

R&D for potential vaccines, therapies and diagnostics in the time of Ebola

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**World Health
Organization**

Ebola R&D in WHO from March to August 2014

- WHO was involved in *ad hoc* discussions and activities
 - With vaccine developers (GSK and Public Health Agency Canada) on candidate products
 - Internally, on prioritization criteria
 - With regulators, on emergency use pathways
- Development of WHO position on convalescent plasma as a potential therapeutic option by the Blood Regulators Network

Ethical considerations for use of unregistered interventions for Ebola viral disease

WHO/HIS/KER/GHE/14.1



Report of an advisory panel to WHO

- “...acceptable on both ethical and evidential grounds to use as potential treatments or for prevention unregistered interventions...”
- “...moral obligation to collect and share all scientifically relevant data generated...”
- “...best possible clinical studies that can be conducted under the circumstances of the epidemic...”

WHO's role from August 2014 onwards:

(1) Gathering and disseminating knowledge

- Since August 2014, WHO held a series of consultations with key international experts and stakeholders to identify potential therapeutic or preventive solutions for Ebola
- Based on concerted expert advice, **WHO prioritized a number of products** for further investigation through human testing:
 - two candidate vaccines
 - a shortlist of antiviral drugs
 - convalescent whole blood and plasma
 - rapid point-of-care diagnostics

One of many significant challenges...

How to compress the usual timeline for unproven interventions from years to months, by working in parallel on:

Development

Testing

Licensure

Use

Issues for consideration

- Availability of therapeutic or preventative substance
 - Preclinical evidence
 - Clinical safety
 - Route of administration
 - Duration of therapy or of protection
 - Storage/transport

... and how to prove that it actually benefits patients...

**Need to (a) stimulate innovative clinical trial design,
(b) de-prioritize many potential interventions**

WHO's role:

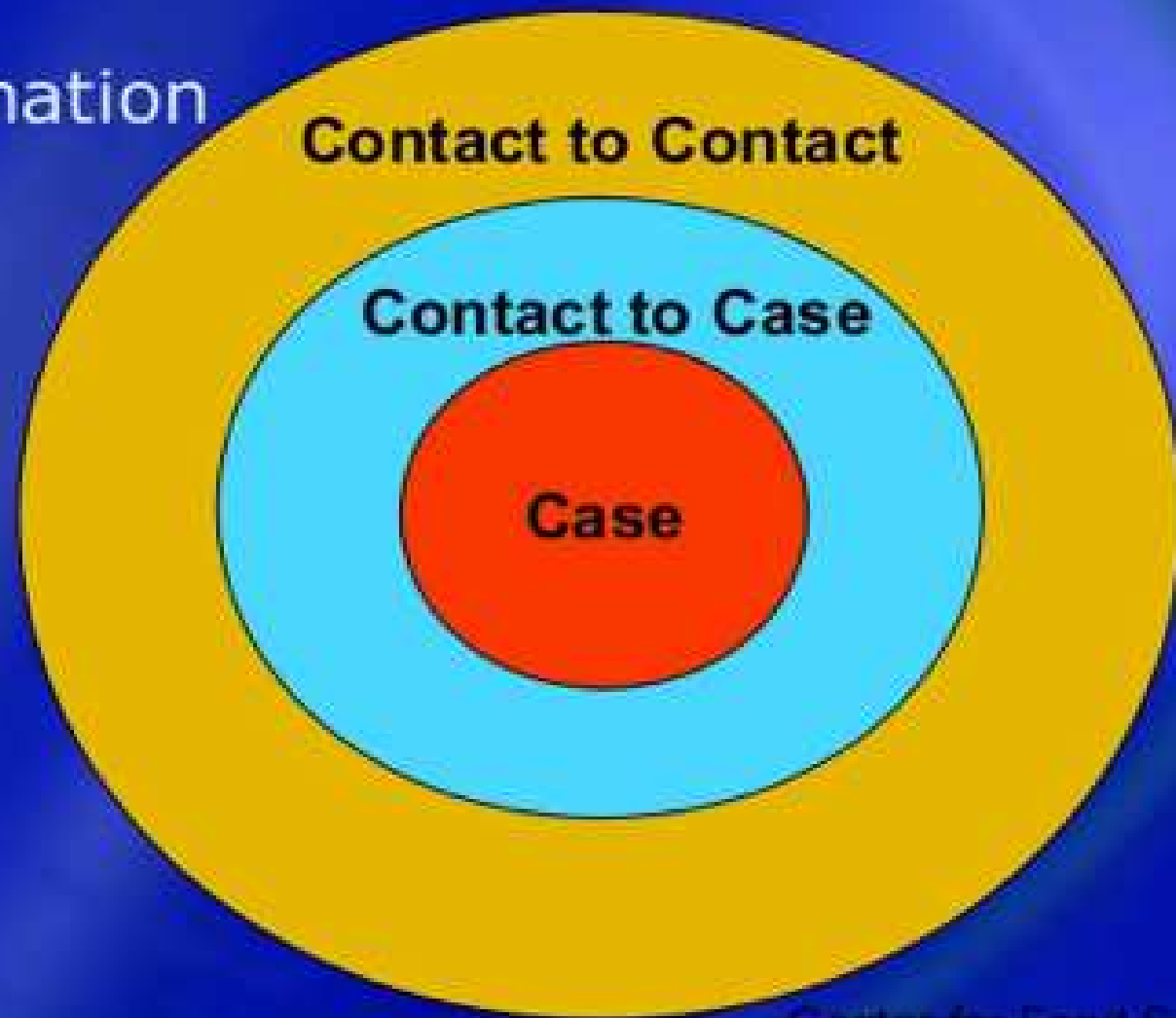
(2) direct support to the R&D response

- Advocating for phase 1 and 2 vaccine trials in Africa
- Facilitating ethical and regulatory review of clinical trial protocols in Africa, including the affected countries (for vaccines)
- Development of target product profiles (for rapid diagnostic tests)
- Development of emergency use and listing procedures to guide procurement decisions (for vaccines; drugs; diagnostics)
- Needs assessments to support R&D (for cold chain)
- Preparing for large-scale deployment of successful interventions (for vaccines)

WHO's role:

(3) Sponsor for ring vaccination Phase 3 clinical trial

- Ring vaccination



Global Achievements

Clinical trials were underway by December 2014 in the three affected countries, each of which were "clinical trial naïve" prior to the epidemic

Prioritized therapeutic products

- Drugs under clinical evaluation :
 - *Favipiravir: Guinea – Trial completed – not to be considered as standard of care.*
 - *Brincidofovir: Liberia – Trial halted, product deprioritized*
 - *Zmapp: “cocktail” of 3 monoclonal antibodies (Liberia; Sierra Leone)*
 - *TKM-100802 (si-RNA); Sierra Leone - Trial completed, product deprioritized*
 - *Interferon: trial initiated in Donka (Guinea): not recruiting*
- Drugs for which clinical evaluation is envisaged:
 - *BCX-4430: adenosine analogue that disrupts viral RNA-dependent RNA polymerase function by chain termination*
 - *MIL-177: cocktail of 3 Mabs (same sequences as Zmapp)*
 - *Antiviral from Gilead*

Blood Products

➤ Convalescent Whole Blood

- *Sierra Leone (MoH); 54 patients transfused. Historical CFR as comparator. Trial halted and switched to convalescent plasma.*

➤ Convalescent Plasma

- *Liberia (Government and US); 6 patients enrolled, 4 matched & treated.*
- *Guinea ("Ebola Tx" - 16 partners); trial initiated mid-February 2015; now completed; disappointing results.*
- *Sierra Leone ("Ebola CP" – 16 partners); trial initiated beginning April*

Vaccine Pipeline

PRE-CLINICAL DEVT.



VLP



Profectus BioSciences, Inc.

rVSV



Rec. rabies



Rec. influenza



Ad5

CLINICAL TRIALS



ChAd3/MVA



ChAd3



VLP



rVSV-ΔG



Ad26/MVA

Two lead candidate vaccines

A- rVSV-ZEBOV – recombinant vesicular stomatitis virus

The rVSV vaccine aims to induce EVD-specific immune responses.

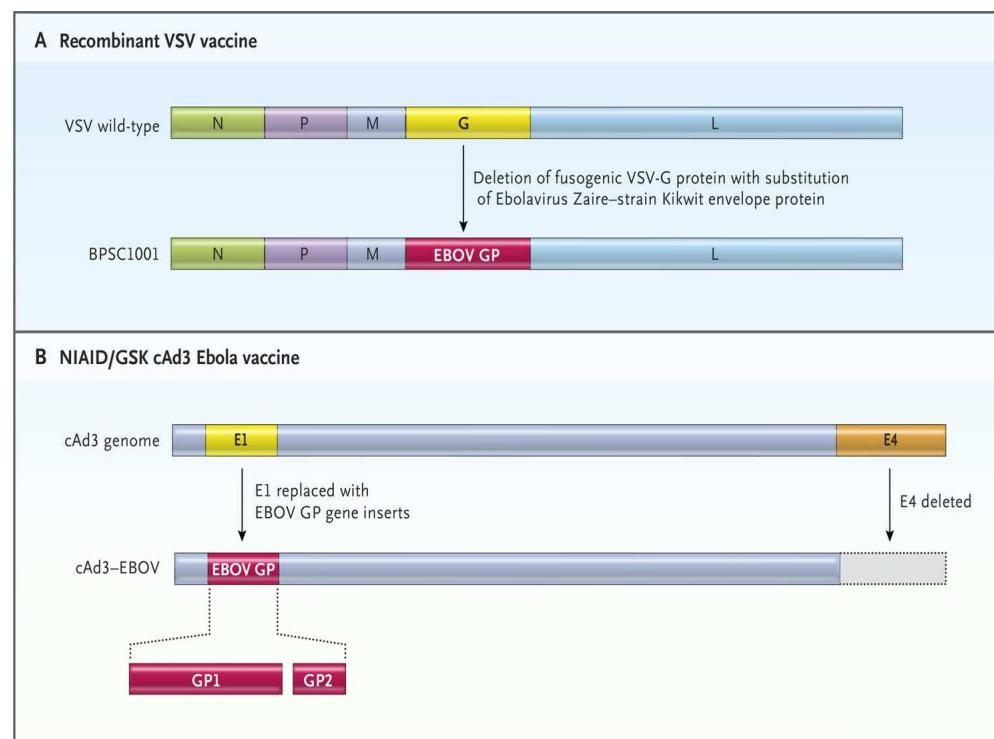
NewLink Pharmaceuticals/Public Health Agency of Canada

800 vials donated to WHO by the Government 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



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

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

Safety summary from Phase I studies

ChAd3- and rVSV-ZEBOV

- No serious adverse events related to immunization
- Arthritis identified as an adverse event of specific interest on rVSV-ZEBOV Phase 1 trials. Generally mild and self-limited.
- Safety monitoring and oversight continues to be a high priority

Vaccine Phase II-III trial designs

- Liberia: Randomized controlled 3-arm trial (VSV vs ChAd3 vs placebo) in the community (Government and US NIH), Started Feb 2015; approx 1500 enrolled
- Sierra Leone:
 - modified stepped-wedge trial with VSV vaccine in health-care workers (Government and US CDC), Enrolment start in early April 2015; target 8,000 subjects
 - Cluster randomized community based study (J&J vaccine) (Government and UK LSTHM), Phase 2 enrolment ongoing; Phase 3 with 800,000 subjects not approved.



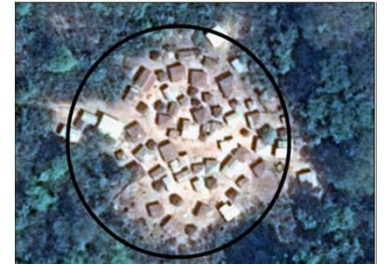
"Ebola ça suffit" –

Ring vaccination
efficacy trial of
rVSV-ZEBOV
candidate Ebola
vaccine in Guinea

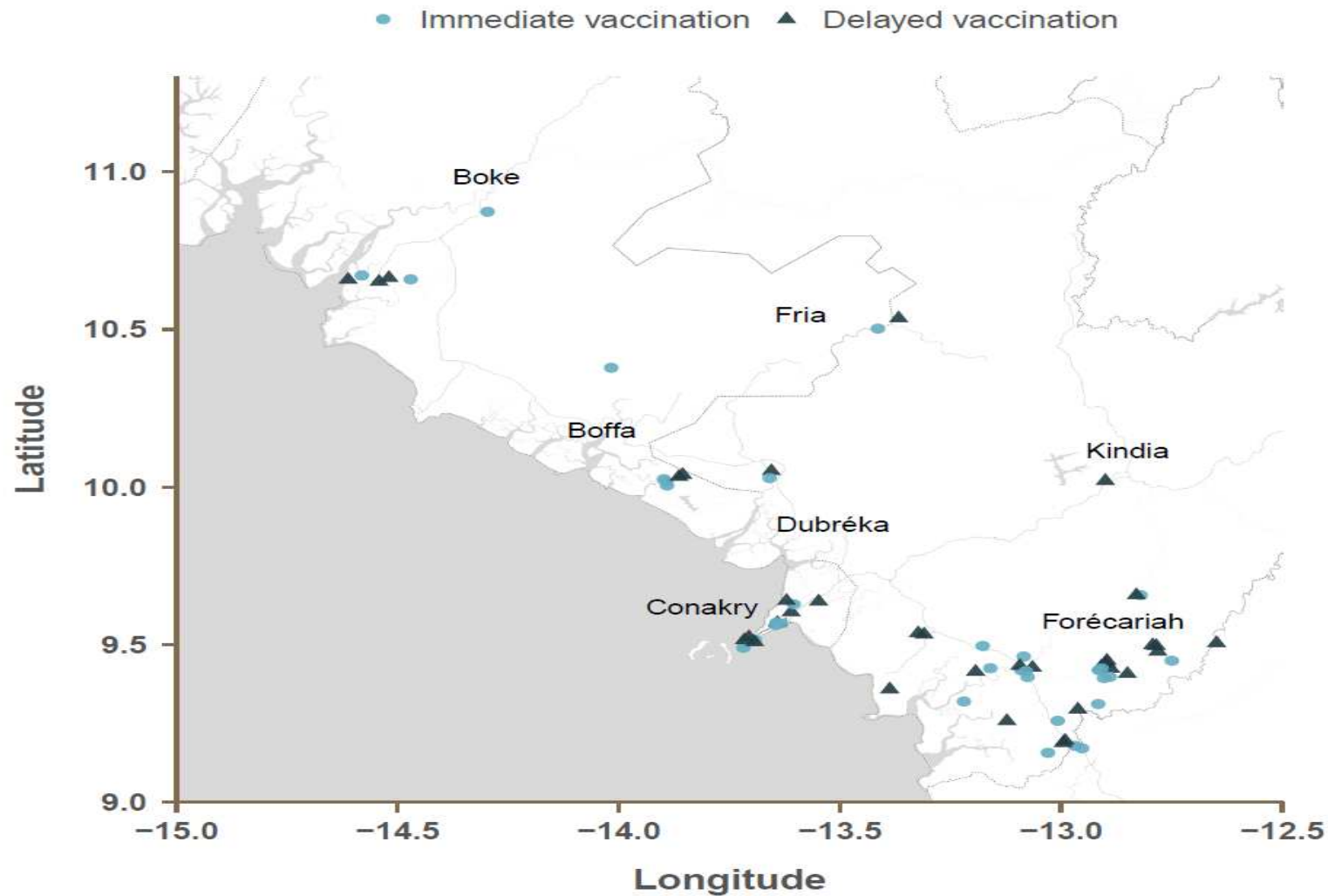
What is a vaccination ring?

A vaccination ring is not necessarily a single geographical site. It comprises:

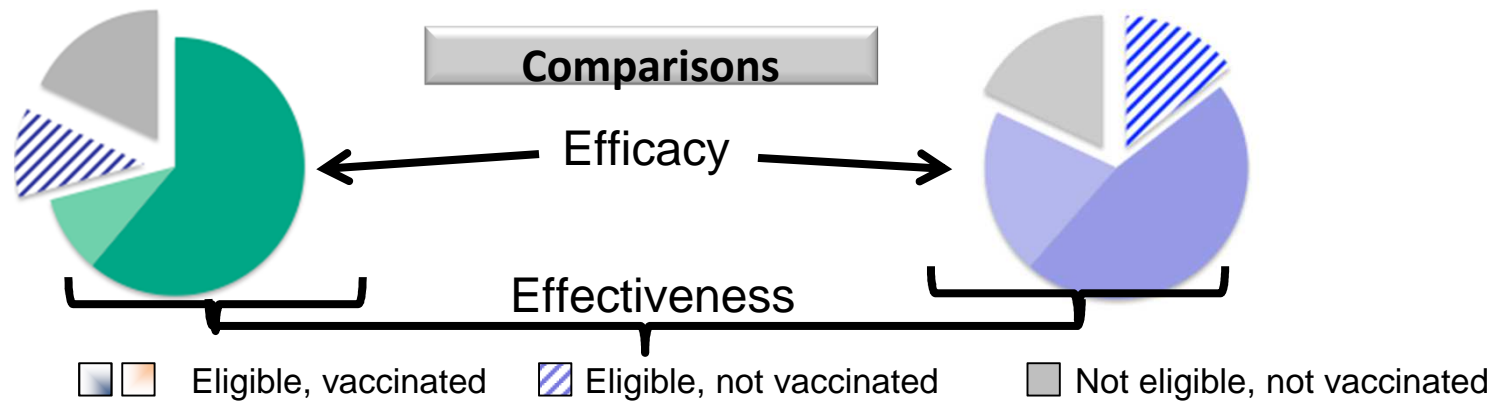
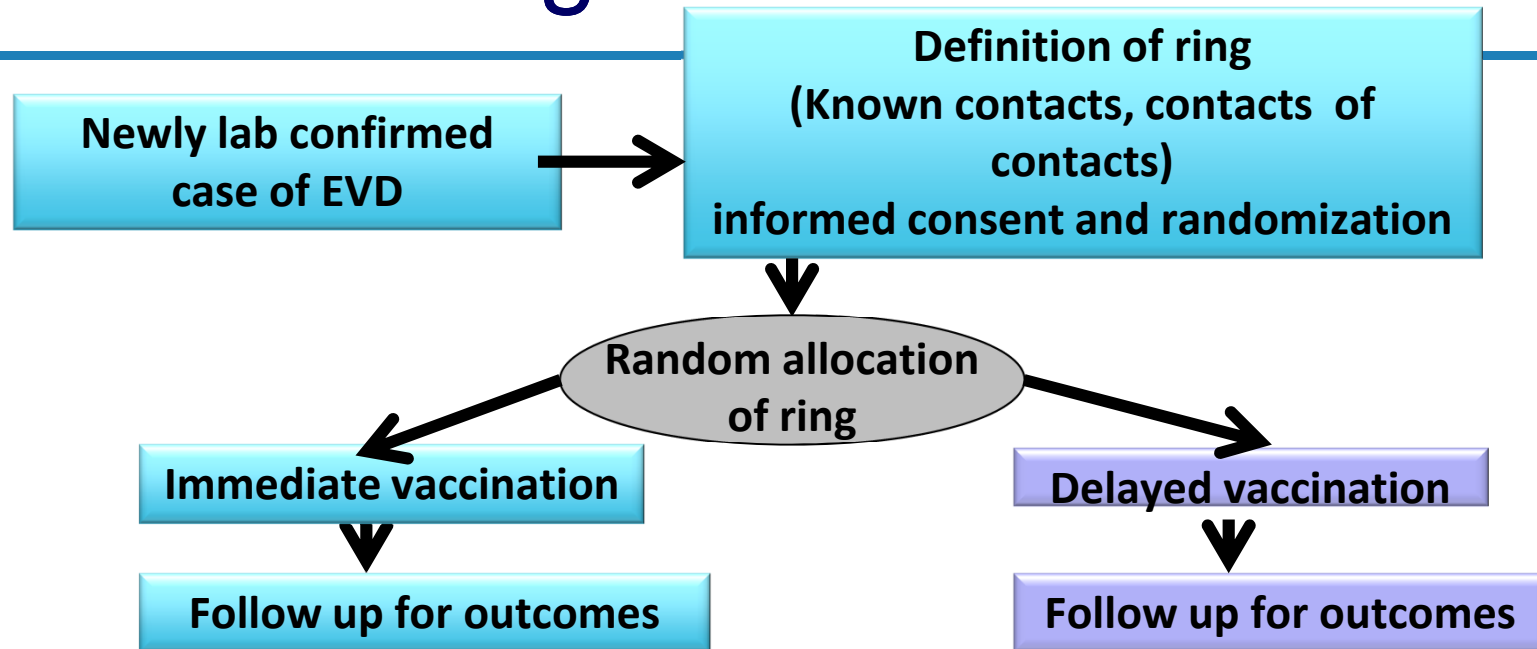
- **all the contacts of an index case of EVD, plus**
- **the neighbours or extended family members to nearest geographic boundary in which the local contacts of the index case reside, plus**
- **household members of any high-risk contact who do not live in the same locality as the case.**



Study area of *Ebola ça Suffit* cluster vaccination trial in Basse-Guinée.



Ring vaccination trial



Kaplan-Meier plots of the cumulative incidence of confirmed Ebola

A: All vaccinated in immediate versus all eligible in delayed (primary analysis)

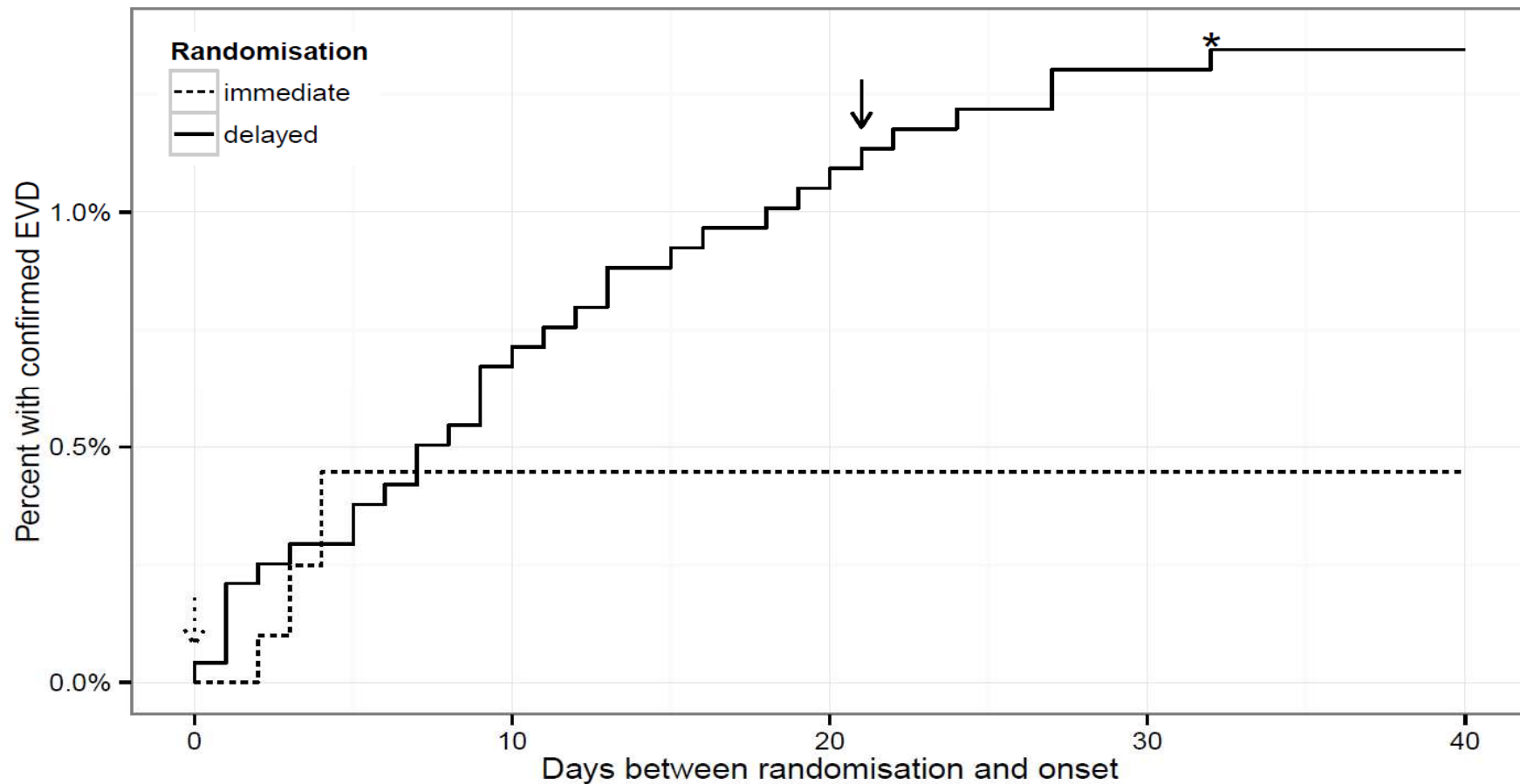


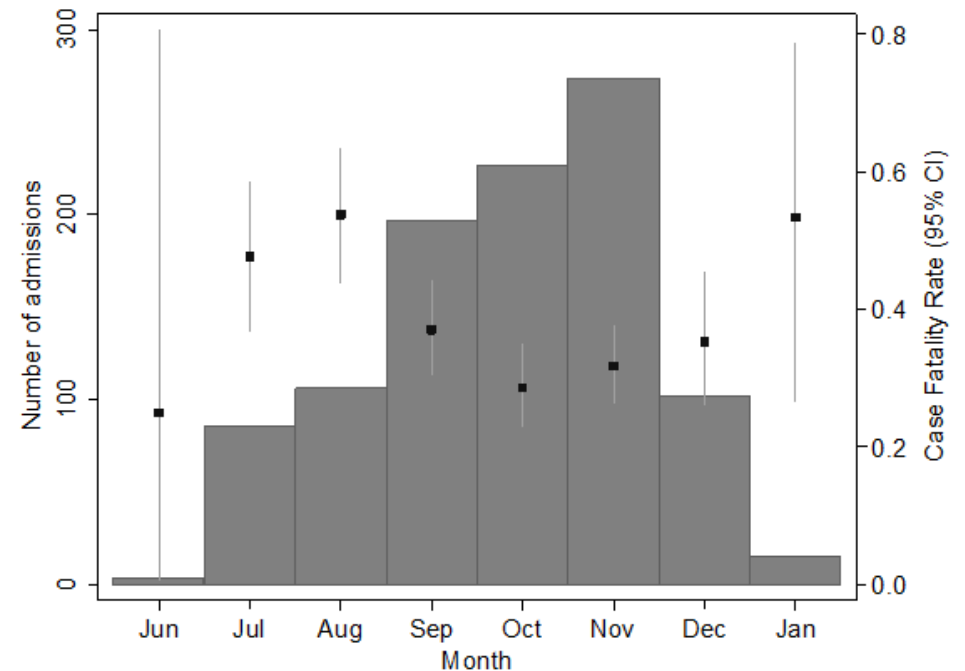
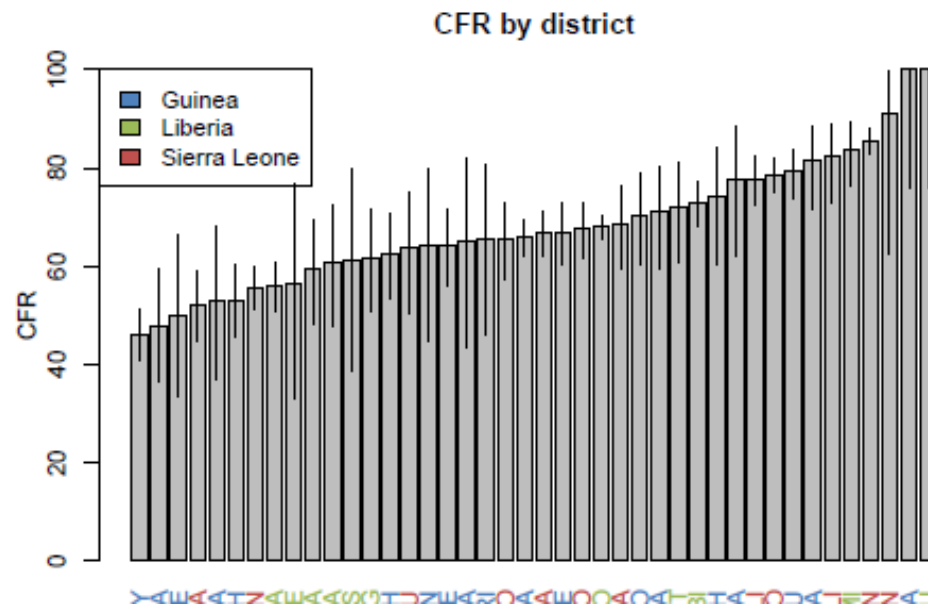
Fig 2 (The Lancet article): calculations of vaccine efficacy and effectiveness in different study populations

	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
<p>*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).</p>				

Challenges for the Present and Future

- Tail-end of the epidemic in the affected countries – implications for current and planned clinical trials
- Case fatality rate changes/obfuscates baseline for judging efficacy of therapeutic interventions from historic data
- Limited /non-availability of some leading candidates delayed start of trials

Case-fatality case is variable : between treatment centers - within individual ETCs



Next steps

- Continued strong emphasis on effectively engaging with communities to build trust and allay concerns about clinical trials.
- Sustaining the momentum to continue the product development work once the epidemic subsides
- Prepare for the inevitable: overcoming obstacles to a timely and effective R&D response : The WHO **R&D Blueprint**

Objectives of the Blueprint

Preempt development of public health emergencies:

- ❖ **Implement roadmap for R&D preparedness,**
- ❖ **Enable prompt roll-out of emergency R&D plan during outbreaks of highly infectious pathogens**

Collaborations welcome!

Five workstreams

1. Mechanism to prioritize pathogens for research and product development
2. R&D preparedness: gap analysis and identification of research priorities for the priority diseases
❖ MERS Roadmap
3. Organization of stakeholders and strengthening of capacities
4. M&E of preparedness level and of interventions
5. Funding options for preparedness and emergency response