Simulation-based trial design to inform an innovative and adaptive statistical strategy

Challenges designing a Phase 3 Ebola vaccine trial

Robin Mogg*, An Vandebosch, Nele Goeyvaerts, Tony Vangeneugden
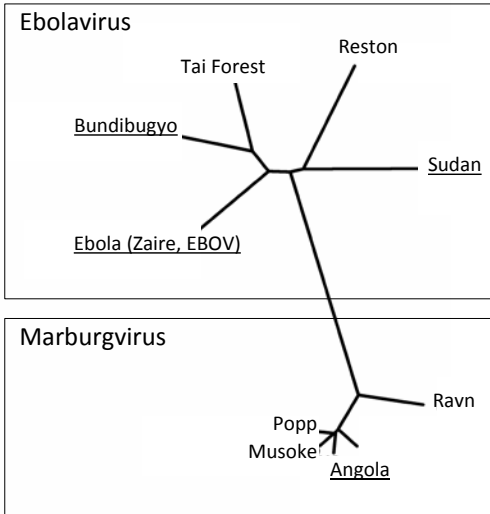
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BASS XXII

November 3, 2015

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Infectious Diseases and Vaccines

Background: Filovirus Disease

4 subtypes responsible for the largest outbreaks

Ebolavirus
- Reston
- Tai Forest
- Bundibugyo
- Sudan
- Ebola (Zaire, EBOV)

Marburgvirus
- Ravn
- Popp
- Musoke
- Angola

Filoviruses can cause severe hemorrhagic fever in humans and NHP.

Two members of virus family have been identified:

Marburg virus disease

- 10 lethal Marburg virus outbreaks recorded since 1967 – generally sporadic, but 2 outbreaks (DR of Congo in 1999 and Angola in 2005) had > 150 cases
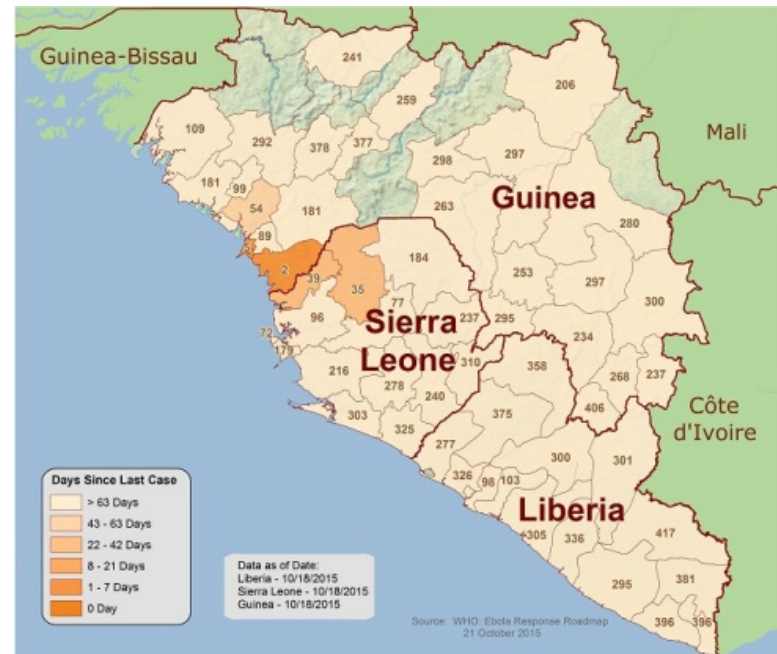
Ebola virus disease

- First identified in 1976, more than 20 lethal Ebolavirus outbreaks recorded since

- 25% to 90% lethality (average: 50%)

- At least 10 outbreaks in last 10 years, with at most 264 reported cases, until…

2014 Ebola Outbreak in West Africa

Total Cases
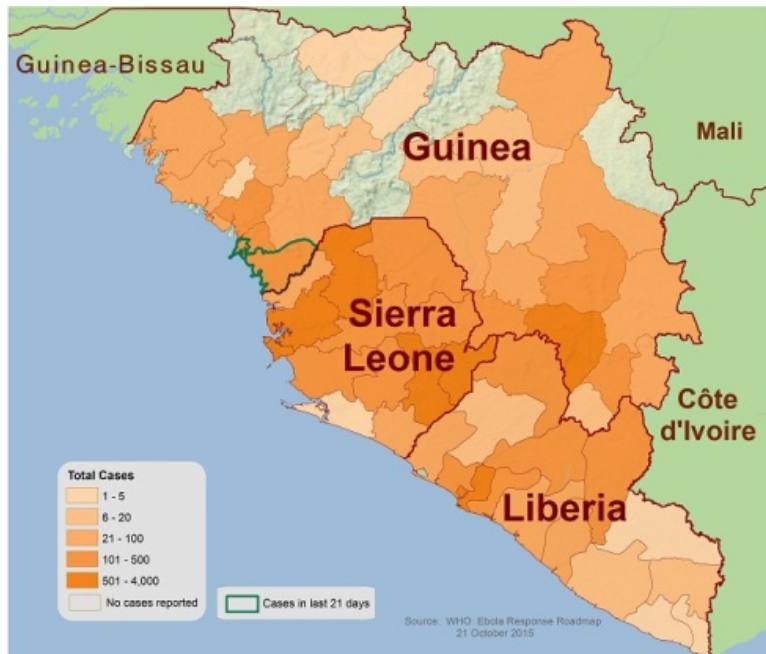
Days Since Last Case

Through Oct 25, 2015, source: CDC (http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/)

- > 28,000 cases , > 11,000 deaths

- Declared as public health emergency of international concern by the WHO in August 2014

- Currently no licensed treatment or vaccine available

2014-2015 Epidemic in Sierra Leone

Figure 5: Confirmed weekly Ebola virus disease cases reported nationally and by district from Sierra Leone

Through Oct 25, 2015, source: WHO
(http://apps.who.int/ebola/current-situation/ebola-situation-report-28-october-2015)
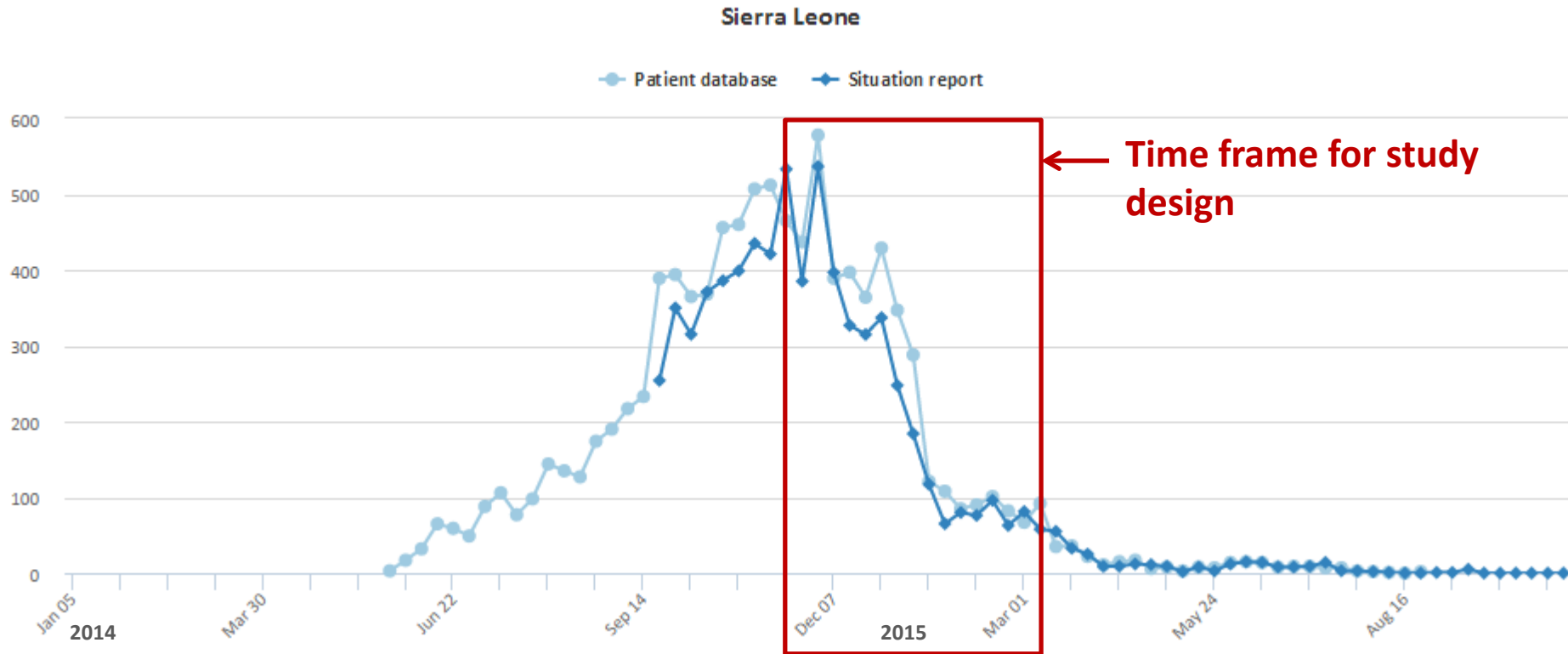
Potential roadblocks for initiating vaccine trials

Ebola outbreak: Guinea health team killed

Africa

19 September 2014 | Africa

http://www.bbc.com/news/world-africa-29256443

Eight members of a team trying to raise awareness about Ebola have been killed by villagers using machetes and clubs in Guinea, officials say.

Correspondents say many villagers are suspicious of official attempts to combat the disease.

Bad science & toxic politics; Misstep that ruined Ghana's Ebola Vaccine Trial

24 October 2015

http://graphic.com.gh/features/opinion/
52057-bad-science-toxic-politics-misstep-that-ruined-ghana-s-ebola-vaccine-trial.html

Presumably, Ghana still awaits the verdict of its Parliament, almost four months after the legislature halted Ebola vaccine trials on the back of fears emanating from arguments of the Ghana Academy of Arts and Sciences (GAAS) that the vaccine trials amounted to importing Ebola Virus Disease (EVD) into Ebola-free Ghana!

In spite of all the science to the contrary, the GAAS, led by its task force, took the position that **"In Phase II Clinical Trials, patients are used as subjects. Ghana has not recorded cases of EVD. The trial being envisaged therefore necessitates either importing patients, who have had the disease or infecting volunteers, and thereby introducing Ebola into a hitherto Ebola-free Ghana."**

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blog.Bioethics.gov

THE BLOG OF THE PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

In Rush to Develop Ebola Therapies, a Debate Over Placebo Control

Written by *Matthew Davis* on *February 5, 2015* — Leave a Comment

This morning the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) resumed consideration of U.S. engagement in the global response to the current Ebola epidemic by examining ethical issues that arise when conducting research during a public health emergency.

As experts move to accelerate development of drugs and vaccines against Ebola, a debate has emerged over whether these therapies should be evaluated with the placebo randomized control approach. This type of research involves clinical trials in which one group of volunteers receives the actual vaccine or drug candidate and another group receives a placebo.

Many clinicians consider the placebo-control approach to be the gold standard for determining the efficacy of a new treatment. But tension in western Africa today involves how scientists and policy makers should prioritize humanitarian and scientific concerns as they address both the immediate crisis and seek evidence that can be applied to future outbreaks.

http://blog.bioethics.gov/2015/02/05/in-rush-to-develop-ebola-therapies-a-debate-over-placebo-control/

Rejection of Ebola Vaccine trial a sad day for science – Prof. Dodoo

Source: Ghana|myjoyonline.com|Edwin Appiah|edwin.appiah@myjoyonline.com
Date: 11-06-2015 Time: 11:06:56:am

http://www.myjoyonline.com/news/2015/June-11th/
rejection-of-ebola-vaccine-trial-a-sad-day-for-science-prof-dodoo.php

Associate Professor of the University of Ghana Professor Alex Dodoo has condemned the reaction of politicians to an Ebola Vaccine trial in Ghana after Parliament ordered its suspension.
"People have gotten it so wrong and it is sad. It is sad for the country, it is sad for science" he lamented.
Parliamentarians took turns yesterday to condemn moves to have an Ebola Vaccine trial in the Volta region.

Some Regulatory Perspective

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Regulatory Pathways for Licensure and Use of Ebola Virus Vaccines During the Current Outbreak FDA Perspective

Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

WHO Consultation on Ebola Virus Vaccines
Geneva, September 29, 2014

http://www.who.int/immunization/diseases/ebola/Finn_WHO_Sept_29_2014.pdf

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Perspective

Evaluating Ebola Therapies — The Case for RCTs

Edward Cox, M.D., M.P.H., Luciana Borio, M.D., and Robert Temple, M.D.

N Engl J Med 2014; 371:2350-2351 | December 18, 2014 | DOI: 10.1056/NEJMp1414145

Share:

Article | References | Citing Articles (10)

The worst Ebola epidemic in history is ongoing. With the number of deaths from Ebola virus

http://www.nejm.org/doi/full/10.1056/NEJMp1414145

- Traditional versus Accelerated Approval versus "Animal Rule" (when human efficacy studies cannot be conducted)
- Expectation of Adequate, Randomized Well-Controlled Studies
  - **Traditional approval:** protection against disease endpoints
  - **Accelerated approval:** use of a surrogate endpoint that is reasonably likely... to predict clinical benefit

Possible study designs
Individually randomized controlled trial (iRCT)

- Widely acknowledged as gold standard for demonstrating vaccine efficacy

- Operationally difficult, but not impossible in Ebola setting

- **Liberia PREVAIL Phase2/3 study:** began March 2015
  - double-blind ~27,000 randomized to placebo, ChAd3-EBOZ (NIAID/GSK) or VSV-ZEBOV (developed by Public Health Agency of Canada, licensed to NewLink Genetics & Merck)
  - Patient recruitment was suspended in September 2015, working to extend into Guinea
  - Initiated natural history study of Ebola survivors in June 2015

- **Sierra Leone STRIVE Phase 3 study:** began April 2015
  - unblinded ~8000 front line workers randomized to immediate or delayed vaccination
  - As of June 2015, ~ 6000 enrolled with half vaccinated

Possible study designs
Ring vaccination trial
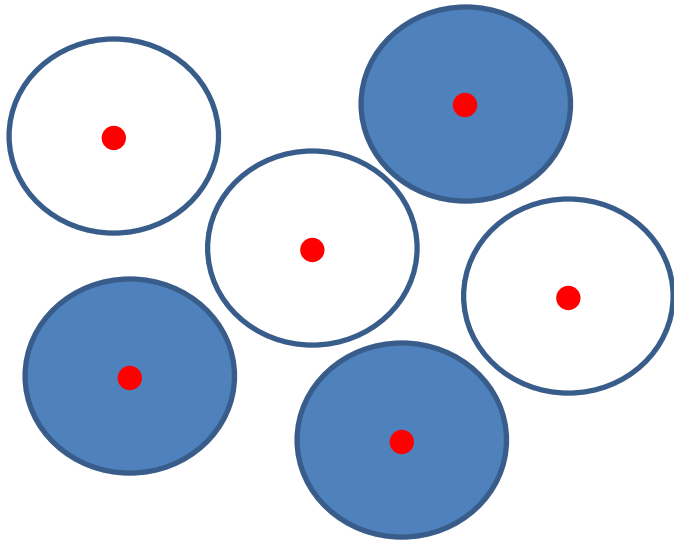
- Recruits those at highest risk of infection (ring), e.g., those socially or geographically connected to a **case**

- The ring is randomized to **immediate** vs delayed (control) vaccination

- Estimate vaccine efficacy by comparing incidence among those enrolled in study, vaccine effectiveness by comparing incidence among all members of rings, including those not eligible for study

- **Guinea Ebola ça suffit ring vaccination trial:**
  - rVSV-ZEBOV vaccine, began April 2015
  - 190 rings, ~10,000 subjects

Possible study designs
Stepped-wedge cluster design

Vaccine	1
Control — Vaccine	2
Control — Vaccine	3
Control — Vaccine	4
Control — Vaccine	5
	...
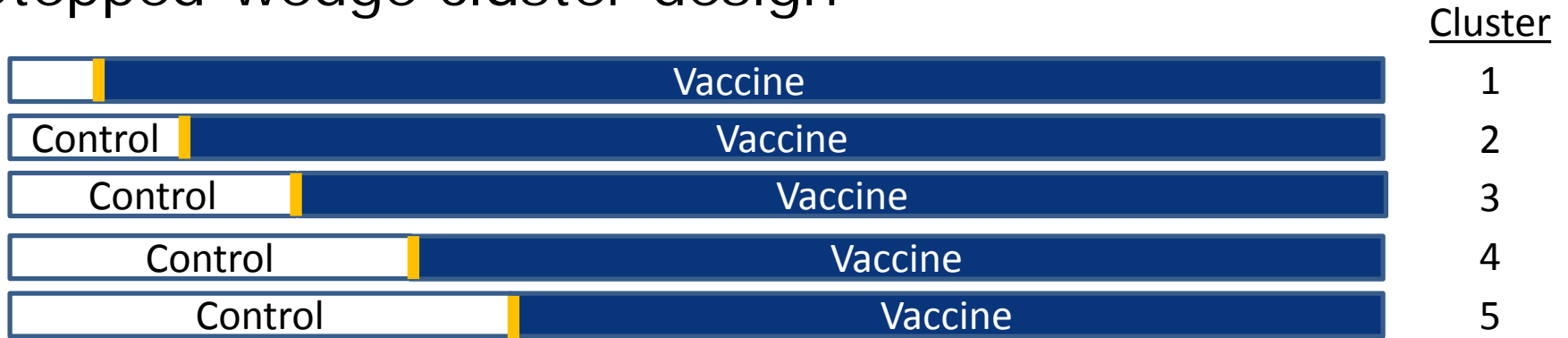
- Highlighted in literature as leading alternative to individual randomization (Cohen and Kupferschmidt, 2014)

- Different clusters sequentially rolled over to vaccination at different times helps logistical constraints

- Potential to reduce sample size: events collected prior to vaccination used as control, vaccine effect can be estimated utilizing both between and within-cluster data

- Challenged (Kotza et al, 2012), requires longer follow-up and other advantages can be achieved with traditional cluster randomized trial

- Power can be significantly reduced with permutation based test since number of clusters may be small (Bellan et al, 2015)

Possible study designs
Classic cluster randomized controlled trial (cRCT)
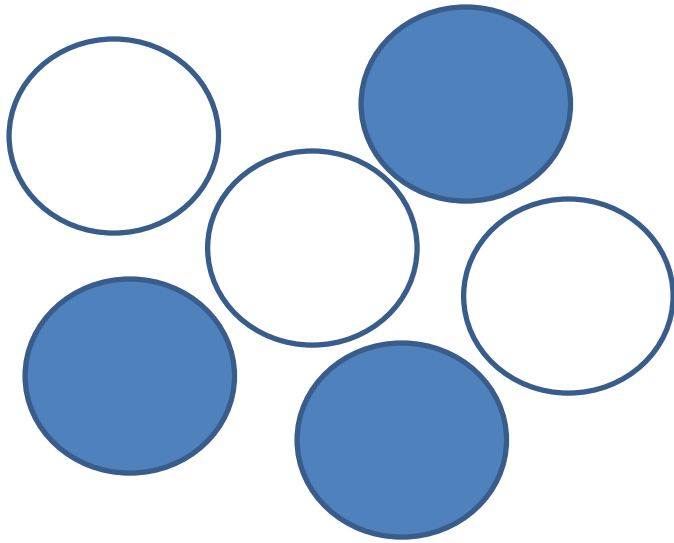
- Recruits larger clusters than ring vaccination design
  - Clusters can be small households, or larger geographical areas such as an entire village

- Clusters are randomized to **immediate** vs control (e.g., delayed vaccination)

- Similar to ring vaccination trial, can estimate vaccine efficacy by comparing incidence among those enrolled, vaccine effectiveness by comparing incidence among all members of cluster

- Alleviates some operational and ethical hurdles relative to iRCT, but requires (potentially much) larger sample sizes than iRCT, stepped-wedge and ring vaccination trials

Phase 3 Ebola Vaccine Trials

Study	Study Design	Doses/Vaccine	Sample Size
Liberia PREVAIL	Double-blind iRCT	ONE DOSE - Placebo - rVSV - ChAd3	~27,000
Sierra Leone STRIVE	Unblinded iRCT	ONE DOSE rVSV (immediate or 3 month delay)	~8000
Sierra Leone MOH/LSHTM/J&J EBOVAC	Cluster randomized (3 stages, 2 arms)	PRIME + BOOST Ad26 + MVA	Stage 3: ~800,000 (clusters of ~5000 people)
Guinea Ebola ça suffit	Ring vaccination	ONE DOSE rVSV (immediate or 21 day delay)	190 rings ~10,000 people

http://www.who.int/immunization/sage/meetings/2015/april/Henao_Restrepo_Trials_design_sageapr2015.pdf

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IA included 90 clusters

- In immediate (delayed) vaccine group, 0 (16) cases of EVD $\geq$ 10 days after randomization from 0 (7) clusters (p-value = 0.0036)

- Pre-defined p-value threshold at IA (O'Brien-Fleming) = 0.0027

- DSMB recommended randomization be stopped and continue trial with immediate vaccination of any new clusters

- Cox proportional hazard with cluster-level frailty used for analysis

Phase 3 Ebola Vaccine Trials

Study	Study Design	Doses/Vaccine	Sample Size
Liberia PREVAIL	Double-blind individually randomized RCT	ONE DOSE - Placebo - rVSV - ChAd3	~27,000
Sierra Leone STRIVE	Unblinded individually randomized RCT	ONE DOSE rVSV (immediate or 3 month delay)	~8000
Sierra Leone MOH/LSHTM/ J&J EBOVAC	Cluster randomized (3 stages, 2 arms)	PRIME + BOOST Ad26 + MVA	Stage 3: ~800,000 (clusters of ~5000 people)
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http://www.who.int/immunization/sage/meetings/2015/april/Henao_Restrepo_Trials_design_sageapr2015.pdf

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Janssen/Bavarian Nordic Ebola Vaccine Program

Accelerated development of heterologous prime-boost regimen in response to current Ebola Zaire outbreak

1. Janssen's monovalent Ad6.ZEBOV component

2. Multivalent Modified Vaccinia ankara Filovirus vaccine manufactured by Bavarian Nordic (MVA-BN-Filo)

Janssen is the sponsor and future license holder of the combination vaccine

Ad26.ZEBOV and/or MVA-BN-Filo

MVA-BN-Filo and/or Ad26.ZEBOV

First in Human (FIH) initiated End Dec 2014

months   0   *
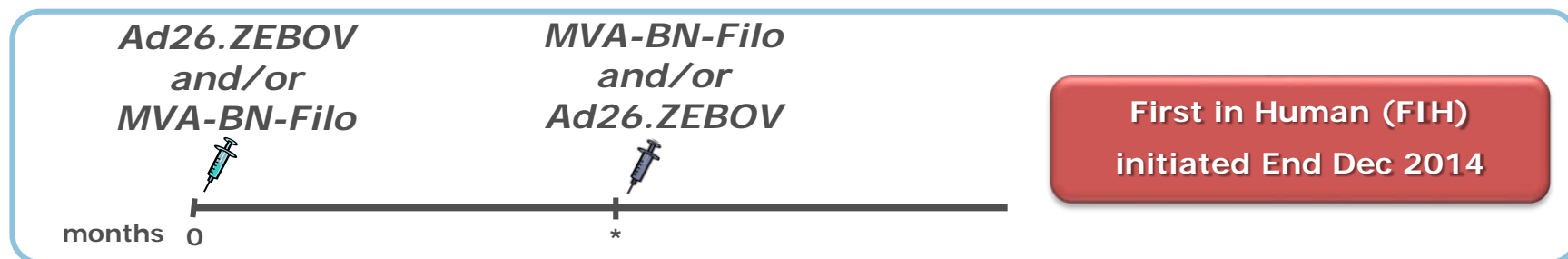
*schedules under investigation: 0/14 days, 0/28 days, 0/56 days

Statistical considerations, design rationale, challenges

- Evaluate the effectiveness of a heterologous prime-boost regimen in preventing laboratory-confirmed EVD

- Ensure unbiased evaluation with sufficient statistical power in minimum time frame

- Considerable debate on the ethical appropriateness of iRCTs in the context of an epidemic, alternative designs advocated

- Infection rates varied substantially both within and between communities (likelihood of unequal exposure to EVD between randomized groups)

- Use of clinical trial simulations as a tool to guide decisions related to study design details

- Use of dynamic transmission models to predict the evolution of the epidemic
  - Incidences likely to reduce over time

Selected study design

- Population based approach: up to 400,000 doses available by Q2 2015

- Open label cluster Randomized Controlled Trial (cRCT), randomize clusters to either

  – Immediate-vaccination

  – Control, with potential for vaccination after period of delay

- Select a number of districts in West Africa. Districts are organized by chiefdoms and they are comprised of sections (sub-regions of size ~5000). These sections were to be randomized stratified by chiefdom on historical incidence

- The vaccine would be offered to the control group in a separate setting, immediately after safety and effectiveness established

- Actual sample size depends on EVD incidence at study start and time of delay

Visual of selected study design

Clusters,
For example
sections (sub-
chiefdoms)

Stratification
Factors
For example
chiefdoms

Targeted
Study Area,
For example
districts
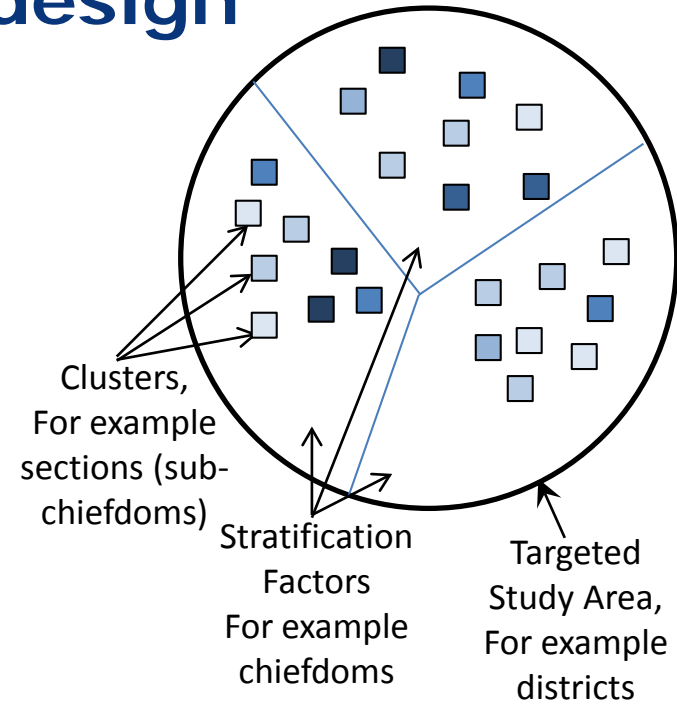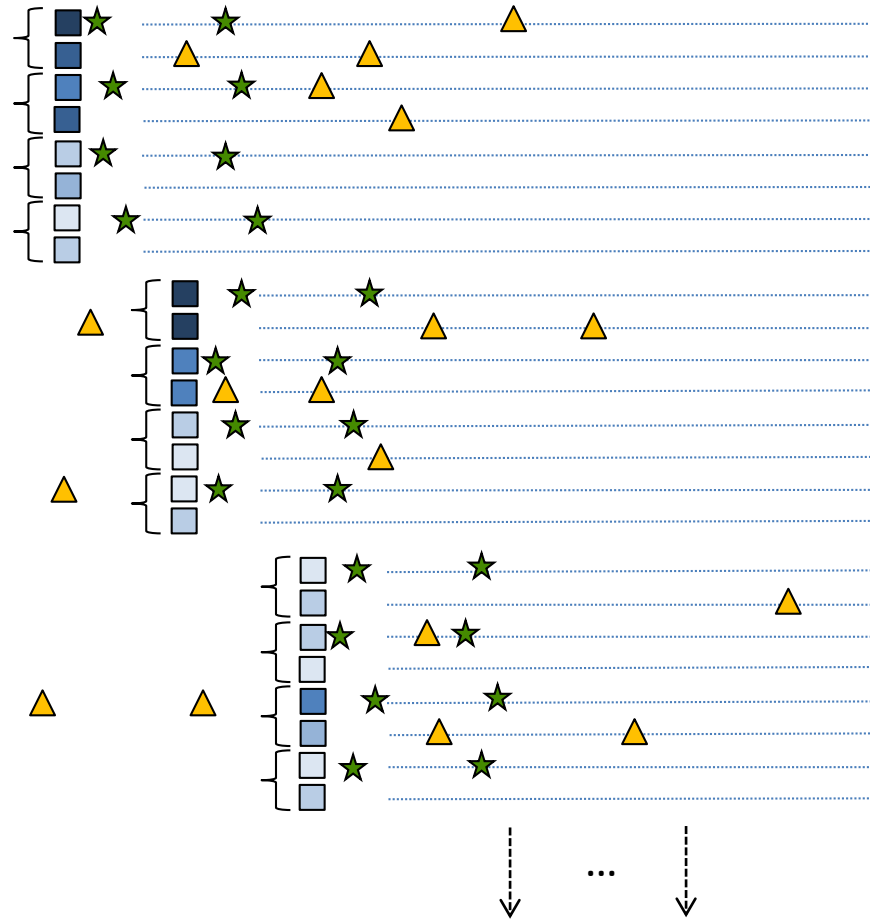
Post-randomization phase:
time-window for primary
randomized comparison

Primary analysis (timepoint derived
based on monitoring control incidence)

...

Routine surveillance for EVD

Legend

Cluster incidence

Low — High

⭐ Prime/boost vaccination

🔺 EVD event

Matched cluster pairs

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Statistical modeling and simulation objectives

- Examine Type I error and power to show vaccine effectiveness > 0 (target 65%) using cluster randomized trial under varying assumptions of EVD incidence

- Evaluate impact of possible unequal EVD exposure between randomized groups on Type I error and power

- Identify optimal timing for analysis (optimal period of delay) for varying assumptions of EVD incidence

- Develop adaptive rules for defining delay period, utilizing real-time monitoring of EVD incidence in clusters randomized to control

- Evaluate possibility of terminating study if feasibility to establish effectiveness unlikely due to low incidence (i.e., "operational futility")

Statistical methods

- **<u>Primary analysis</u>:** compare all observed Ebola cases occurring after randomization in the immediate vaccination clusters with all observed Ebola cases in the same time span in the control group clusters

  - Study under field conditions ⇔ estimating vaccine effectiveness (direct + indirect effects of vaccination) rather than vaccine efficacy (direct effects of vaccination only)

- **<u>Two statistical methods</u>**

  - Conditional Poisson test: commonly used in vaccine development to monitor rare safety and/or disease events; assumes sum (over clusters) of the binomial means are equal for both groups, which is approximate at best

  - Permutation test: likely to suffer loss of power compared to conditional Poisson test, but will be valid even with differential exposure between randomized groups

Statistical methods (cont.)

- **<u>Conditional Poisson test</u>:**

  - Number of cases within each cluster $Binom(n_{Vi}, \pi_{Vi})$ and $Binom(n_{Cj}, \pi_{Cj})$ for cluster i within vaccine arm and cluster j within control arm

  - Assuming clusters are independent, the total number of cases in vaccine and control arm, respectively, $V = \sum_{i \in V\ arm} V_i$ and $C = \sum_{j \in C\ arm} C_j$, can be approximated by Poisson distributions with rate parameters $\lambda_V = \sum_{i\ \epsilon\ V\ arm} n_{Vi}\pi_{Vi}$ and $\lambda_C = \sum_{j\ \epsilon\ C\ arm} n_{Cj}\pi_{Cj}$

    - Conditional on the total number of cases $T = C + V$ observed, $V \sim Binom(T, p = \lambda_V/(\lambda_V + \lambda_C))$. With (approximately equal sample sizes), H_0: $VE = 0$ is equivalent to the simple binomial test H_0: $p = 0.5$

- **<u>Permutation test</u>:**

  - Treatment assignments of the clusters randomly permutated many (e.g., 5000) times, VE calculated and p-value = proportion of permutations with VE at least as large as observed VE

Statistical methods (cont.)

IMPORTANT NOTE:

- Both methods rely on observed Ebola cases only

  - No knowledge of actual number of subjects within each cluster

  - Requires assumption that number of subjects within each cluster is distributed equally across randomized groups

  - Realistic? Not sure. Advantageous? Yes, as number of subjects in the control arm (and full number in vaccination arm) would be unknown and based on most recent population census

    - For Sierra Leone, most recent census is 2004

Control incidence rates and projections

Sierra Leone weekly reported confirmed and probable cases up to July 12, dynamic transmission model fit and projections (source: LSHTM)

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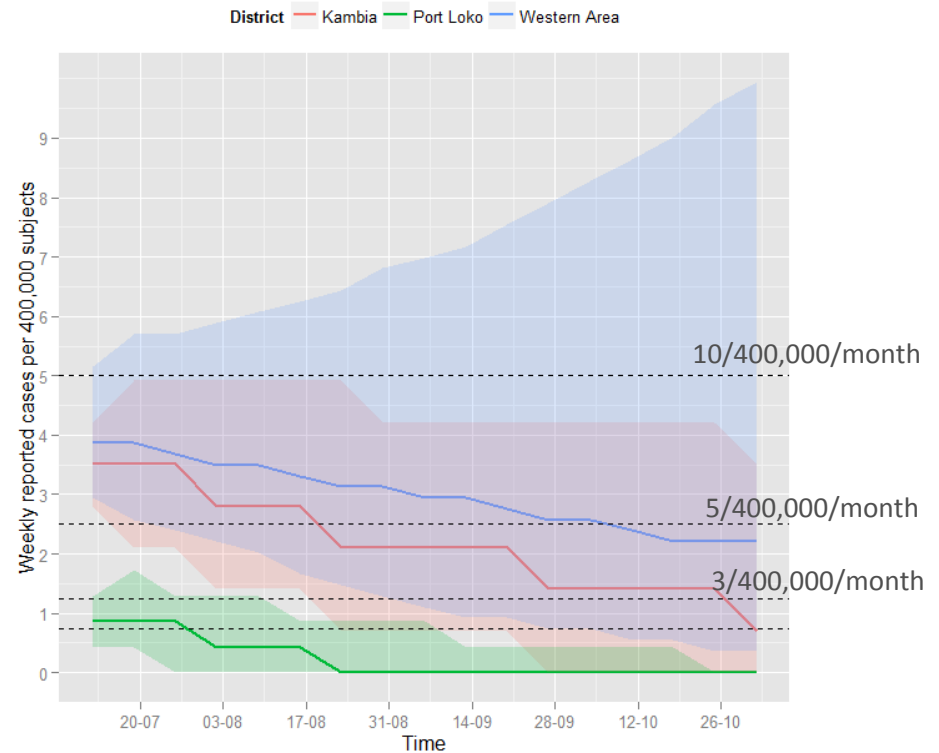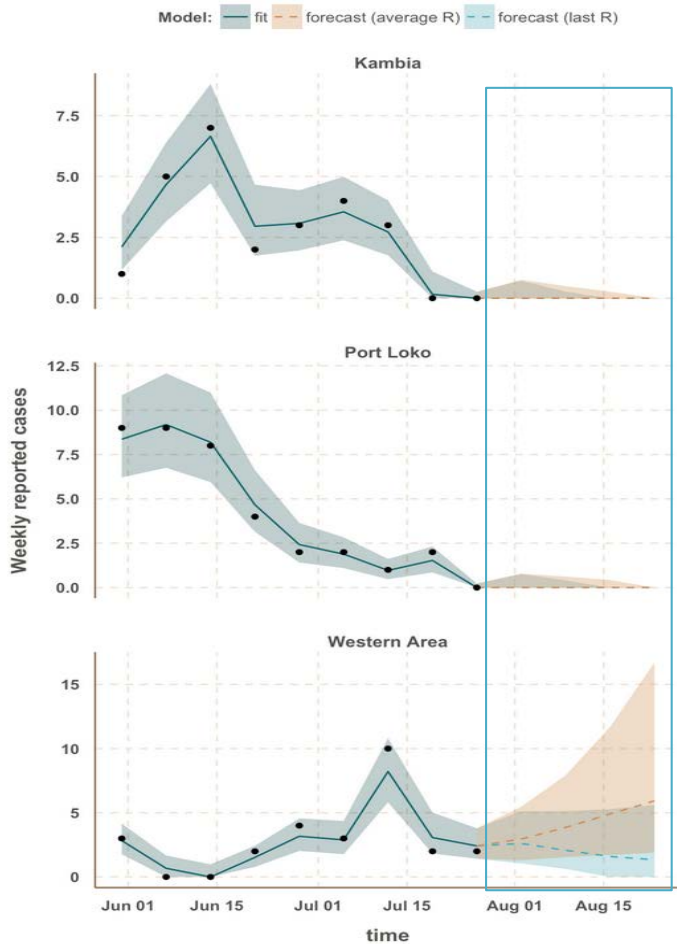
Details of simulation study

- Vaccine availability of 400,000 $\Rightarrow$ 160 clusters of size 5000 simulated, 80 assigned immediate vaccination and 80 control; 12 weeks to vaccinate all subjects

- **Intra-cluster correlation not constant!** We attempted to simulate considerable heterogeneity with mixture and random effects (+/- 20% of overall mean)

Average Control Incidence (/100,000 person-months)	Within Cluster Control Incidences (/100,000 person-months)		
	Low Incidence Clusters (+/- 20%)	Moderate Incidence Clusters (+/- 20%)	High Incidence Clusters (+/- 20%)
5	2	10	16
2.5	1	5	8
1.25	0.5	2.5	4
0.75	0.25	1.5	2.75

  - Two randomization schemes: "controlled" ensures equal exposure between groups, and "simple" may result in differential exposure

- For each subject, generate event time for EVD under control using exponential. If randomized to vaccine, multiply event time by 1-VE, VE varied maximum 50%, 65%, 80%

  - Count number of events within each cluster and defined follow-up

Simulation results: Type I error

Average Control Incidence (/100,000 person-months)	Controlled Randomization Conditional Poisson			Simple Randomization Conditional Poisson			Simple Randomization Permutation Test		
Follow-up Time (weeks):	12w	16w	20w	12w	16w	20w	12w	16w	20w
5	2.2	2.1	2.3	7.5	8.5	9.8	2.0	2.3	2.4
2.5	1.7	1.9	1.9	4.9	5.1	5.7	1.9	2.4	2.3
1.25	1.5	2.0	1.7	2.7	3.3	4.1	1.6	1.6	1.8
0.75	1.8	1.8	2.1	2.5	2.7	3.3	1.7	1.6	1.8

Based on 5000 simulations, with 80 clusters of size 5000 per study arm
Assumes 12 weeks to vaccinate (prime) all immediate vaccination clusters and (0, 28) day prime/boost schedule
Controlled Random Allocation accounts for heterogeneity through matching on baseline Ebola incidence
Simple Random Allocation does not account for heterogeneity through matching on baseline Ebola incidence
Low, Moderate and High incidence clusters account for 70%, 20%, and 10% of total clusters, respectively
12 w, 16 w 20 w corresponds to 12, 16 and 20 weeks minimum follow-up time, respectively

- Permutation test required to control Type I error

Simulation results: Power

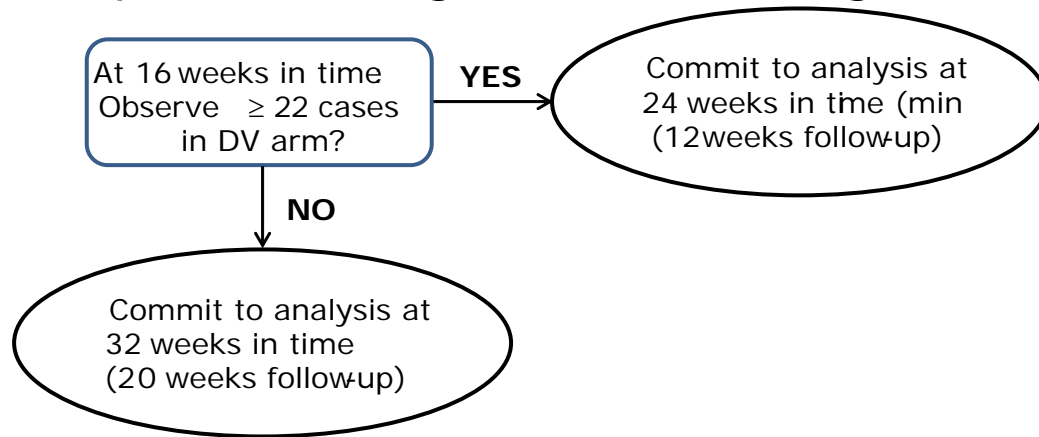| Average Control Incidence (/100,000 person-months)	65% VE Conditional Poisson			65% VE Permutation Test			80% VE Permutation Test		
Follow-up Time (weeks):	12w	16w	20w	12w	16w	20w	12w	16w	20w
5	99.6	99.9	>99.9	97.7	98.9	99.3	99.8	>99.9	>99.9
2.5	92.6	96.8	98.4	86.8	92.9	95.2	95.1	99.0	99.9
1.25	68.3	78.5	85.1	62.3	71.4	78.5	75.6	90.1	96.1
0.75	45.1	54.9	62.8	35.8	46.2	53.4	49.7	67.1	80.2
Based on 5000 simulations, with 80 clusters of size 5000 per study arm Assumes 12 weeks to vaccinate (prime) all immediate vaccination clusters and (0, 28) day prime/boost schedule with Simple Random Allocation Low, Moderate and High incidence clusters account for 70%, 20%, and 10% of total clusters, respectively 12 w, 16 w 20 w corresponds to 12, 16 and 20 weeks minimum follow-up time, respectively									

- Slight reduction in power when using Permutation test

- Incidence of 1.25/100,000 person-months provides at least ~80% power to conclude vaccine is effective (true VE = 65%)

- 12 weeks follow-up sufficient for incidence of at least 2.5/100,000, need 20 weeks follow-up for incidence of 1.25/100,000 or less

Adaptive decision rule

- The follow-up time used in the study was proposed to be adaptive in nature

  - Based on a statistical decision rule at a specific point in time (e.g., 4 weeks after all subjects in immediate vaccinated arm are vaccinated)

  - Based on evaluating incidence in the control arm where minimum follow-up time could be maintained or extended to ensure sufficient power

- Various rules were assessed through simulation

Adaptation rule

Flexible follow-up monitoring rule (assuming 12 weeks to vaccinate):

At 16 weeks in time
Observe ≥ 22 cases
in DV arm?

YES → Commit to analysis at 24 weeks in time (min (12 weeks follow-up)

NO → Commit to analysis at 32 weeks in time (20 weeks follow-up)

Average Control Incidence (/100,000) person-months	Probability define minimum follow-up time equal to		Type I error	Power	
	12w	20w		65% VE	80% VE
5	> 99.9	< 0.1	2.0	97.7	99.8
2.5	65.6	34.4	2.0	92.6	99.0
1.25	0.8	99.2	1.9	78.5	96.1
0.75	< 0.1	> 99.9	1.8	53.4	80.2

Based on 5000 simulations, with 80 clusters of size 5000 per study arm
Assumes 12 weeks to vaccinate (prime) all immediate vaccination clusters and (0, 28) day prime/boost schedule with Simple Random Allocation
Low, Moderate and High incidence clusters account for 70%, 20%, and 10% of total clusters, respectively
12 w, 16 w 20 w corresponds to 12, 16 and 20 weeks minimum follow-up time, respectively

Operational futility

- Can we evaluate possibility of terminating study if feasibility to establish effectiveness unlikely due to low incidence (i.e., "operational futility")

- Turns out this yields a non-trivial reduction in power, and >5% probability of stopping study when there was adequate statistical power to show vaccine effectiveness

- Declaring futility not predictive of later study success (highly undesirable)

- Operational futility rules not further considered

Discussion

- A cluster randomized controlled trial implemented with permutation based inference can provide robust inference with less efficiency than an iRCT (higher sample size), but with the advantage of greater operational ease and potentially wider community acceptance

- The long tail of epidemic makes implementing efficacy/effectiveness trials difficult, but also highlights importance of durability of protection and wide spatial coverage

- A large scale population based approach may potentially provide best protection to prevent further EVD transmission

- Modeling and simulating the trial design under various scenarios and assumptions based on the most currently available data was extremely useful in guiding study design decisions

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Stijn Vansteelandt (Ghent University)

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Conall Watson (LSHTM)   John Edmunds (LSHTM)

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