Statistical design challenges of a Phase 2/3 randomized placebo-controlled Ebola vaccine trial

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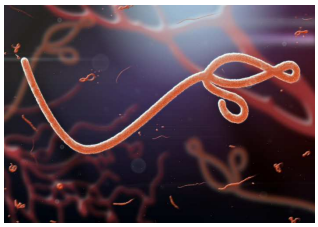
Contents

Introduction
The PREVAIL I study
Study design
Randomization and blinding
Data Safety Monitoring Board
Current status
Next steps
Bridging efficacy from NHP to humans

Filoviruses

- Enveloped, negative strand RNA viruses (Filoviridae family) of filamentous shape
- 2 family members:
  - Ebola virus (5 subspecies)
    - Zaire ebolavirus (EBOV)
    - Sudan ebolavirus (SUDV)
    - Taï Forest ebolavirus (TAFV)
    - Bundibugyo ebolavirus (BDBV)
    - Reston ebolavirus (RESTV) (not virulent in humans)
  - Marburg virus (MARV)

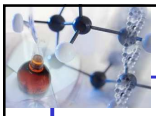


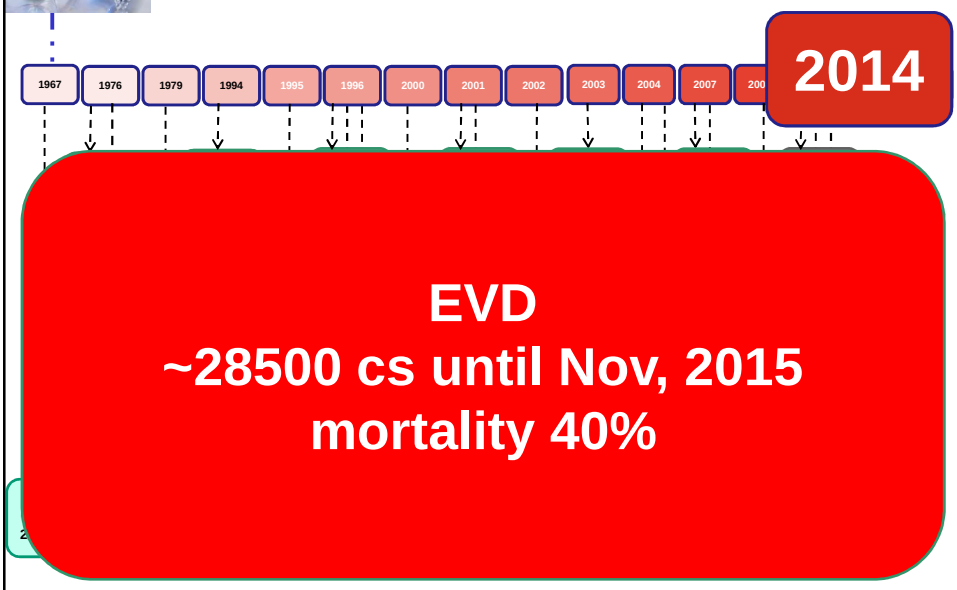
http://www.newsworks.org

Ebola virus disease (EVD)

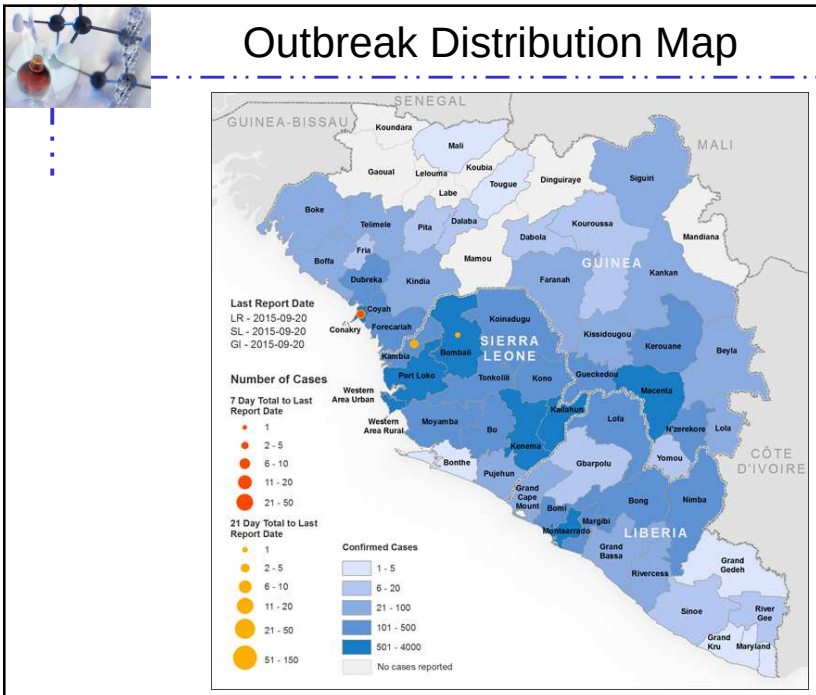
- Incubation 2-21 days, probably function of viral inoculum
- Essentially an aspecific febrile syndrome, with gastroint. symptoms. Difficult to diagnose in absence of hemorrhagic symptoms, which are rarely observed (<6%) Unexplained bleeding reported in 18%.
- Interval for onset of symptoms to hospitalization is 5.0+/-4.7 days
- Interval for onset of symptoms to hospital discharge is 16.4+/-6.5 days
- Interval for onset of symptoms to death is 7.5+/-6.8 days

The story so far…



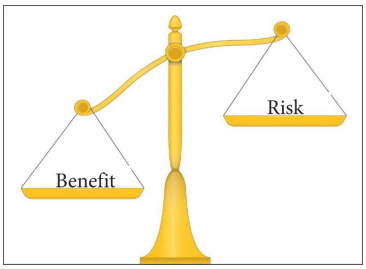


Outbreak Distribution Map



Developing a vaccine

- Types of vaccines:
  - Prophylactic vaccines: prevent the disease
  - Therapeutic vaccines: cure the disease
- For Ebola we want to develop a prophylactic vaccine
  - Vaccinate “healthy” subjects



Questions in vaccine development

- Is the product safe ?
- Does the product induce an immune response ?
  - Immunogenicity
  - Persistency of immune response (booster dose needed ?)
- Is the product efficacious in preventing the disease ?
  - Vaccine efficacy
- Compare to a control group to answer these questions:
  - New Product: Placebo or Vaccine against other disease
  - Existing product: Competitor
  - Control period before vaccination

Phase III Ebola studies

- Liberia: « PREVAIL I» study
  - Double-blind, individually randomized, placebo-controlled
- Guinea: « Ebola ça suffit »
  - Ring vaccination trial (Cluster-randomized, open-label)
  - Immediate versus delayed (21 days) vaccination
- Sierra Leone: « STRIVE » study
  - Open, individually randomized trial with phased introduction of the vaccine (6 months)

Contents

Introduction

The PREVAIL I study

Study design

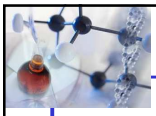
Randomization and blinding

Data Safety Monitoring Board

Current status

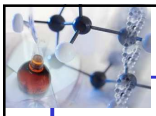
Next steps

Bridging efficacy from NHP to humans



The PREVAIL I study

- Partnership for Research on Ebola Virus in Liberia
  - NCT02344407
- Phase 2/3
- Randomized, double-blind, placebo-controlled trial
- Two candidate vaccines
  - ChAd3-EBO Z vaccine
  - VSVΔG-ZEBOV vaccine
- Sample size: 28170 subjects
  - ~1500 in a Phase 2 substudy
- Study population: Volunteers ≥ 18 years in West Africa at risk of Ebola infection
- Primary objective: To determine the efficacy and safety of the two vaccines as compared to placebo



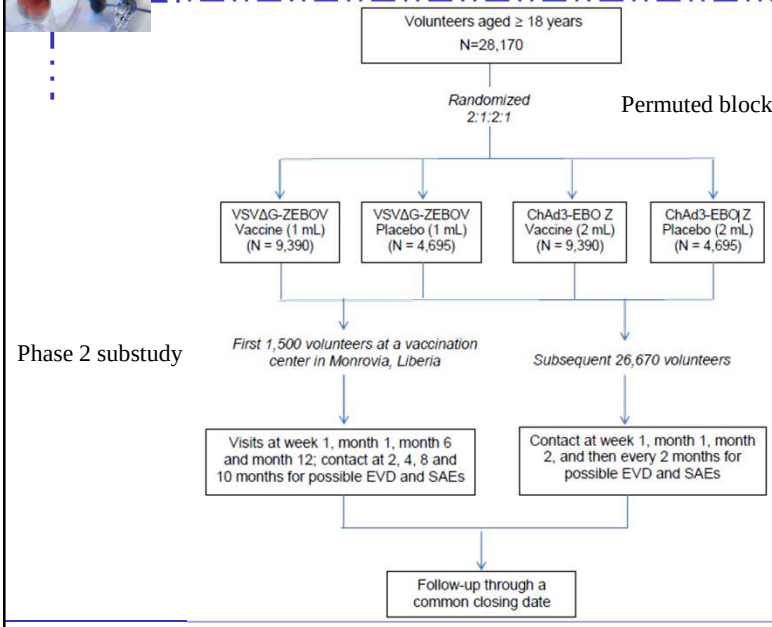
Main inclusion/exclusion criteria

- Inclusion criteria
  - Informed consent
  - Age ≥ 18 years
  - Likely to be in the surrounding area of the vaccination center for at least one year
- Exclusion criteria
  - Fever > 38.0º Celsius
  - History of EVD (self-report)
  - Current pregnancy
  - Breast-feeding an infant
  - Any condition which would limit the ability of the participant to meet the requirements of the study protocol (for example, any serious illness)

Study cohort

- Study initiated in existing health facilities in West Africa
- Widespread communication about the trial
  - To encourage volunteers to go to a vaccination center
- Significant outreach efforts
  - Health care workers
  - Other persons likely to have contact with patients with EVD
    - Ambulance drivers
    - Burial crews
  - Efforts will be made to include high risk individuals

Study design overview



Study schedule

	Phase 2 substudy	All (Phase 2 and 3)
Baseline (Day 0)		
Informed consent / Demographics / Contact information / Indicators of increased risk		X
Clinical information / Blood sample / HIV pre-counseling	X	
Week 1 and Month 1		
Clinical information / Blood sample / AEs / HIV and syphilis post-counseling referral	X	
Days 3, 10 and 14		
Blood sample for VSV viral RNA measurement (subset)	X	
Week 2		
Interview on targeted symptoms and signs (subset)	X	
Month 6 and Month 12		
Blood sample for immunogenicity testing	X	
Week 1, Month 1, Month 2 and every 2 months afterwards through study end		
EVD events / SAEs / Deaths		X

Rationale for study design

- Randomization implemented in a practical, simple manner
  - Syringes prepared in a central pharmacy
  - For each comparison: blocks were prepared
    - E.g., blocks of 12: 4 ChAd3; 4 VSV; 2 each Placebo
- Design implementation had to be made as simple as possible
  - Urgency setting: phase I--> III; need to embed a phase II
  - Need to have simple procedures (short timeframe)
  - Epidemic setting with deadly disease
    - Data collection thought to be challenging
    - Limit data collection to absolute needs to avoid burden

Rationale for study design

- Experts at the WHO Consultation on Ebola vaccines
  - These two vaccine candidates be rapidly evaluated for their efficacy and safety
  - Without compromising international standards
  - If feasible, randomized controlled trials (RCT) should be the design of choice
    - They would provide the most robust data
    - In the shortest amount of time
- VRBPAC 12 May 2015
  - RCTs would provide the most direct evidence of VE
  - Additional approaches are available and under consideration
- A lot of debate on RCT in context of Ebola
  - Adebamowo C et al., Lancet 2014; 384:1423-4
  - Cox et al., NEJM 2014; 371: 2350-1

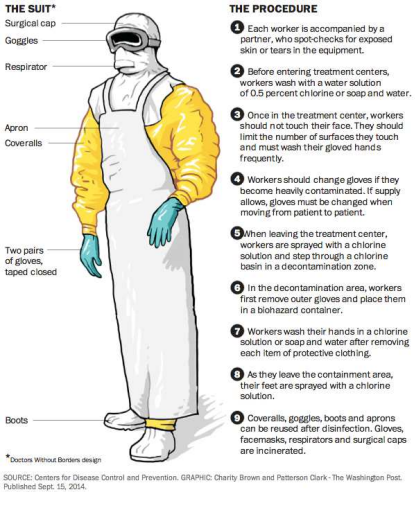
Rationale for study design

- Is randomization ethical in the context of Ebola outbreak ?
  - Different perspectives in NEJM and Lancet
  - NEJM: « Evaluating Ebola Therapies — The Case for RCTs »
  - Lancet: « Randomised controlled trials for Ebola: practical and ethical issues »
- In the context of prophylactic vaccines:
  - « Healthy » subjects
  - Before Phase III only limited safety and immunogenicity data
  - No evidence of efficacy in humans, only in animal models
  - “Such randomisation is ethical when there is equipoise”
    - When there is genuine uncertainty about whether an untested treatment has benefits or risks that exceed those of conventional care

Randomization and blinding

- Randomization
  - Remove the potential bias in treatment assignment (selection bias)
  - Randomization tends to produce comparable groups
- Blinding
  - Increase objectivity (assessment bias)
  - Subjective nature of some of the targeted symptoms

Conventional care to prevent Ebola

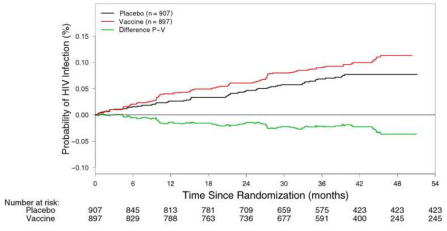


Is there equipoise on risks ?

- Phase I data available to quantify possible risks
- Study design should not impact on « Convential care »
- Blinded trial ensures no assessment bias
  - No false-positive feeling of protection
  - No difference in health seeking behaviour
  - Preventive measures will continue to be applied
  - No difference in disease exposure
  - No difference in risk behaviour
- Blinding versus another control vaccine is difficult
  - Hence the placebo-controlled study

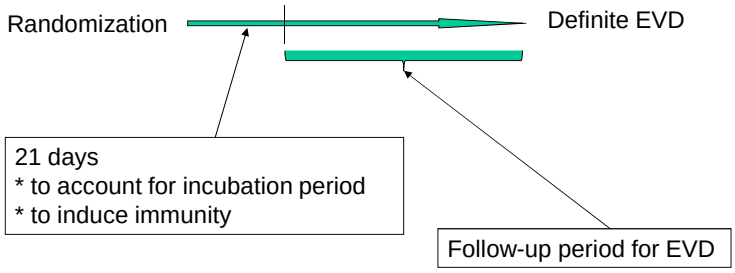
Is there equipoise on benefits ?

- No evidence of efficacy in humans, only in animal models
- A prior study of a recombinant adenovirus investigational vaccine for HIV
- Unexpected result that those receiving the vaccine had an increased incidence of infection.
- This was despite evidence of protection in the non-human primate model
- This emphasizes the uncertainty in moving from animal studies to human studies



Primary efficacy endpoint

- Definite EVD occurring 21 days or more following randomization
  - All Ebola cases reviewed by an Endpoint Review Committee (ERC)
  - Classification in Definite (PCR or ELISA test) or Probable EVD



Primary analysis

- Modified intention to treat (mITT) using EVD outcomes that occur 21 days or more following randomization
  - ITT will be a sensitivity analysis
- A Cox model for time to EVD to estimate hazard ratio (HR)
- Vaccine efficacy: VE = (1-HR)x100%
- VE for each pair-wise comparison
  - ChAd3 EBO-Z vaccine versus pooled placebo
  - VSVΔG-ZEBOV vaccine versus pooled placebo

Sample size

- 1:1 randomization ratio for each comparison
  - Pooled placebo group (1ml and 2ml)
- Type I error: 0.025 (2-sided) for each comparison
  - Bonferroni correction
- 90% power to detect VE=50% (HR=0.5)
- Freedman formulae: 112 events

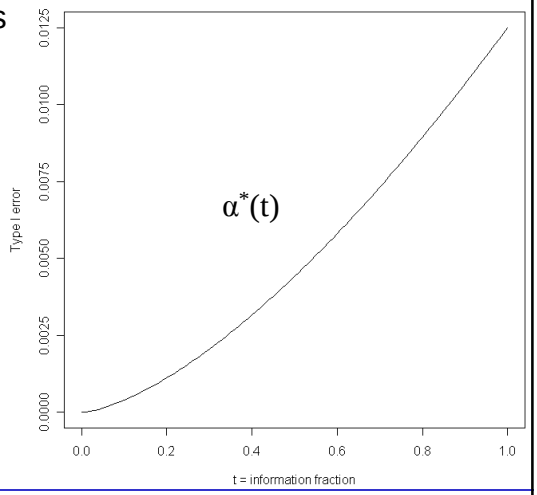
$$d = \frac{(Z_{\alpha/2} + Z_{\beta})^2 (HR + 1)^2}{(HR - 1)^2}$$

Sample size

- 1.0% of volunteers in the pooled placebo group will develop EVD after 12 months
- Enrollment period 4 months
- Follow-up period minimum of 8 months
  - average follow-up is 10 months
  - range is 8 to 12 months
- Deaths unrelated to EVD and losses to follow-up will occur at the rate of 1% per month
- 28170 volunteers need to be enrolled
  - 9390 per active vaccine arm
  - 4695 per each of the two placebo groups
- Sample size re-estimation based on blinded data possible

Group sequential methodology

- Agreement to have several interim analyses
- At each interim analysis
  - Test statistic Z_k
  - Boundary B_k
- Lan-DeMets method
  - α-spending approach



Group sequential methodology

- Calculation of boundaries

$$B_1 : P(Z_1 > B_1) = \alpha^*(t_1)$$

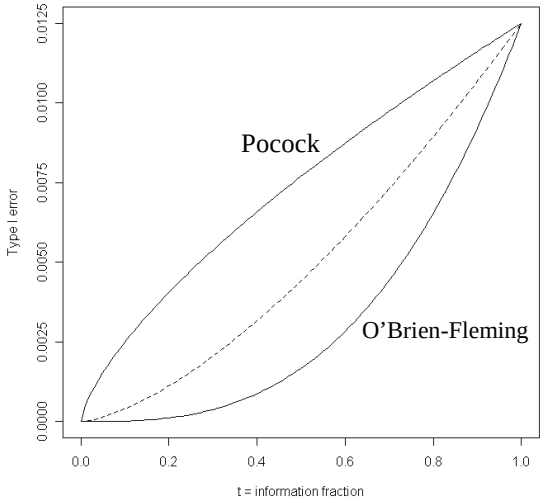
$$B_2 : P(Z_1 \leq B_1, Z_2 > B_2) = \alpha^*(t_2) - \alpha^*(t_1)$$

$$B_k : P(Z_1 \leq B_1, Z_2 \leq B_2, \ldots, Z_{k-1} \leq B_{k-1}, Z_k > B_k) = \alpha^*(t_k) - \alpha^*(t_{k-1})$$

$$\begin{aligned} & P(\text{Crossing a bound ever}) \\ = \; & \alpha^*(t_1) + (\alpha^*(t_2) - \alpha^*(t_1)) \\ & + \ldots + (\alpha^*(t_K) - \alpha^*(t_{K-1})) = \alpha^*(1) = \alpha \end{aligned}$$

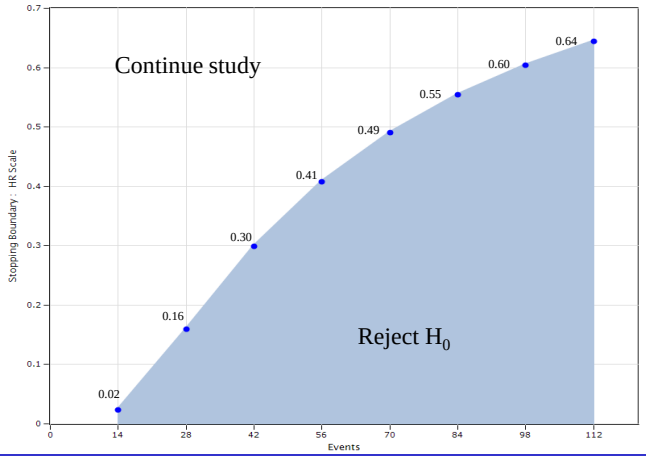
Group sequential methodology

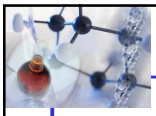
- Two commonly used spending functions



Interim analyses

- 7 interim analyses + final analysis
  - ~12.5%, 25%, 37.5%, 50%, 62.5%, 75% and 87.5%
- Estimated boundaries (HR scale)





Contents

Introduction

The PREVAIL I study

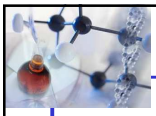
- Study design
- Randomization and blinding

Data Safety Monitoring Board

Current status

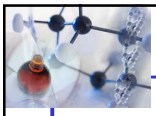
Next steps

- Bridging efficacy from NHP to humans



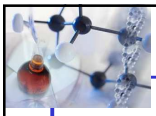
Data monitoring

- Protocol team
  - Blind to interim results by treatment group
  - Monitor enrollment and follow-up of subjects
  - Monitor pooled event rate
    - Make recommendation on sample size re-estimation
    - Request DSMB to convene (e.g., in case of related SAEs)
- Independent Data Safety Monitoring Board (DSMB)
  - DSMB received interim treatment comparisons from unblinded statisticans
  - The protocol team prepared an open report for the DSMB
  - Participated in an open session with the DSMB



Data Safety Monitoring Board

- Will review study design before study initiation
- Will convene every 2-4 weeks
  - Review safety data from substudy
  - Make recommendation of expansion to other sites
  - Review safety throughout the study
  - Review of efficacy data if # cases triggers an analysis
    - Separate for each comparison vaccine versus placebo
    - Flexible Lan-DeMets approach to determine α spent
- DSMB will not communicate whether efficacy data was reviewed
  - Recommend continuing the study as planned
  - or modifying the study
  - or terminating the study

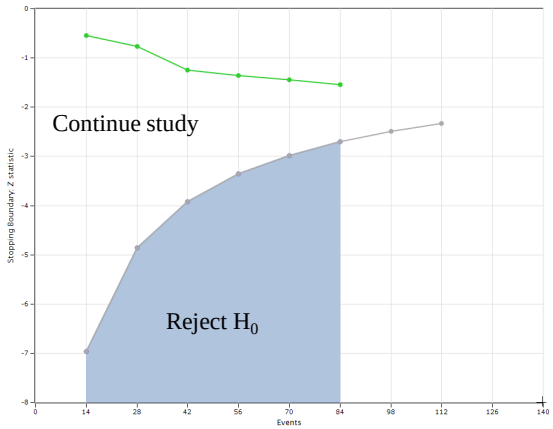


Data Safety Monitoring Board

- Early stopping of one vaccine could impact ability to determine efficacy and safety of other vaccine
  - Pooled placebo group
- E.g., one vaccine is efficacious (boundaries crossed) and the other not
  - DSMB will assess risk/benefit of each vaccine
  - They can recommend to continue the study
    - E.g., increase information on a less effective but safer vaccine
  - Or recommend to stop the study and cross-over to effective vaccine
- Conditional power estimates can be used to guide DSMB

Data Safety Monitoring Board

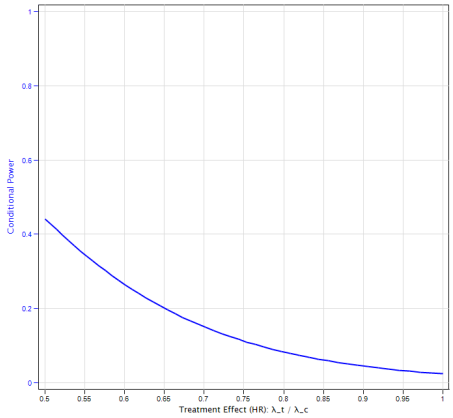
- Conditional power
  - Probability(Reject H_0|data accumulated so far)
- Example: one vaccine has ~30% VE

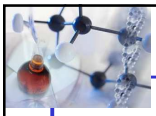


Events	VE	CP_CT	CP_HA
14	0.25	21%	88%
28	0.25	19%	83%
42	0.32	38%	83%
56	0.30303	29%	75%
70	0.292683	22%	63%
84	0.285714	14%	44%
98	0.310345		
112	0.30303		

Data Safety Monitoring Board

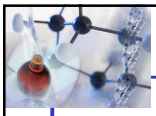
- If CP under alternative (50% VE) < 60%
  - Ask DSMB to recommend stopping study
  - Releasing the data on the efficacious vaccine
  - CP under current trend will also be considered





Data Safety Monitoring Board

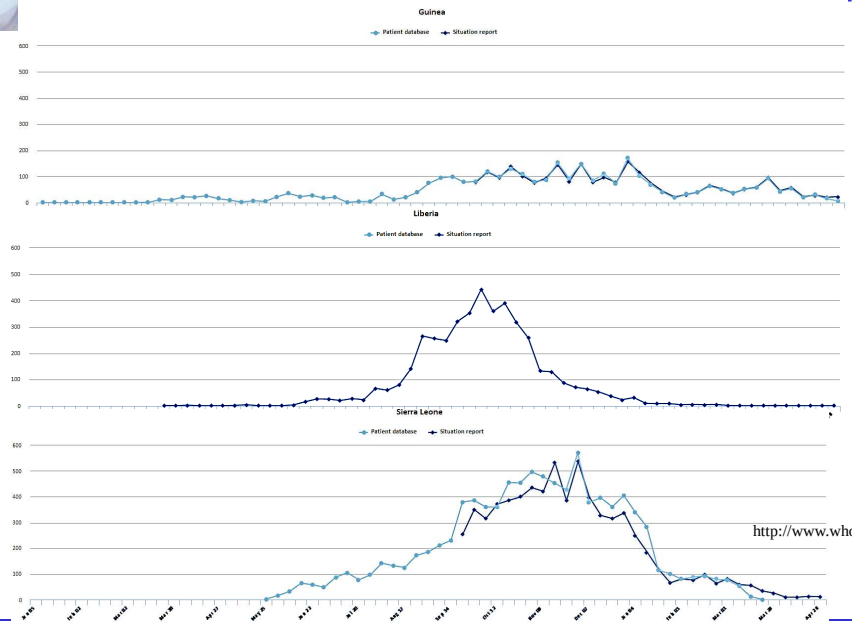
- If one vaccine has an unacceptable rate of SAEs or a rate of EVD and/or all-cause mortality greater than placebo
  - Enrolment to that arm will be terminated
  - Allocation will be 1:1 for subsequent enrolments to the other vaccine and placebo
- The DSMB is provided with these guidelines (not rules)
- DSMB will use their expert and independent judgment
  - Concerning early termination of one of the vaccine arms
  - Not every situation can be foreseen
    - Consistency of primary endpoint findings in subgroups
    - Treatment differences for major secondary outcomes



Contents

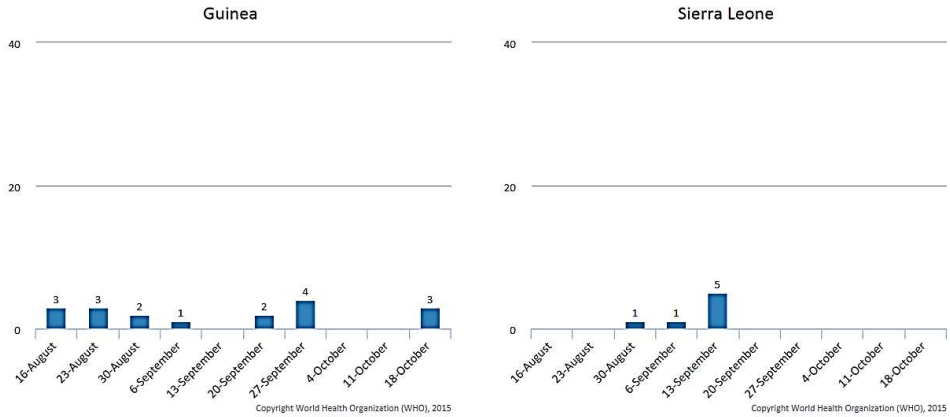
Introduction
The PREVAIL I study
Study design
Randomization and blinding
Data Safety Monitoring Board
Current status
Next steps
Bridging efficacy from NHP to humans

Situation over time



http://www.who.org

Latest situation reports



Current status

- Study started 2 February 2015
- Recommendation for expansion on 20 March 2015
- Because of Liberia being ebola-free, no expansion to Phase III part of the study

http://www.nydailynews.com/

Contents

Introduction

The PREVAIL I study

Study design

Randomization and blinding

Data Safety Monitoring Board

Current status

Next steps

Bridging efficacy from NHP to humans

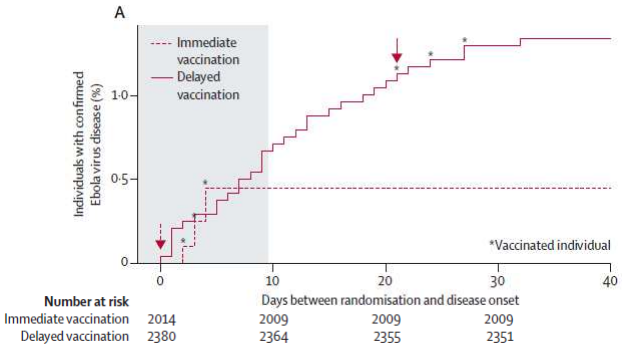
Next steps

- December 2014 FDA Workshop
- VRBPAC May 2015
  - If phase 3 clinical trials yield inconclusive results (due to low Ebola virus attack rates or other factors), the FDA may need to consider other approaches to demonstrating effectiveness for licensure
  - Preliminary results of Ebola vaccines suggest the vaccines can induce human immune responses at levels comparable to protective responses in NHPs
  - NHP studies are important for evaluating mechanisms of protection and for mimicking human infections

Guinea trial showed efficacy

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

Ana Maria Henao-Restrepo, Ira M Longini, Matthias Egger, Natalie E Dean, W John Edmunds, Anton Camacho, Miles W Carroll, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Stefanie Hossmann, Mandy Kader Kondé, Souleymane Kone, Eeva Kuisma, Myron M Levine, Sema Mandal, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, Conall H Watson, Sakoba Kéïta, Marie Paule Kieny, John-Arne Røttingen**



Bridging NHP to human efficacy

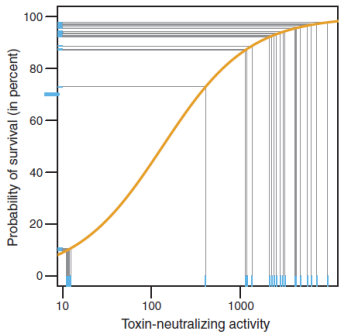


Fig. 5. Graphical representation of first row in Table 3. Orange logistic line is the predicted survival based on setting 3 (rabbits). The lines going from the horizontal axis to the logistic curve, then to the vertical axis represent the TNA values for the 29 cyno monkeys in setting 6. Random noise was added to the lines close to TNA = 11.5 (half the limit of detection), and those lines represent eight monkeys, five that died and three that survived. The sky blue tick on the vertical axis represents the mean predicted survival (70.1) for cyno macaques based on rabbit efficacy data.

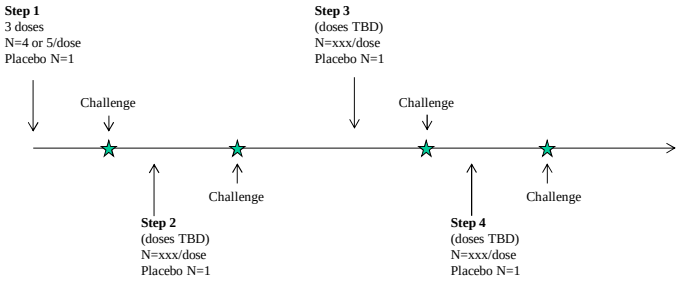
- Logistic regression in NHP
- Average predicted protection level in humans (%)

Bridging NHP to human efficacy

- Challenges
  - Humans and NHP may need different vaccine doses to reach comparable immune response
  - Generate a relatively wide range of antibody titers
  - Avoid that all NHP survive or die
- A Bayesian adaptive design was implemented to overcome these challenges

Bridging NHP to human efficacy

- 4-step Bayesian adaptive design



Bridging NHP to human efficacy

- After each step:
  - Evaluate survival rate
  - Evaluate antibody titers
  - Adapt #NHP/dose for next step
    - Standard error of the slope
    - Survival rate

Logistic regression

$$\log(\pi/(1-\pi)) = \alpha + \beta \log(\text{titer})$$

$$\alpha \sim N(\theta_{0,\alpha}, \theta_{1,\alpha})$$

$$\beta \sim N(\theta_{0,\beta}, \theta_{1,\beta})$$

ANOVA model

$$\log(\text{titer})|\text{dose} \sim N(\mu_{\text{dose}}, \sigma^2_{\text{dose}})$$

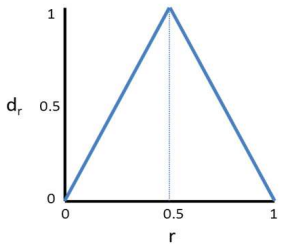
$$\mu_{\text{dose}} \sim N(\theta_{0,\mu}, \theta_{1,\mu})$$

$$\sigma^2_{\text{dose}} \sim \Gamma(\theta_{0,\sigma^2}, \theta_{1,\sigma^2})$$

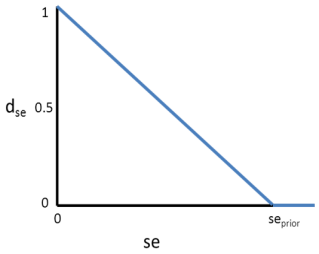
Bridging NHP to human efficacy

- Desirability approach

Survival rate



Precision slope



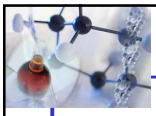
- Overall desirability used to determine dose allocation

Next dose allocation

- Simulate next step based on what we know
- The scenarios are:

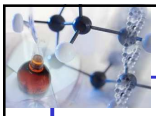
Scenario	Dose 1	Dose 2	Dose 3	Relationship	Survival
1	1	1	11	?	?
2	1	2	10	?	?
3	1	3	9	?	?
…	…	…	…	?	?

- Select the one that would give the best compromise between quality of the fit and a survival rate close to 50%



Conclusion

- PREVAIL I Phase 2/3 study
- Phase 3 part not yet started due to Liberia ebola-free
- One vaccine shown to be efficacious in another Phase III
- Other vaccine bridging from NHP to human efficacy



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