola vaccine clinical trials in Guinea, Liberia, and Sierra Leone., 30 March 2015	http://www.who.int/medicines/ebola-treatment/4th_teleconference_vaccine_clinical_trials.pdf?ua=1
Fifth Teleconference on Vaccine Clinical Trials Design in Guinea, Liberia and Sierra Leone. 21 July 2015	http://www.who.int/medicines/ebola-treatment/meetings/fifth_tel-conf_clinictrials/en/
Report on the 2nd WHO Consultation on Biobanking: Focus on West Africa, 6-7 August 2015	http://www.who.int/entity/medicines/ebola-treatment/meetings/2nd_who_biobaking-consultation/en/index.html
Developing Global Norms for Sharing Data and Results during Public Health Emergencies 1-2 September 2015	http://www.who.int/entity/medicines/ebola-treatment/data-sharing_phe/en/index.html

The following set of activities were deemed important and were initiated by the international community:

- Use of Parallel Phase 1-2 trials had to be launched in sites with optimal first-in-human clinical management facilities, followed as quickly as possible by Phase 1-2 in Africa. These trials were to be conducted on highly expedited timelines. The trials were to be larger than usual Phase 1 trials, to allow for simultaneous safety, immunogenicity and dose finding evaluations.
- Given the lack of a standardised assay, centralised laboratory facilities were chosen to allow for head-to-head comparability evaluations between all clinical trial sites, and different vaccines.
- Data management by investigator-initiated trials were to be promoted, with data transfer to the entities responsible for licensure submission. Independent oversight including Data Safety Monitoring Boards (DSMB) and Good Clinical Practice (GCP)

monitoring needed to be established. All regulatory and ethics oversight steps would need to occur to the same high standards but in greatly compressed timelines

- The trial protocols were adapted to take into consideration safety and immunogenicity results of the phase 1 trial as they became available and the evolution of the epidemic.

4. Preparing for the deployment of vaccines

To rapidly implement campaigns in the affected countries once vaccine becomes available, public health officials needed to be planning the most optimal vaccination strategies for vaccine deployment as soon as feasible.

The essential objective of the collaborative deployment planning has been to finalize development of a framework to enable roll out of a vaccine in public health Ebola emergencies, as soon as vaccines are regulatory approved and recommended for use. This overarching framework could subsequently be included in the country preparedness plans for Ebola response activities.

Vaccination strategies may require triage of vaccine to those at highest risk of exposure, depending on availability of vaccine doses, with expansion to additional populations over time as more doses arrive. If triage of vaccination is necessary, early engagement of in-country community leaders in shaping the strategy or strategies will be critical to the success of any vaccination campaign.

In the last quarter of 2014, while phase 1/2 clinical trials yielded promising results and the most advanced vaccine candidates prepared to enter Phase 3 trials, it was deemed essential, to start considering preparations for public health deployment, if and as soon as appropriate as part of the measures to control the outbreak and to support future Ebola prevention and control activities.

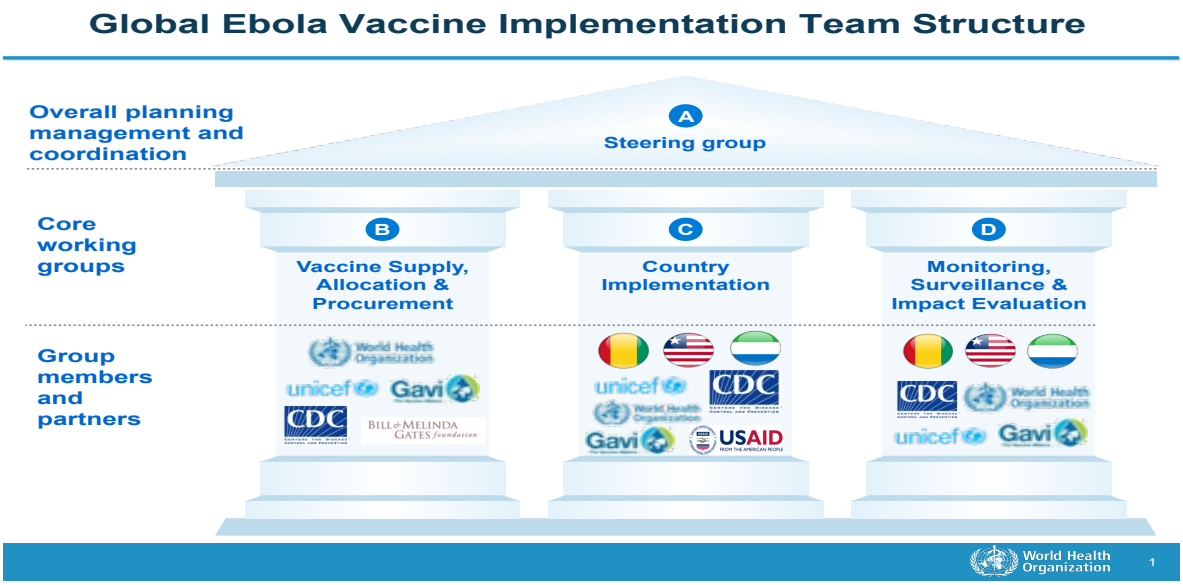


Figure 3: Global Ebola Vaccine Implementation Team (GEVIT) structure

Early in the process, it was clear that in order to be successful such effort would have to be highly collaborative and a Global Ebola Vaccine Implementation Team (GEVIT) was created with WHO leadership in order to facilitate the collaborative planning for the potential introduction of Ebola vaccines[2].

GEVIT associated countries most affected by the ongoing Ebola Virus Disease (EVD) outbreak and key partners, who would be closely involved in procuring and introducing an Ebola vaccine (Figure2).

A Steering Group was established to provide leadership and coordination to a global team organized in three Working Groups:

(1) Vaccine Supply, Allocation and Procurement;

(2) Country Implementation; and

(3) 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:

(i) to support development and dissemination of tools and guidelines, synthesis of evidence to inform strategies and policies, and community engagement strategies;
(ii) to provide capacity and work with Ministries of Health and partners to develop and implement their country plans, enabling and facilitating in-country planning, management, and coordination mechanisms, as and when relevant.

The plans and tools are near finalization and are intended for use during the ongoing outbreak or as a framework for deployment in public health Ebola emergencies, particularly in resource-limited settings.

B. SUMMARY OF KEY ACHIEVEMENYS TO DATE

C.

The timelines achieved for the two most advanced candidate vaccines were absolutely unprecedented in vaccine evaluation, and all those involved have thereby learnt that the previously accepted norms for expedited evaluation can be greatly accelerated by international partnerships, emergency funding and leadership by WHO.

Each regulator, ethics committee, scientist, partner and funding agency deserves to be commended for responsiveness to the crisis. Notably both GSK and Newlink/Merck responded in exceptional timeframes to their responsibilities as part of the vaccine development matrix.

[2] First workshop of the partners group on Ebola vaccines deployment. Summary report, 24-26 February 2015. http://www.who.int/healthsystems/publications/vaccines-deployment-workshop/en/)

1.Unprecedented and diligent design, review and implementation of clinical trials

Regulatory and ethics timelines were faster than ever before achieved in many cases. In one example a first-in-human Phase 1 was authorized in 4 working days by regulators in the UK, including initial assessment, and time to review responses by the applicant. Surging human resources into the assessment process achieved this; the rigour of the assessment process was maintained with the emphasis on product quality and participant safety.

Protocol development occurred within a few weeks thanks to the involvement of many of the leading scientists and methodologists globally.

Clinical trial investigators in Africa requested that Phase 1 data was available from Europe or North America before trial start in Africa; in practice an interval of about 4-6 weeks was achieved between clinical trial start dates in high income countries, and in Africa.

Five Phase 1 trials of ChAd3 and eight Phase 1 rVSV trials were initiated between September and December 2014 in North America, Europe and Africa. Centralised laboratory testing occurred at several laboratories.

Safety and immunogenicity data was available by February 2015 from most of these trials. The first publication was a preliminary report of the first ChAd3 trial, which was published in a journal at the end of November 2014. The information available by February allowed for dose selection data-informed decisions to be made for the three Phase 2-3 trials

Phase 2 and 3 trials were planned and initiated in record time in each of the three worst affected countries (Liberia and Sierra Leone and Guinea)

The first trial initiated was in Liberia (PREVAIL) in February, 2015 only 6 months after the global public health emergency was declared, followed by the STRIVE trial in Sierra Leone and the "Ring Vaccination trial" in Guinea which started in March 2015.

These trials are an example of international partnerships with researchers and authorities from the Ebola affected countries at the core of the same.

2. Encouraging results on safety, immunogenicity and preliminary results on efficacy and effectiveness

The safety and immunogenicity of the ChAd3-EBO-Z and the rVSV-ZEBOV have been evaluated in multiple Phase 1 clinical trials in the United States, Europe and West Africa.

Initial results indicate that these vaccines are immunogenic and do not present safety concerns that would prevent their evaluation in larger Phase 2 and Phase 3 clinical trials.

In addition, while unpublished, multiple promising two-dose schedules have been evaluated in the clinic, and these may be of relevance where long term protection is required. These two dose schedules include Ad26/MVA, ChAd3/MVA and a two-dose recombinant protein vaccine.

No further details on two-dose schedules are given as results are not yet published.

Global Advisory Committee on Vaccine safety (GACVS)

Safety of two candidate Ebola virus vaccines[1]

Phase 1 studies of the ChAd3 vaccine began in September 2014 with limited data already published. A total number of 271 healthy adults were vaccinated with ChAd3-EBO-Z in Phase 1 studies in the United States, the United Kingdom, Mali and Switzerland, with doses ranging from 1010 to 1011 viral particles. An additional Phase 1 study including 2 arms testing monovalent ChAd3-EBO-Z (n=34) was undertaken in Uganda. Based on safety and immunogenicity data from Phase 1 studies, the viral particle dose was selected for further clinical testing. Phase 2 studies in healthy adults and in children are planned in West African countries adjacent to the current outbreak zone. A Phase 2/3 study, in collaboration with the U.S. National Institutes of Health, was begun in Liberia in February 2015 but safety data were not available at the time of the GACVS meeting. In the Phase 1 studies, dose-related reactogenicity was observed, with injection-site pain and fever mainly occurring within the first 24 hours after vaccination. In most recipients, fever resolved within 24 hours. Transient clinically non-significant reductions in lymphocyte and platelet counts were observed, as is seen with many live virus vaccines. No serious adverse events ascribed to the vaccine or other unexpected serious adverse reactions were found.

Phase 1 studies of the rVSV-ZEBOV-GP vaccine began in October 2014 with limited data already published.11, 12 In total, 248 volunteers were vaccinated across 7 studies in the United States, Switzerland, Germany, Gabon, Kenya and Canada; enrollment for all studies was completed by May 2015. Collection of long-term safety and immunogenicity data from these studies is ongoing. A Phase 1b dose-ranging study, with 256 volunteers receiving doses of rVSV-ZEBOV ranging from 3 x 103 to 3 x 106 or placebo (n=74) was initiated in the United States in December 2014.

In those studies, pain at the injection site was common as were systemic symptoms including fever, malaise, and "flu-like symptoms" (chills, myalgia, headaches and fatigue) were common after vaccination and generally lasted 1 to 3 days. Administration of rVSV vaccine results in viraemia that is detectable by polymerase chain reaction (PCR) during the first and sometimes second week after vaccination, with a peak found on day 2. Vaccine virus was detected by PCR in urine and saliva in <10% of subjects. No vaccine-related serious adverse reactions have been reported to date from Phase 1 or 1b studies. Arthralgia, arthritis, dermatitis, rash and cutaneous vasculitis were reported, with varying frequency between study sites, in the 2nd week following vaccination; these reactions are associated with vaccine virus replication in the joints and the skin as demonstrated by PCR testing of specimens collected from those sites and evidence of local viral gene expression documented by immunohistochemistry. In subjects with arthritis, pain generally lasted 2–3 weeks, but occasionally more than 3 months. Joint reactions did not occur more frequently with higher doses of vaccine, but were more common among older subjects. A small number of skin vesicles and mouth ulcers were also observed and limited data did not indicate that virus had been detected by PCR. Transient, non-clinically significant reductions in neutrophil and lymphocyte counts were found in some recipients in the first few days following vaccination.

The rVSV vaccine is currently being tested in Phase 2/3 studies in Liberia, Guinea, and Sierra Leone; safety data are not yet available from those studies. Additional assessment of joint and skin events is planned in upcoming clinical studies. Safety data from Phase 1 studies of both ChAd3 and rVSV vaccines indicate an acceptable safety profile in healthy adults. Ongoing studies will provide additional experience in adults, and will allow more extensive assessment of safety. No data are currently available regarding the safety of these vaccines in subjects with underlying disease or medical conditions. There are also no data regarding the safety of these products in paediatric and pregnant subjects.

Phase 1 trials

ChAd3

Phase 1 trials confirmed a dose response in terms of both reactogenicity and immunogenicity from 1x10(10) vp to 1x10(11) vp (Table 1). Given that toxicity was not limiting at higher doses, and immunogenicity at 1x10(11) was approaching the range where non-human primates were reliably protected from challenge, this higher dose of 1x10(11) vp was chosen for further Phase 2/3 evaluation.

Unlike rVSV several hundred humans have received the identical ChAd3 backbone in Hepatitis C and RSV Phase 1 trials, with no SAE causally related to vaccination, and no unexpected safety signal.

Table 4. Overview of ChAd3 Phase 1 trials to evaluate safety and immunogenicity in healthy adults

Phase of Trial	Site	ChAd3 EBO Z dose level	Subjects Enrolled as of 22 Sep 2015	Preliminary results published
Phase 1 adults	VRC – USA (bivalent)	$2x10^{10}$ $2x\ 10^{11}$	20	N Engl J Med. 2014 Nov 26.
	Oxford – UK	$1\ x10^{10}$ $2.5\ x10^{10}$ $5\ x10^{10}$	76	N Engl J Med. 2015 Jan 28
	CVD – Mali	$1\ x10^{10}$ $2.5\ x10^{10}$ $5\ x10^{10}$ $1\ x10^{11}$	91	In press
	Lausanne – Switzerland	$2.5\ x10^{10}$ $5\ x10^{10}$	100	In press
	University of Maryland – USA	$1\ x10^{10}$ $1\ x10^{11}$	20	
	MUWRP - Uganda	$1\ x10^{10}$ $1\ x10^{11}$	34	
	2^{nd} Oxford study - UK	$2.5\ x10^{10}$	32	
	CHUD Dakar - Senegal	$2.5\ x10^{10}$ $3.7\ x10^{10}$	40	
Phase 2 adults	Senegal, Mali, Nigeria, Cameroon	$1\ x10^{11}$	722 enrolled /3000 planned	
Phase 2 paediatric	Senegal, Mali, Nigeria, Cameroon, Ghana	$1\ x10^{11}$	Not started	

rVSV Vaccine

For rVSV reactogenicity was dose related, but the dose response from 3x10(5) pfu to 5x10(7) pfu was rather flat in terms of IgG binding antibodies as measured by ELISA (Table 2). There was a dose response seen in terms of neutralising activity, with the highest response seen at 2x10(7). Unlike for ChAd3, an unexpected safety signal was detected in the rVSV trials, namely mild to moderate and generally short lived arthritis or arthralgia of onset during the second week after vaccination, in a small minority of individuals (20% in one site and less than 5% in other sites). This was confirmed to be related to dissemination of non-mutated rVSV-ZEBOV vaccine virus to joints, and is most likely caused by the known tropism of ebola virus for joints. Thus the chimeric virus shares tropism from the VSV backbone and the Ebola glycoprotein. The arthritis/arthralgia is not dose related as it was seen at a similar frequency in vaccinees that received 3x10(5) as for those receiving 5 x10(7) pfu. The decision was therefore taken to modify protocols to include solicited data collection for this adverse event, and to continue Phase 2/3 at 2x10(7) pfu.

Table 5. Overview of rVSV Phase 1 trials to evaluate safety and immunogenicity in healthy adults

Phase of Trial	Site	rVSV dose level	Subjects Enrolled as of Sep 2015	Preliminary results (D28 from partial enrolment)
Phase 1	WRAIR – USA	$3x10^6$ $2x10^7$ $1x10^8$	30	December 2014 N Engl J Med. 2015 Apr 1
	NIAID - USA	$3x10^6$ $2x10^7$ $1x10^8$	30	December 2014 N Engl J Med. 2015 Apr 1
	Geneva - Switzerland	$3x10^5$ $1x10^7$ $5x10^7$	100	January 2015 N Engl J Med. 2015 Apr 1 Lancet Infect Dis. 2015 Aug 3
	Germany	$3x10^5$ $3x10^6$ $2x10^7$	30	January 2015 N Engl J Med. 2015 Apr 1
	Gabon	$3x10^3$ $3x10^4$ $3x10^5$ $3x10^6$	115 (40 paediatric)	January 2015 N Engl J Med. 2015 Apr 1

Phase of Trial	Site	rVSV dose level	Subjects Enrolled as of Sep 2015	Preliminary results (D28 from partial enrolment)
		$2x10^7$		
	Kenya	$3x10^6$ $1x10^7$	40	February 2015 N Engl J Med. 2015 Apr 1
	Canada	$1x10^5$ $5x10^5$ $3x10^6$	30	
	NewLink-1b multiple sites - USA	$3x10^3$ $3x10^4$ $3x10^5$ $3x10^6$ $9x10^6$ $2x10^7$ $1x10^8$	442	

Phase 2/3 trials

The NIAID, the Liberia College of Physicians and Surgeons and the Liberian Institute for Biomedical Research are conducting a study in Liberia that started early February 2015. The study is called Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) and is a Phase 2/3 clinical trial designed to evaluate the safety and efficacy of two investigational vaccines intended to prevent Ebola virus infection: the ChAd3 and the rVSV vaccines.

The US Centers for Disease Control and Prevention (CDC), the Sierra Leone College of Medicine and Allied Health Sciences (COMAHS), and the Sierra Leone Ministry of Health and Sanitation (MoHS) are conducting a study in Sierra Leone that started in April 2015. This phase 3 study is called the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE). It is an event-driven, unblinded, randomized, phased introduction vaccine trial to assess the safety and efficacy of the rVSV Ebola vaccine among health care and other frontline workers.

The STRIVE and PREVAIL studies are designed to assess vaccine efficacy based on clinical disease endpoints, and serum samples will be collected for immunogenicity analysis. In addition to the 2 large Phase 3 trials sponsored by the US government,

The Guinea Consortium, a large international partnership including the Government of Guinea and the World Health Organization (WHO) is implementing a cluster randomised trial (*Ebola ça suffit* ring vaccination trial) in Guinea using the rVSV-ZEBOV vaccine.

In this novel adaptive trial design, rings are randomised 1:1 to (a) immediate vaccination of individuals at raised risk of infection due to their connection to a case or (b) vaccination delayed by 21 days.

Vaccine efficacy against disease is assessed in participants over equivalent periods from the day of randomisation. In addition a prospective cohort study among frontline workers is being conducted to obtain additional evidence on the safety and immunogenicity of rVSV.

Table 6. Overview of Phase 3 Ebola vaccine trials (1)

Study	Design	Schedule / Vaccine(s)	Sample Size (Target)	Target popn	Age inclusion criteria	Primary end points	Follow up period
Liberia PREVAIL	Double blinded, individually randomized controlled	One dose rVSV ChAd3 (Placebo)	Phase 2: 500 rVSV 500 ChAd3 (Phase 3: 27,570)	Individuals at risk for EVD	≥ 18 years	Safety, Immuno-genicity (lab confirmed EVD)	Monthly follow-up through event driven closing date
Sierra Leone STRIVE	Individually randomized,(unblinded) to immediate vs delayed arm (6 months)	One dose rVSV	Phase 3: 9000	Health Care Workers	≥ 18 years	Safety, Sub-group immu-nogenicity (lab confirmed EVD)	One year
Sierra Leone EBOVAC MoH/LSH TM/J&J	Cluster randomized in 3 stages and 2 arms to immediate vs delayed arm (6 months)	Prime + Boost Ad26 + MVA	Stage 1: (40) Stage 2: (400) Stage 3: (3160) (Phase 3: 800,000, clusters of approx. 5,000 people)	General population	Stage 1: ≥ 18 years (Stage2 & Stage 3: >12 months)	Safety, Immuno-genicity (lab confirmed EVD)	Stage 1 & Stage 2: 1year Stage 3: 5 months, with 1 year in sentinel groups
Guinée Ebola ÇA SUFFIT -essai Clinique*	Cluster randomized in areas with EVD - to immediate vs delayed arm (21 days) Cohort study among FLWs	One dose rVSV (ChAd3)	(190 rings Approx. 10,000 people) 1200	Eligible individuals who are contacts and contacts of contacts of lab conf. EVD cases	≥ 18 years & since August 2015: 13-17 yrs. 6-12 yrs.	(lab confirmed EVD) Safety, Immuno-genicity	84 days after vaccination

* Sierra Leone trial extension since September 2015

Table 6. Overview of Phase 3 Ebola vaccine trials (2)

Study	Exclusion criteria	Number of subjects enrolled to date	Status
Liberia PREVAIL	Fever (38.0 Celsius) History of EVD Pregnancy (negative urine pregnancy test required)	Phase 2: Started January 2015, Enrolment completed: 600 volunteers (Phase 3: not initiated)	Closed, Analysis ongoing (Searching new location)
Sierra Leone STRIVE	History of EVD or HIV Fever (algorithm for evaluation) *Pregnancy*	Started April 2015 Enrolment completed: 9000 volunteers, 4500 vaccinated in immediate arm, vaccinations in delayed arm on-going	Ongoing
Sierra Leone EBOVAC MoH/LSHTM/J&J	Pregnancy, individuals, medically unfit for vaccination through chronic illness	To start in September 2015	Not recruiting yet
Guinée Ebola ÇA SUFFIT -essai clinique*	Fever Pregnancy History of EVD or HIV History of immunosuppression Disease requiring hospitalization at the time of vaccination	Ring- Started March 2015 Enrolments and vaccinations completed in randomized rings in July 2015, non-randomized immediate rings continuing FLWs – started March 2015, Enrolment completed: 1200 volunteers Trial extension with safety only for new enrolments	Ongoing Interim results published Lancet. 2015 Aug 29

* Sierra Leone trial extension since September 2015

From the declaration of the public health emergency to the publication of interim results of efficacy from the Guinea ring vaccination trial the interval was less than 12 months, even though not a single person had been enrolled in a clinical trial when the emergency was declared.Between April 1, 2015, and July 20, 2015, 90 clusters, with a total population of 7651 people were included in the planned interim analysis. 48 of these clusters (4123 people) were randomly assigned to immediate vaccination with rVSV-ZEBOV, and 42 clusters (3528 people) were randomly assigned to delayed vaccination with rVSV-ZEBOV.

In the immediate vaccination group, there were no cases of Ebola virus disease with symptom onset at least 10 days after randomisation, whereas in the delayed vaccination group there were 16 cases of Ebola virus disease from seven clusters, showing a vaccine efficacy of 100% (95% CI 74·7–100·0; p=0·0036). No new cases of Ebola virus disease were diagnosed in vaccinees from the immediate or delayed groups from 6 days post-vaccination.

At the cluster level, with the inclusion of all eligible adults, vaccine effectiveness was 75·1% (95% CI −7·1 to 94·2; p=0·1791), and 76·3% (95% CI −15·5 to 95·1; p=0·3351) with the inclusion of everyone (eligible or not eligible for vaccination).

	All vaccinated in immediate versus all eligible in delayed (primary analysis)	All eligible and consented	All eligible (eligible adults, contacts and contacts of contacts)	All (all contacts and contacts of contacts)
Number of individuals (clusters)				
Immediate	2014 (48)	2048 (48)	3035 (48)	4123 (48)
Delayed	2380 (42)	1930 (42)	2380 (42)	3528 (42)
Number of cases at <10 days (affected clusters)				
Immediate	9 (4)	10 (5)	18 (9)	21 (9)
Delayed	16 (12)	6 (5)	16 (12)	25 (13)
Number of cases at ≥10 days (affected clusters)				
Immediate	0 (0)	0 (0)	6* (3)	8* (4)
Delayed	16† (7)	11† (5)	16† (7)	21† (7)
Vaccine efficacy/ effectiveness‡ (%; 95% CI)	100% (74·7 to 100)	100% (70·8 to 100)	75·1% (–7·1 to 94·2)	76·3% (–15·5 to 95·1)
p value§	0·0036	0·0194	0·1791	0·3351

*All cases occurred in unvaccinated individuals. †Four cases were vaccinated and developed symptoms on day 0, 2, 6, or 6 after vaccination. ‡From fitting a β-binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (first two columns); from Cox proportional hazards model to estimate vaccine effectiveness (last two columns). §From Fisher's exact test (two-sided).

Table 7. Calculations of vaccine efficacy and effectiveness based on different study populations 9preliminary results), Ring vaccination trial, Guinea.

According to Fisher's exact test comparing the proportions of clusters with one or more eligible case, the p value for the efficacy estimate was 0 ·0036 and did not cross the interim analysis threshold of p=0 ·0027. The estimated vaccine efficacy in all members of the 90 clusters is 76 ·3% (95% CI –15 ·5 to 95 ·1, p=0 ·3351.

The full data on the secondary outcomes for efficacy and effectiveness and safety will be part of a future report once follow-up is completed for all participants and analyses have been done and follow-up is completed for all participants and analyses have been done.

The continued enrolment, immediate vaccination, and follow-up of clusters will generate additional data about the effectiveness of ring vaccination to protect communities through herd immunity.

This trial is thought to serve as a proof of concept for a novel ring vaccination cluster-randomised trial design. This trial design is logistically feasible, even in resource-poor settings and in a crisis situation.

3. Plans and tools in preparation for vaccine deployment

Significant progress has been made in the three areas of work.

First, in terms of vaccine supply, allocation and procurement:

(i) models of supply capacity and timing of availability have been developed, closely engaging with manufacturers of advanced vaccine candidates, to be refined as new information arise;
(ii) potential demand scenarios based on a range of vaccination strategies are being considered in close collaboration with mathematical modelers;
(iii) an International Coordinating Group (ICG) for Ebola vaccine has been established, its terms of reference and processes are being defined based on the experience with ICGs for vaccines against other epidemic diseases such as meningitis or cholera; and
(iv) vaccine procurement modalities are being developed.

Second, in terms of country implementation: a guidance document has been drafted based on experience with vaccination activities during outbreak response for other infectious diseases. The guidance is organized around four main areas:

(i) vaccines and vaccination strategies;
(ii) overall planning for deployment including infection control measures;
(iii) cold chain and logistics, including provision for ultra-cold temperature equipment and related power supply, with particular attention to sustainability, flexibility and alignment with the health system needs;
(iv) shaping community engagement and risk communication strategies building on experience from both the Ebola response and the vaccine trials, including key messages and addressing possible responses to questions, concerns and perceptions.

Third and last, in terms of monitoring and evaluation, guidance documents have been drafted to address the following three areas: (i) monitoring and evaluation of the Ebola vaccination delivery strategy; (ii) evaluation of the impact of the vaccine use and potentially efficacy, with attention to elements and definitions to be adapted or added to the surveillance system; and (iii) vaccine safety surveillance including the development of case definitions for Adverse Events Following Immunization (AEFI) and guidelines to strengthen AEFI Monitoring and Evaluation.

GEVIT will now seek to reach consensus on the documents and tools, so that the blueprint be completed by December 2015.

A regional workshop will be a significant milestone to advance and integrate plans together with countries, using case studies and simulation exercises. It will be held in Brazzaville just after the October 2015 meeting of the WHO's Strategic Advisory Group of Experts on Immunization (SAGE) to benefit from their draft recommendations on Ebola vaccines and vaccination.

C. PREPARING FOR THE INEVITABLE – BUILDING AN R&D LINE OF DEFENCE FOR GLOBAL HEALTH THREATS

WHO R&D blueprint for epidemics

Objectives:

- To develop and implement a roadmap for R&D preparedness,
- To enable roll-out of an emergency R&D plan as early as possible during future public health emergencies due to highly infectious pathogens

Five Work-streams:

1. Mechanism to prioritize pathogens for research and product development

- Identification of the top priority infectious diseases for which R&D should be conducted urgently for better preparedness. This work will build on prioritization exercises conducted by various organizations.
- Development of a methodology, based on explicit criteria, for revising these R&D priorities annually or when needed, in order to take into consideration new emerging pathogens.

2. R&D preparedness: gap analysis and identification of research priorities

- Production of a template for a fully developed roadmap for R&D preparedness for priority infectious pathogens, including priority research as well as product R&D. One of the identified priority pathogens (MERS-CoV) will be used as an example to articulate the main elements of this roadmap.

3. Organization, coordination of stakeholders and gap analysis of capacities

- Investigation of a stakeholder engagement plan and governance structure that efficiently allows for National and International actors to work in concert in support of a global effort.
- Mapping of capacities, platforms, tools and templates needed to enable conduct of an efficient research response during a public emergency. This will facilitate the last steps of R&D for identified priority diseases, as well initiation of R&D for previously unknown pathogens

4. Assessment of preparedness level and (Impact assessment) of interventions

- Development of a mechanism for monitoring and evaluation of the effectiveness of the outputs over the near- and longer-terms will be developed

5. Funding options for preparedness and emergency response

- Exploration of options for complementary funding models from centrally pooled resources in R&D funds, to joint planning with individual implementation by different entities in line with the agreed blueprint activities, and agreed roles and responsibilities for different agencies.