Ebola vaccines and vaccination

Ana Maria Henao-Restrepo
Marie-Pierre Preziosi
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on behalf of all experts, partners, scientists, developers, pharmaceutical companies, national authorities, governments, non government organisations, foundations, institutions and WHO colleagues, that have worked on Ebola vaccines R&D

8 August 2014
WHO declared a public health emergency of international concern

OUTLINE

Overview of the global efforts

Summary of the available evidence

Next steps and challenges

"The Ebola R&D effort has mobilised people, institutions and resources in ways never seen before. This is one positive outcome in an otherwise horrific human calamity.

.....New tools have been developed with unprecedented speed, though the window of opportunity for testing some is closing.

.....The job 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...."

Margaret Chan

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

AUG
Ethical considerations for use of unregistered interventions for Ebola virus disease

SEP
WHO Consultation on potential Ebola therapies and vaccines
WHO Consultation on Ebola vaccines

OCT
First WHO High-level meeting on Ebola vaccines access and financing,
Development of technical document on Ebola vaccines to inform Gavi Alliance Board decision

NOV
WHO Meeting of the STAC on Ebola Experimental Interventions
First meeting of WHO Ebola Science Committee
WHO Technical Consultation: Heterologous Prime-Boost Immunization in Ebola vaccine development and testing, licensure and use
The VSV Ebola Consortium (VEBCON)

JAN
Second WHO High-level meeting on Ebola vaccines access and financing

MAR
WHO Ebola Science Committee, 3-4 March 2015

MAY
WHO Ebola R&D summit

SEP
Developing Global Norms for Sharing Data and Results during Public Health Emergencies

OCT
SAGE Working Group on Ebola Vaccines and Vaccination

Consultations to discuss regulatory pathways and oversight of planned Ebola vaccines trials

OCT First teleconference on regulatory approaches for expediting development and availability of Ebola vaccines

NOV African Vaccine Regulatory Forum (AVAREF)

Report of the joint review facilitated by WHO for the GSK ChAd3 Ebola Vaccine clinical trials application

DEC WHO hosts joint review of Phase II clinical trial application for GSK Ebola vaccine

JAN Second teleconference on regulatory approaches for expediting development and availability of Ebola vaccines

The AVAREF joint review process of Ebola clinical trial applications

MAR WHO Informal Consultation on regulatory considerations for evaluation of Ebola Vaccines intended for emergency use, WHO/HQ Geneva

Consultations to discuss clinical trial design and progress with the conduct of the Ebola vaccines trials

WHO consultation on potential Ebola therapies and vaccines

SEP First teleconference on vaccine clinical trial designs in Guinea, Liberia, and Sierra Leone

OCT Second teleconference on vaccine clinical trials design for Guinea, Liberia, and Sierra Leone

NOV Third teleconference on vaccine clinical trials design for Guinea, Liberia, and Sierra Leone

DEC

JAN The rVSV vaccine selected for Guinea trial according to a framework developed by the WHO STAC-EE

MAR Fourth teleconference on Ebola vaccine clinical trials in Guinea, Liberia, and Sierra Leone

JUL

AUG Fifth Teleconference on Vaccine Clinical Trials Design in Guinea, Liberia and Sierra Leone.

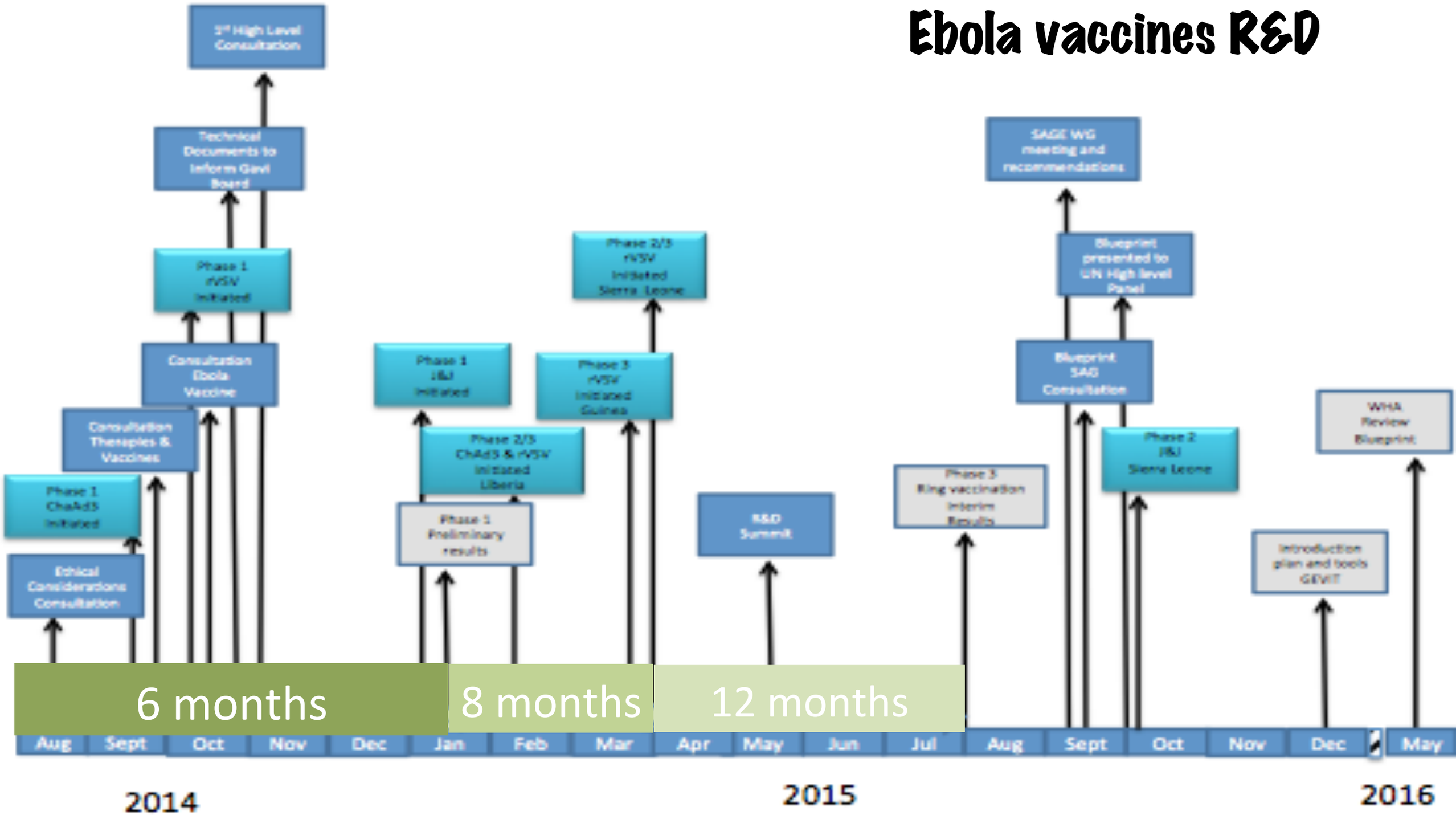
SEP Report on the 2nd WHO Consultation on Biobanking: Focus on West Africa,

Developing Global Norms for Sharing Data & Results during Public Health

Preparing for the deployment of vaccines

Collaborative efforts, adaptation of the traditional R&D model, compressed timeframes and, unprecedented partnerships formed.

Ebola vaccines R&D



Ebola vaccines pipeline then…

NON- CLINICAL EVAL.

CLINICAL EVALUATION

Protein Sciences CORPORATION

VLP

Profectus BioSciences, Inc.

rVSV

Jefferson THOMAS JEFFERSON UNIVERSITY

Rec. rabies

VAXART

Ad5

J&J

Ad26/MVA

gsk

ChAd3

NewLink GENETICS

rVSV-ΔG

Ebola vaccines pipeline now…

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RESEARCH INSTITUTE OF INFLUENZA · MINISTRY OF HEALTHCARE OF THE RUSSIAN FEDERATION

Rec. Influenza

VAXART

Ad5

J&J

Ad26/MVA

NOVAVAX

Creating Tomorrow's Vaccines

VLP

CanSinotech

gsk

ChAd3

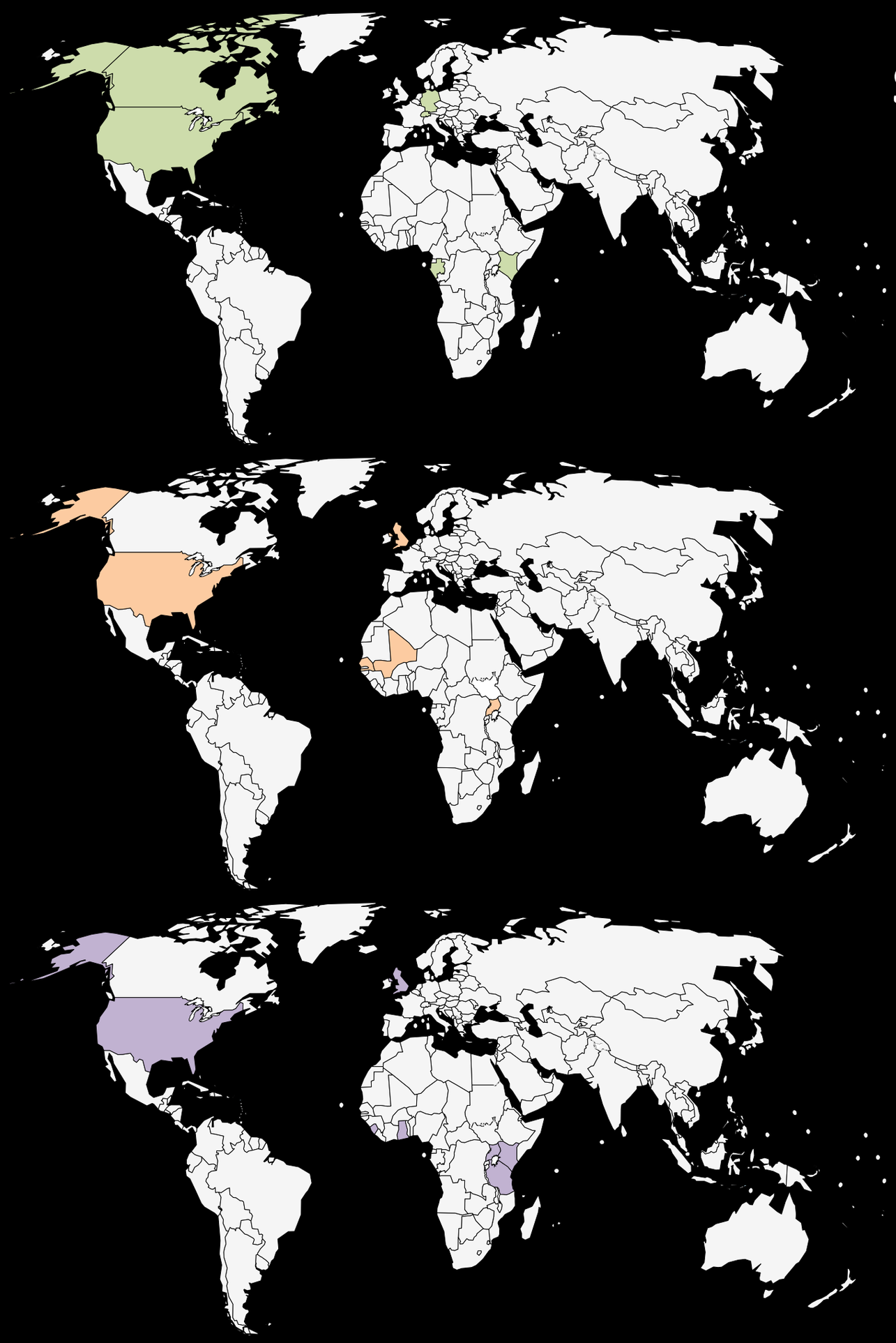
NewLink GENETICS

MERCK Be well

rVSV-ΔG

Characteristics of most advanced candidate Ebola vaccines in clinical development (1)

Product	rVSV-ZEBOV	ChAd3-ZEBOV	Ad26.ZEBOV and MVA-BN-Filo	Ad5-ZEBOV
Principle	Recombinant vector viruses expressing EBOV envelope glycoproteins			
Vector	Replication-competent recombinant vesicular stomatitis virus (VSV)	Replication-defective recombinant chimpanzee adenovirus serotype 3 (rChAd3)	Replication-defective recombinant human adenovirus serotype 26 (Ad26) [primer] and Modified Vaccinia Ankara (MVA) [booster]	Replication-defective recombinant human adenovirus serotype 5 (Ad5)
Expressed filovirus GP	ZEBOV (Zaire)	ZEBOV (SUDV not tested in 2014–2015 trials)	Ad26: ZEBOV MVA: ZEBOV, SUDV, Marburg virus	ZEBOV (Zaire)
Number of doses	1	1	2, heterologous prime & boost (14,28,56 days apart)	1



Sites of Ebola vaccine Phase 1 trials

rVSV-ZEBOV (827 participants)

CANADA (3-dose levels, 30 participants)	GERMANY (3-dose levels, 30 participants)
USA, Multiple sites (7-dose levels, 442 participants)	SWITZERLAND, Geneva (3-dose levels, 100 participants)
USA, WRAIR (3-dose levels, 40 participants)	KENYA (2-dose levels, 40 participants)
USA, NIAID (3-dose levels, 30 participants)	GABON (5-dose levels, 115 participants)

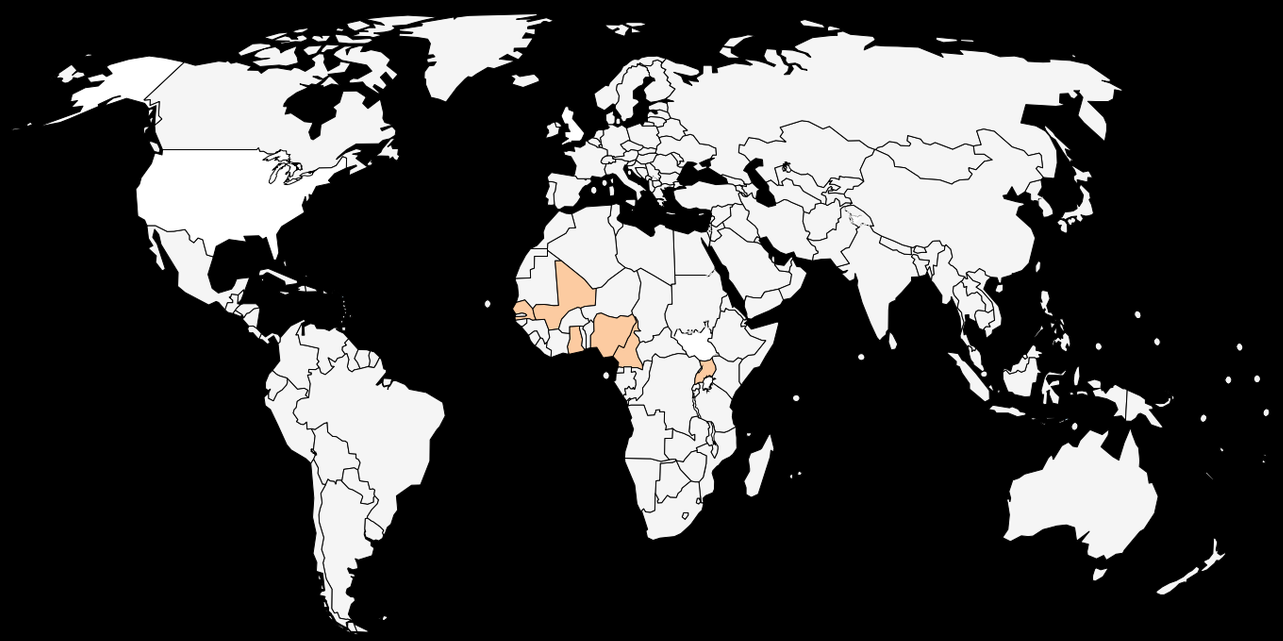
ChAd3-ZEBOV (413 participants)

USA, VRC (2-dose levels, 20 participants)	SWITZERLAND, Lausanne (2-dose levels, 100 participants)
USA, U. of Maryland (2-dose levels, 20 participants)	SENEGAL, CHUD (2-dose levels, 40 participants)
UK, Oxford (3-dose levels, 76 participants)	MALI, CVD (4-dose levels, 91 participants)
UK, Oxford (1-dose level, 32 participants)	UGANDA, MUWRP (2-dose levels, 34 participants)

Ad26.ZEBOV and MVA-BN-Filo (779 participants)

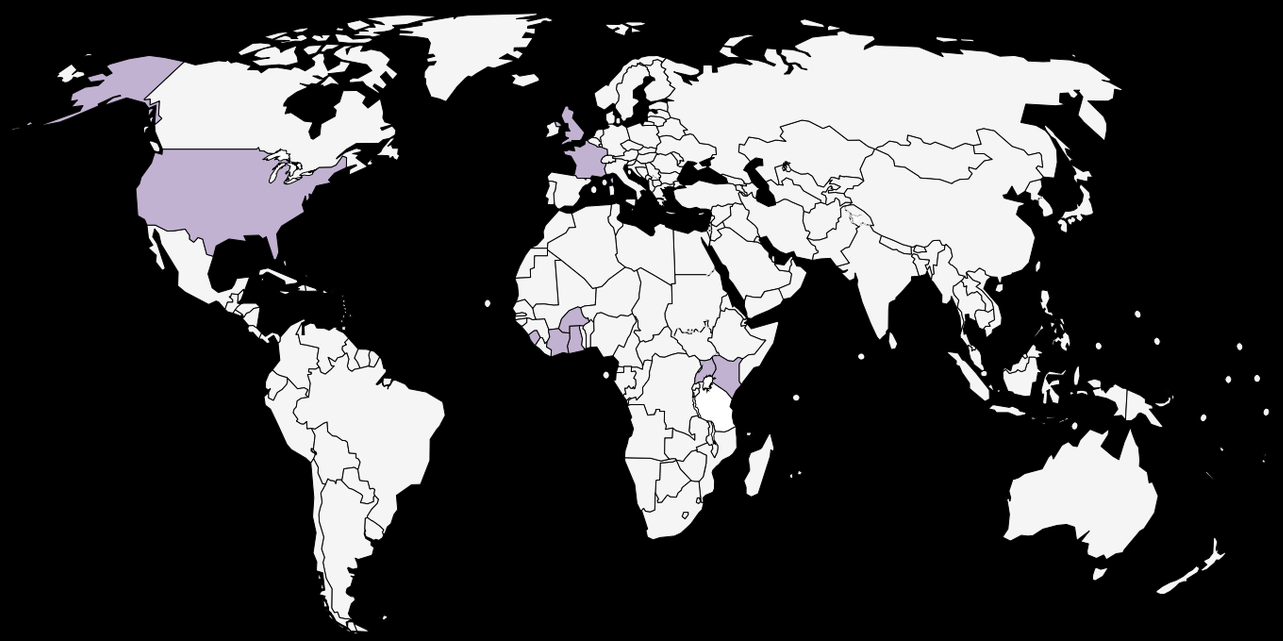
USA (2-dose levels, 128 participants)	GHANA/KENYA (1-dose level, 72 participants)
UK, Oxford (1-dose level, 87 participants)	TANZANIA/UGANDA (1-dose level, 72 participants)
	SIERRA LEONE (440 participants)

Sites of Ebola vaccine Phase 2 trials



ChAd3-ZEBOV (>3,000 participants)

SENEGAL, MALI, NIGERIA & CAMEROON (3,000 participants)	SENEGAL, MALI, NIGERIA, CAMEROON & GHANA (planned, in children)

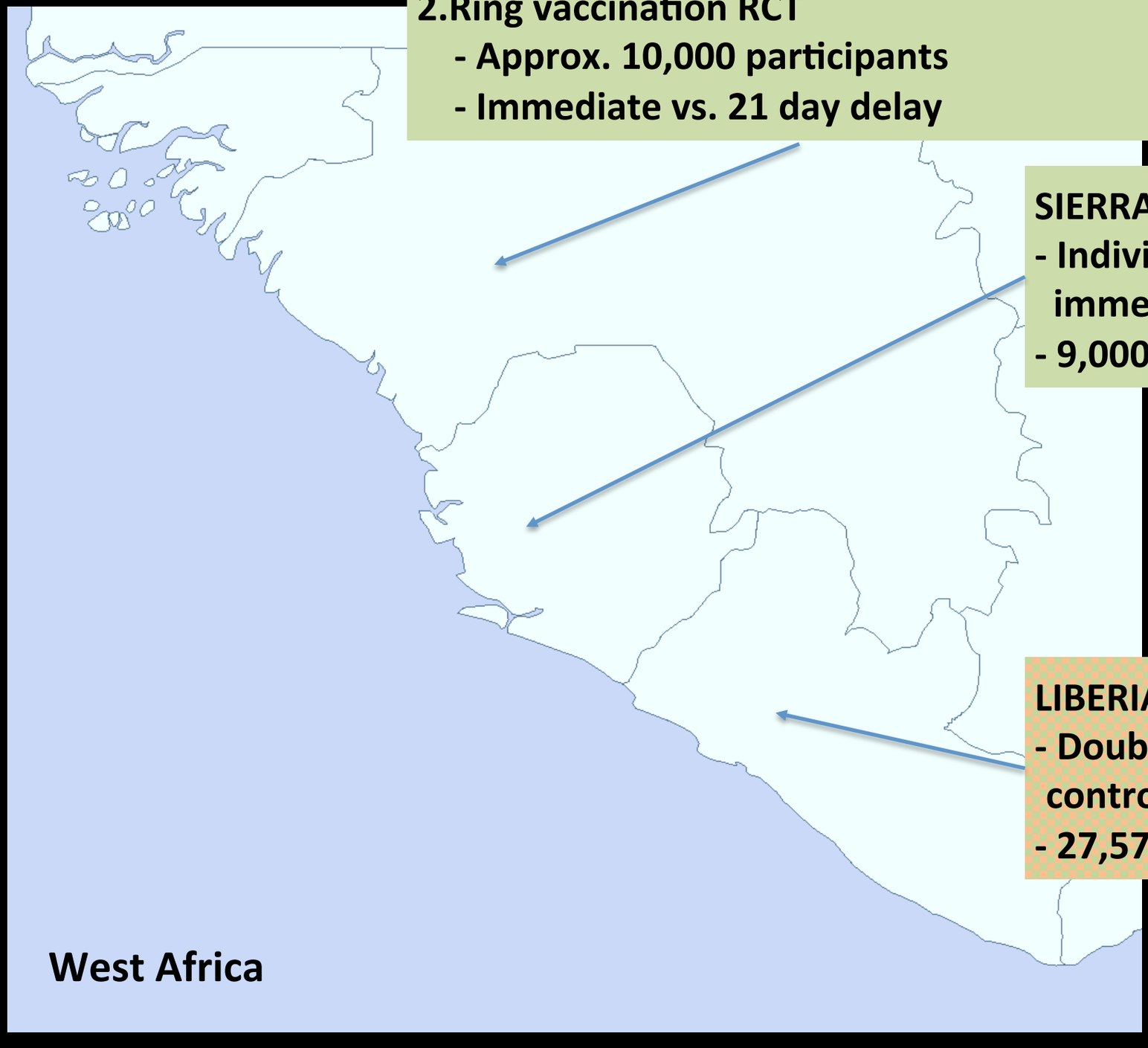


Ad26.ZEBOV and MVA-BN-Filo (6,094 participants)

USA (525 healthy adults)	SIERRA LEONE (3,440 healthy adults and children)
USA (329 healthy adults)	IVORY COAST, BURKINA FASO, KENYA, UGANDA & GHANA (1,188 participants aged 1–17 years)
UK/FRANCE (612 healthy adults)	

Sites of Ebola vaccine Phase 3 trials

GUINEA, "Ebola ça suffit" (rVSV-ZEBOV)
1.Cohort study among Front Line Worker - Approx. 3,500 participants
2.Ring vaccination RCT
- Approx. 10,000 participants
- Immediate vs. 21 day delay



SIERRA LEONE, "STRIVE" (rVSV-ZEBOV)
- Individually randomized (un-blinded) to immediate vs delayed arm
- 9,000 health care workers

LIBERIA, "PREVAIL" rVSV/ChAd3/Placebo)
- Double blinded, individually randomized controlled
- 27,570 individuals at risk

Overview of participants in Ebola vaccines trials*

Participants (sites)	rVSV-ZEBOV	ChAd3-ZEBOV	Ad26.ZEBOV and MVA-BN-Filo	Ebola/Makona GP nanoparticle vaccine
Phase 1	777 adults (8) 40 children (1)	413 adults (8)	404 adults (6)	230 adults (Australia)
Phase 2		40 adults (4) Children (4, not yet started)	1,188 persons aged 1–70 years (6) 612 adults (2). Planned children 1-17, HIV+ve adults	
Phase 2/3	500 adults (Liberia, Ph 2) 4,500 adults (Sierra Leone) Adolescents and adults (Guinea)	500 adults (Liberia, Ph 2)	440 persons aged 1–65 years (Sierra Leone) 850 adults (US)	

*** As of October 2015**

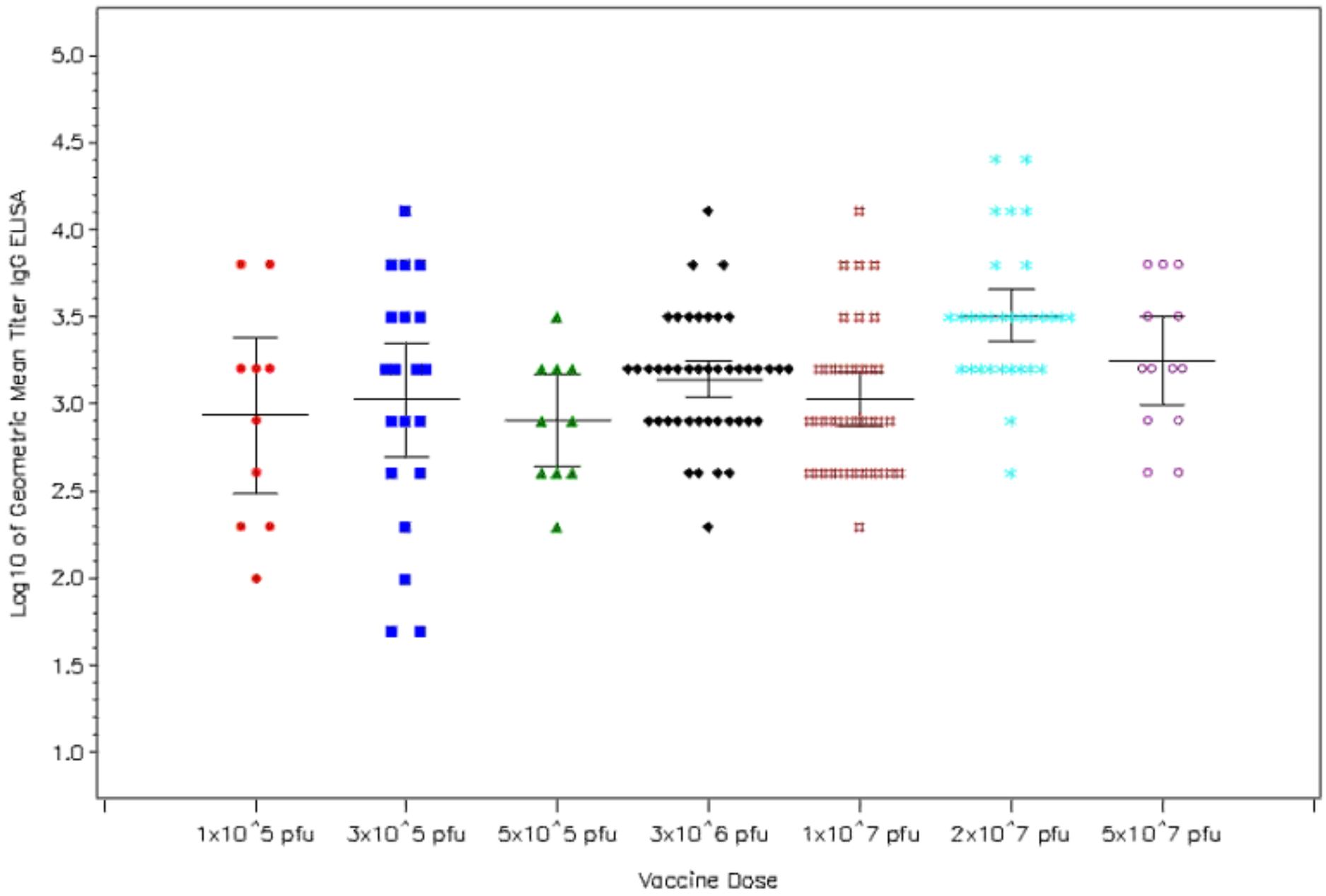
Source: rVSV and ChAd3, SAGE WG report; Ad26/MVA and GP nanoparticle, clinicaltrials.gov

Immunogenicity results

Dose Response of IgG ELISA
Preliminary Analysis of Pooled Data (D28)

Figure 3a

Geometric Mean ELISA IgG End Point Titers at Day 28 by BPSC1001 Dose Level



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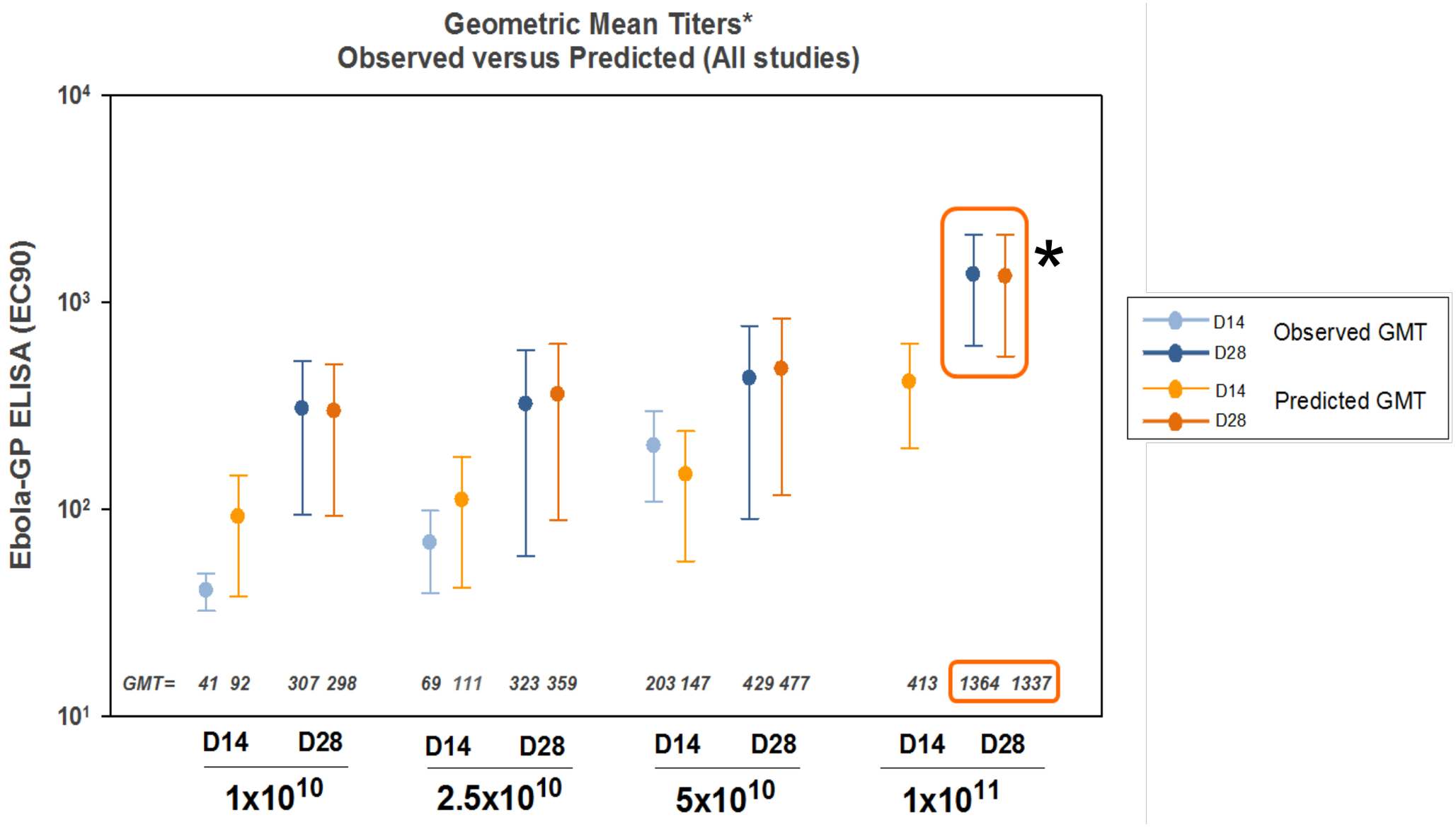
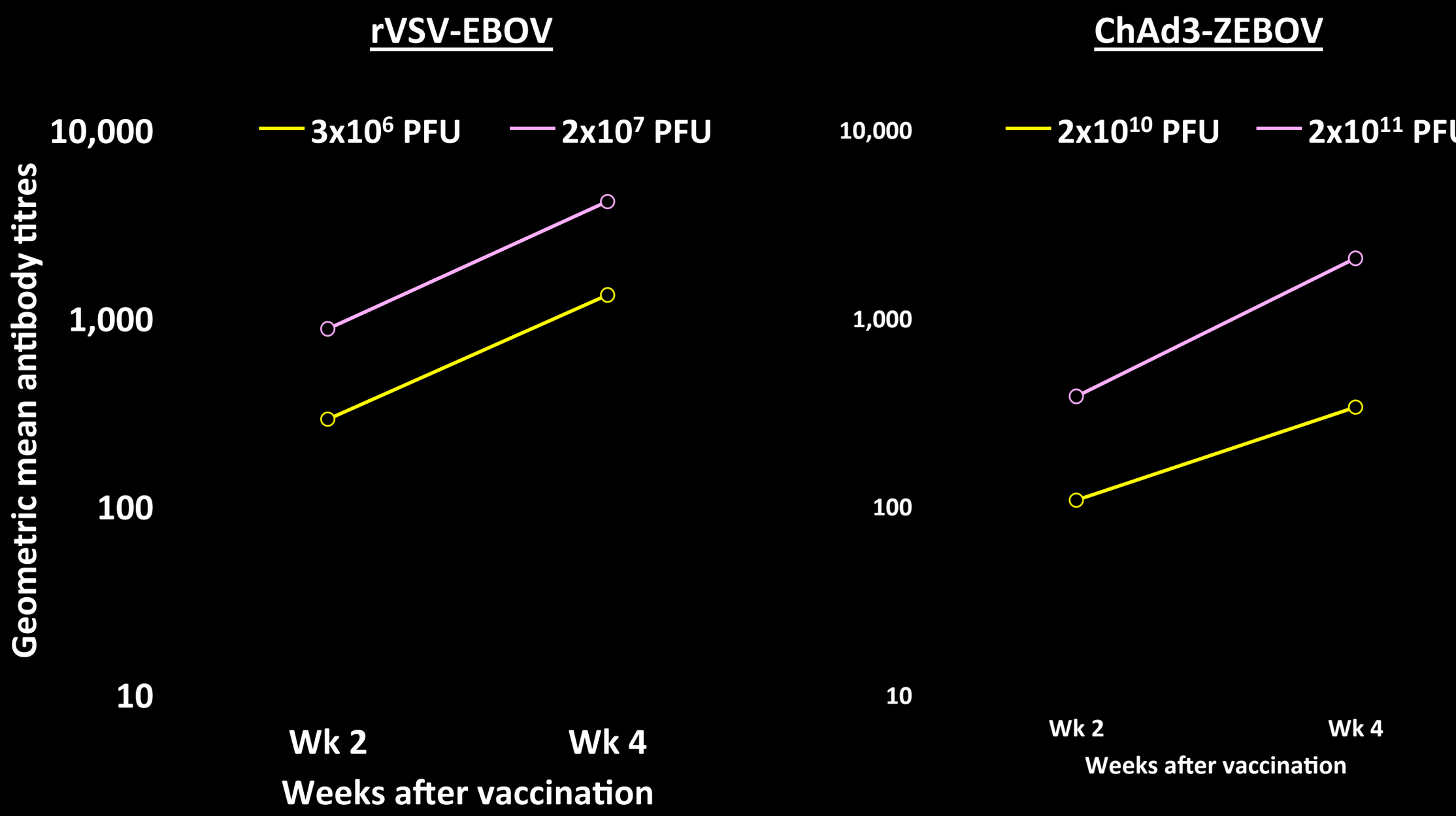
Anti-GP ELISA : model based GMTs versus observed GMTs

VRC ELISA, based on data available on March 4, 2015



* Predicted GMT = 1347.5. Titers of 967 to 6600 associated with full protection in cynomolgous macaques after vaccination with 2e10 vp dose (Stanley, Nat Med 2014). Similar to levels reported after a recombinant VSV vaccine (GMT 1429) (Regules, NEJM 2015).

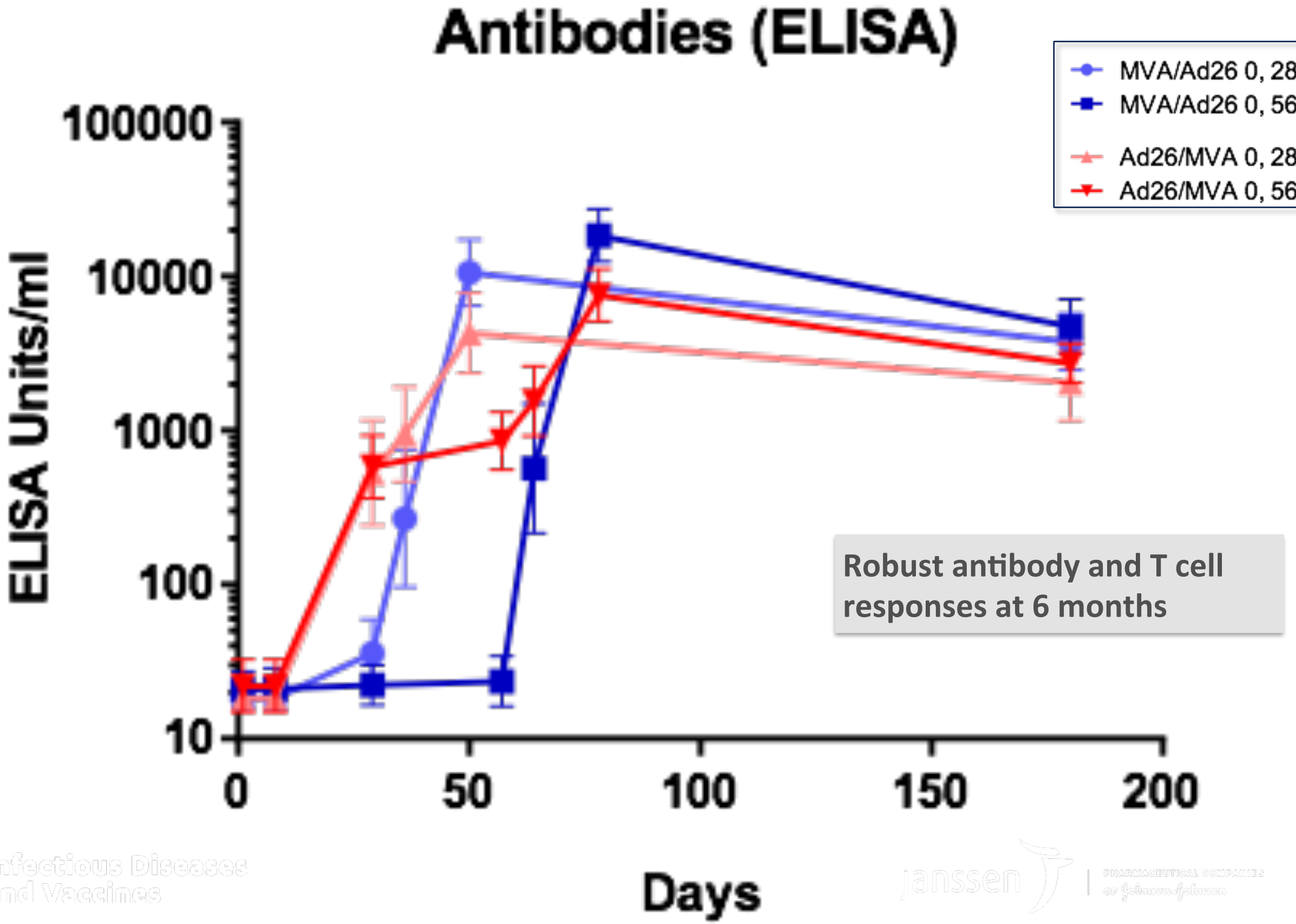
Immunogenicity appears to be dose-dependent



Note: Antibody titres are not comparable between trials.

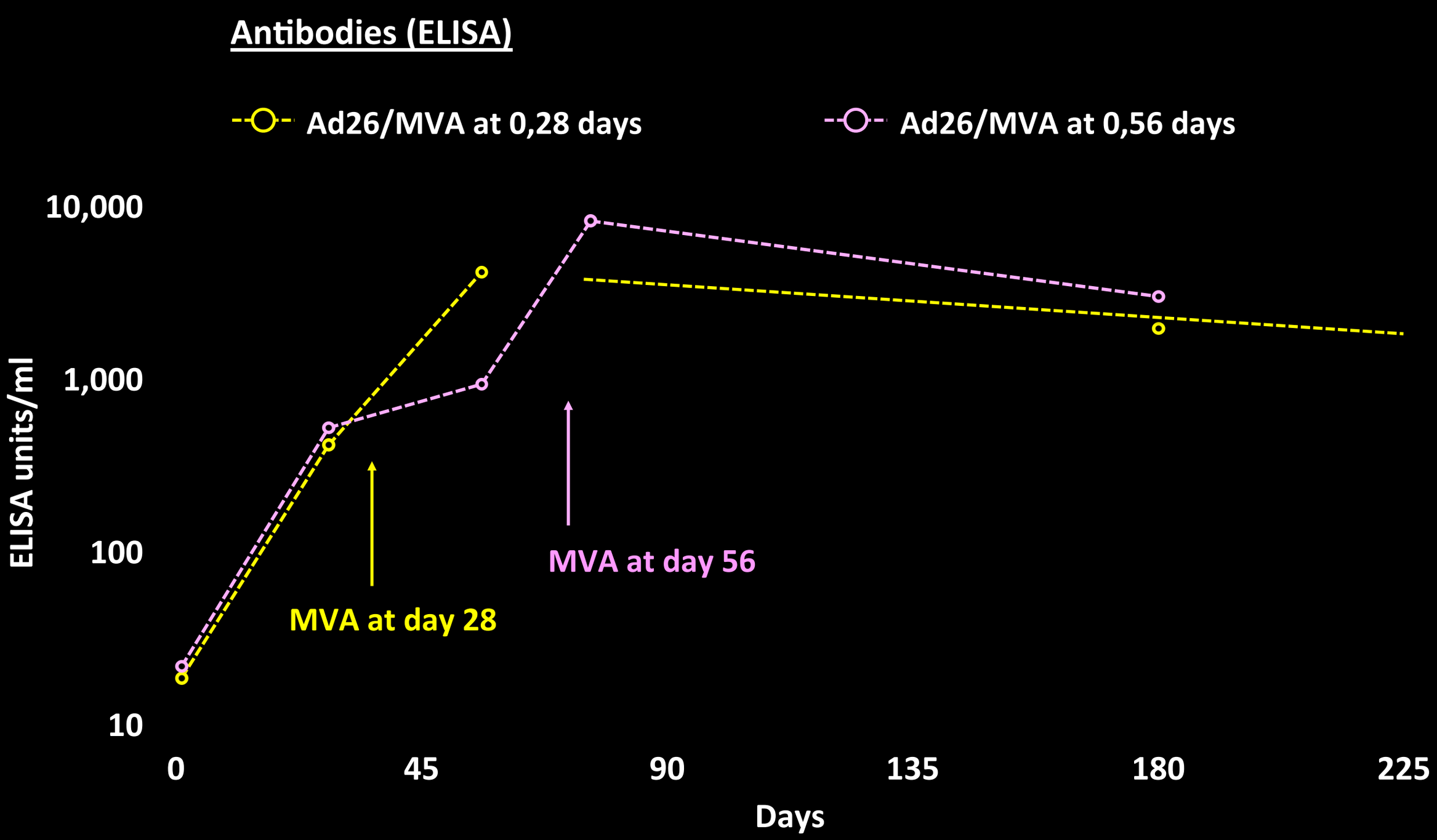
rVSV-EBOV: Regules et al., NEJM 2015 (1 Apr); ChAd3-ZEBOV : Ledgerwood et al., NEJM 2014 (26 Nov)

6-month evaluation of Ad26/MVA immune responses



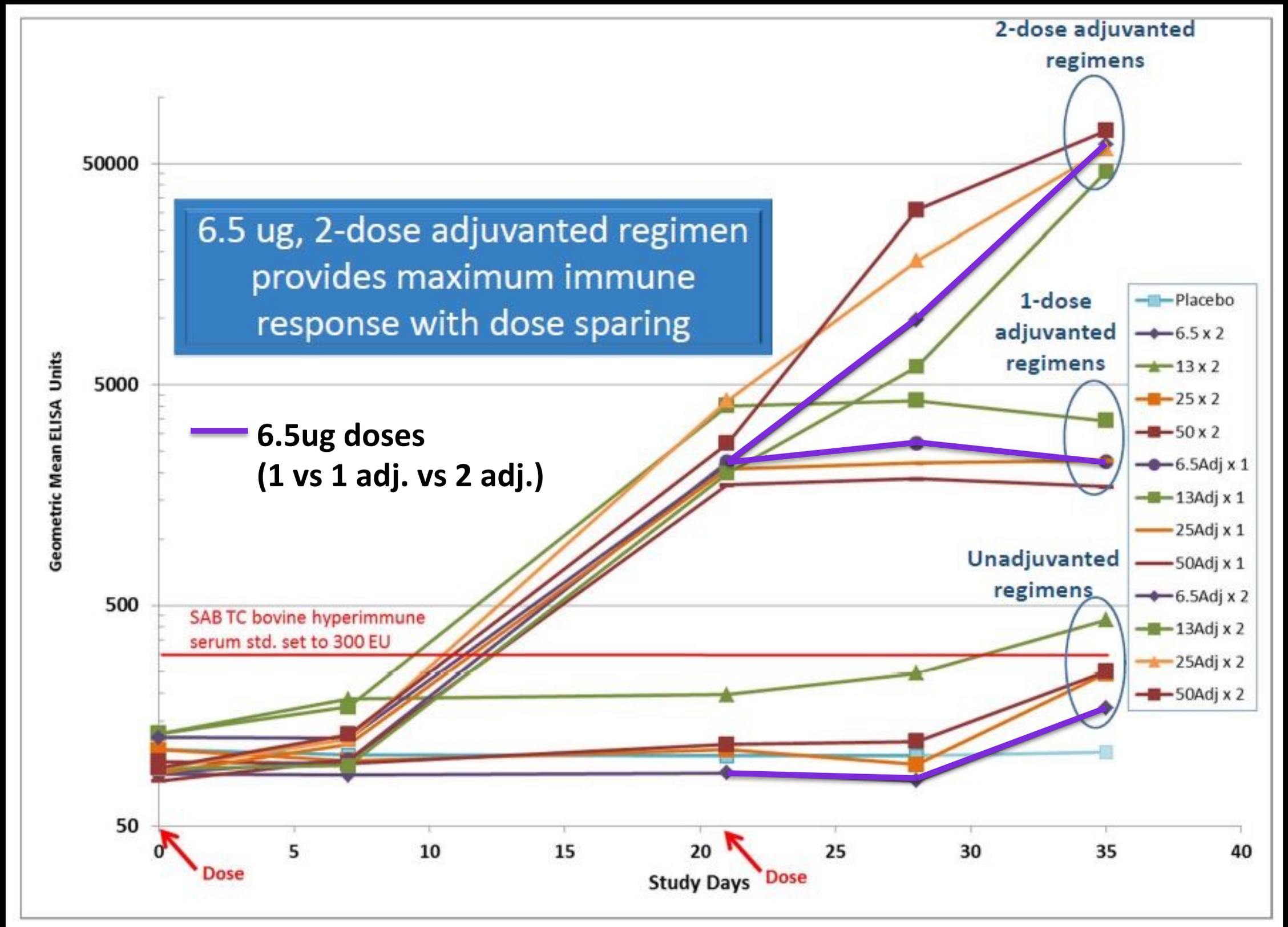
Robust antibody and T cell responses at 6 months

6-month evaluation of Ad26/MVA immune responses



Note: Preliminary results presented by Janssen Ebola Vaccine Program on 18 October 2015

Immunogenicity of Ebola/Makona GP nanoparticle vaccine



Safety results

Safety summary from ChAd3-ZEBOV

- No serious adverse events related to Ebola vaccine to date
- Trend for dose-related reactogenicity (injection site pain, feverishness, malaise) generally occurring within first 48 hours

- Transient minor reductions in lymphocytes and platelets (class effect seen with many live vaccines, including those based on adenovirus)

Safety Summary of rVSV-ZEBOV

No vaccine-related SAEs to date in all ongoing trials

Most AEs are consistent with acute “flu-like” symptoms

Arthralgia / arthritis cases reported in 2nd week post-vaccination frequency varying by site and study

- Transient and low-moderate severity events, not dose-dependent, and appear to be virally mediated
- Highest frequency reported at Geneva site (~20%)
- 0-10 % at other sites

Ebola vaccines - safety summary

No serious adverse events vaccine related

Reactive arthritis cases identified as an adverse event in Geneva VSV Phase 1 trial. Spontaneous resolution with good prognosis.

Safety data from Phase 1 studies of both ChAd3 and rVSV vaccines indicate an acceptable safety profile in healthy adults and children older than 5 years of age.

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 younger children and pregnant subjects.

Ongoing studies will provide additional experience in adults, and will allow more extensive assessment of safety.

Source : GACVS report June 2015

Ebola vaccine, Phase 3 trial, Guinea

on behalf of
Ebola ça suffit-essai clinique:
L’équipe de l’Essai du Vaccin

Design of a ring vaccination trial

Newly laboratory confirmed Ebola case

Definition of the ring: list of contacts and contacts of contacts

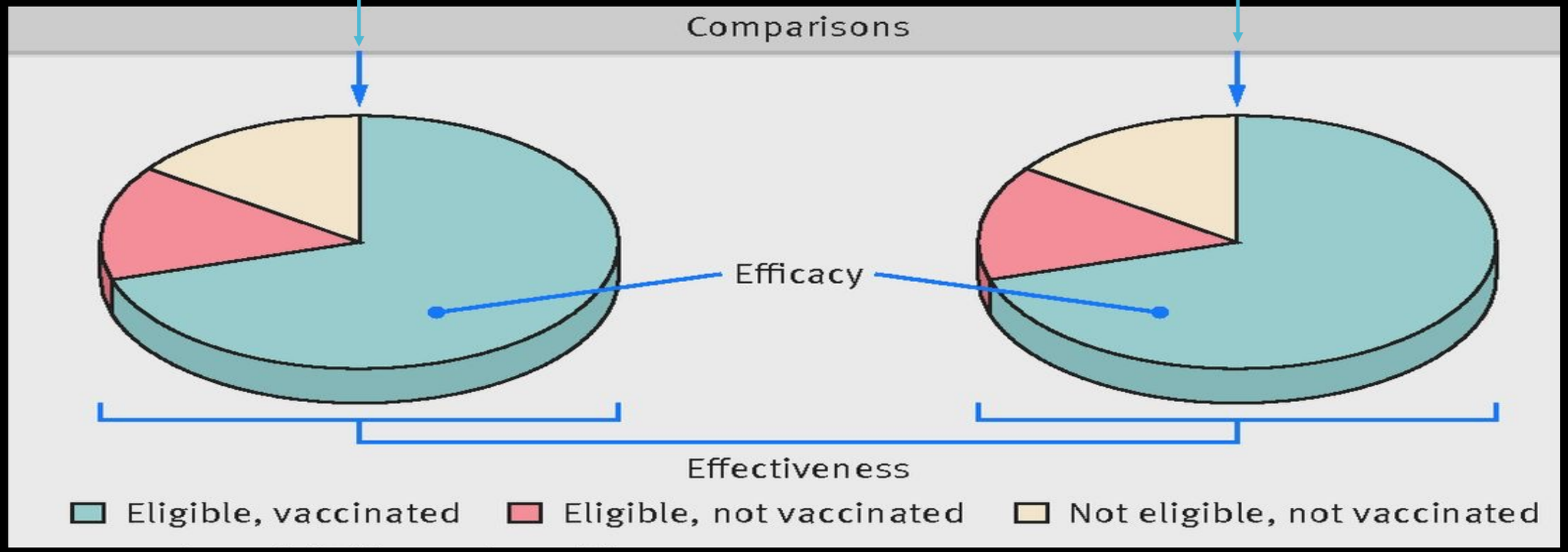
Random allocation of the ring

Immediate vaccination

Follow-up for outcomes

Immediate vaccination

Follow-up for outcomes



Ebola ça suffit ring vaccination trial consortium BMJ 2015;351:bmj.h3740

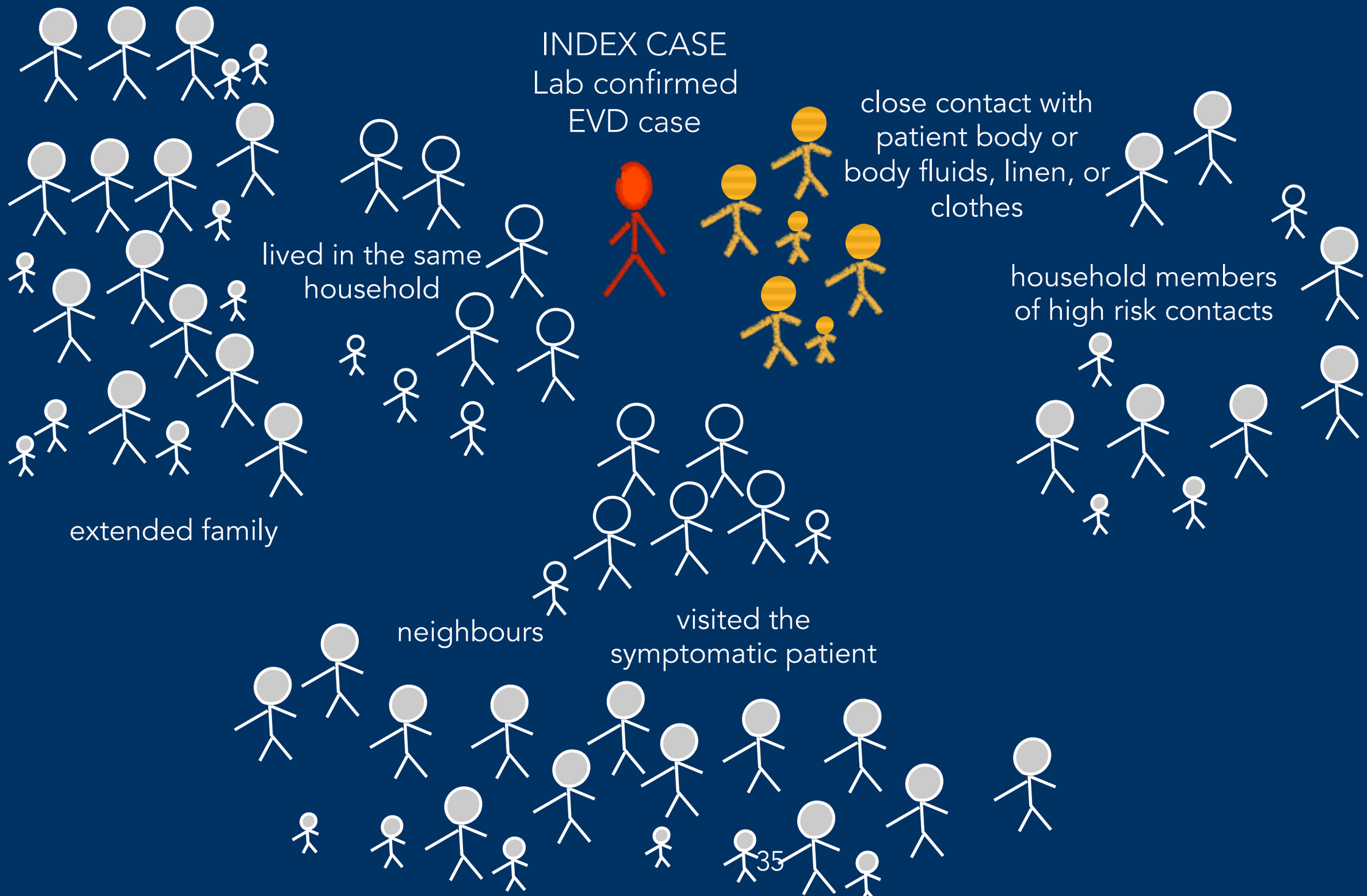
Each laboratory confirmed case of EVD is reported to the study team

Local social mobilisers explain the trial rationale and implications for participation

A list of contacts and contacts of contacts is prepared , often starting with the contact tracing list

What is a vaccination ring?

Contacts and contacts of contacts



The ring definition team calls the study headquarters and randomisation takes place

Vaccination is administered immediately or after

3 weeks as defined by randomisation outcome

Each participant receives an identification card

dates for follow - up visits

emergency phone numbers

reminder vaccine is experimental with unknown efficacy
need to maintain infection

prevention control measures

Participants are visited at home for follow up visits on days 3, 14, 21, 42, 63 and 84

In the ring vaccination trial, teams go to communities with a recently confirmed Ebola case

446 confirmed cases of Ebola virus disease

350 excluded
237 not considered for inclusion: distance too large, delayed reporting, inadequate capacity
84 already included in an existing cluster
10 negative attitude of community or other security issues
11 under consideration for new cluster
5 negative tests at reference laboratory
3 pilot clusters

96 clusters randomised

50 clusters allocated to immediate vaccination

46 clusters allocated to delayed vaccination

2 clusters (24 people) excluded from interim analysis (not yet entered into the database)

4 clusters (182 people) excluded from interim analysis (not yet entered into the database)

48 CLUSTERS IMMEDIATE
4123 contacts + contacts of contacts

42 CLUSTERS DELAYED
3528 contacts + contacts of contacts

1088 individuals ineligible for vaccination
981 aged <18 years
107 pregnant or breastfeeding

1148 individuals ineligible for vaccination
1081 aged <18 years
67 pregnant or breastfeeding

3035 individuals eligible for vaccination

2380 individuals eligible for vaccination

1021 not vaccinated
987 no consent given or absent
34 withdrew consent

882 not vaccinated
450 no consent given or absent
0 withdrew consent
212 consented but absent for vaccination
220 consented but not yet due for vaccination

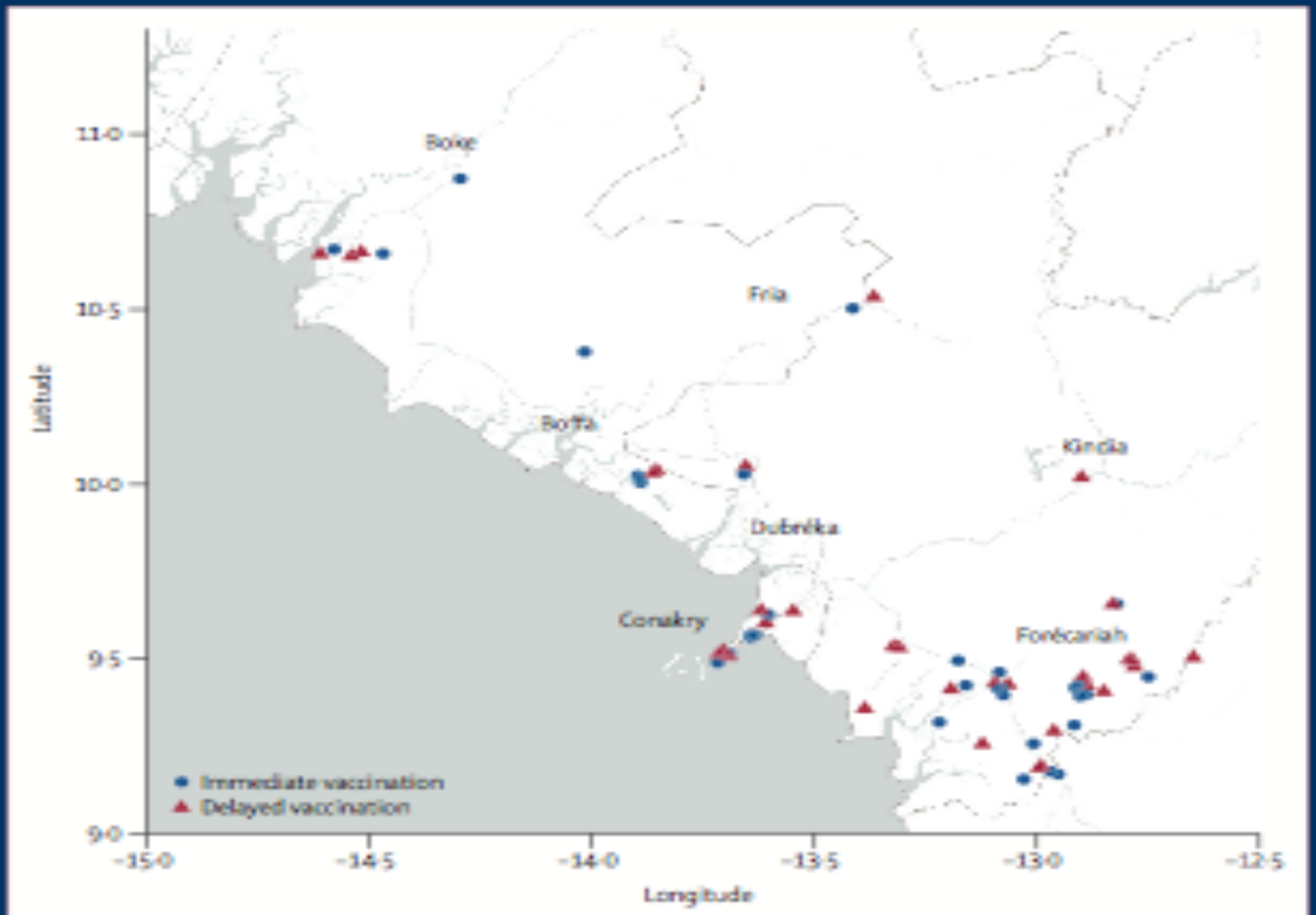
2014 individuals vaccinated

1498 individuals vaccinated

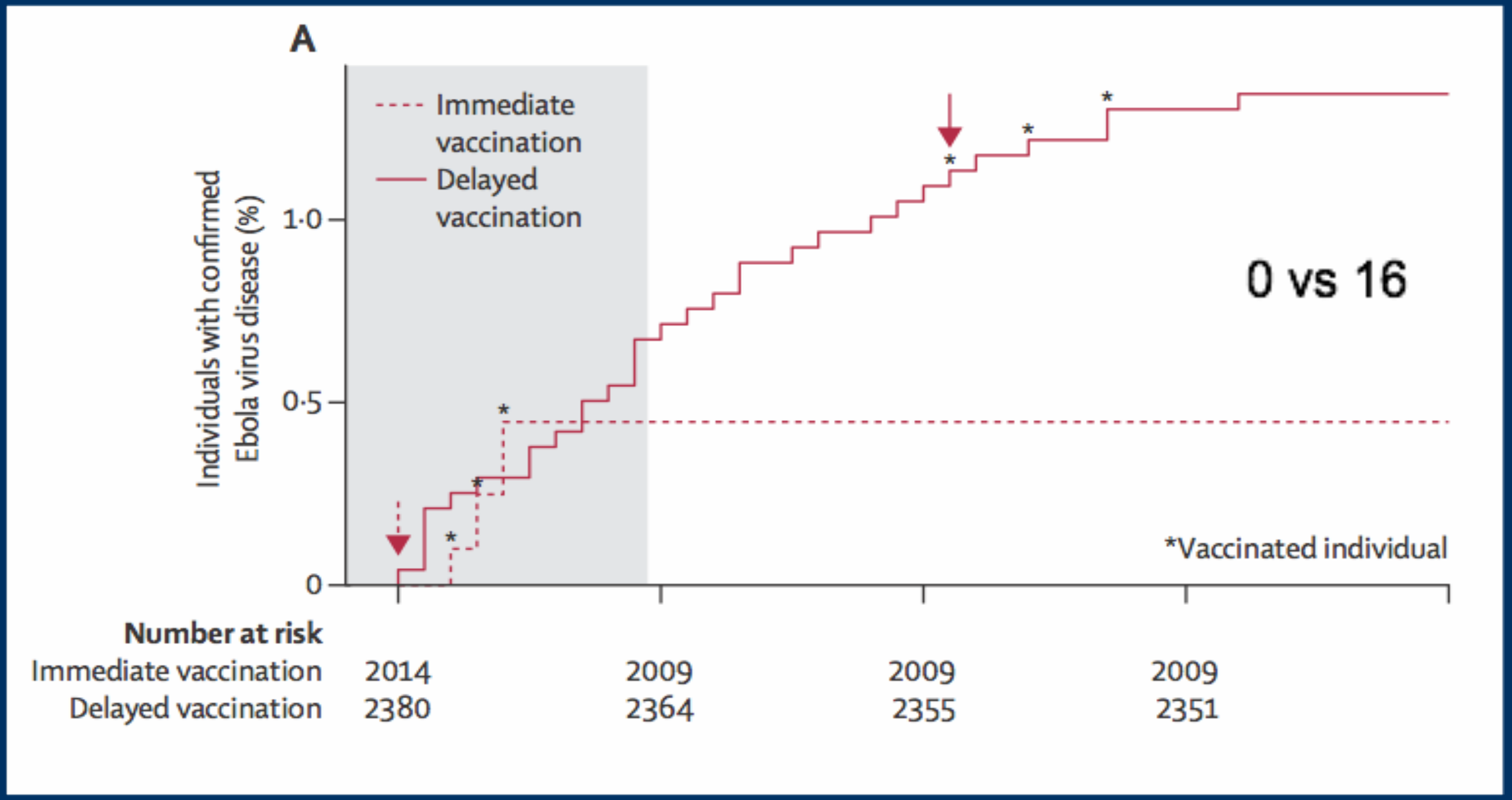
Individuals included in analyses:
2014 individuals who were vaccinated immediately
2048 individuals who were eligible and consented
3035 eligible individuals
4123 contacts and contacts of contacts

Individuals included in analyses:
1930 individuals who were eligible and consented
2380 eligible individuals
3528 contacts and contacts of contacts

Location of the rings



All vaccinated adults assigned to immediate vaccination versus all eligible individuals assigned to delayed vaccination



†Four cases were vaccinated and developed symptoms on day 0, 2, 6, 6

	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,

Plans and tools in preparation for Ebola vaccines deployment

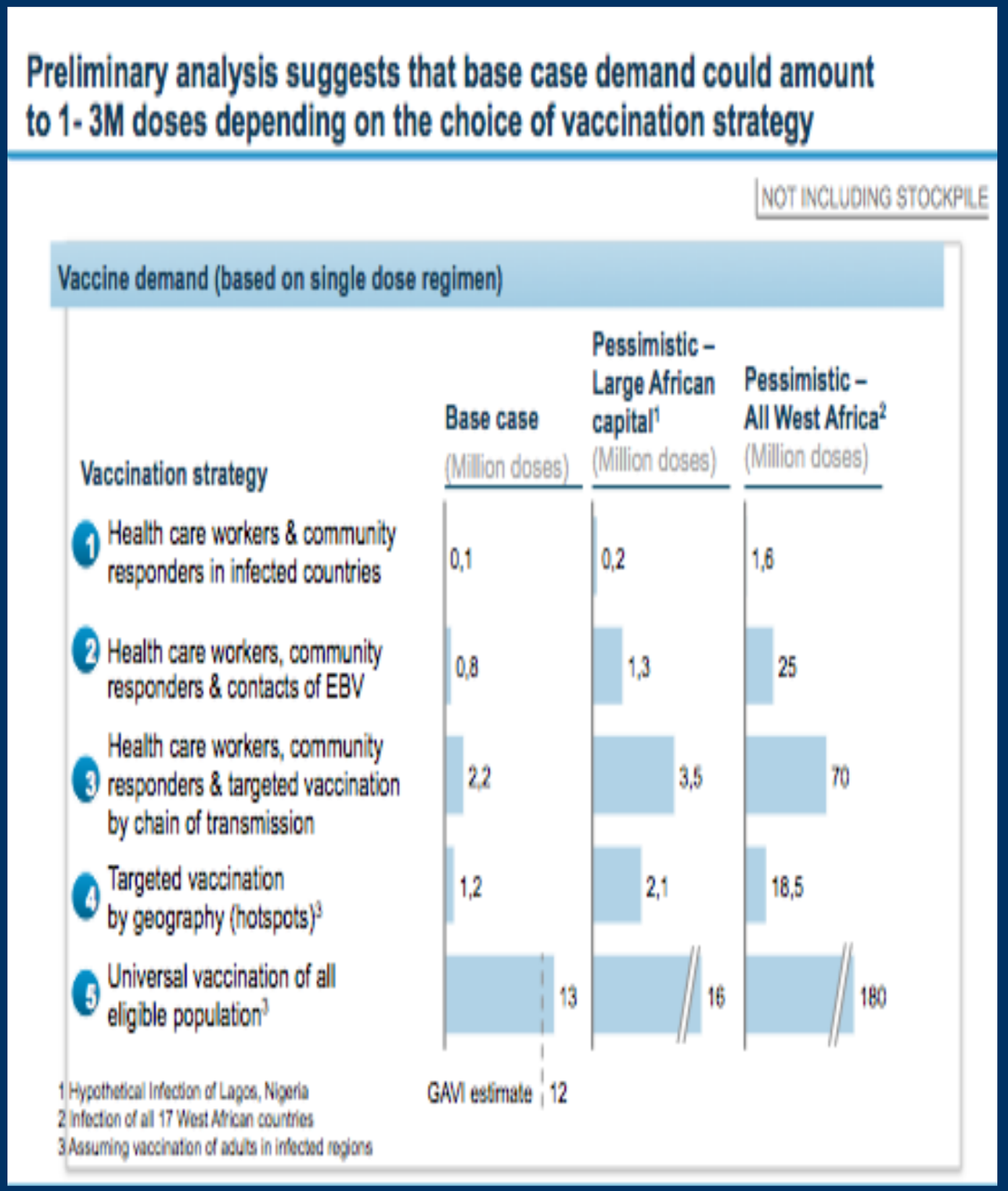
Significant progress in terms of vaccine supply, allocation and procurement

Models of supply capacity and timing of availability

Potential demand scenarios

An International Coordinating Group (ICG) for Ebola vaccine has been established

Vaccine procurement modalities



A guidance document for vaccination activities during this Ebola outbreak and as a response for future outbreaks of other infectious diseases

What does the guidance document include?

vaccines and vaccination strategies

overall planning for deployment including infection control measures

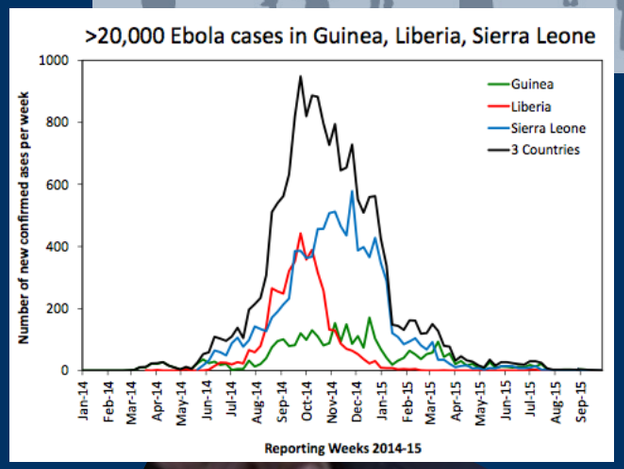
cold chain and logistics

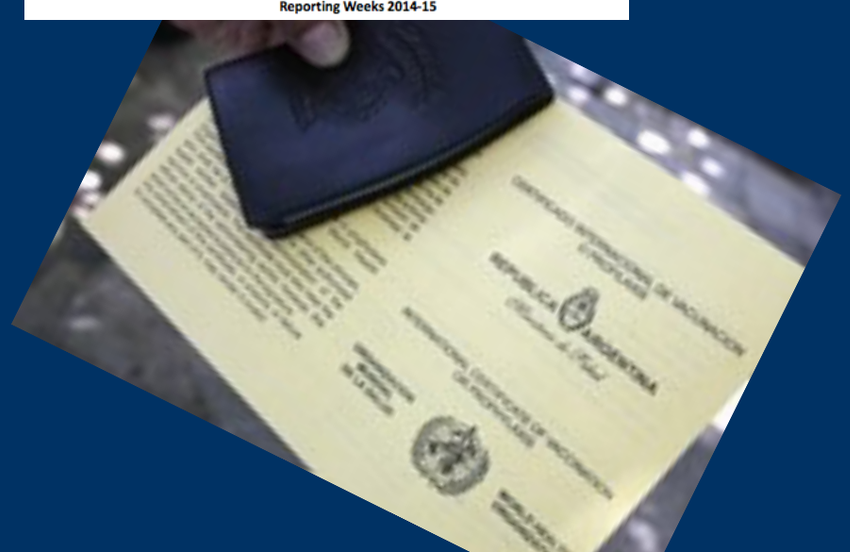
provision for ultra-cold temperature equipment and related power supply

shaping community engagement and risk communication strategies

building on experience from both the Ebola response and the vaccine trials

Guidance document for monitoring activities during vaccine deployment





What does the guidance document include?

monitoring and evaluation of the Ebola vaccination delivery strategy

evaluation of the impact of the vaccine use and potentially effectiveness

vaccine safety surveillance

Preparing for the deployment of vaccines
Next steps

A regional workshop to advance and integrate plans together with countries will be held after the **October 2015** meeting SAGE .

GEVIT will seek to reach **consensus on the documents and tools,** by **December 2015.**

Ebola vaccines

Next steps

Next steps

1. Complete the ongoing and planned trials

Additional information on safety, immunogenicity, efficacy and effectiveness will become available, including critical data on special populations

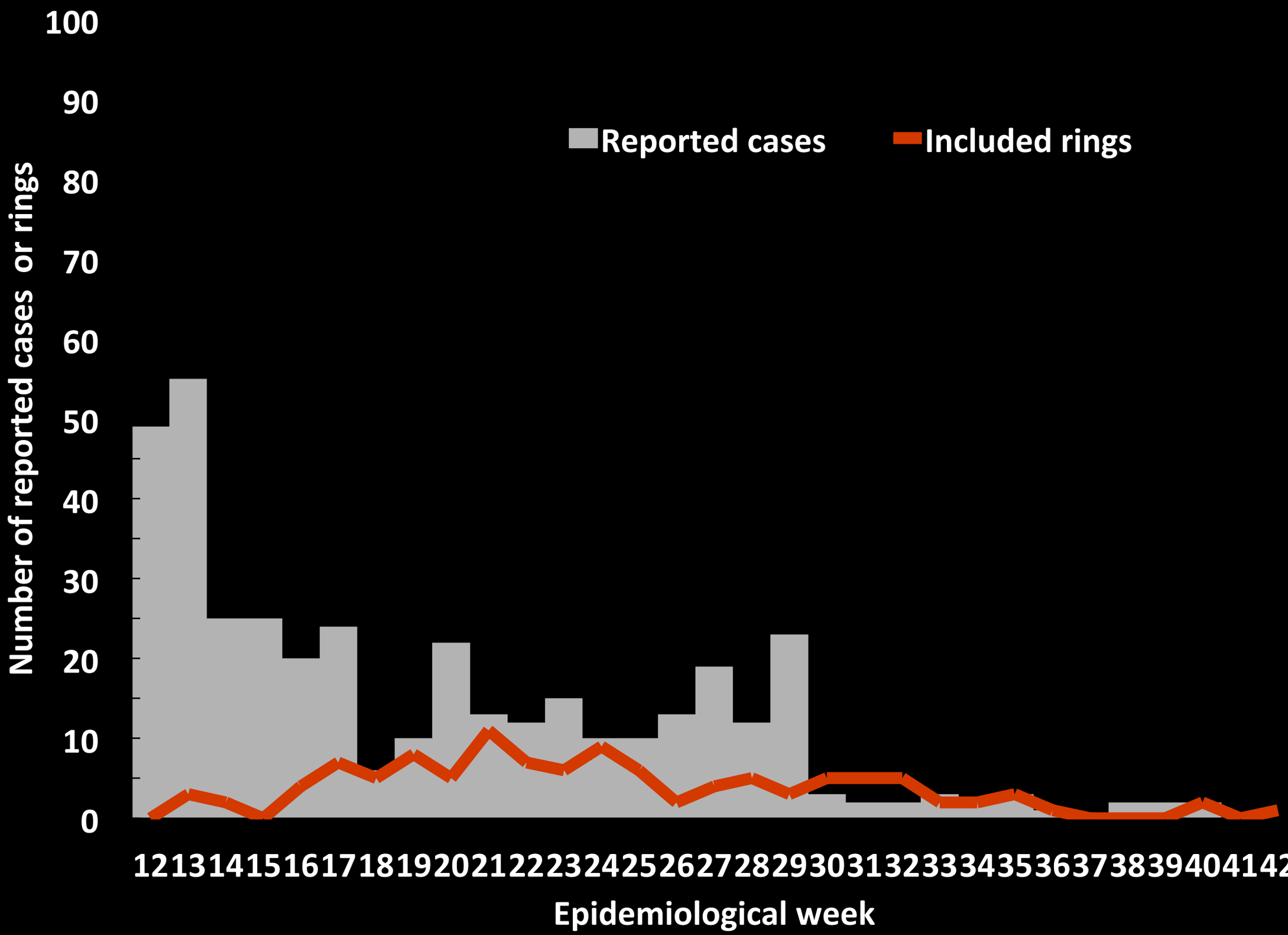
Next steps

2. The Phase III ring vaccination trial is continuing

Randomisation stopped on 26 July, 2015 to allow for all eligible contacts and contacts of contacts in the newly-defined rings to receive the vaccine immediately.
Ring vaccination trial extended to Sierra Leone

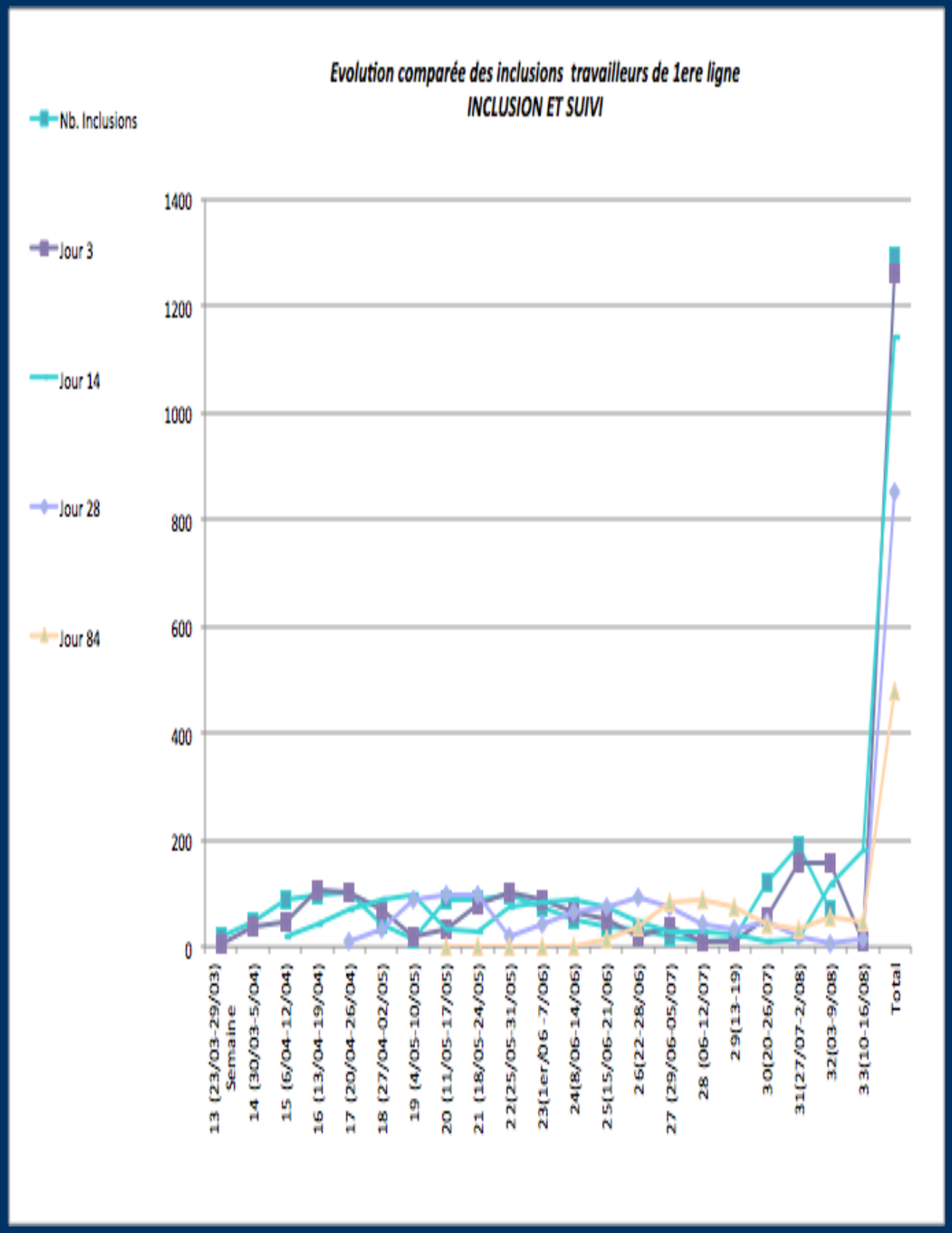
Children 6 years and older are eligible for the trial since September 2, 2015

Number of reported cases and ring included in Guinea



Next steps

3. MSF and WHO obtained an amendment of the 'front-line workers' study protocol i order to vaccinate 2,000 additional front-line workers in Guinea



Options being considered for potential access to rVSV outside clinical trials

1. Full regulatory approval
2. Emergency Use Authorization (EUA) by FDA or other NRA
3. Emergency Use Authorization Listing (EUAL) by WHO
4. Expanded access programme

The initiation of any regulatory review procedure is the role and responsibility of the vaccine manufacturer.

Implementation of any option to secure access to the rVSV vaccine requires:

- Vaccine availability
- Clarification on which regulatory path will be followed-up
- Preparation of required documentation for the NRA review.
- Setting up of processes for assuring human subject protections for all
- Examination of the evidence on populations at risk, potential vaccine impact, **risks and benefits** and definition of intended use

Ebola vaccines and vaccination

HTTP://WWW.THEGUARDIAN.COM/GLOBAL-DEVELOPMENT/GALLERY/2015/JUL/31/GUINEA-EBOLA-VACCINE-TRIAL-IN-PICTURES

Photos: SEAN HAWKEY