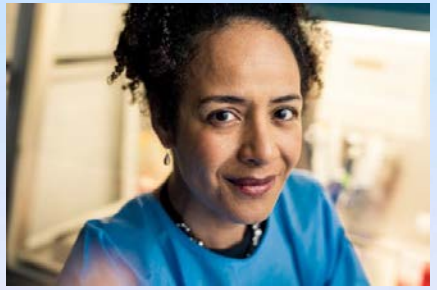
Zentrum für Innere Medizin I, Infektiologie, Emerging Infections



Berthold Fabricius

Prof. Dr. Marylyn Addo

25th Annual AGAH Meeting Berlin. April 2016

Experience of vaccine development against Ebola virus

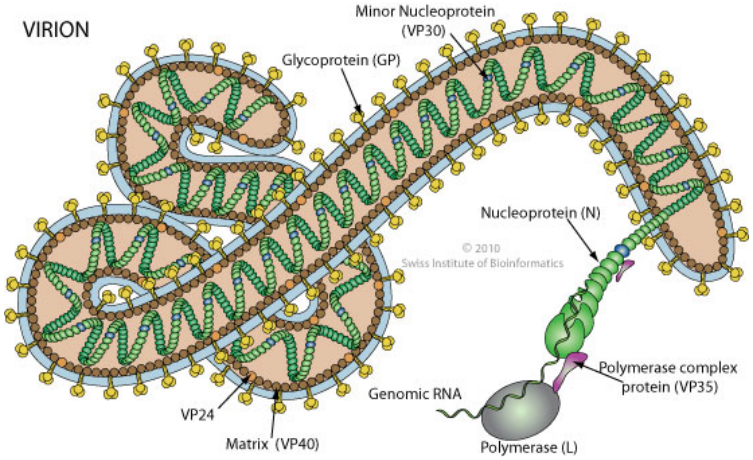
Dr. Christine Dahlke

German Center for Infection Research
TTU Emerging Infections

Universitätsklinikum Hamburg-Eppendorf

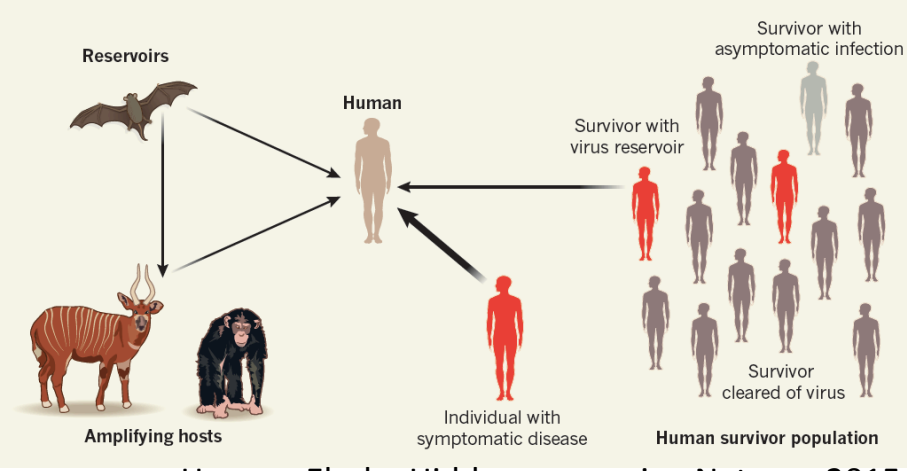
Ebola Virus

- Filovirus
- Small RNA genome
- Five Ebola virus species
  - *Association with diseases*
    - Zaire Ebola virus (ZEBOV / EBOV)
    - Sudan Ebola virus (SEBOV)
    - Bundibugyo Ebola virus
  - *No association with diseases*
    - Reston Ebola viurs
    - Tai Forest Ebola virus



Transmission

- Natural reservoir host & transmission routes are not identified.

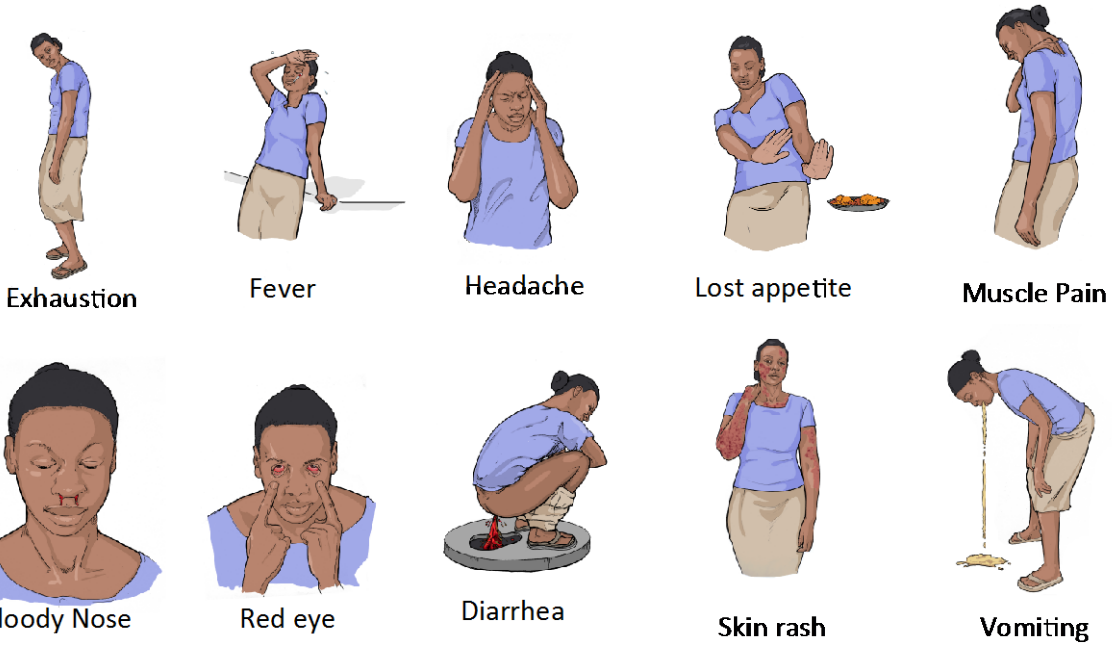


Heeney;Ebola: Hidden reservoirs, Nature, 2015

- Hypothesis:
  - Fruit bats are natural reservoir
  - Spillover Event:
    - First patient becomes infected through contact with infected animal.
- Human-to-human transmission: through direct contact.

Ebola Virus Disease

Symptoms can appear from 2 to 21 days after exposure



Source: CDC

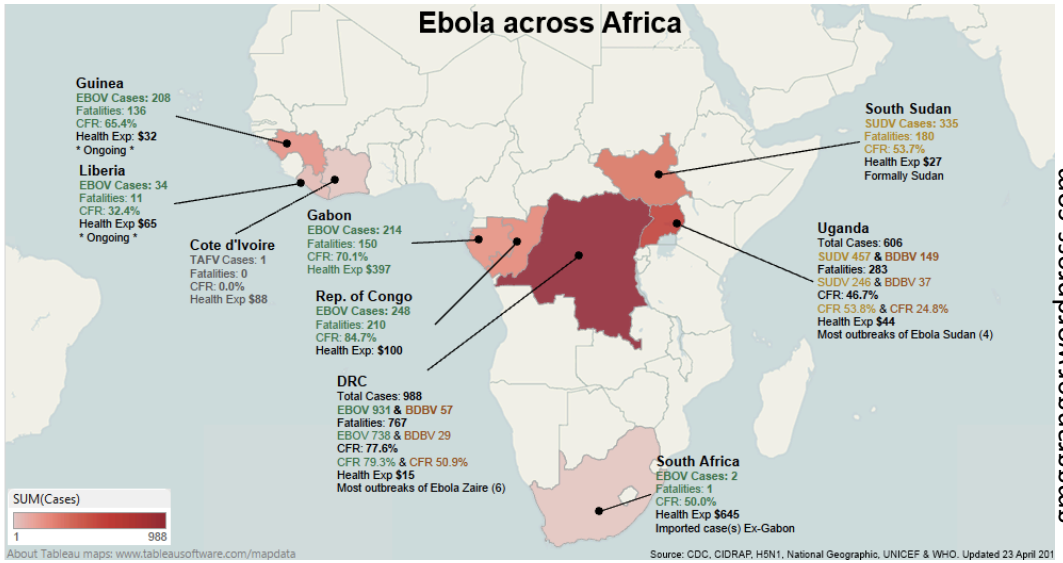
Case Fatality Rate vary from 25% to 90%

EVD timeline of outbreaks

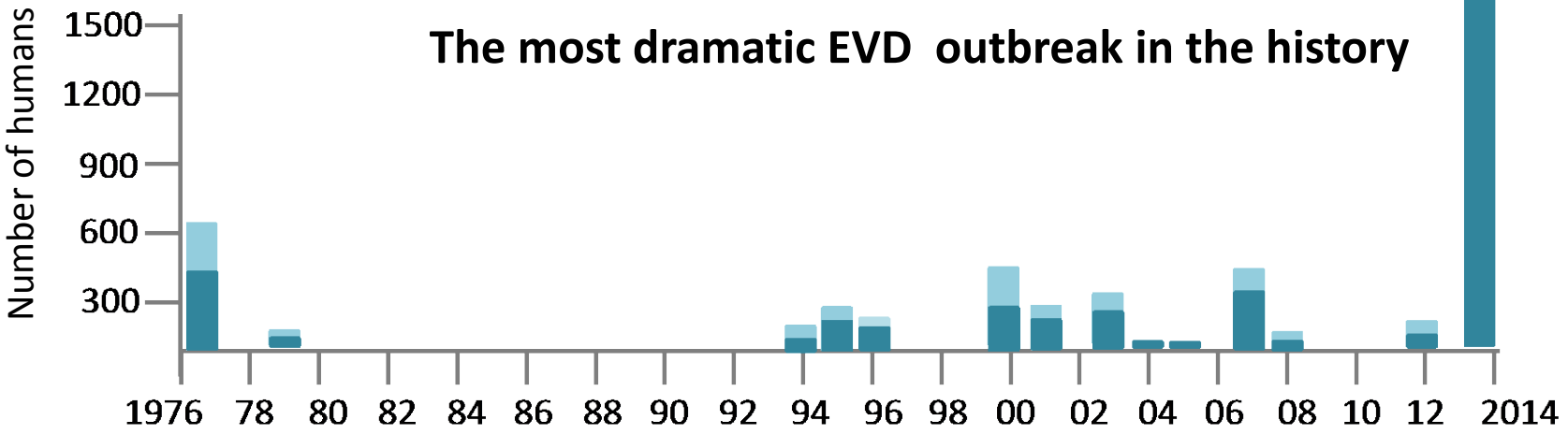
For 40 years Ebola viruses have been responsible for sporadic outbreaks of severe and often fatal hemorrhagic fever in humans in Africa. (Mire et al., 2016)

28 646 cases

11 323 deaths



gmggranger.wordpress.com



West African EVD outbreak

Blaize et al. N Engl J Med. 2014 Oct

December 2013

A „mysterious“ disease began slightly spreading in a small village in Guinea.

January 2014

First investigations: Cholera

March 2014

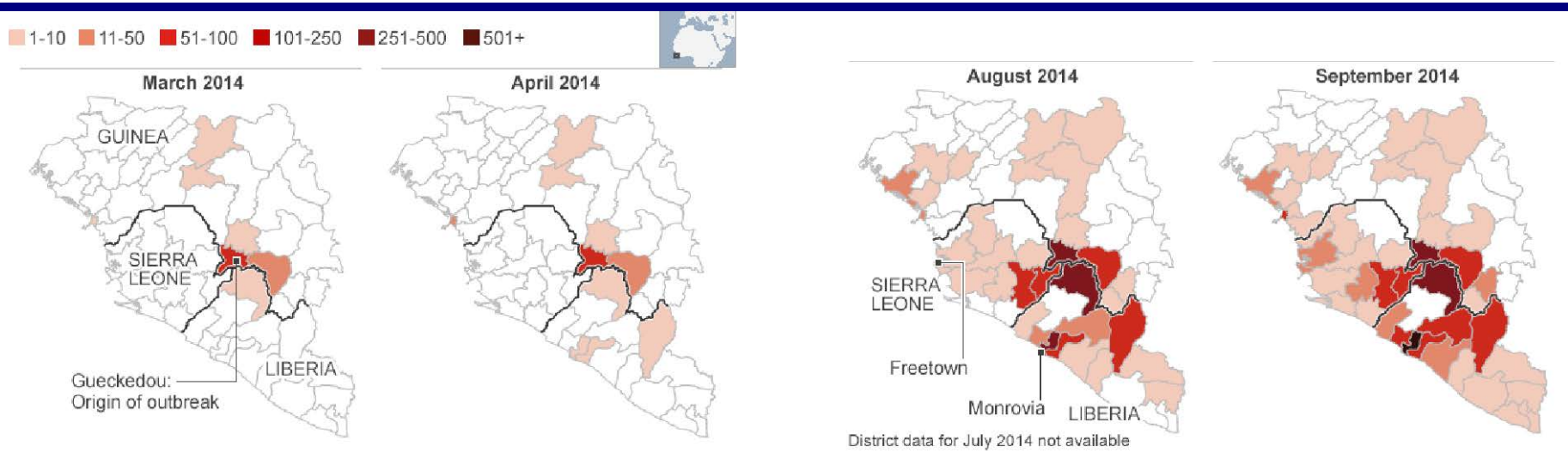
Reports of „hick ups“ – an exclusion criteria for Cholera

21st : Pasteur Institute confirmed the causative agent: Filovirus

23rd : First reports about EVD outbreak in Guinea

29th : First cases in Liberia and Sierra Leone

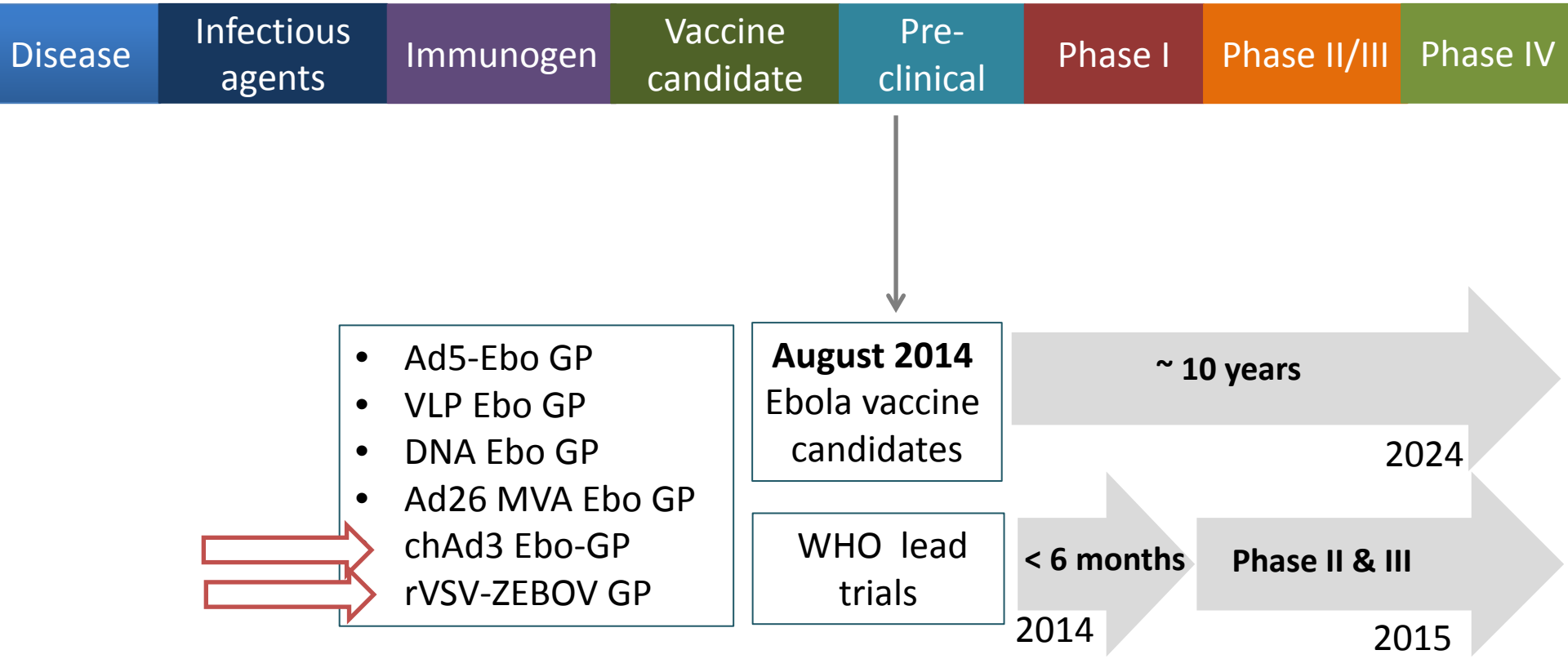
West African EVD outbreak



In June 2014, the oubreak was out of control.

In August 2014, WHO director Margaret Chan declared the current outbreak of EVD a public health emergency of international concern.

Accelerate development, testing and clinical assessment and deployment of potential in vitro diagnostics, therapeutics and vaccines.



Only **two** candidates possess clinical grade 1 material for **Phase 1** clinical studies & provide data about high level protection in NHP

VEBCON – VSV-Ebola Consortium

4 IIT

Aim:

Assess safety, tolerability and immunogenicity of rVSVΔG-ZEBOV-GP in healthy adults from **Europe** and **Africa:**

- different doses of vaccine
- different genetic background
- with and without history of prior EVD outbreaks

WHO

University of Marburg

University of Tübingen

Institute for Infection and Immunity University of London

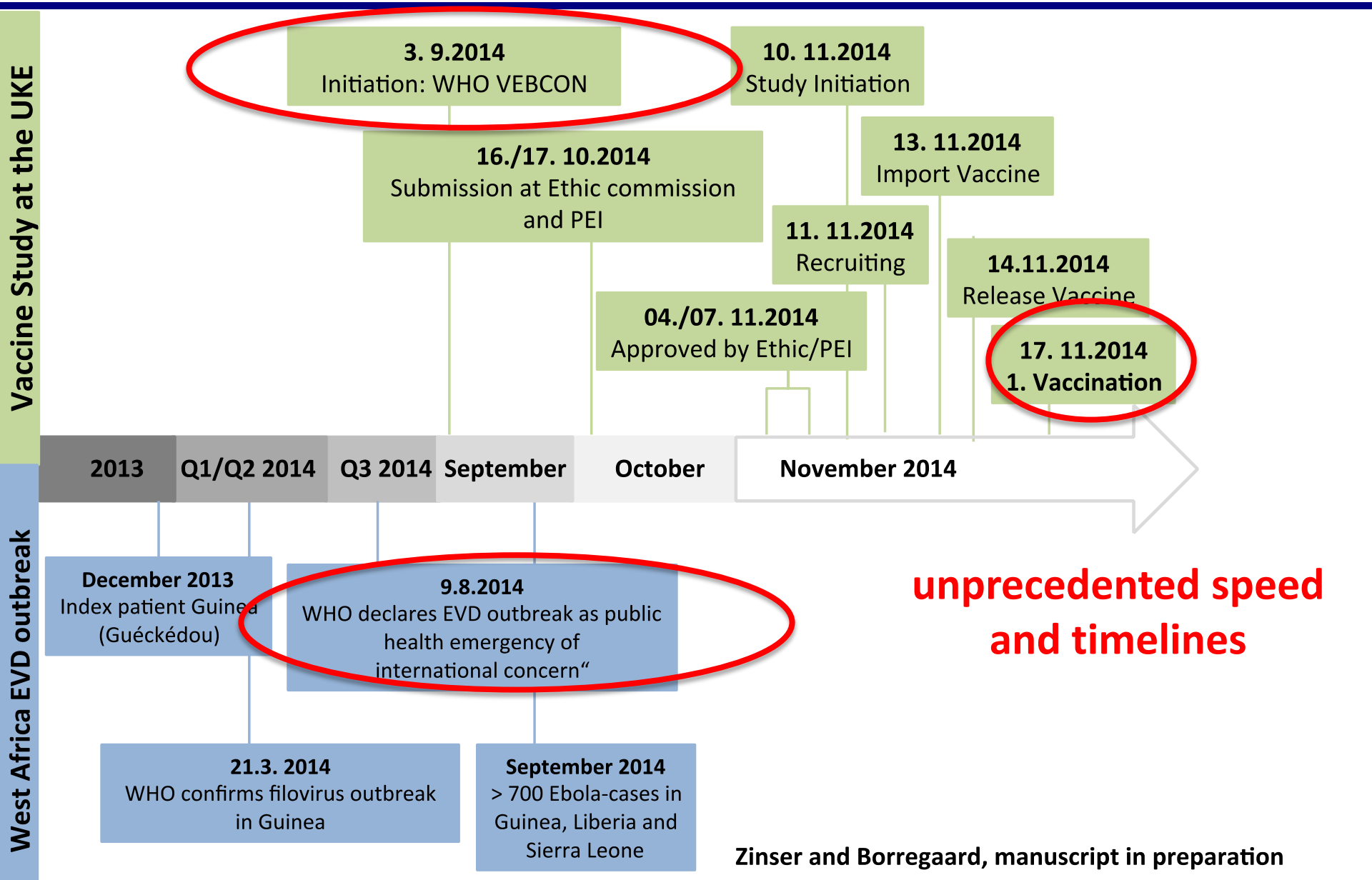
University of Geneva Switzerland

KEMRI WELLCOME Kenya

Cermel Gabon

UKE Germany

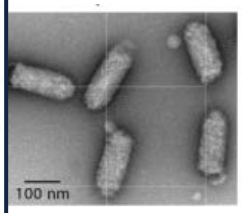
Phase I trial in Hamburg - timeline



unprecedented speed and timelines

Zinser and Borregaard, manuscript in preparation

rVSV –
recombinant Vesicular Stomatitis Virus

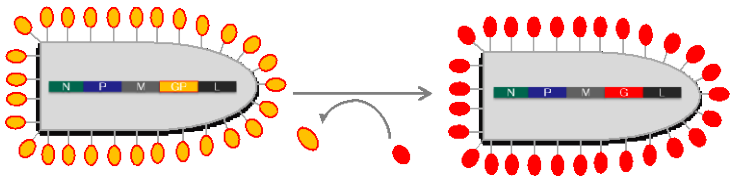


rVSV/EBOV-GP

- VSV is a non-segmented negative-strand RNA virus belonging to *Rhabdovirus* family
- Simple genome structure
- Causes vesicular lesions in livestock
- VSV infection in humans is rare and is either asymptomatic or causes mild illness
- rVSV platform has been shown to be effective in several animal studies

rVSV ZEBOV - live attenuated vaccine

VSV wt 



DRAWBACK

- Safety concern (replication competent vaccine)
- New World Virus
- Bringing a new virus to humans

BENEFIT

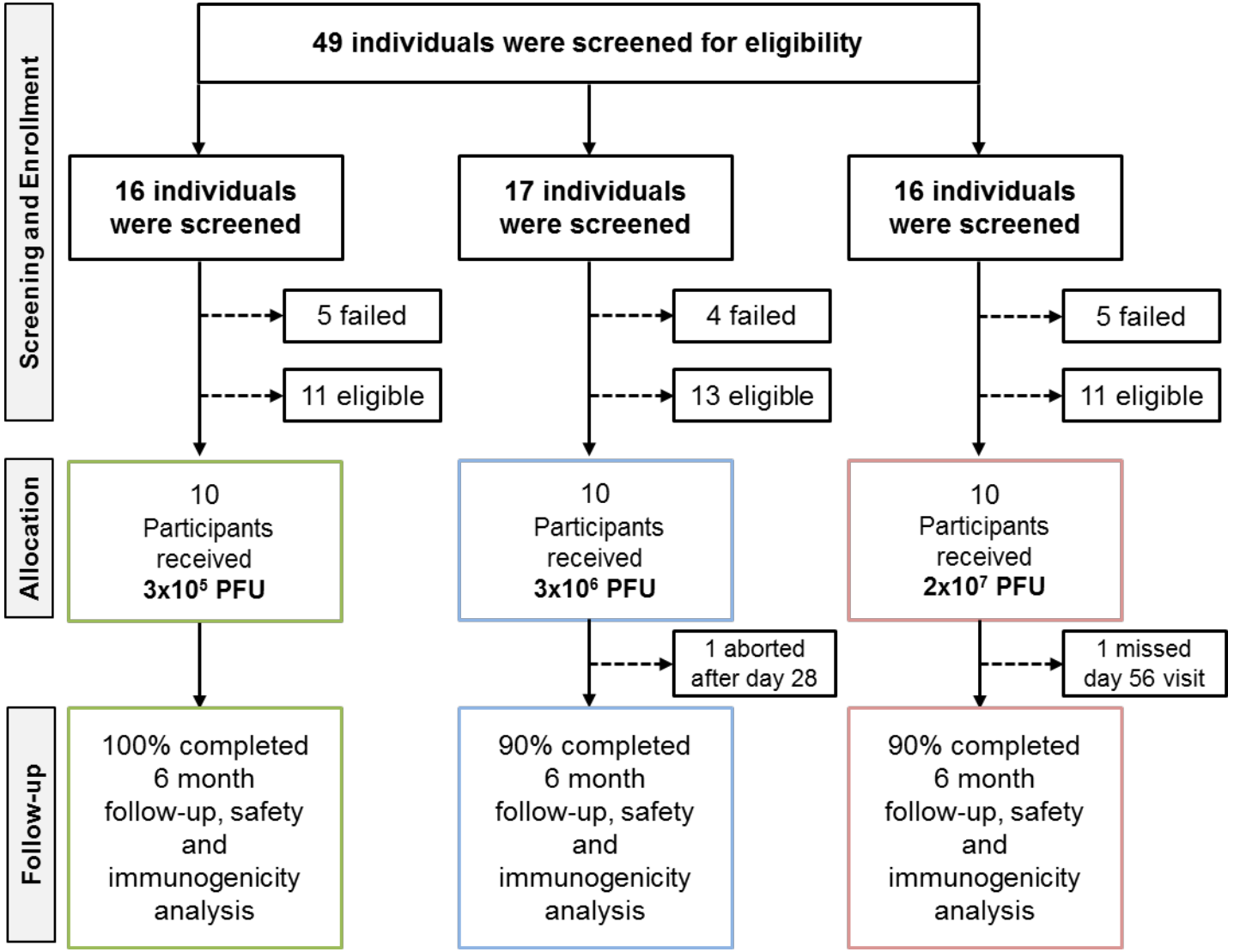
- Grows to high titers
- Replication in the cytoplams (no integration)
- Limited seroprevalence
- Lack of serious pathogenicity in humans
- Single injection might be sufficient
- Post-exposure prophylaxis

Phase I Trial of rVSV vaccine expressing Ebola glycoprotein

CLINICAL TRIAL CENTER NORTH

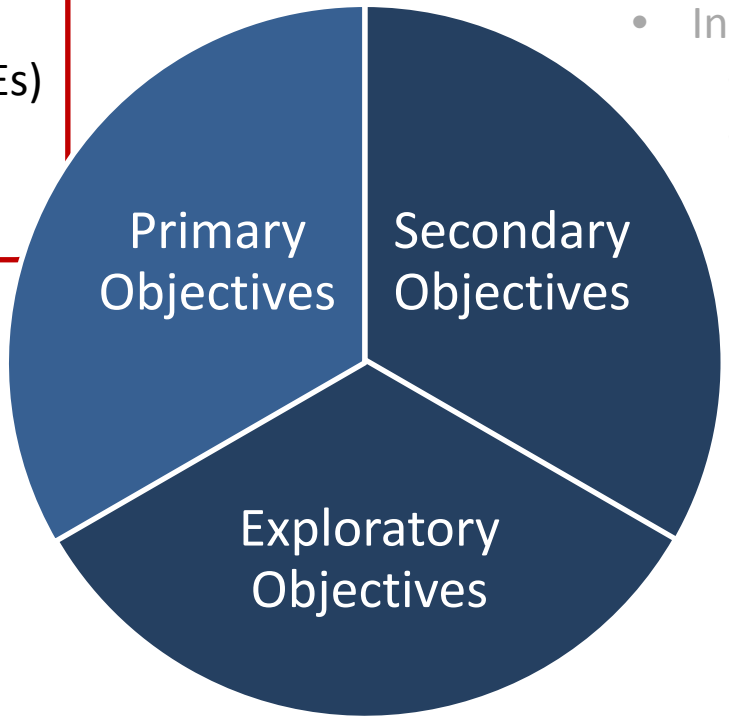
UKE HAMBURG

Clinical Trial Profile



Objectives of the clinical phase I study

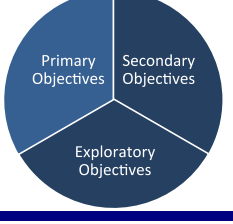
- Safety & tolerability
  - Adverse Events (AEs)
  - Blood safety
- Viremia & excretion



- Induced antibody responses
  - ZEBOV-GP-specific
  - Neutralizing Ab

- Cell subset phenotypes & function
- EBOV-GP-specific T cell immunity

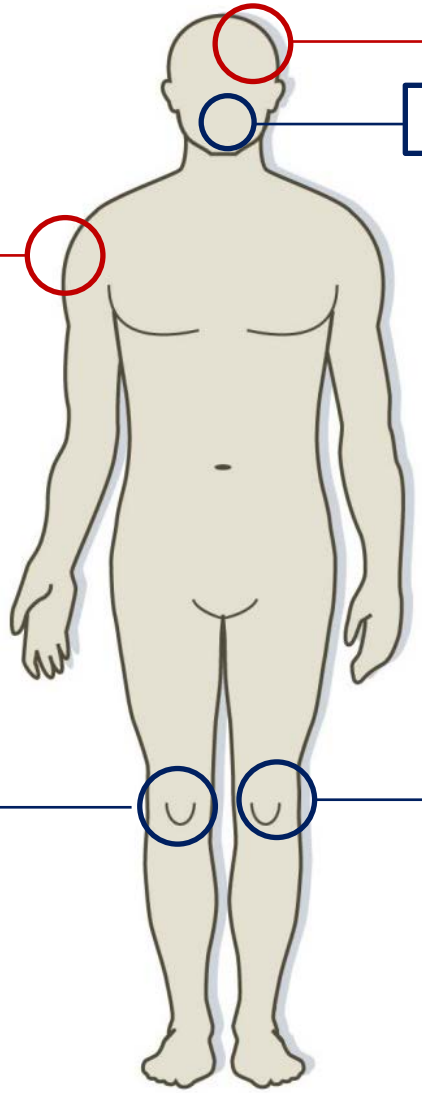
Adverse Events



Adverse Events:
Mild: 116
Moderate: 19
Severe: 4

Localized Adverse Events

- Pain at Injection Site (37%)
- Erythema (13%)
- Swelling (7%)



Headache (57%)

Oral vesicle (10%)

Systemic Adverse Events

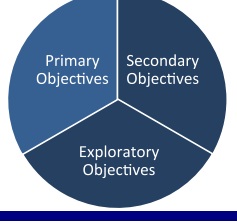
- Fever (17%)
- Chills (20%)
- Fatigue (20%)
- Myalgia (57%)

Arthritis (3%)

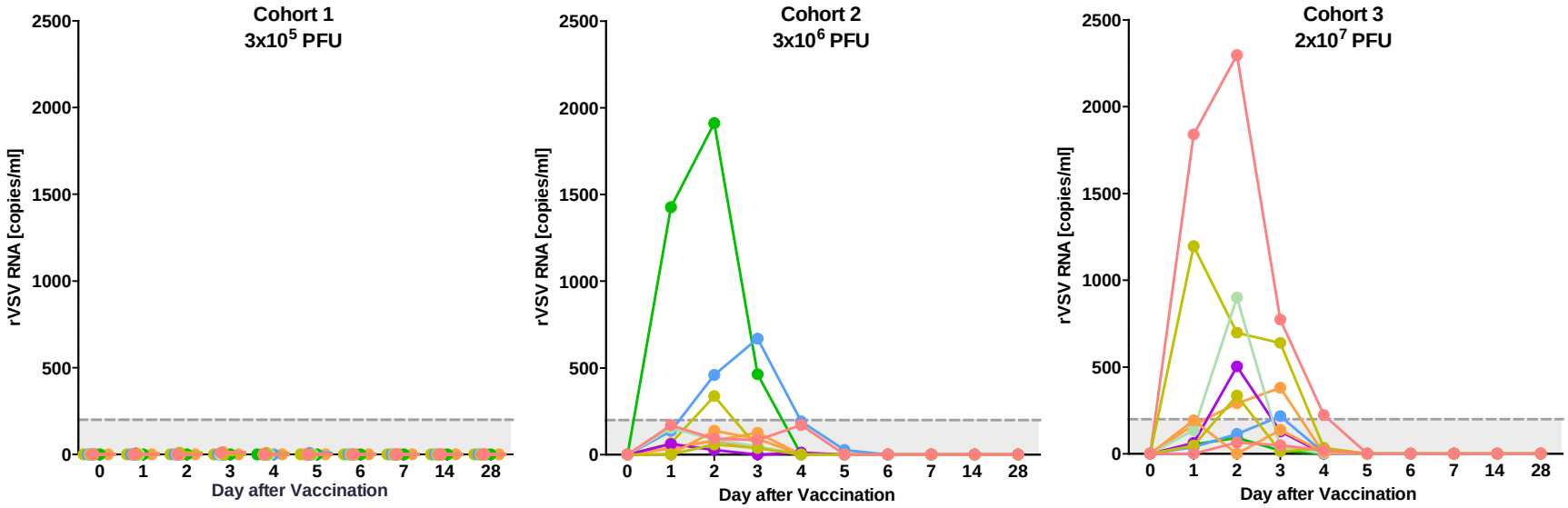
Arthralgia (10%)

No serious adverse event (SAEs)

Viremia & Viral Shedding



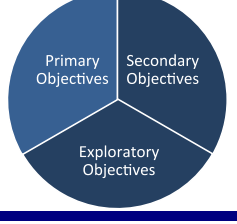
RT TaqMan qPCR of total RNA derived from plasma



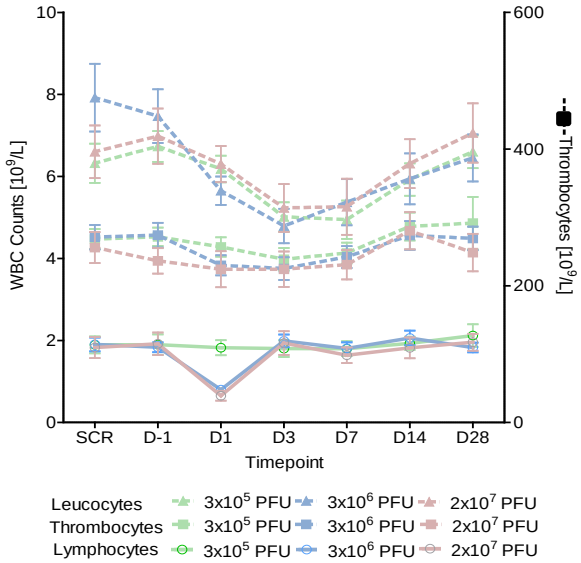
Viremia is observed in the two higher dose cohorts.

No excretion into urine or saliva (data not shown).

Biologic Monitoring



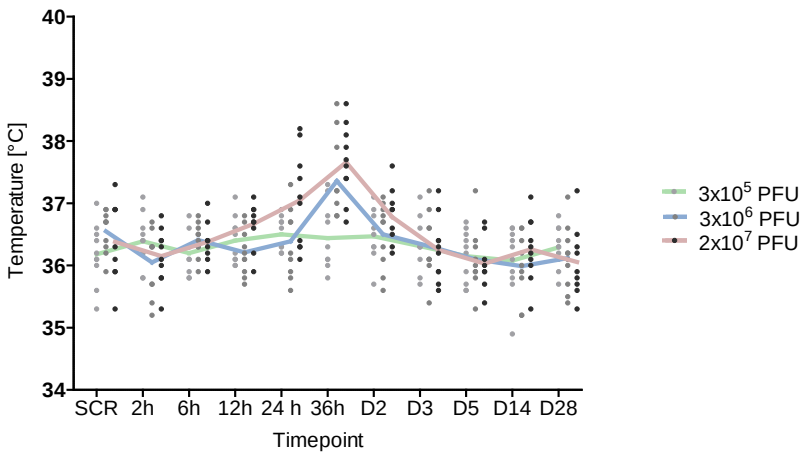
Lymphocytes



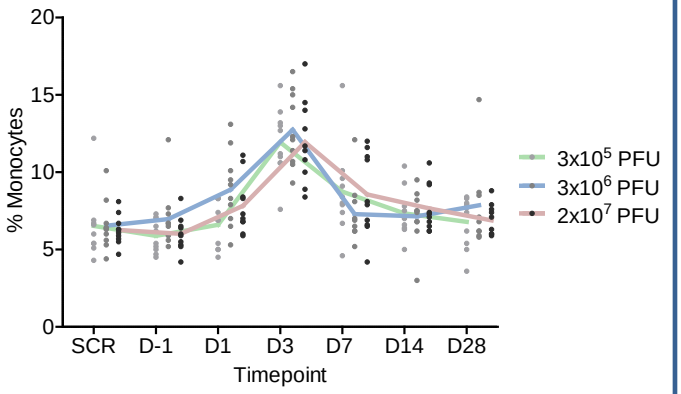
Dose cohort	Lymphocytes		
	SCR	D1	p-value SCR to D1
3x10^5 pfu	1.620 (1.41 – 2.29)	1.800 (1.57 – 2.13)	NS
3x10^6 pfu	1.815 (1.46 - 2.17)	0.742 (0.65 - 0.92)	***
2x10^7 pfu	1.660 (1.34 - 2.46)	0.545 (0.43 - 0.76)	***

SCR and D1 values are expressed as median (IQR).
p-value determined by Mann-Whitney Test.

Temperature



Monocytes



SCR= Screening

Objectives of the clinical phase I study

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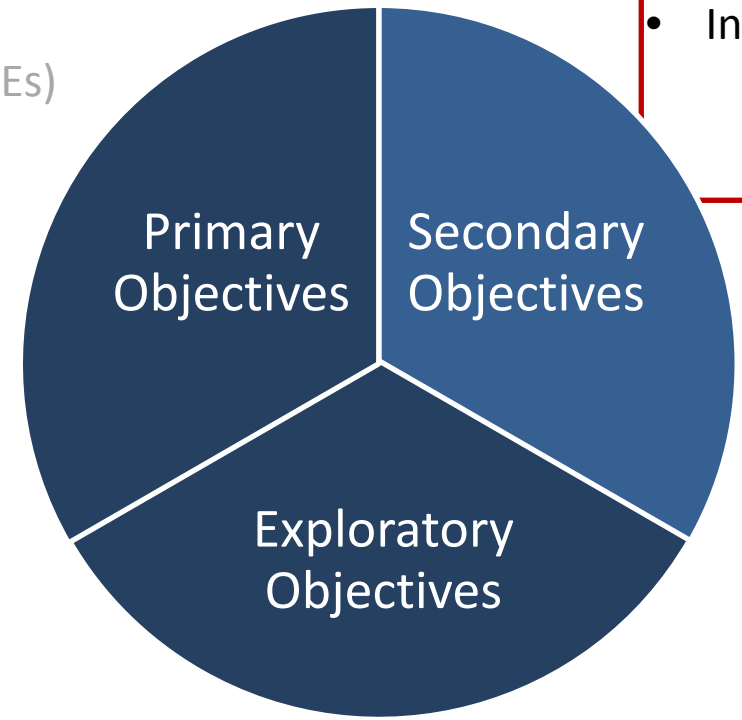


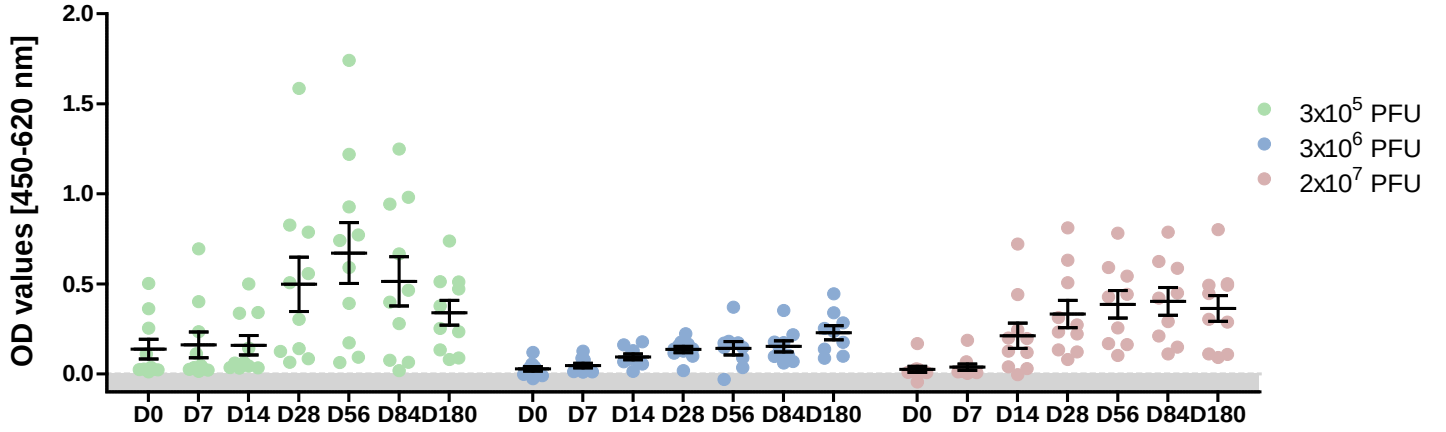
- Induced antibody responses
  - ZEBOV-GP-specific AB
  - Neutralizing AB

- Vector immunity
- Cell subset phenotypes & function
- EBOV-GP-specific T cell immunity

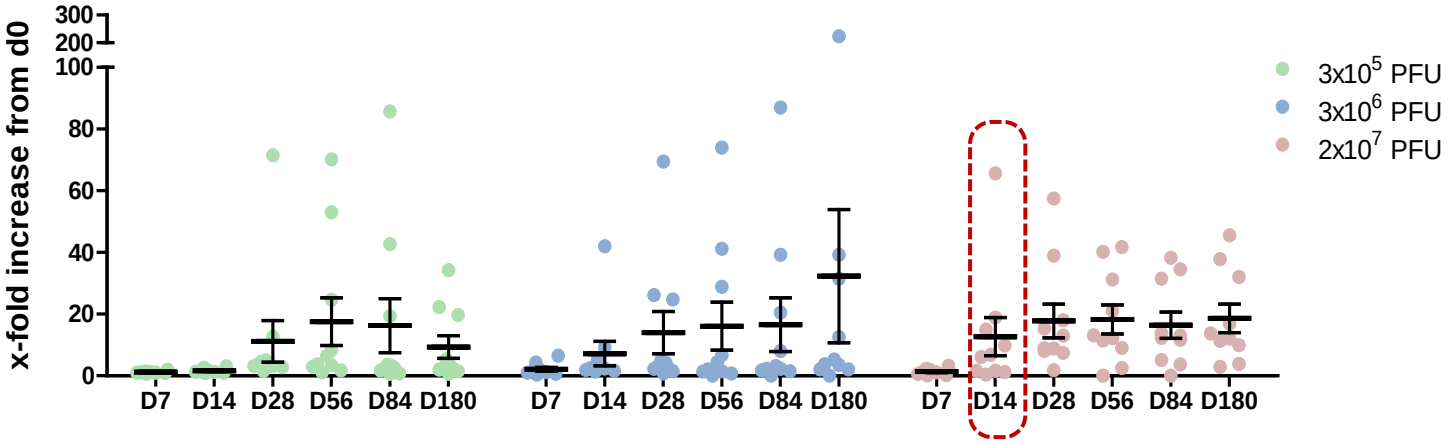
ZEBOV-GP-specific Antibodies

ELISA using inactivated whole virions of the Zaire-Guéckédou strain

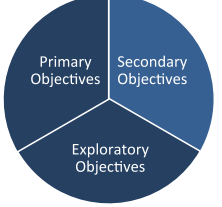
OD values



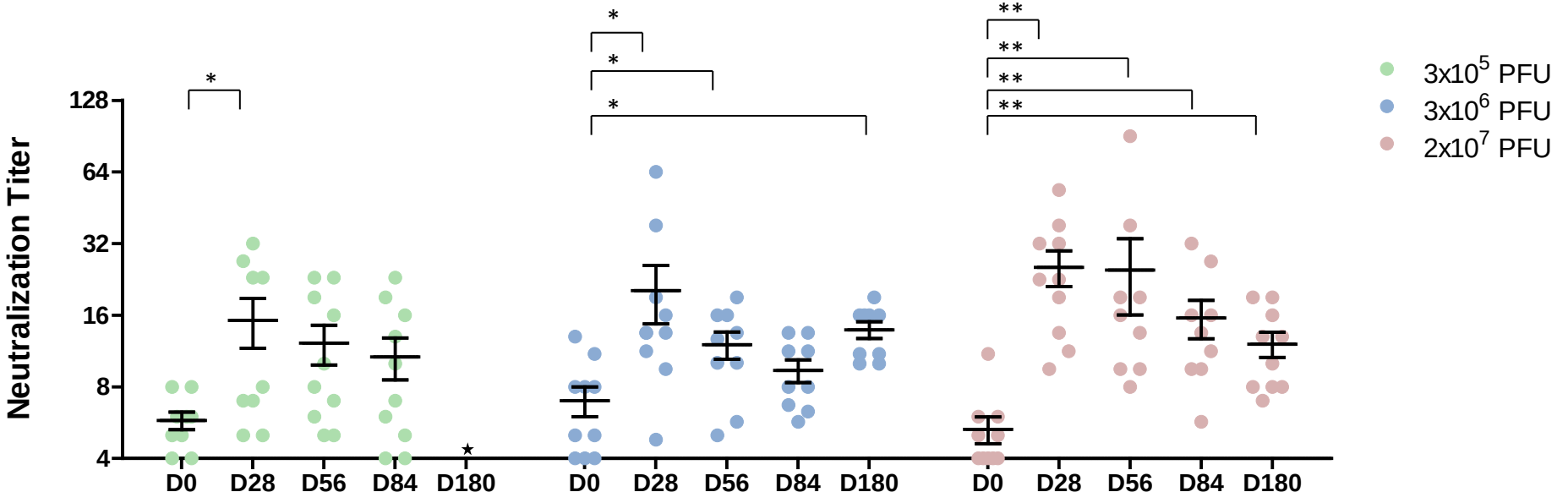
X-fold increase



Neutralizing Antibodies



Neutralization assay using infectious EBOV isolate

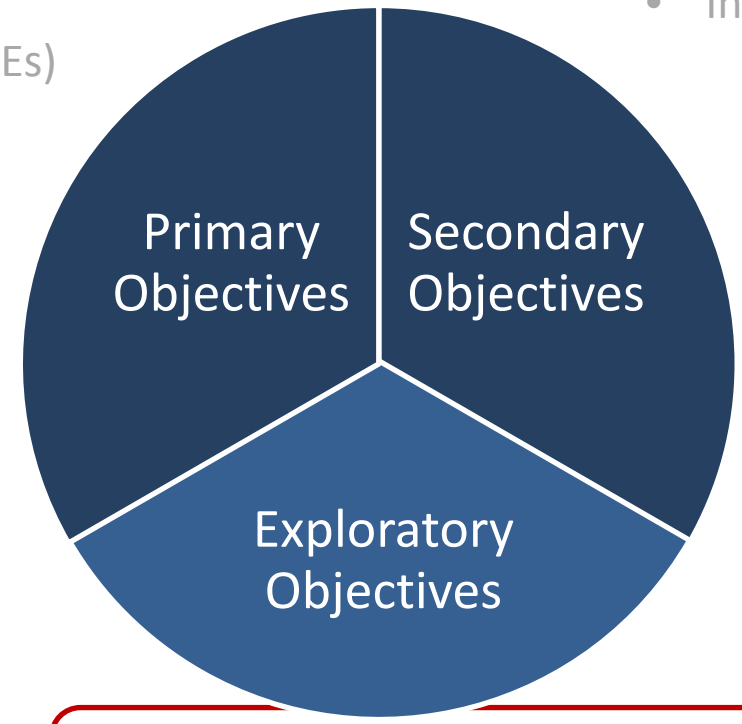


Neutralizing antibodies are detectable
in all subjects of $2x10^7$ dose cohort up to 6 months

★ = under investigation

Objectives of the clinical phase I study

- Safety & tolerability
  - Adverse Events (AEs)
  - Blood safety
- Viremia & excretion



- Induced antibody responses
  - ZEBOV-GP-specific
  - Neutralizing Ab

- Cell subset phenotypes & function
- EBOV-GP-specific T cell immunity

Conclusion

1. VSV-EBOV is safe and immunogenic. (Agnandji et al., NEJM, 2015)

2. Early and persistent **antibody** and **neutralizing antibody** productions.

3. Low magnitude of **T cell responses.**
   - $2x10^7$ PFU cohort: broader responses to all 4 peptide pools compared to lower dose cohorts

4. The highest dose cohort showed **early responses**.
   - T cell and antibody assays revealed responses 14 days after vaccination ($2x10^7$ PFU).
   - Delayed responses for the lower dose cohorts.

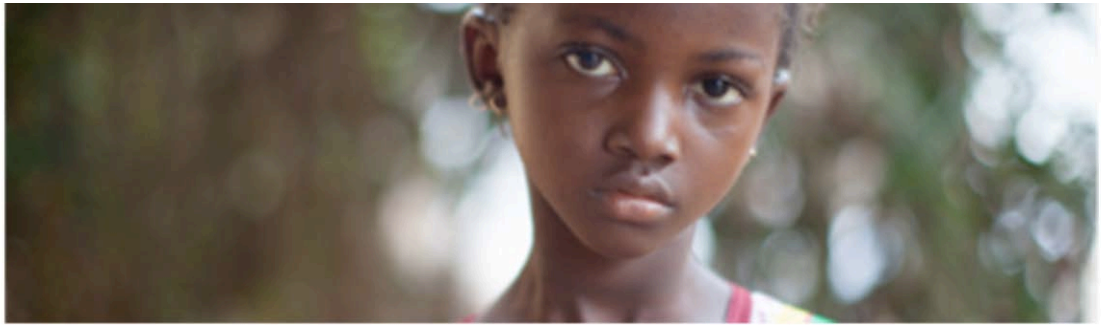
5. Assay Responder: $2x10^7$ PFU cohort showed consistent **positive responses in all assays.**
   - Our data guided the decision of dose selection for Phase II/III trials.

6. **Our results provide supportive human data for the rVSV platform**.

Open Questions

1. What are the correlates of protection?
   - Antibody responses seem to be more crucial than T cell responses.
   - IgG levels correspond to survival in mouse and guinea pig challenges. (Wong et al., Vaccine 2014)
   - Cell mediated immunity does not appear critical to protections. (Marzi et al., PNAS. 2013)
2. Did the tremendously speed of Phase I initiation have an impact on the outbreak?
   - Although Phase II/III trials were too late to include high numbers of patients, rVSV-EBOV could be tested in Guinea.
3. Are we prepared for the next Ebola virus epdiemic?
   - Davos Deal: GAVI (Vaccine Alliance) signs 5 Million $ deal to purchase Ebola vaccine
4. What did the world learn from Ebola?

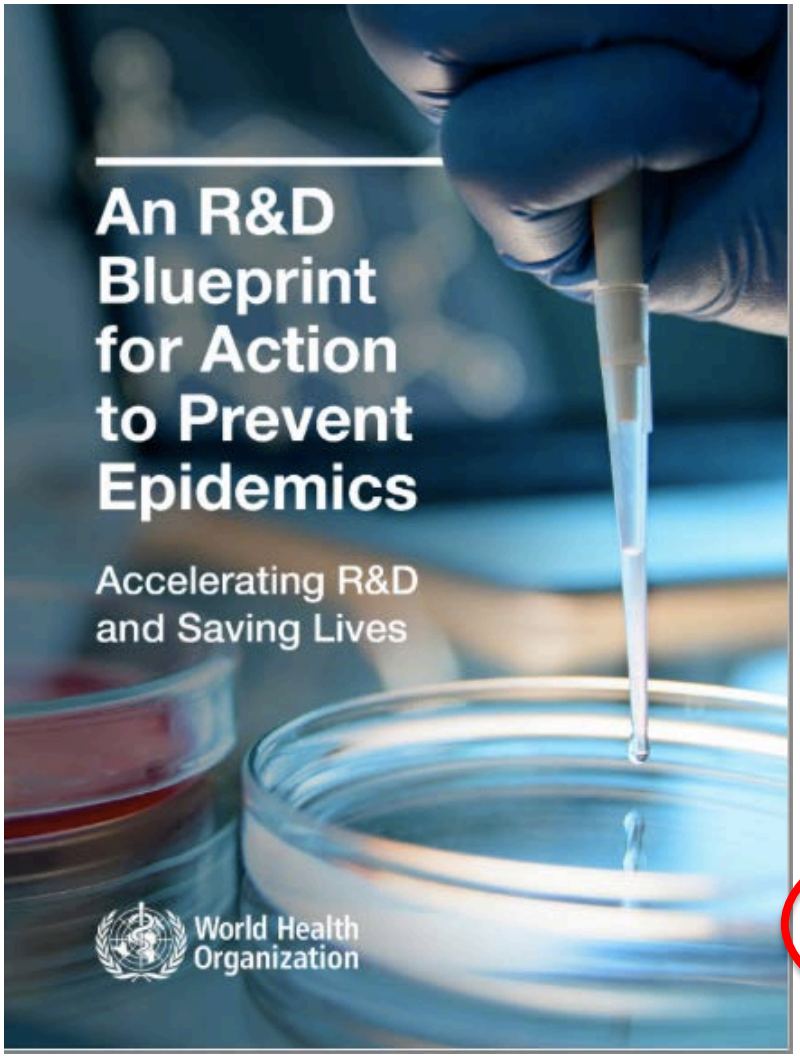
What did the world learn from Ebola



"We should never again experience a crisis like the West Africa Ebola Epidemic. The world needs a more dynamic approach to R&D for life-saving drugs, vaccines and diagnostics."

Dr Mimi Darko, Food and Drugs Authority, Ghana

World Health Organization



WHO publishes list of top emerging diseases likely to cause major epidemics

WHO HQ SHOC Room

WHO /Christopher Black

A panel of scientists and public health experts convened by WHO met in Geneva this week to prioritise the top five to ten emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist. These diseases will provide the basis for work on the WHO Blueprint for R&D preparedness to help control potential future outbreaks.

The initial list of disease priorities needing urgent R&D attention comprises: Crimean Congo haemorrhagic fever, Ebola virus disease and Marburg, Lassa fever, MERS and SARS coronavirus diseases, Nipah and Rift Valley fever. The list will be reviewed annually or when new diseases emerge.

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Emerging Infections

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wellcome trust

...we thank all volunteers for their participation!

Thank you for your attention