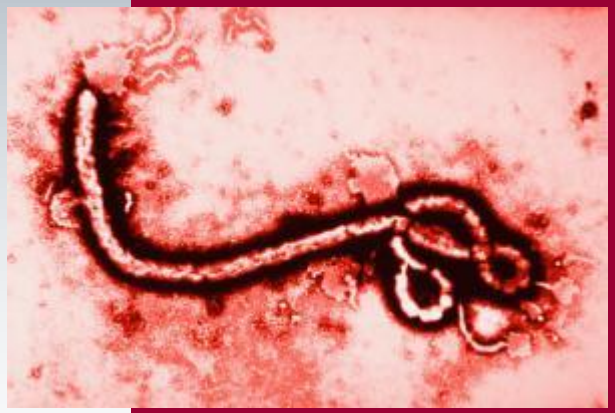

ATTENTION !
EBOLA !
Beaufort
UN
UN

Ebola Vaccines

Prof John McBride

James Cook University




VE DISTRICT #13
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FIRST RESPONDER
EMERGENCY MEDICAL SERVICES INC.

The Virus

- Family FILOVIRUS
  - Includes Marburg and genus Ebolavirus
  - 5 species – **Zaire, Sudan**, Tai Forest (Ivory Coast), Bundibugyo and Reston
  - Non segmented Single stranded –ve sense RNA
  - Similar to Paramyxoviruses and Rhabdoviruses

Host and Transmission

- Unknown maintainance host – bats suspected
- Marburg found in bats (eg Uganda cave)
- Most epidemics start after contact with infected animals (non human primates) – particularly in relation to their use as “bush meat”

Transmission

- Direct contact of broken skin or mucous membranes with virus containing fluids (blood, vomit, urine, faeces, semen, sweat)
- NOT aerosol
- Traditional washing/ handling of the dead
- Absent or misuse of protective equipment amongst HCWs

Pathogenesis

- Many target cells – but macrophages/ Dendritic cells initially
- Virus suppresses Interferon response
- Abundant release of cytokines and chemokines ➡ SIRS
- Tissue factor release ➡ Coagulation with D-dimer detection. Eventually Liver failure

Clinical

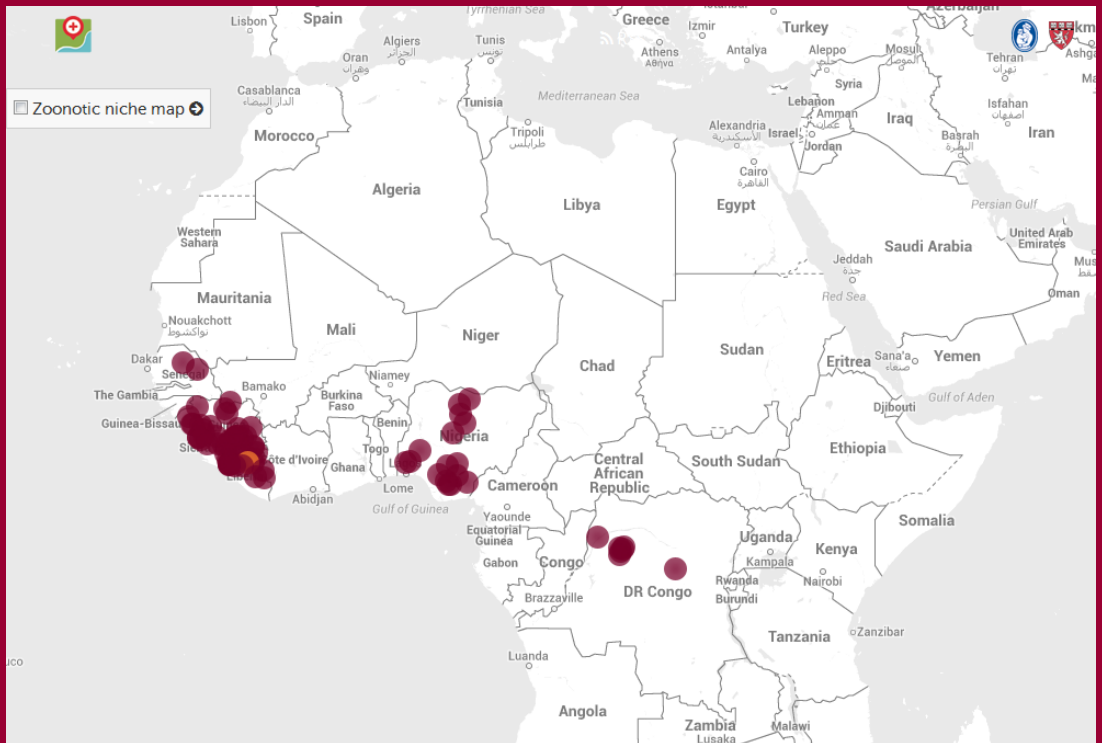
- Incubation 2-21 days. No contagion till symptomatic
- Fever, malaise, headache, backpain
- Rash common – erythematous
- Diarrhoea, nausea, vomiting
- Bleeding late in illness
- Hiccups somewhat characteristic

Laboratory

- Lymphopenia, leucopenia with immature forms
- Thrombocytopenia (50-100,00/uL)
- AST>ALT
- Prolonged APTT PT, increased FDPs
- Proteinuria
- Virus persists in semen up to 3 months (viable) – even 9 months (by PCR)

CS 252971

* As of July 18, 2015



http://healthmap.org/ebola/#timeline

28,633 cases
11,314 deaths

November 23

WEST AFRICA OUTBREAK *

United Kingdom 1 case

Spain 1 case

Guinea 3804 cases 2536 deaths

Sierra Leone 14122 cases 3955 deaths

Senegal 1 case

Mali 8 cases 6 deaths

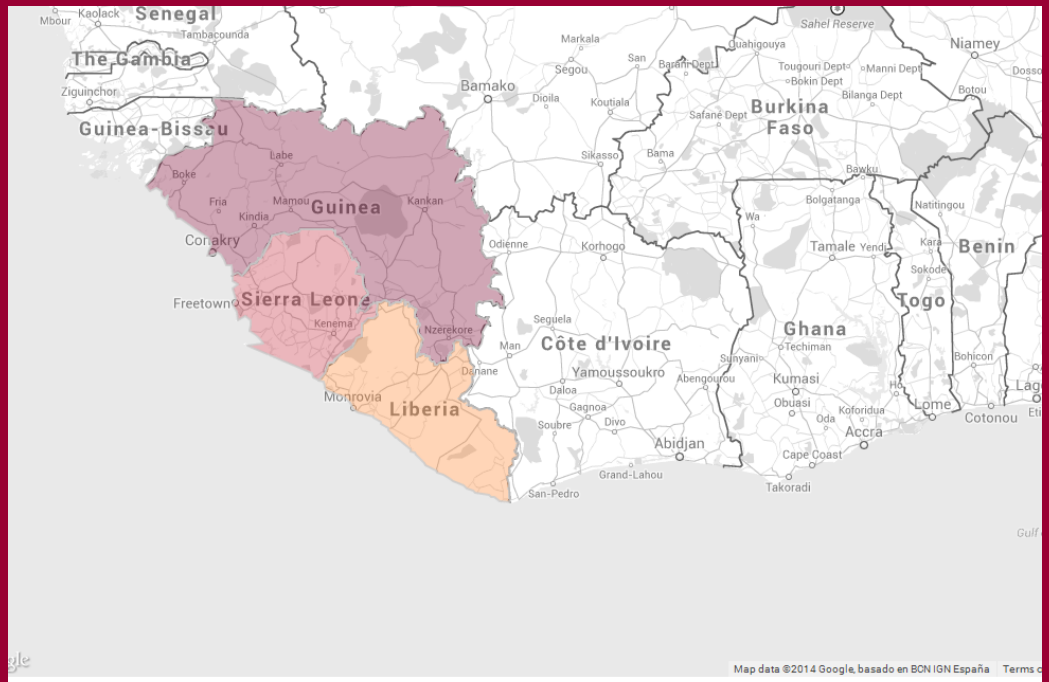
Liberia 10672 cases 4808 deaths

Nigeria 20 cases 8 deaths

United States 4 cases 1 death

DR CONGO OUTBREAK *

68 cases 41 deaths



TIMELINE | PROJECTION

Modeling Ebola in West Africa: Cumulative Cases by Date of Reporting

Modeling Method: IDEA (Fisman et al. 2013) | Generation Time: 18 days | Interpolation Method: Exponential | Data Source: WHO

Countries

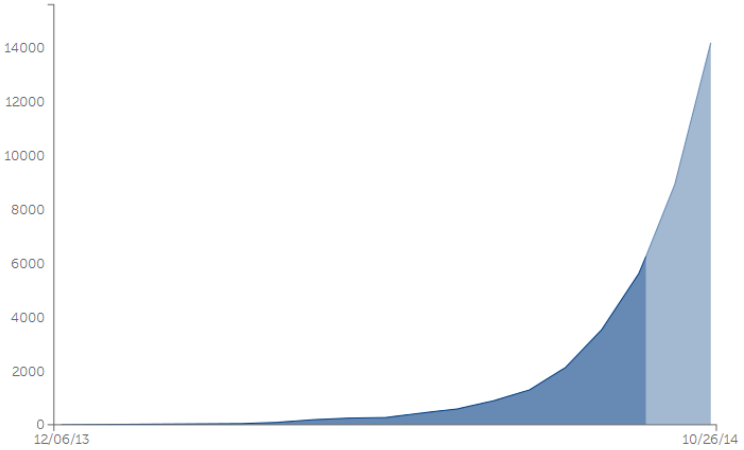
- ○ Guinea
- ○ Liberia
- ○ Sierra Leone
- ● All Affected Countries

Change in Control Efforts

- ● No Change
- ○ Deterioration in Control
- ○ Improved Control, Type 1
- ○ Improved Control, Type 2

Legend

The dark color shows real cases and the light color shows projected.



Treatment

- Mortality estimated 70%
- Supportive
- Immune serum – not as efficacious as reported
- Zmapp
- Some more experimental Rx – siRNA, polymerase inhibitor (BCX4430), GS-5734

Nicotiana benthamiana

Zmapp-macaques

Compound	Schedule (days post infection)	Survival
Zmapp 1	**3, 6, 9**	**6/6**
Zmapp 2	**3, 6, 9**	**5/6**
Control	**3, 6, 9**	**0/2**
ZMapp	**3, 6, 9**	**6/6**
ZMapp	**4,7,10**	**6/6**
ZMapp	**5,8,11**	**6/6**
Control	**4,7,10**	**0/3**

LB-2. Nucleotide Prodrug GS-5734 is a Broad-Spectrum Filovirus Inhibitor that Provides Complete Therapeutic Protection Against the Development of Ebola Virus Disease (EVD) in Infected Non-human Primates

Session: Oral Abstract Session: Late Breaker Oral Abstract Session
Saturday, October 10, 2015: 10:40 AM
Room: 7--AB

Background: The high case-fatality rate during the recent Ebola virus (EBOV) outbreak in West Africa is due in part to the lack of effective antiviral therapies. Antiviral screening against EBOV identified GS-5734, a prodrug of adenine nucleotide analog, as an inhibitor of pathogenic filoviruses.

Method: In vitro activity was tested in filovirus-infected human endothelial cells, liver cells, and macrophages using quantitative GFP expression, PCR, and/or immunostaining. Intracellular metabolism was determined by LC/MS/MS and polymerase (pol) inhibition was tested in biochemical assays. Efficacy was assessed in blinded, placebo-controlled studies in EBOV-infected rhesus monkeys. Animals infected on Day 0 (N= 6 per treatment group) were treated once-daily for 12 days by intramuscular (IM) or intravenous (IV) injection. Survival (Day 28 post infection), plasma viral RNA, and signs of Ebola virus disease (EVD) were monitored.

Result: GS-5734 inhibits Ebola virus (Kikwit and Makona variants), Sudan, and Marburg virus (EC_{50} = 0.01 to 0.20 μM), and exhibits low cytotoxicity (CC_{50} = 2 to > 20 μM) in multiple human cell types. The compound undergoes fast intracellular conversion to the nucleoside triphosphate metabolite that persists in cells ($T_{1/2}$ > 10 h) and inhibits a surrogate viral RNA pol from respiratory syncytial virus (IC_{50} = 1 μM), but not host mitochondrial RNA or DNA pols (IC_{50} > 200 μM). IM treatment of EBOV-infected monkeys with 3 mg/kg GS-5734 initiated after the detection of systemic viremia (Day 2 to 4) resulted in 50% survival compared to no survival in placebo-treated control animals ($P < 0.003$). Administration of 10 mg/kg GS-5734 IV initiated on Day 3 was associated with 100% survival, mean plasma viral RNA reduction of up to 5 $\log_{10}$ copies/mL relative to placebo ($P < 0.001$), and a profound suppression of EVD signs including thrombocytopenia, coagulopathy and serum chemistry alterations.

Conclusion: GS-5734 represents the first small-molecule antiviral agent that demonstrates robust therapeutic efficacy in a monkey model of EVD. Coupled with the potential for broad-spectrum anti-filovirus activity, further development of GS-5734 for the treatment of EBOV and other hemorrhagic filovirus infections is warranted.

ZEBOV

ChAd3

The winding road to an Ebola vaccine

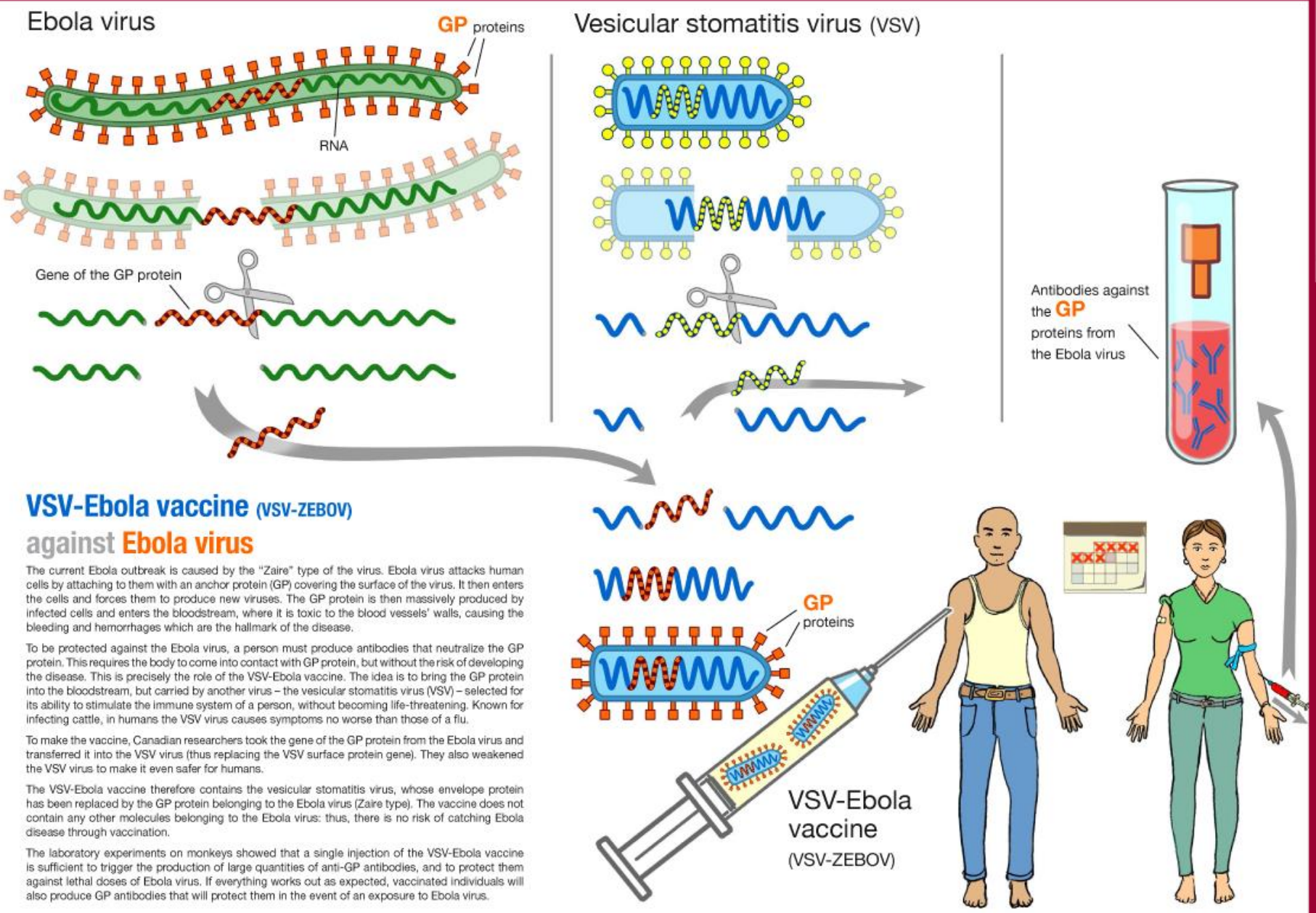
These phase II and phase III trials may yield additional information needed for regulatory approval.

VACCINES/LOCATION	TARGET ENROLLMENT	START DATE	DESIGN	STATUS
Merck, GSK/Liberia	27,000 in general population	February 2015	Randomized controlled with placebo arm	Stopped at 1500. Blood collection continues
Merck/Sierra Leone	8700+ front-line workers	April 2015	Immediate versus deferred	Immediate arm vaccinated, deferred in fall
Merck/Guinea	190 clusters of potential contacts	April 2015	Ring vaccination, immediate versus deferred	Control arm halted after analysis of first 90 clusters, all offered vaccine
Merck/Guinea	1200 frontline workers	March 2015	Safety and immune responses	May add 2000 more
GSK/Mali, Senegal, Ghana, Cameroon, Nigeria	3000 adults	June 2015	Safety and immune responses	Plan to add 600 children in October

ZEBOV

- Recombinant Vesicular Stomatitis Virus with surface Gp ZEBOV – 1 dose
- Cluster randomized contacts – immediate vs delayed- 21 days (2014 vs 1498 vaccinated)
- 0 vs 16 cases
- 100% vaccine efficacy
- Delayed vaccination now ceased
- Only 1 SAE (fever)

http://dx.doi.org/10.1016/S0140-6736(15)61117-5



VSV-Ebola vaccine (VSV-ZEBOV) against Ebola virus

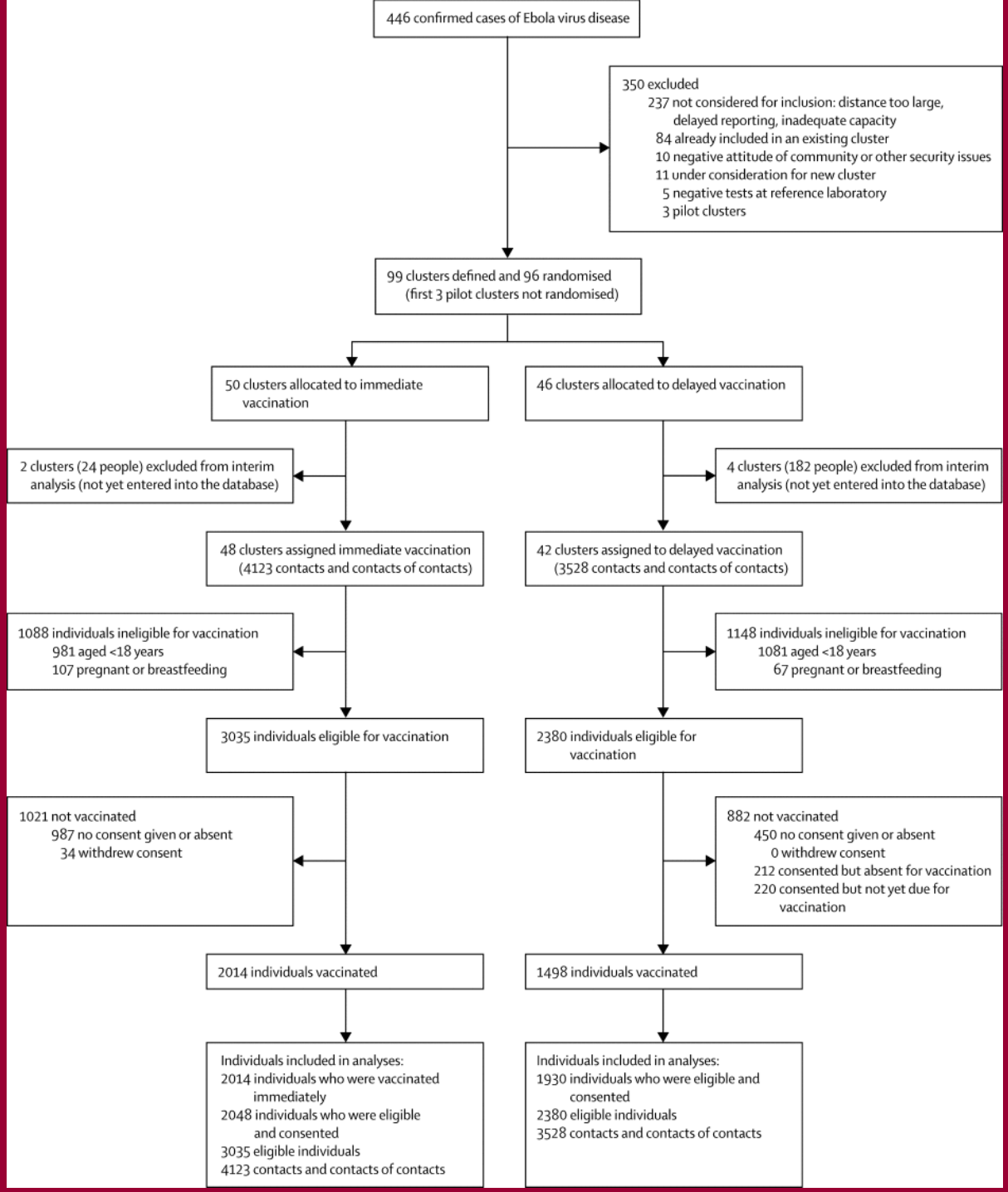
The current Ebola outbreak is caused by the "Zaire" type of the virus. Ebola virus attacks human cells by attaching to them with an anchor protein (GP) covering the surface of the virus. It then enters the cells and forces them to produce new viruses. The GP protein is then massively produced by infected cells and enters the bloodstream, where it is toxic to the blood vessels' walls, causing the bleeding and hemorrhages which are the hallmark of the disease.

To be protected against the Ebola virus, a person must produce antibodies that neutralize the GP protein. This requires the body to come into contact with GP protein, but without the risk of developing the disease. This is precisely the role of the VSV-Ebola vaccine. The idea is to bring the GP protein into the bloodstream, but carried by another virus – the vesicular stomatitis virus (VSV) – selected for its ability to stimulate the immune system of a person, without becoming life-threatening. Known for infecting cattle, in humans the VSV virus causes symptoms no worse than those of a flu.

To make the vaccine, Canadian researchers took the gene of the GP protein from the Ebola virus and transferred it into the VSV virus (thus replacing the VSV surface protein gene). They also weakened the VSV virus to make it even safer for humans.

The VSV-Ebola vaccine therefore contains the vesicular stomatitis virus, whose envelope protein has been replaced by the GP protein belonging to the Ebola virus (Zaire type). The vaccine does not contain any other molecules belonging to the Ebola virus: thus, there is no risk of catching Ebola disease through vaccination.

The laboratory experiments on monkeys showed that a single injection of the VSV-Ebola vaccine is sufficient to trigger the production of large quantities of anti-GP antibodies, and to protect them against lethal doses of Ebola virus. If everything works out as expected, vaccinated individuals will also produce GP antibodies that will protect them in the event of an exposure to Ebola virus.


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
99 clusters defined and 96 randomised (first 3 pilot clusters not 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 assigned immediate vaccination (4123 contacts and contacts of contacts)
42 clusters assigned to delayed vaccination (3528 contacts and 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

Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial

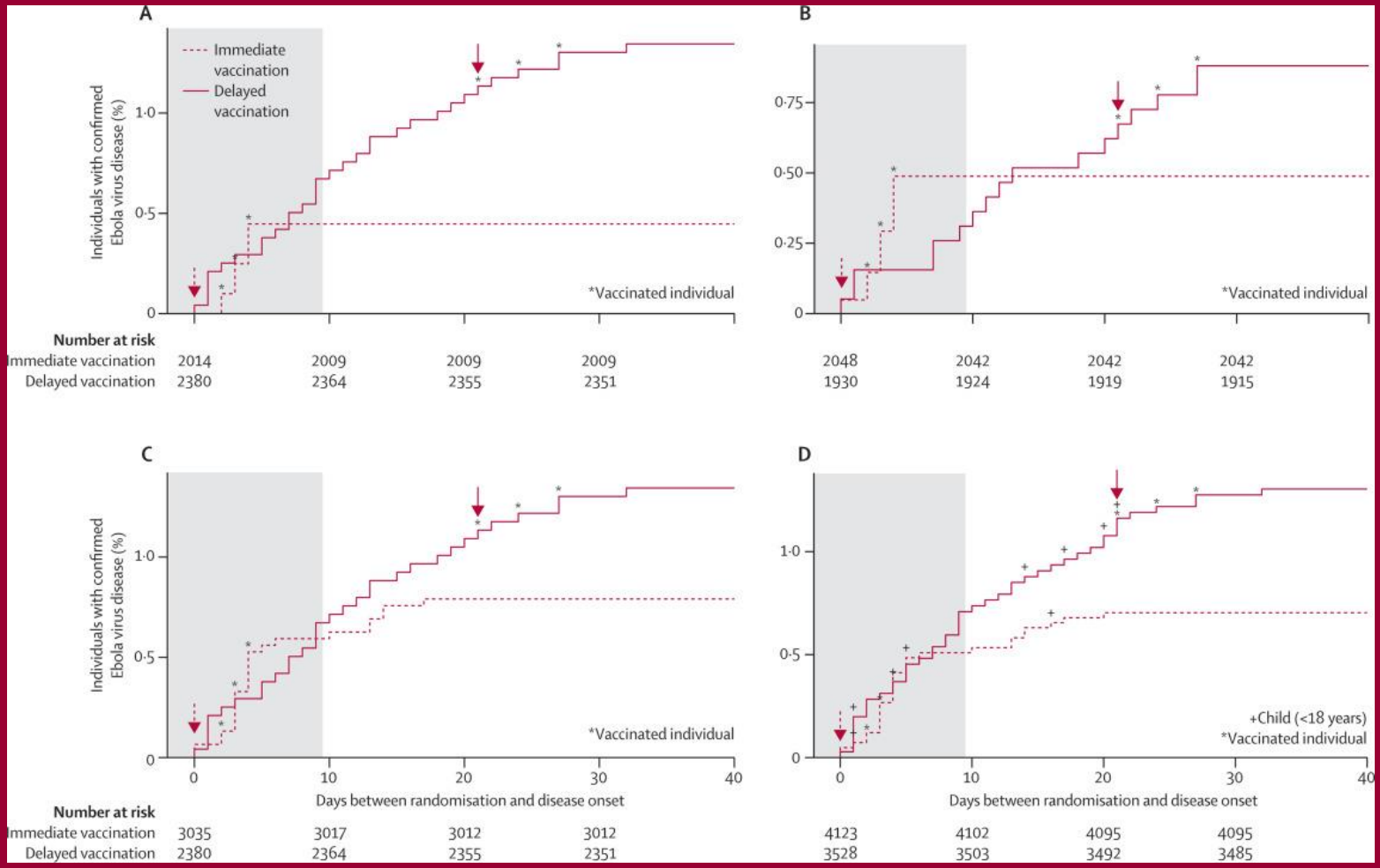
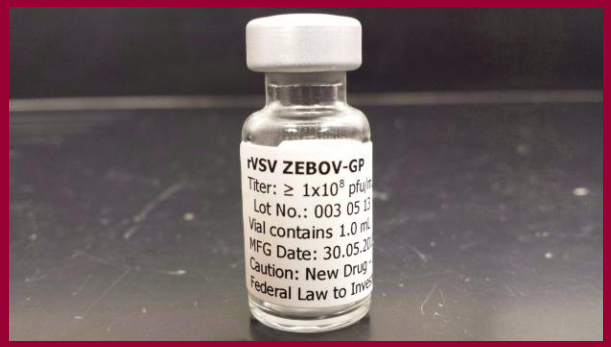


Figure 3. Kaplan-Meier plots of the cumulative incidence of confirmed Ebola virus disease in different study populations (A) All vaccinated individuals assigned to immediate vaccination versus all eligible individuals assigned to delayed vaccination (primary analysis). (B) All eligible and consenting individuals. (C) All eligible individuals. (D) All individuals. Arrows indicate immediate (day 0) and delayed (day 21) vaccination. The shaded area shows the period excluded from analyses

http://dx.doi.org/10.1016/S0140-6736(15)61117-5

ZEBOV issues

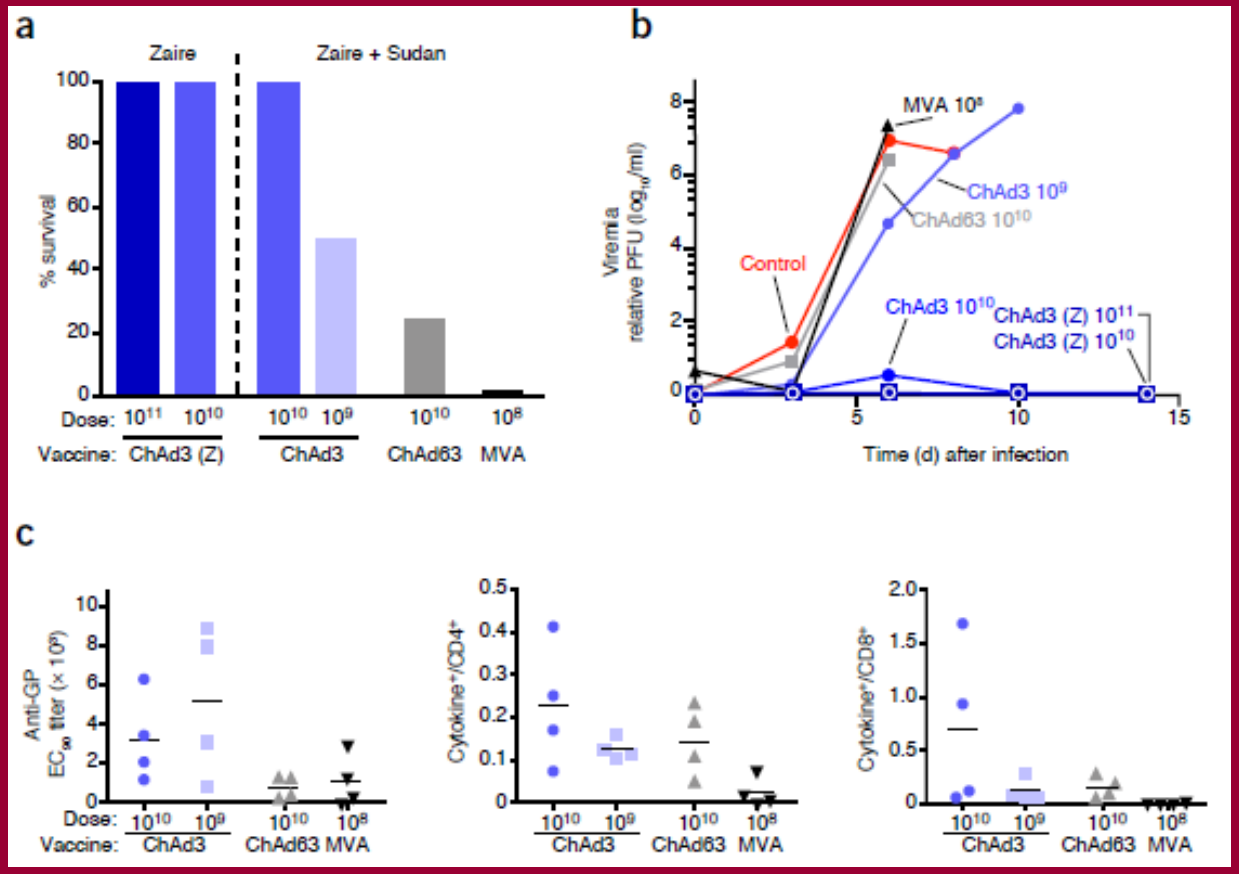


- Storage and transport at -80C
- Although only 1 SAE attributed to vaccine (fever):
- Swiss volunteer study – 13/51 had delayed (day 10) reactive arthritis, 7 with rash[1].
- In a US study – no SAE's but around 25% had gr1/2 arthralgia – 1 had mild delayed arthralgia[2]

1. http://dx.doi.org/10.1016/S1473-3099(15)00154-1
2. http://dx.doi.org/**10.1056/NEJMoa1414216**

Vaccine

- Recombinant chimpanzee adenovirus expressing ebolavirus glycoprotein (ChAd-3)



Challenge occurred 5 weeks post vax, At 10 months best response was 50% So – single shot does not give durable protection

http://dx.doi.org/10.1038/nm.3702

2 dose schedule

- Different boosting strategies used – including use of Modified vaccinia Ankara (MVA)

Table 1 Durable vaccine protection against EBOV

Vector	Dose (PU)		Protection[a]
Single shot			
ChAd3	1×10^{11}	2/4	50%
ChAd3	1×10^{10}	0/4	0%
Prime-boost			
ChAd3/ChAd3	$1 \times 10^{10}/1 \times 10^{10}$	1/3	33%
ChAd3/ChAd63	$1 \times 10^{10}/1 \times 10^{10}$	1/4	25%
ChAd3/MVA	$1 \times 10^{10}/1 \times 10^{8}$	4/4	100%

Animals in single-shot groups were vaccinated with ChAd3 at the doses indicated and exposed to a lethal dose of EBOV 10 months after the prime vaccination. Animals in prime-boost groups were primed with ChAd3, boosted 8 weeks later and exposed to a lethal dose of EBOV as in the single-shot groups.

Use of ChAd3-EBO-Z Ebola virus vaccine in Malian and US adults, and boosting of Malian adults with MVA-BN-Filo: a phase 1, single-blind, randomised trial, a phase 1b, open-label and double-blind, dose-escalation trial, and a nested, randomised, double-blind, placebo-controlled trial

Lancet Infect Dis 2015

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November 3, 2015
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See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(15)00408-9

*Contributed equally

Interpretation 1×10^{11} pu single-dose ChAd3-EBO-Z could suffice for phase 3 efficacy trials of ring-vaccination containment needing short-term, high-level protection to interrupt transmission. MVA-BN-Filo boosting, although a complex regimen, could confer long-lived protection if needed (eg, for health-care workers).

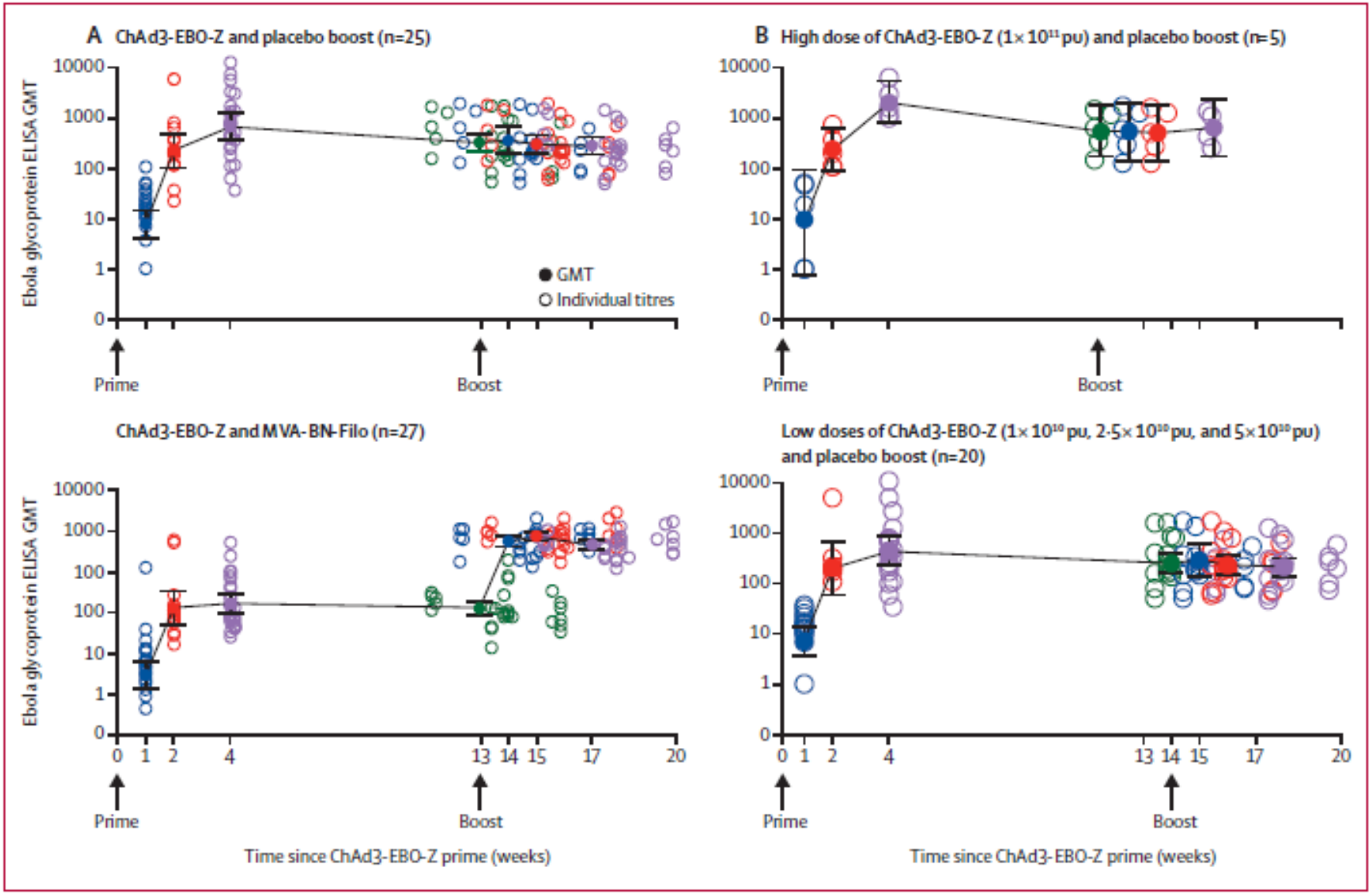

Figure 2: **Anti-Zaire Ebola virus glycoprotein ELISA titres (background subtracted) for the Malian participants in the nested MVA-BN-Filo booster trial**

- Titres>1:1000 in 91% after 10^{11} Chad3

Safety

- 1 unrelated SAE
- Nearly all AE's were mild – fatigue and headache most common.
- Temp >38.5C in 3/111 of Chad3 recipients and 0/52 in MVA recipients

- “Bavarian Nordic (Martinsried, Germany) provided 30 scarce doses of MVA-BN-Filo (which expresses Zaire Ebola virus and Sudan Ebola virus glycoproteins and other filovirus proteins)”.

FDA thinking

- Approval under the "animal rule" (21 CFR 601.90/91/92) may be considered for products for certain serious or life-threatening conditions when definitive human efficacy studies are not ethical or feasible ….. This regulation permits FDA to license vaccines based on adequate and well controlled animal studies when the results of those animal studies establish that the vaccine is ***reasonably likely*** to produce clinical benefit in humans, provided that safety in humans has been established.

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Dispatch

Effectiveness of Ring Vaccination as Control Strategy for Ebola Virus Disease

Adam J. Kucharski, Rosalind M. Eggo, Conall H. Watson, Anton Camacho, Sebastian Funk, and W. John Edmunds

Author affiliations: London School of Hygiene and Tropical Medicine, London, UK

Suggested citation for this article

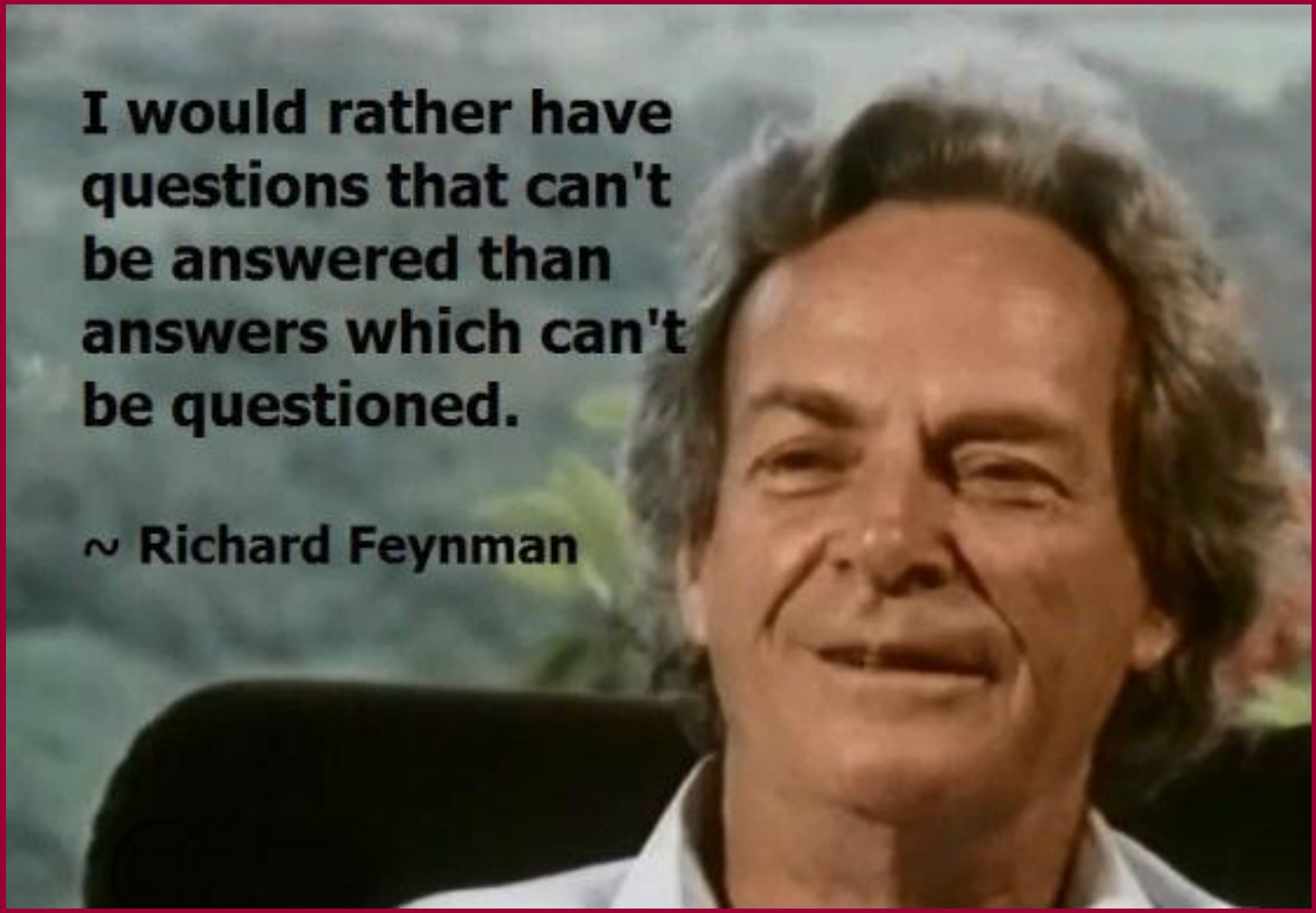
Abstract

Using an Ebola virus disease transmission model, we found that addition of ring vaccination at the outset of the West Africa epidemic might not have led to containment of this disease. However, in later stages of the epidemic or outbreaks with less intense transmission or more effective control, this strategy could help eliminate the disease.

Interesting facts and resources

- "We believe that Ebola virus has killed probably tens of thousands of Great Apes in the past 20 to 30 years in Central Africa" (about 1/3 world's Gorilla population)
- Great apes-fruit-bats & Faeces as monitoring tool
- http://www.voanews.com/content/ebola-great-apes-24sept14/2460717.html


"THANK
YOU
SCIENCE!"


I would rather have questions that can't be answered than answers which can't be questioned.
~ Richard Feynman