Norwegian Institute of Public Health

The Ebola Vaccine Experience: Cluster Randomisation and Implications for HCV Trial Design

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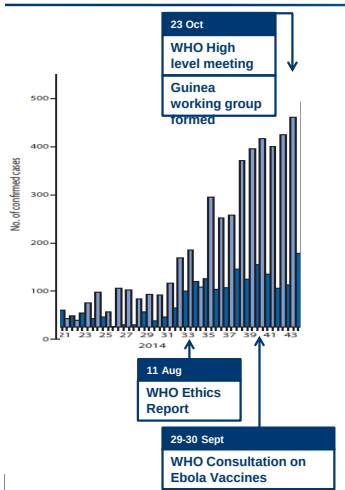
Foto: Daniel Berehulak, The New York Times


The Ebola epidemic 2014-2016
28 646 cases
11 323 deaths
(March 27, 2016)
Foto: Daniel Berehulak, The New York Times

Challenging to predict outbreak curve and future needs

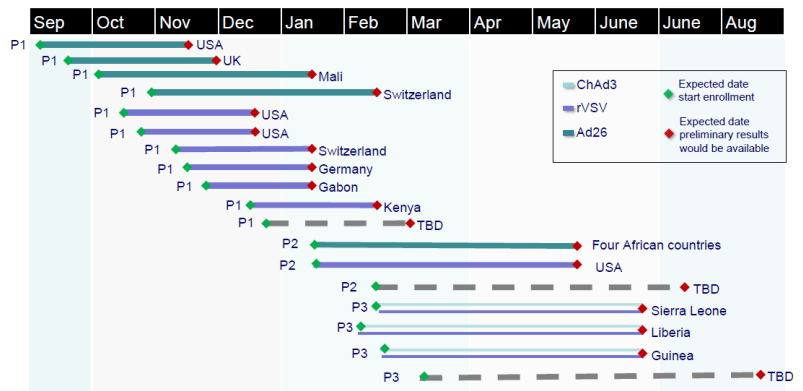


Predictions

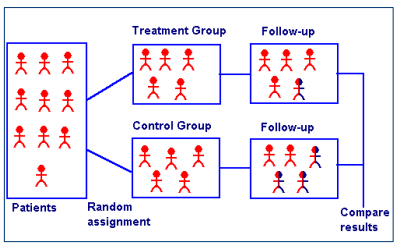
WHO: **20 000** before Nov-14

CDC : 500'-**1.4 mill** before Jan-15

16-18 clinical trials in a year



Randomized controlled trial (RCT) is the gold-standard for clinical vaccine trials

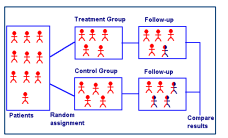


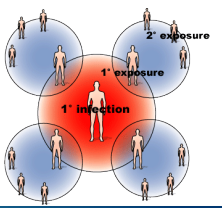
- Scientific validity
  - Causality assessment
  - Balancing confounding factors
  - Minimizing bias
  - Regulatory requirements
- Fair subject selection

Is an RCT optimal in outbreak settings?

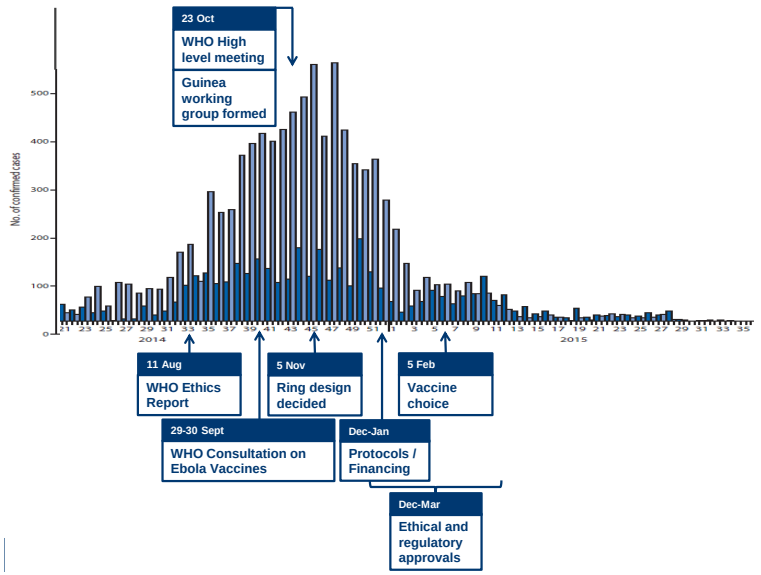
What is the ideal study design?

- **Randomized controlled trial**
  - Classical clinical trial
  - Placebo group
  - Large sample size
- **Stepped wedge**
  - Secures vaccination of all participants
  - Gradual introduction of vaccine; unvaccinated serve as control
  - Large sample size
- **Ring vaccination**
  - Smallpox eradication
  - Secures vaccination of all participants
  - Delayed vaccination of half of rings
  - Lower sample size due to high attack rate

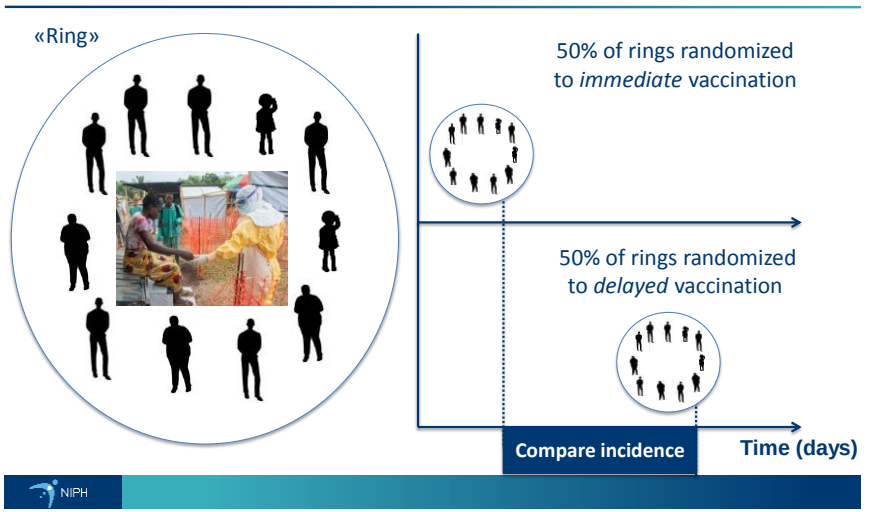




Planning an efficacy study during an epidemic



Guinea vaccine trial working group *Ebola ça suffit!*
Ring vaccination



Advantages with ring vaccination - reactive cRCT vs proactive iRCT

- Prioritize vaccine to those at highest risk
- Distributive justice with randomization
- Experimental comparison of vaccinated and non-vaccinated
- All participants receive vaccine (3 weeks delay for control group)
- Timely results - attack rate at the level of the ring is higher (higher risk individuals)
- Contact tracing as recruitment facilitates active community engagement

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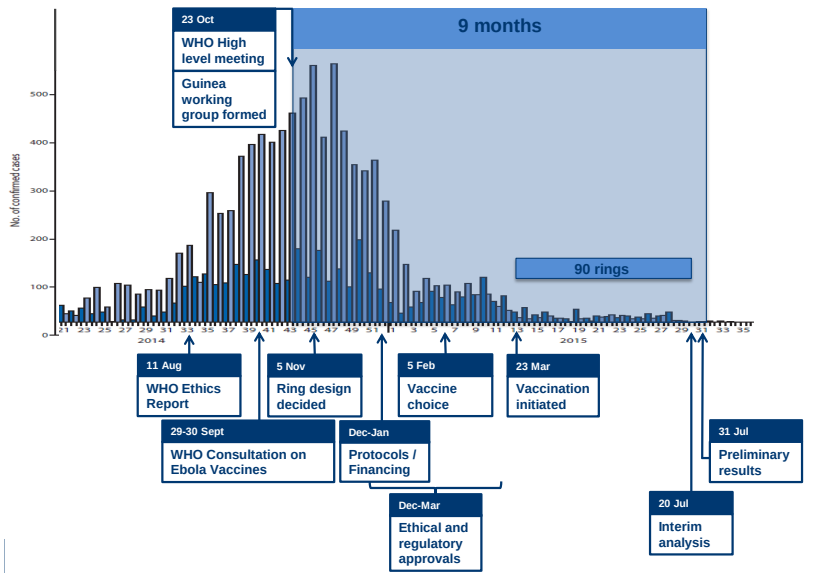
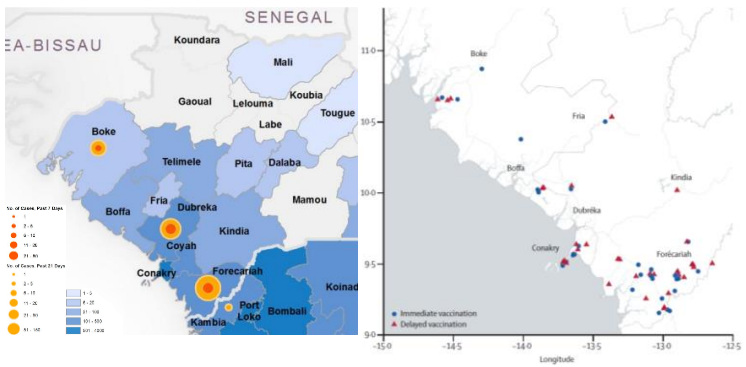
Planning an efficacy study during an epidemic

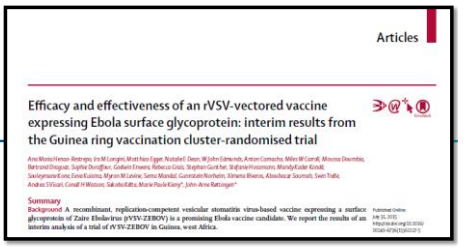


Trial design follows the outbreak geographically



Each ring visited **at days 0, 3, 14, 21, 42, 63, and 84** post-vaccination to document the potential occurrence of any serious adverse events

Inclusion of study subjects


Articles

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

Summary

Total *n* = 7651 included

Randomized immediate vaccination

n = 4123

Excluded (<18 yrs, pregnant/ breast-feeding) : 1088

Remaining *n* = 3035

Vaccinated individuals : *n* = 2014

Randomized delayed vaccination

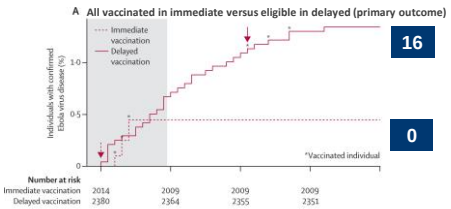
n = 3528

Excluded (<18 yrs, pregnant/ breast-feeding) : 1148

Remaining *n* =2380

Vaccinated individuals : *n* = 1498

Interim results for 90 rings per 20th July 2015



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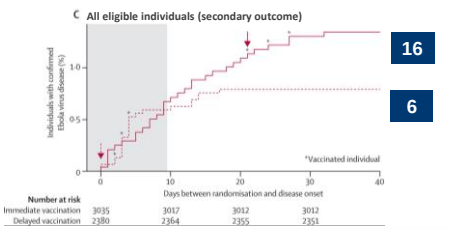
Vaccine *efficacy*: 100%
95% CI 74.7 – 100%
***p* = 0.0036**



16

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Vaccine *effectiveness*: 75%
95% CI -7.1 – 94.2
***p* = 0.1791**

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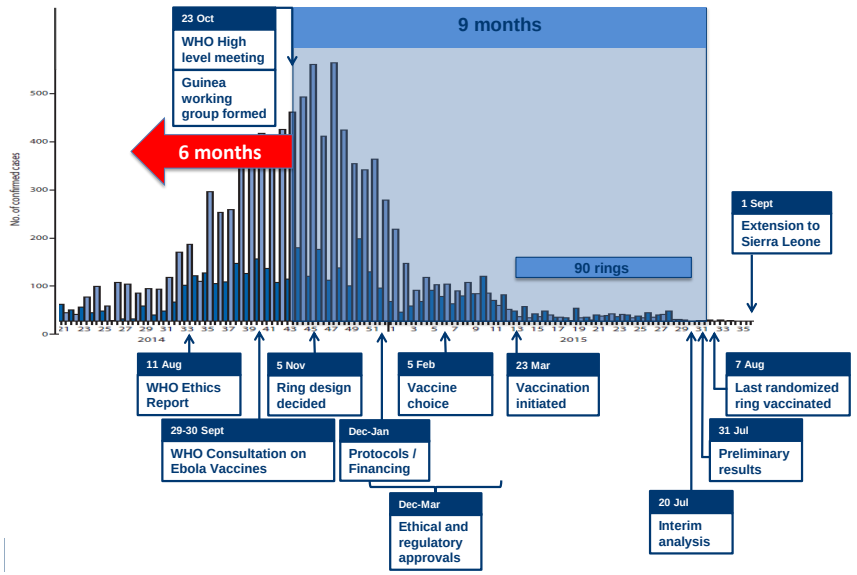
Henao-Restrepo et al. Lancet July 31st 2015

Planning an efficacy study during an epidemic



What can this teach us regarding treatment as prevention (TasP) for Hepatitis C in PWIDs?

Experience with TasP for HIV

- Treatment as prevention (TasP) for the global elimination of HIV
- WHO and UNAIDS
  - elimination threshold at one new HIV infection per 1000 individuals per year
  - diagnosing 90% of the individuals currently infected with HIV
  - treating 90% of the diagnosed
  - achieving viral suppression in 90% of treated individuals

TasP for HIV
- effect on transmission on individual level

Landmark clinical trial HPTN 052 (Cohen et al, 2011)

- 1763 couples in which one partner was HIV-1-positive and the other was HIV-1-negative
- **Intervention**: antiretroviral therapy immediately (early therapy) vs antiretroviral therapy after a decline in the CD4 count or the onset of HIV-1-related symptoms (delayed therapy).
  - The primary prevention end point was linked HIV-1 transmission in HIV-1-negative partners
- **Results**: treated individuals are less likely than untreated individuals to transmit HIV to their sex partners
  - Treating the HIV-infected partner in a discordant couple (ie, a couple in which only one partner is infected) was 96% effective in preventing HIV infection.

TasP for HIV
- effect on transmission on individual level

Prospective cohort studies

- Rural KwaZulu-Natal, South Africa (Tanser et al, Science 2013)
  - Follow up of 16,667 individuals HIV-uninfected at baseline, observing individual HIV seroconversions over the period 2004 to 2011.
  - **Results**: individual HIV acquisition risk declined significantly with increasing ART coverage in the surrounding local community.
- FSW, Kenya (McClelland et al, AIDS 2015)
  - Association between community ART coverage and FSW's risk of becoming HIV infected
    - Increasing general population ART coverage was associated with lower HIV incidence in FSWs.

TasP for HIV
-effect on transmission on population level

- ART is effective at preventing transmission in stable heterosexual couples
  - Not clear whether ART will be similarly effective at preventing HIV transmission at the population level
- Currently, four clinical trials are evaluating the effectiveness of TasP on reducing incidence
  - Interim results from the different studies are conflicting (International AIDS Conference, Durban 2016)

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TasP for HIV
-effect on transmission on population level

Modelling (Okano et al, Lancet 2016)

- Population-based study of the Danish HIV epidemic in men who have sex with men
- TasP can substantially reduce a country's HIV epidemic, and bring it close to elimination under optimal conditions: very high treatment coverage, and exceptionally high (98%) viral suppression rate.
- Unless these extremely challenging conditions can be met in sub-Saharan Africa, the WHO's global elimination strategy is unlikely to succeed.

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TasP for HIV
-effect on transmission on population level

Modelling

- The contribution of ART and reductions in injecting risk for reducing HIV incidence in PWID (Fraser et al, Int J Epidemiol, 2016)
  - Projections suggest
    - Decrease in injecting risk reduced HIV incidence by 76% (63-85%) and ART further reduced HIV incidence by 8% (2-19%), or on its own by 3% (-34 - 37%)
  - Conclusion
    - Observed declines in HIV incidence in Vancouver between 1996 and 2007 should be seen as a success for intensive harm reduction, whereas ART probably played a small role.

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What can this teach us regarding (early vs delayed) treatment as prevention (TasP)

for Hepatitis C in PWIDs?

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Impact of HCV treatment on population level -evidence of effect

- Mathematical modelling
  - Numerous epidemiological modelling studies in different target groups (PWID, prisons, msm) support decrease in population prevalence through treatment as prevention (TasP)
- However, no empirical data to support effect of treatment as prevention (TasP) on population prevalence

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Need empirical evidence to demonstrate that early treatment as prevention (eTasP) works for Hepatitis C in PWIDs–

Models not enough given implementation and adherence challenges

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Possible study designs for eTasP for HCV

- iRCT – early versus delayed treatment
  - Not possible to measure effect on population level – *de facto* one cohort
- Cohort – treat as many as possible early
  - Measure effect on population level by interrupted time series (ITS) design
- Controlled interrupted time series (cITS)
  - Compare cities with and without early treatment
- cRCT: identify clusters/networks of active PWID
  - Randomize clusters to early vs delayed treatment
  - Measure incidence in both groups

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Summary

- Ebola
  - Community based effectiveness trials can be conducted under difficult circumstances and demonstrate population benefits
- HIV TasP
  - Effects on individual level demonstrated in close follow up
  - Effects on population level incidence (prevention)
    - Conflicting results from models
    - Lack of empirical data – interim results not so promising
- HCV eTasP
  - Models support decrease in population incidence
  - Need for multi centre trials to establish empirical evidence for effect on population level

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C E P I

Coalition for Epidemic Preparedness Innovations

Norwegian Ministry of Foreign Affairs

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