Lecture 10
Design and analysis of randomized vaccine trials for emerging infectious disease epidemics: The case of Ebola and COVID-19

Ira Longini

University of Florida

CENTER FOR INFERENCE & DYNAMICS OF INFECTIOUS DISEASES

UF UNIVERSITY of FLORIDA

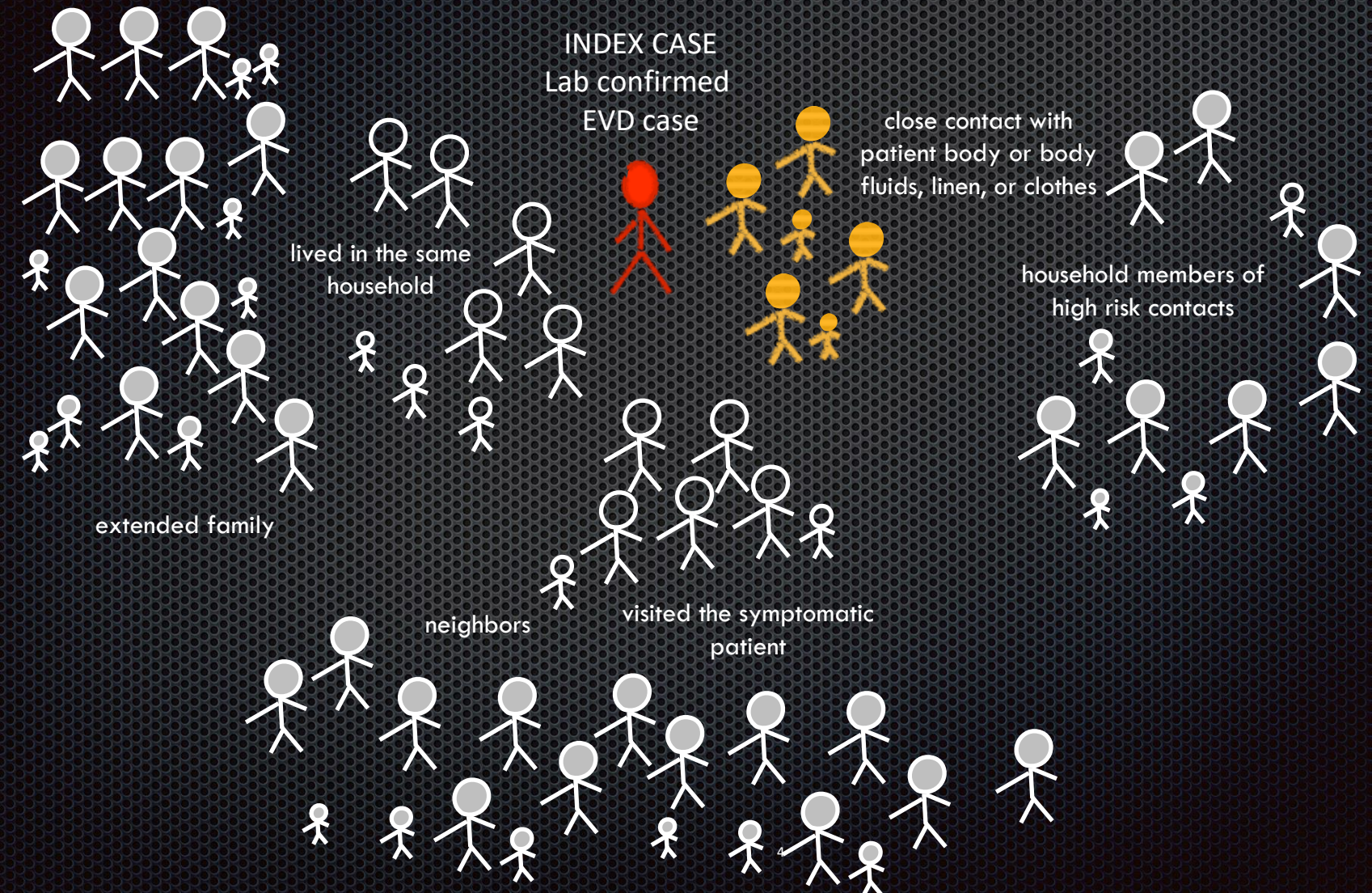
Phase III Ebola Vaccine Trial

Ring Vaccination

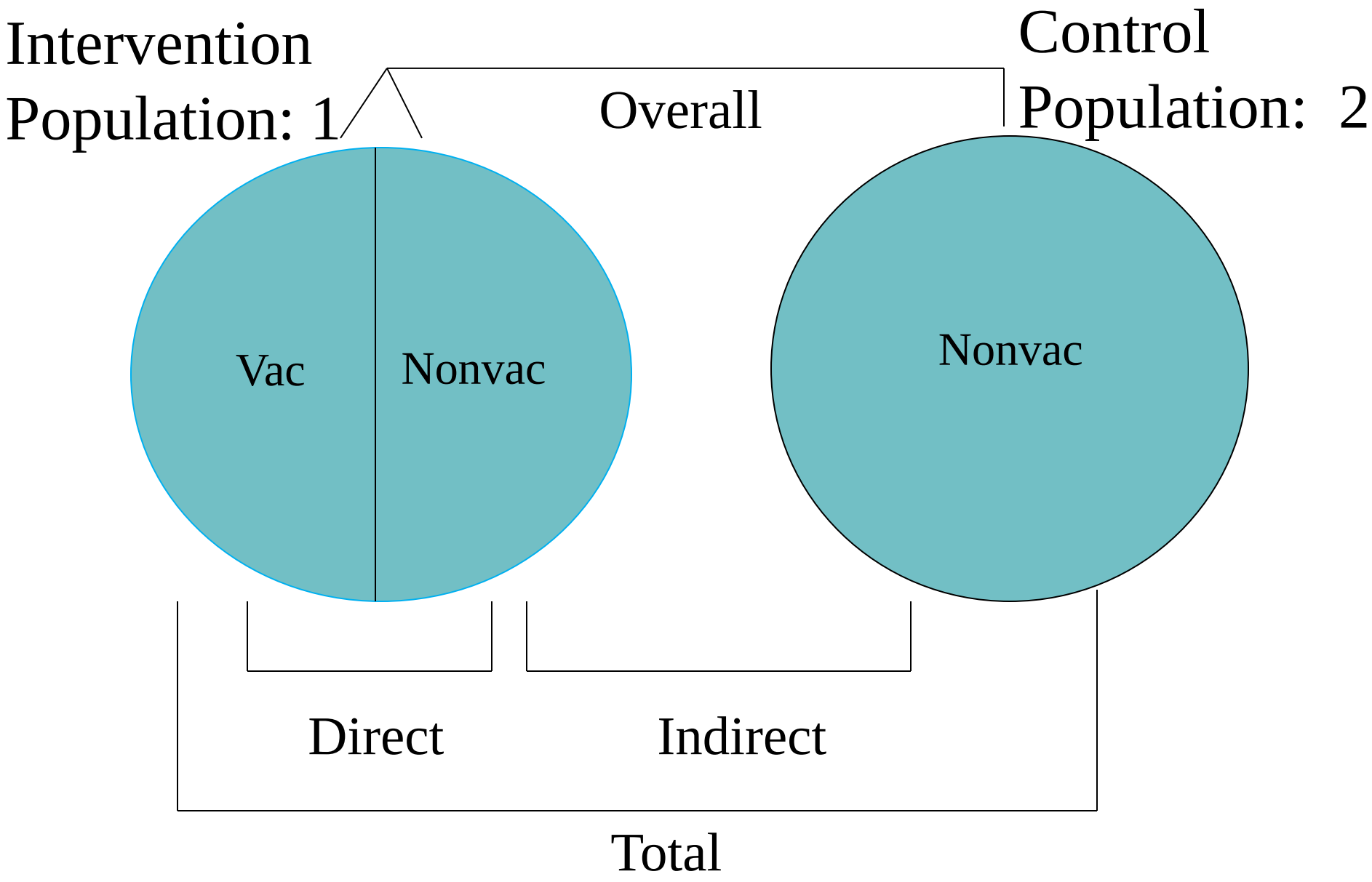
- First used during the consolidated phase of smallpox eradication in the 1970's
- Special case of surveillance and containment
  - Isolate cases
  - Quarantine contacts
- Instead of quarantine, vaccinate the contacts and contacts of contacts of index cases that are isolated

What is a vaccination ring?

Contacts and contacts of contacts

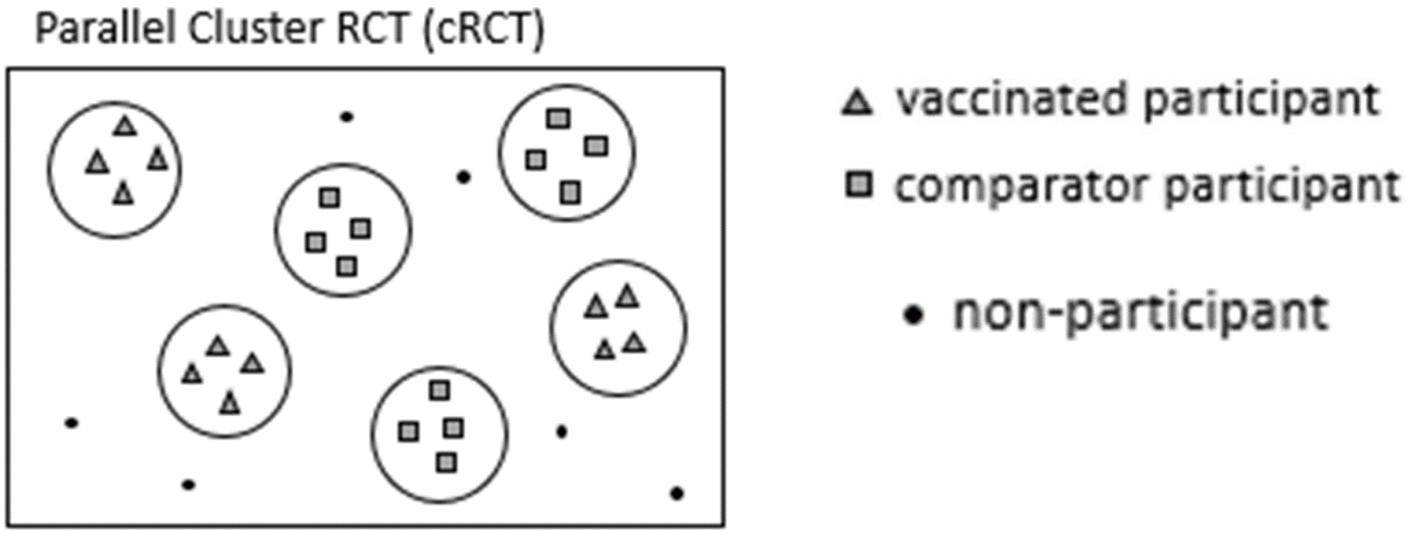


Vaccine Effectiveness



Ring vaccination randomization scheme

- Randomization across rings



Estimate total and overall effectiveness

Ebola vaccine trail in Guinea, West Africa: Case Study

Infectious disease factors for Ebola

- Transmissibility: R_0 = 1.4 - 2.0
- Speed of transmission: 10-12 days, incubation period 6 days
- Type of contact: direct to bodily fluids
- Pathogenicity: Close to 100%
- Stage of epidemic: Late
- Heterogeneity in transmission: close contact networks

Vesicular Stomatitis Virus vaccine (rVSV-ZEBOV) Merck

- Vaccine action: protection against disease; leaky
- Number of doses: one
- Immunity ramp up period: 4-7 day
  Non-human primate challenge studies
  Phase I and II human vaccine trials

thebmj

BMJ 2015;351:h3740 doi: 10.1136/bmj.h3740 (Published 27 July 2015)

RESEARCH METHODS & REPORTING

The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola

Ebola ça suffit ring vaccination trial consortium

Abstract

A World Health Organization expert meeting on Ebola vaccines proposed urgent safety and efficacy studies in response to the outbreak in West Africa. One approach to communicable disease control is ring vaccination of individuals at high risk of infection due to their social or geographical connection to a known case. This paper describes the protocol for a novel cluster randomised controlled trial design which uses ring vaccination

disease within a few weeks. When implemented as a targeted programmatic public health measure, such an approach is described as "ring vaccination."

A surveillance-containment strategy using ring vaccination was central to smallpox eradication in the 1970s. This contributed to the interruption of transmission in Africa, South America, and Asia.[2] Ring vaccination with an efficacious vaccine might similarly help to control other communicable diseases by

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*

Summary

Background A recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus (rVSV-ZEBOV) is a promising Ebola vaccine candidate. We report the results of an interim analysis of a trial of rVSV-ZEBOV in Guinea, west Africa.

Methods For this open-label, cluster-randomised ring vaccination trial, suspected cases of Ebola virus disease in Basse-Guinée (Guinea, west Africa) were independently ascertained by Ebola response teams as part of a national surveillance system. After laboratory confirmation of a new case, clusters of all contacts and contacts of contacts were defined and randomly allocated 1:1 to immediate vaccination or delayed (21 days later) vaccination with rVSV-ZEBOV (one dose of 2×10^7 plaque-forming units, administered intramuscularly in the deltoid muscle). Adults (age ≥18 years) who were not pregnant or breastfeeding were eligible for vaccination. Block randomisation was used, with randomly varying blocks, stratified by location (urban *vs* rural) and size of rings (<20 *vs* >20 individuals). The study is open label

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*These authors contributed equally

World Health Organization, Geneva, Switzerland (A M Henao-Restrepo MD,

Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

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

Summary

Background rVSV-ZEBOV is a recombinant, replication competent vesicular stomatitis virus-based candidate vaccine expressing a surface glycoprotein of Zaire Ebolavirus. We tested the effect of rVSV-ZEBOV in preventing Ebola virus disease in contacts and contacts of contacts of recently confirmed cases in Guinea, west Africa.

Methods We did an open-label, cluster-randomised ring vaccination trial (Ebola ça Suffit!) in the communities of Conakry and eight surrounding prefectures in the Basse-Guinée region of Guinea, and in Tomkolili and Bombali in Sierra Leone. We assessed the efficacy of a single intramuscular dose of rVSV-ZEBOV (2×10^7 plaque-forming units administered in the deltoid muscle) in the prevention of laboratory confirmed Ebola virus disease. After confirmation of a case of Ebola virus disease, we definitively enumerated on a list a ring (cluster) of all their contacts and contacts

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*Contributed equally

WHO, Geneva, Switzerland (A M Henao-Restrepo MD,

“...three challenges...

three fixes...”

Challenge 1

The way cases had surged in different geographic areas, thwarting efforts to design a randomized trial in which participants in each district faced the same infection risk.

Fix 1

Randomization within small groups of people – that is, among small groups of people projected to have a similar risk of exposure to the virus

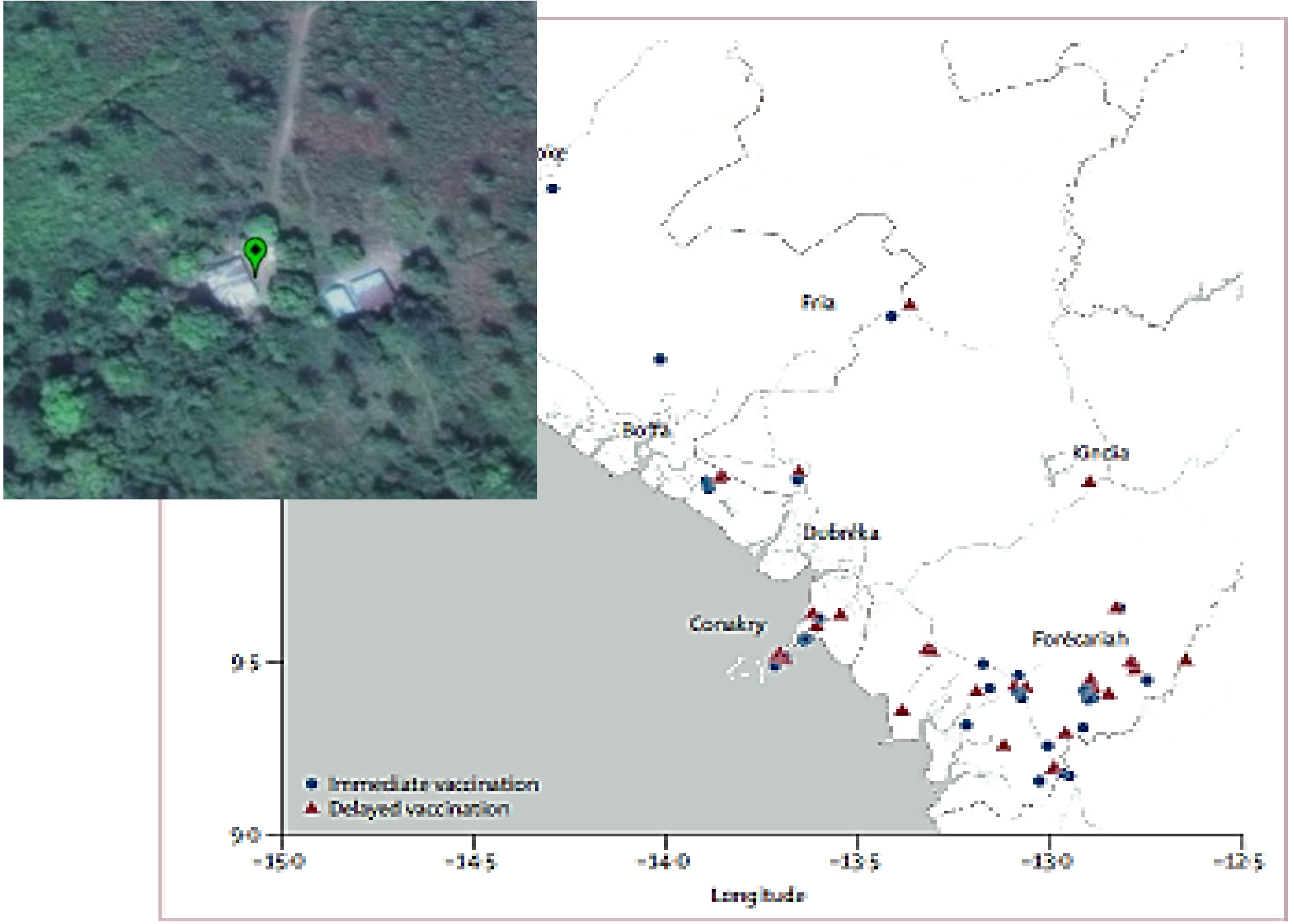
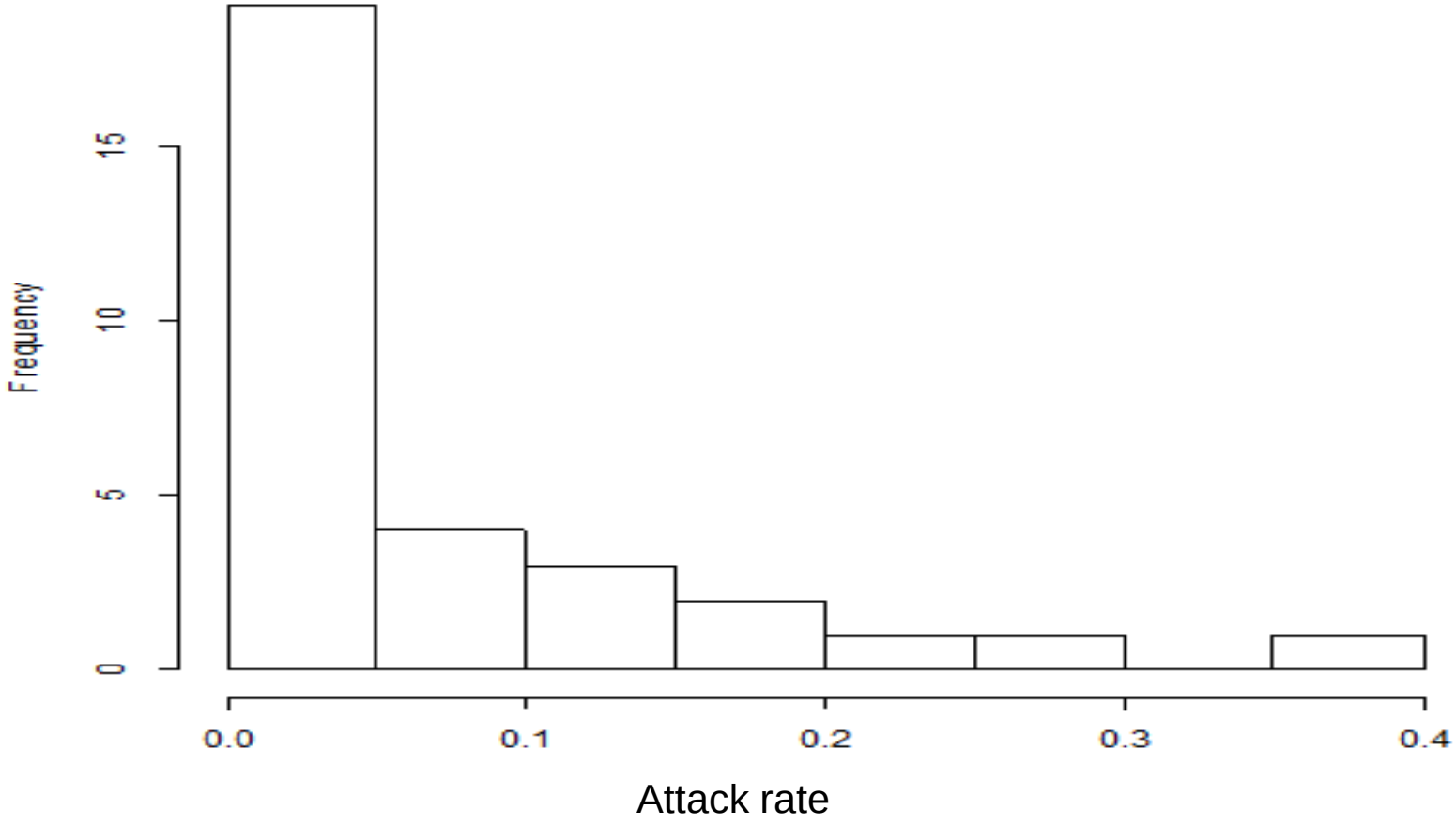


Figure 2: Study area of Ebola ça Suffit cluster vaccination trial in Basse-Guinée

Clustering: Distribution of attack rates among known contacts of Ebola cases in Guinea



Median = 0.034, Mean = 0.065, Intraclass correlation = 0.065

*Source: WHO contact tracing teams in Guinea.

How was the ring vaccination trial implemented?

The social mobilization teams explain the trial and trial procedures to the community before any action starts

Vaccination is administered immediately or after 3 weeks as defined by randomisation outcome

Why “ring” vaccination trial for Ebola epidemics in terms of numbers?

Transmission can be intense but is usually clustered in transmission units, e.g., rings, households, contact networks

Ebola epidemic in West Africa

28,454 cases of EVD so far in a combined population of 22 million people: AR = 0.13%

For RCT: Sample size per arm ≈ 21,000

- (VE = 0.7, power = 0.90, $\alpha = 0.05$ two sided)

Where do we do the trial?

Ring vaccination follows the transmission

For ring vaccination trial: AR in rings is 1-2% with a lot of variation, ICC = 0.05

Sample size per arm:

≈ 95 rings (5,000 people): two orders of magnitude smaller than RCT assuming VE = 0.7, power = 0.90, $\alpha = 0.05$ two sided, ICC = 0.05)

≈ 36 rings (1,800 people) if VE = 1.00

Actual trial at interim analysis (half-way point): For the primary analysis, there where 4,394 people in the two arms, in 90 rings*

*Henao-Restrepo, Longini, Egger, Dean, et al. Lancet (2015)

Challenge 2

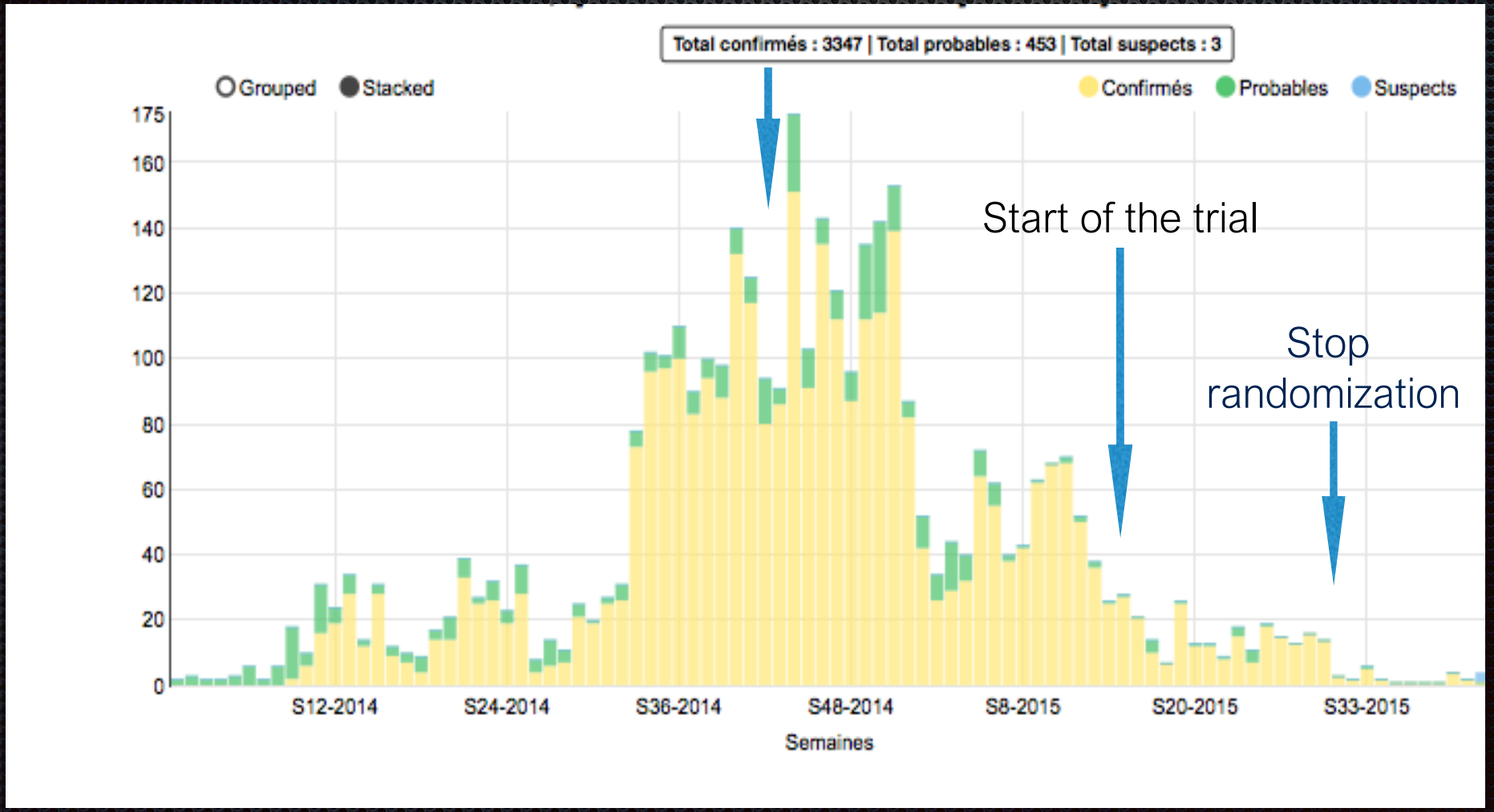
The unprecedented outbreak outpaced the speed with which clinical trials could be implemented

Fix 2

Randomization within small groups of people – that is, among small groups of people projected to have a similar risk of exposure to the virus

Cases of Ebola by week of notification of cases, Guinea 2014-15

Decision to conduct trial

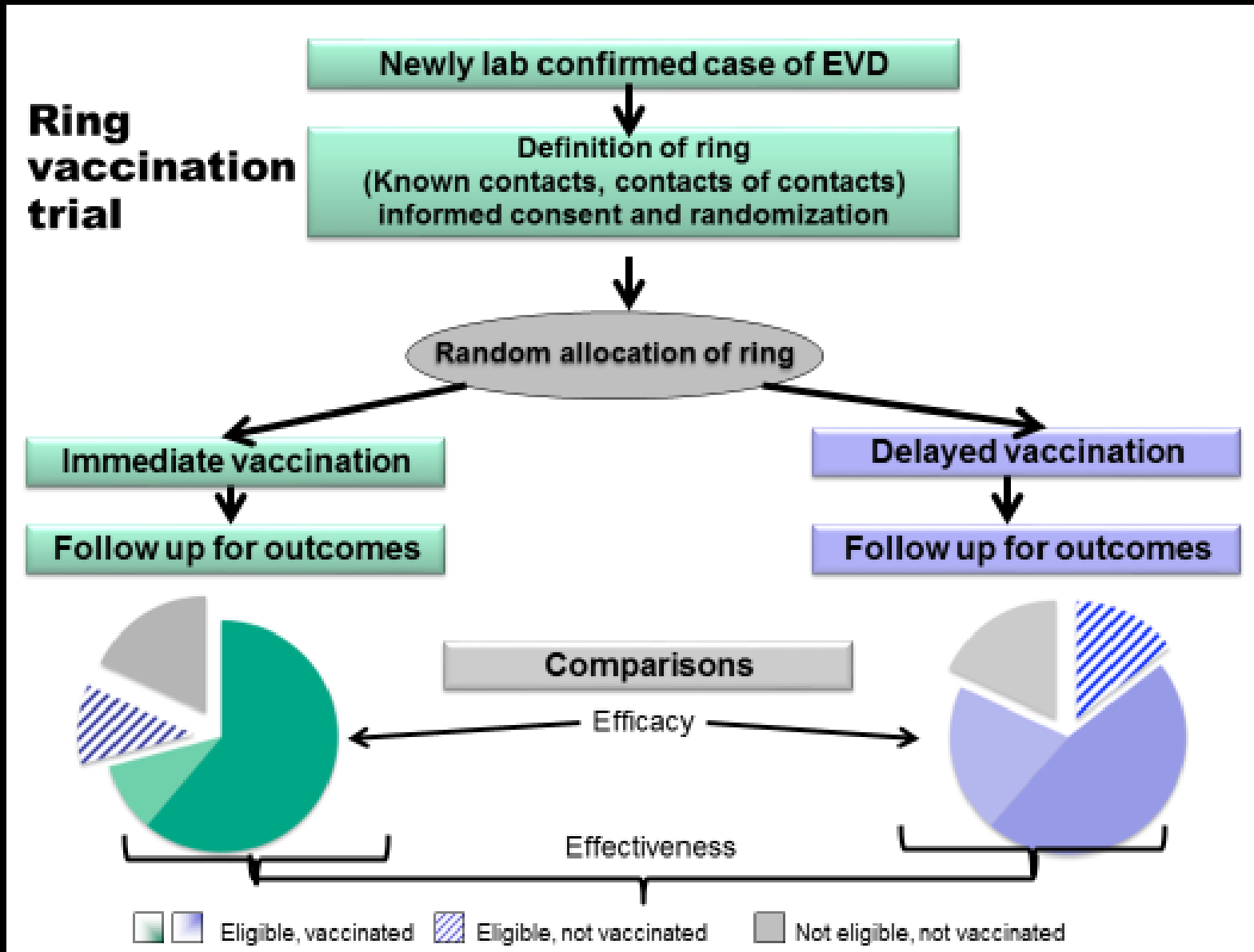


Challenge 3

The uncertainty in predicting future infection incidence

Fix 3

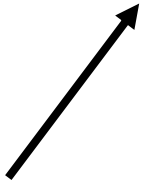
Adaptive design with real-time modifications, based on a predetermined interim analysis of study data.


Ring vaccination trial
Newly lab confirmed case of EVD
Definition of ring
(Known contacts, contacts of contacts)
informed consent and randomization
Random allocation of ring
Immediate vaccination
Delayed vaccination
Follow up for outcomes
Follow up for outcomes
Comparisons
Efficacy
Effectiveness
Eligible, vaccinated
Eligible, not vaccinated
Not eligible, not vaccinated

In the ring vaccination trial, teams go to communities with a recently confirmed Ebola case

Hazard function

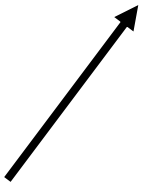
$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$



Random effect, E(Z_h) = 1

Hazard function

$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$



Hazard rate to comparison group

Hazard function

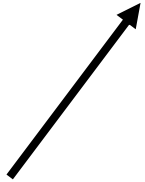
$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$

Participation indicator

Can be a function of time delays due to incubation period and immune ramp-up period

Hazard function

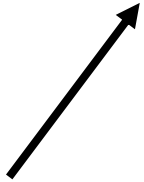
$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$



Vaccine effect, 1 - VE

Hazard function

$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$



Covariates if needed

Statistical approach for cluster-randomized trials or studies

Vaccine efficacy: $\widehat{VE} = 1 - \widehat{\lambda_1}/\widehat{\lambda_0} = 1 - \hat{\theta}$

$\widehat{\lambda_1}$ = the estimated hazard of confirmed illness in the vaccinated

$\widehat{\lambda_0}$ = the estimated hazard confirmed illness in the unvaccinated

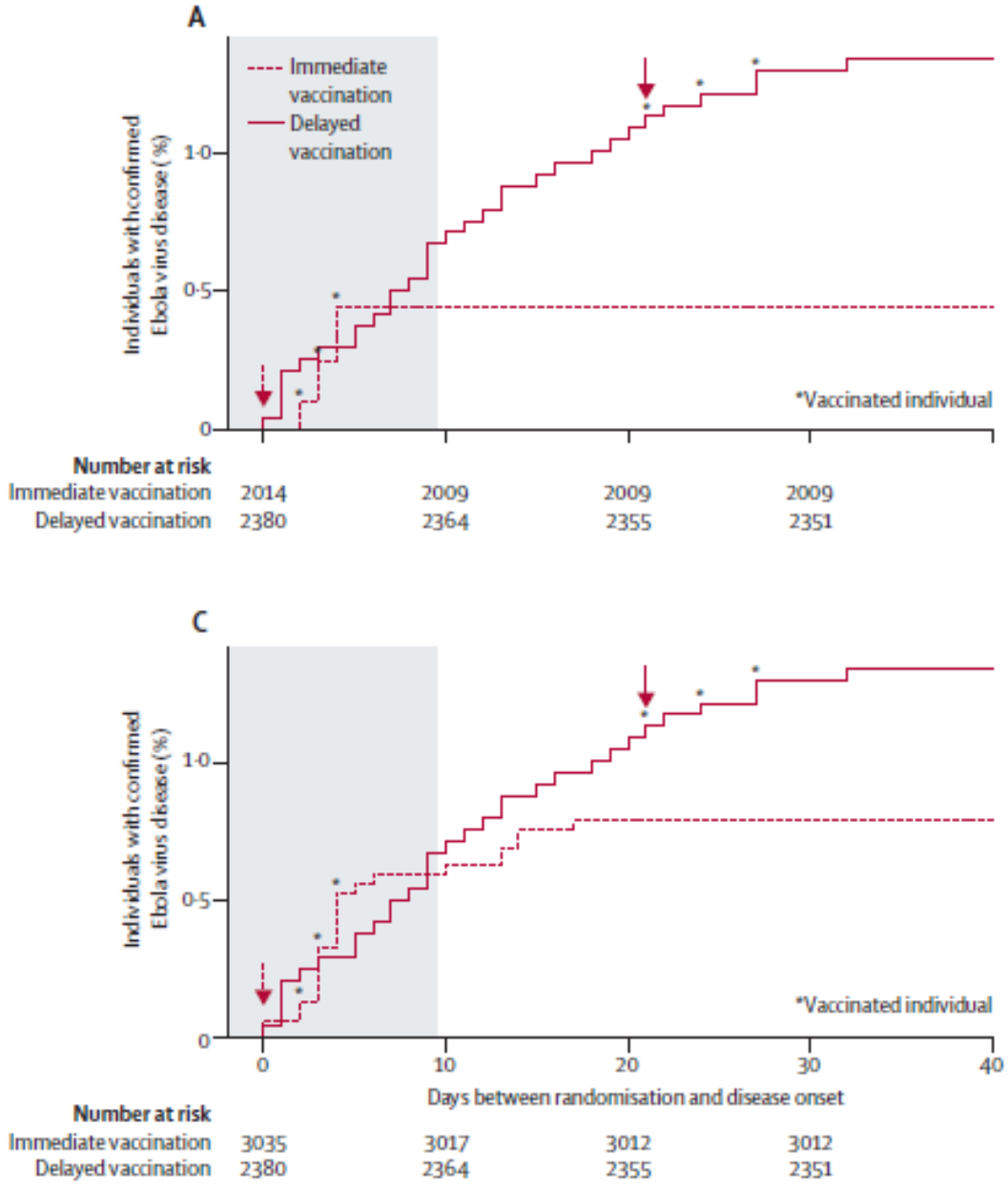
Model will be a mixed-effects, time-dependent, Cox regression model with a random effect (frailty) when there is clustering, or small sample equivalent using cumlative incidence (logist reg).

H_0: $VE = 0$ versus H_a: $VE \neq 0$.

Estimated *VE* and 95% CI

Adaptive α spending boundaries (e.g., O'Brien-Fleming)

Cumulative risk, estimates, statistics



Primary outcome:
Vaccine efficacy = 100%
95%CI [75% - 100%]
p = 0.0036

Secondary outcome:
Overall Vaccine effectiveness = 75%
95%CI [– 7% - 94%]
p = 0.1791

Source: Henao-Restrepo, Longini, Egger, Dean, *et al.* *Lancet* (2015)

What does this mean?

Vaccine efficacy is high: 75 - 100%

Ring-level overall protection is 75% with about 50% coverage

Mobile stockpile of Ebola vaccine is being used to contain and mitigate future Ebola introductions and outbreaks

Over 350,000 people have been vaccinated in the 2019 - 2021 outbreaks of Ebola in the DRC and Guinea

rVSV-ZEBOV vaccine is now licenced

Subsequent Ebola outbreaks:
All controlled with ring vaccination

Year	Country	EVD	Cases	Deaths	Case fatality
2021	Guinea	Zaire			
2021	Democratic Republic of the Congo	Zaire			
2020	Democratic Republic of the Congo	Zaire	130	55	42%
2018-2020	Democratic Republic of the Congo	Zaire	3481	2299	66%
2018	Democratic Republic of the Congo	Zaire	54	33	61%
2017	Democratic Republic of the Congo	Zaire	8	4	50%

These outbreaks are over

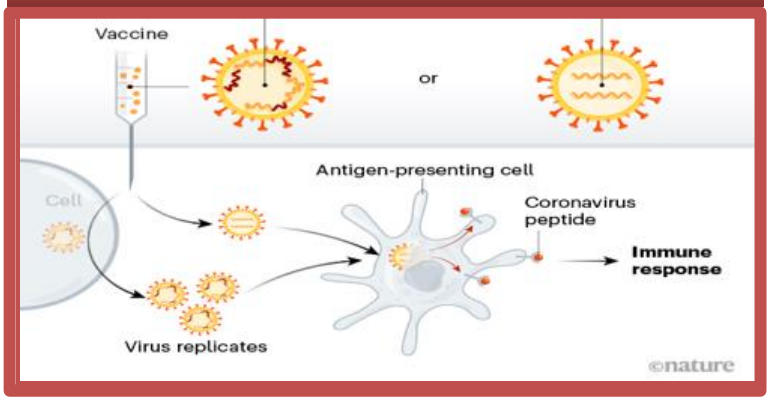
Estimate VE of rVSV-ZEBOV vaccine > 90% from observational studies

The development and deployment of COVID-19 vaccines:

Types of COVID-19 vaccines

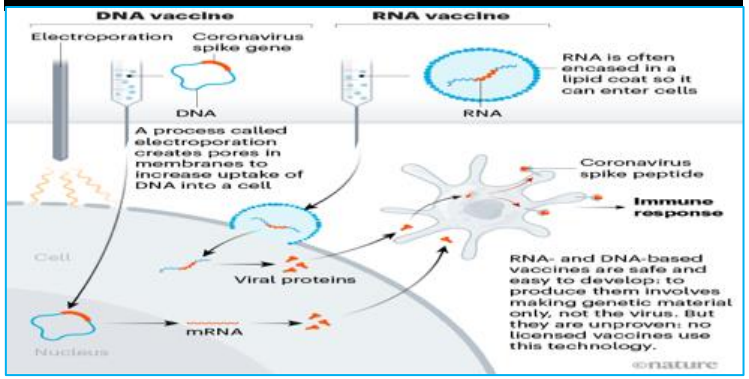
VIRUS VACCINES

Live-attenuated virus Inactivated virus



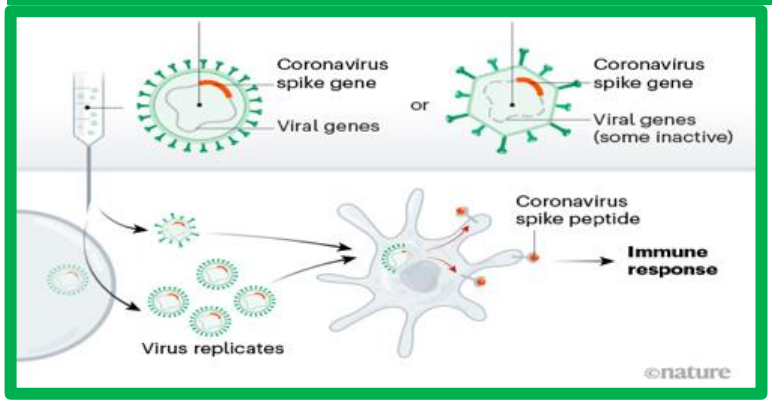
NUCLEIC ACID VACCINES

DNA and RNA vaccines



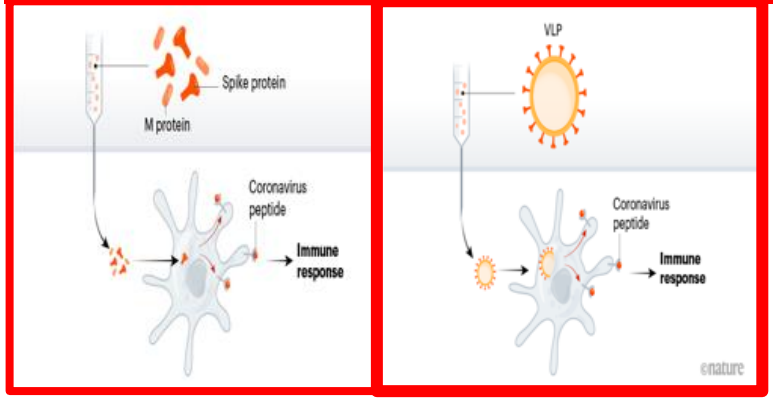
VIRAL VECTOR VACCINES

Replicating viral vector Non-replicating viral vector



PROTEIN-BASED VACCINES

Protein subunits Virus-like particles



Phase III COVID-19 Vaccine Trials and Observational Studies

Shapiro J, Dean NE, Madewell ZJ, Yang Y, Halloran ME, Longini IM. Efficacy estimates for various COVID-19 vaccines: What we know from the literature and reports. MedRxiv (2021) doi: https://doi.org/10.1101/2021.05.20.21257461

The following COVID-19 vaccines are being rolled out on a global scale, by manufacturer:

- Pfizer; mRNA, two dose
- Moderna; mRNA, two dose
- Johnson & Johnson; human Ad26, one dose
- AstraZeneca; chimp ChAdOx1, two dose
- Sputnik; human Ad26 prime, with Ad5 boost, two dose
- Novavax; protein subunit, adjuvant, two doses
- Sinovac; inactivated with adjuvant, two doses
- Sinopharm; inactivated with adjuvant, two doses

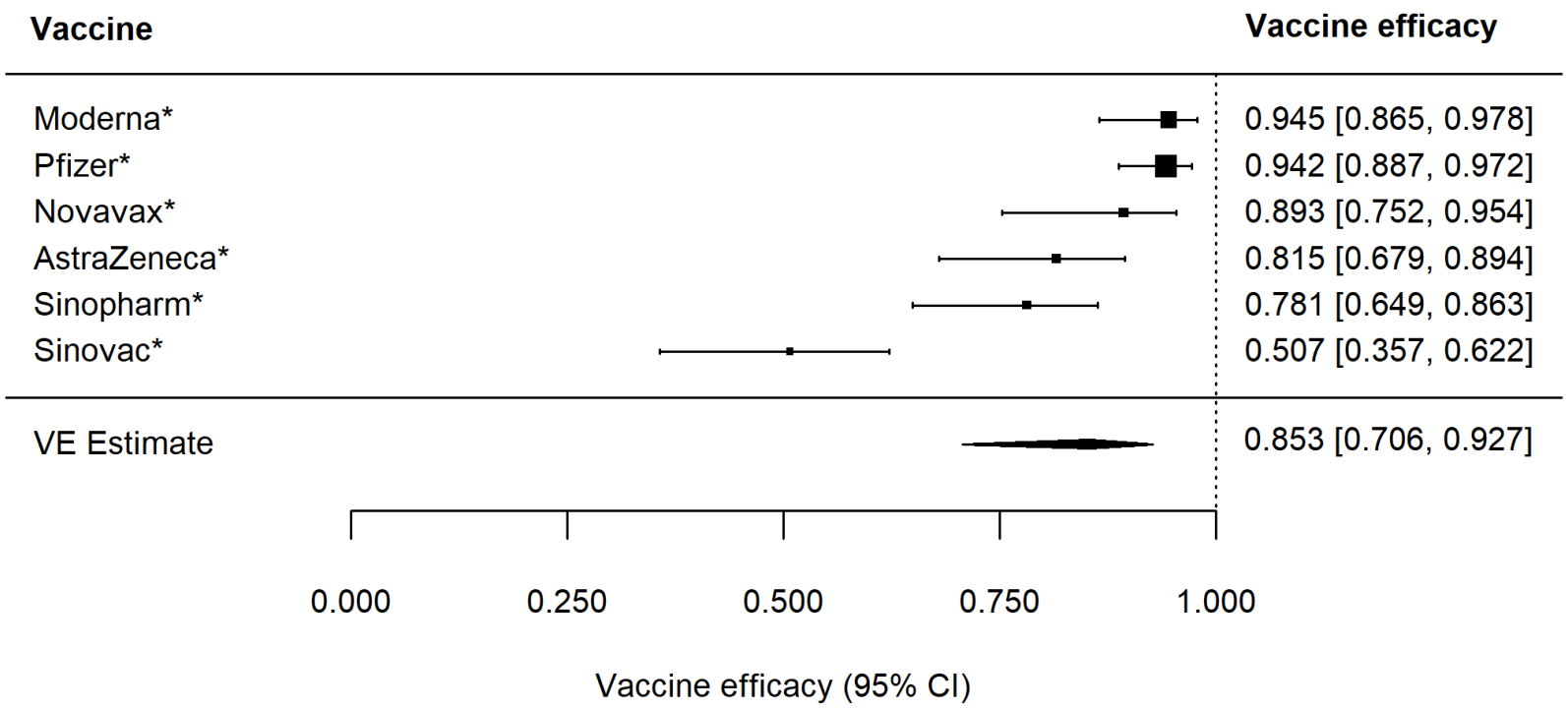
The state of the pandemic

- Global distribution of vaccines is very uneven with rich countries getting most of the vaccine
- Most middle income and developing countries will have enough vaccine to cover at most 20% population
- Several evolving and current variants of concern have some level of immune escape
- We need more and better vaccines
- We need targeted vaccination strategies that rely on local epidemiology and priorities

What we need to know about vaccine efficacy

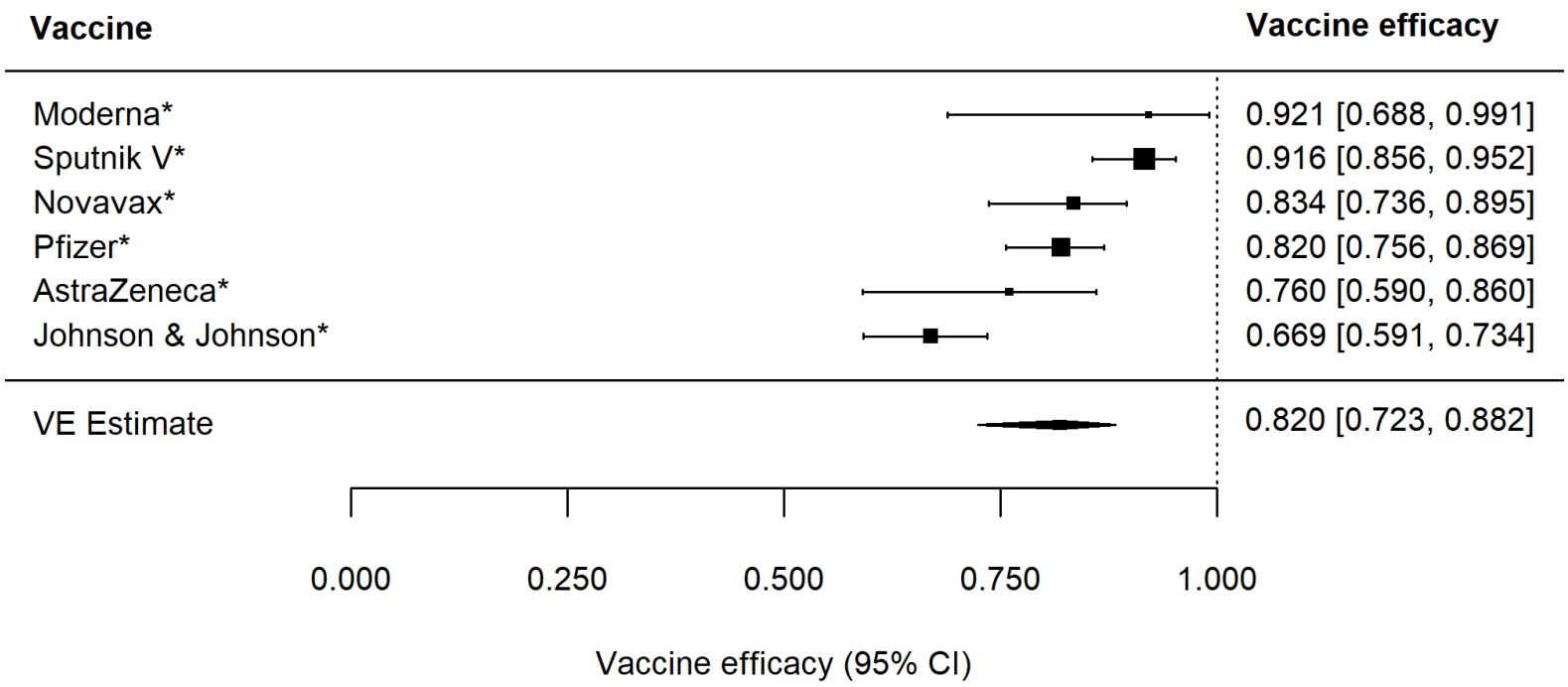
- VE_S vaccine efficacy against infection
- VE_P vaccine efficacy against clinical disease/infection; can be for general disease, severe disease, hospitalization, death
- VE_{SP} vaccine efficacy against clinical disease in those infected (primary endpoint in phase III trials)
  - $VE_{SP} = 1 - (1 - VE_S)(1 - VE_P)$ in the multiplicative world
- VE_I vaccine efficacy against transmission to others/infection

VE_{SP} after two doses

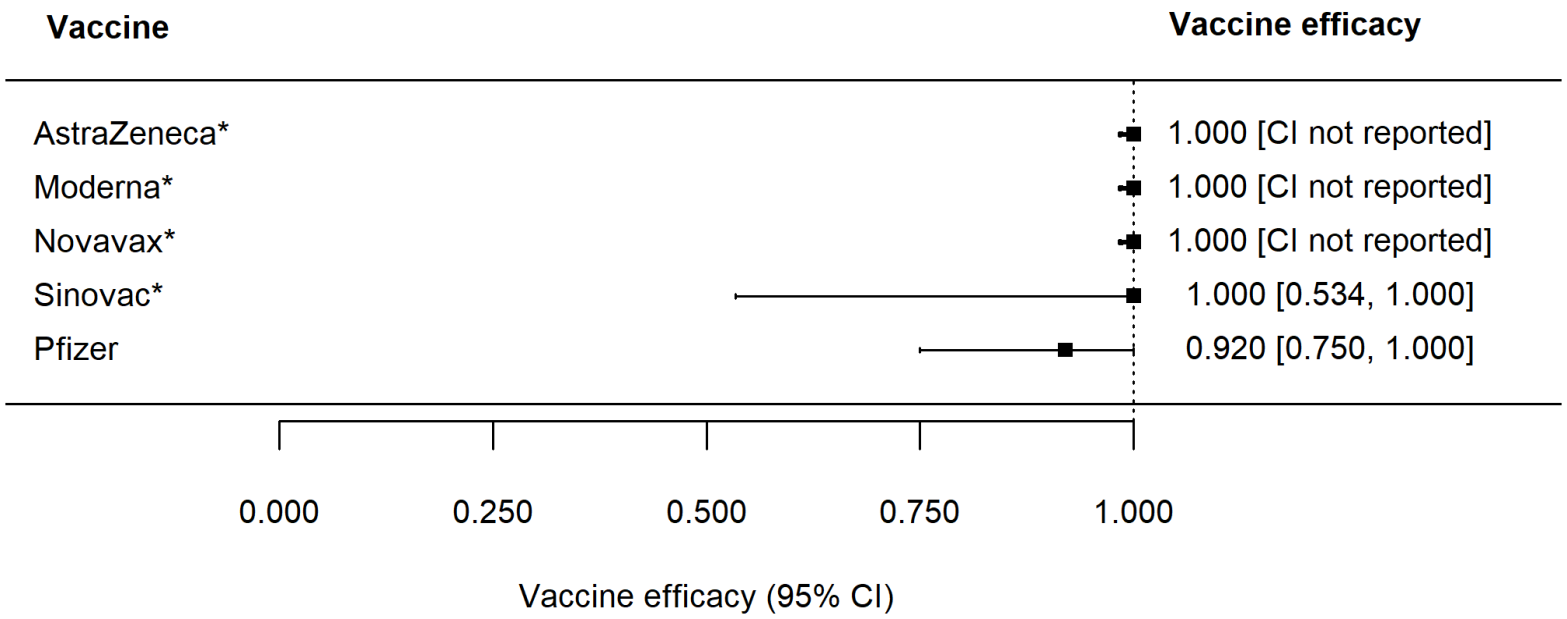


* indicates double-blinded, randomized vaccine trial

VE_{SP} after one dose

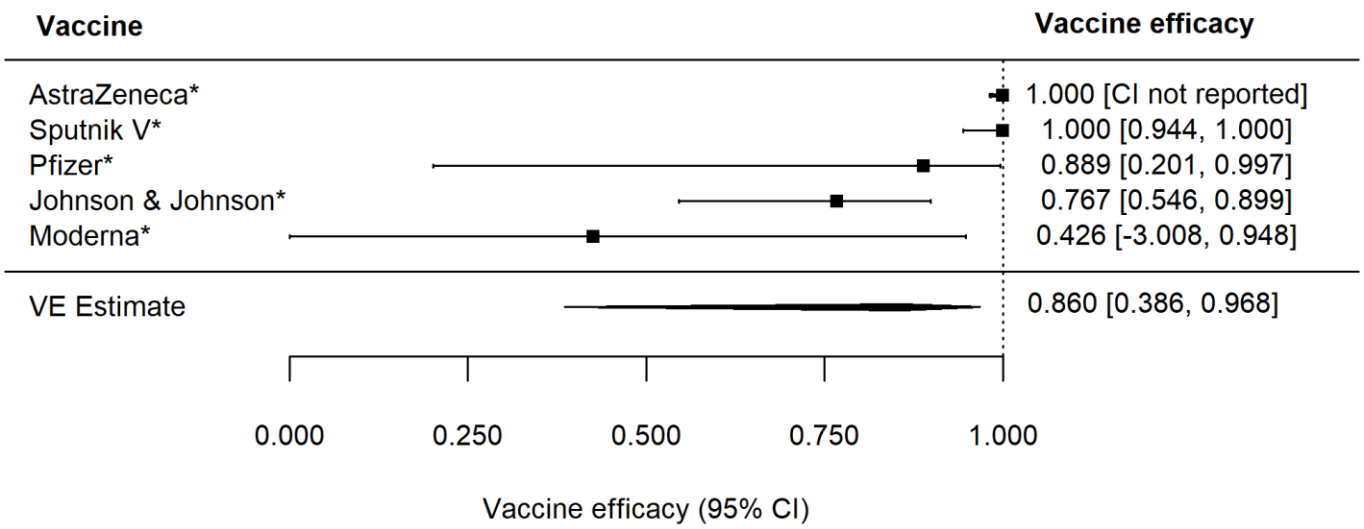


VE_{SP} against severe disease after two doses

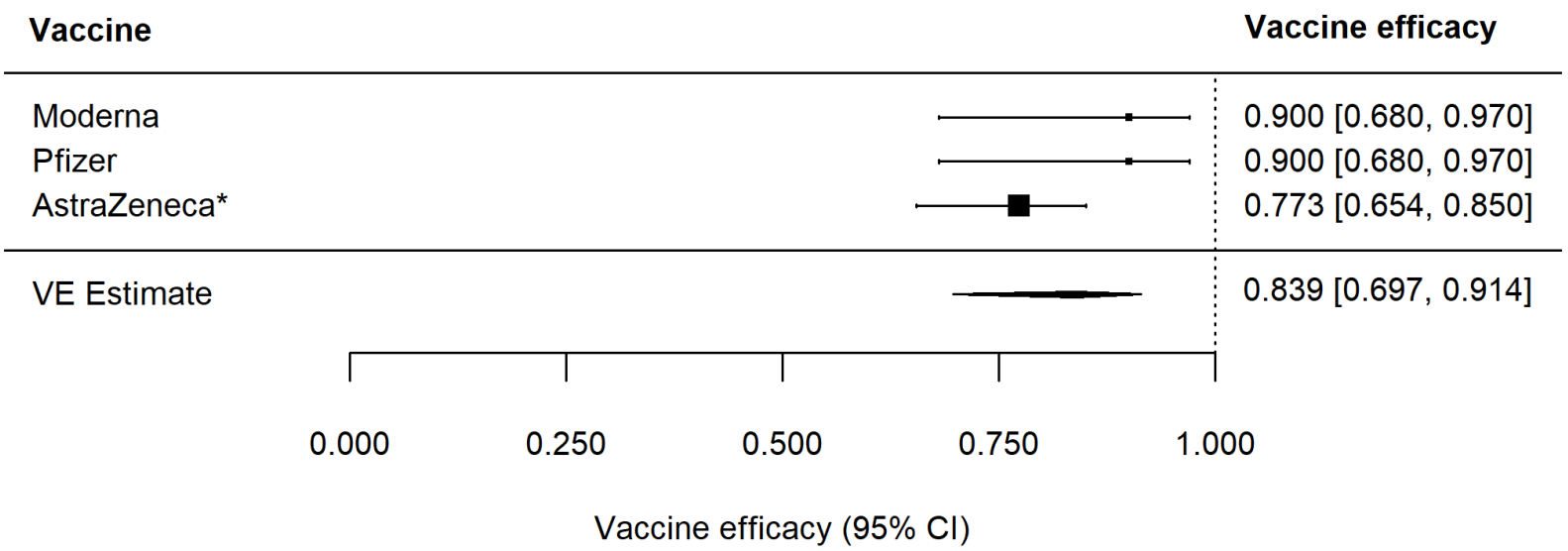


Note: Numbers are small from randomized trials, but VE_{SP} tends to appear high for severe disease, hospitalizations and deaths

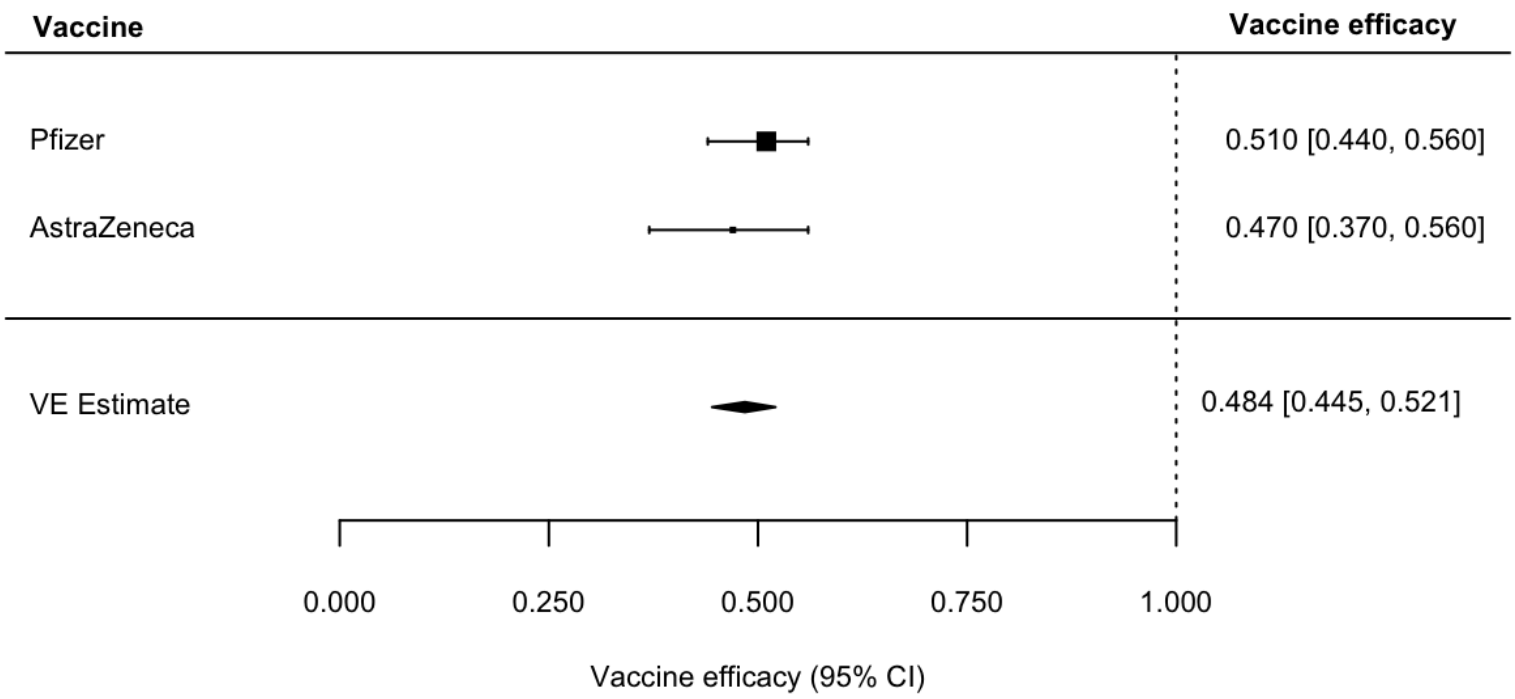
VE_{SP} against severe disease after one dose



VE_S

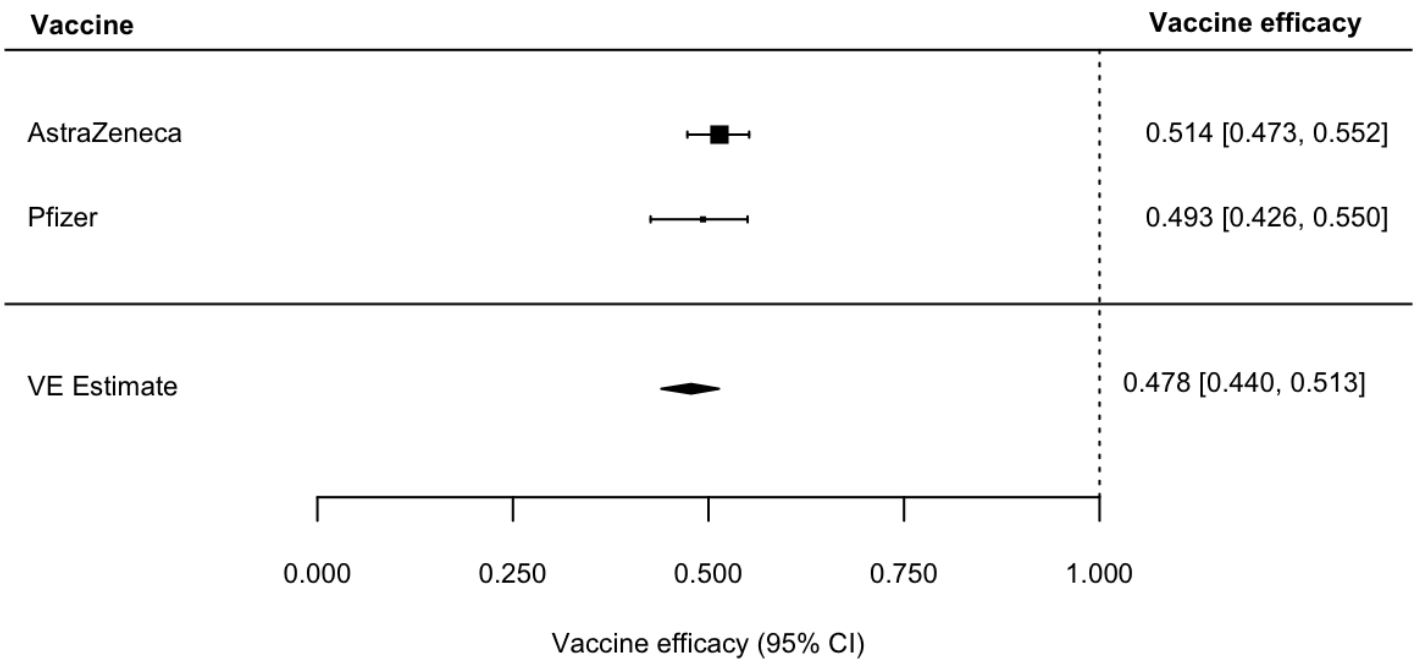

Vaccine
Vaccine efficacy
Moderna
Pfizer
AstraZeneca*
VE Estimate
0.900 [0.680, 0.970]
0.900 [0.680, 0.970]
0.773 [0.654, 0.850]
0.839 [0.697, 0.914]
0.000
0.250
0.500
0.750
1.000
Vaccine efficacy (95% CI)

VE_I

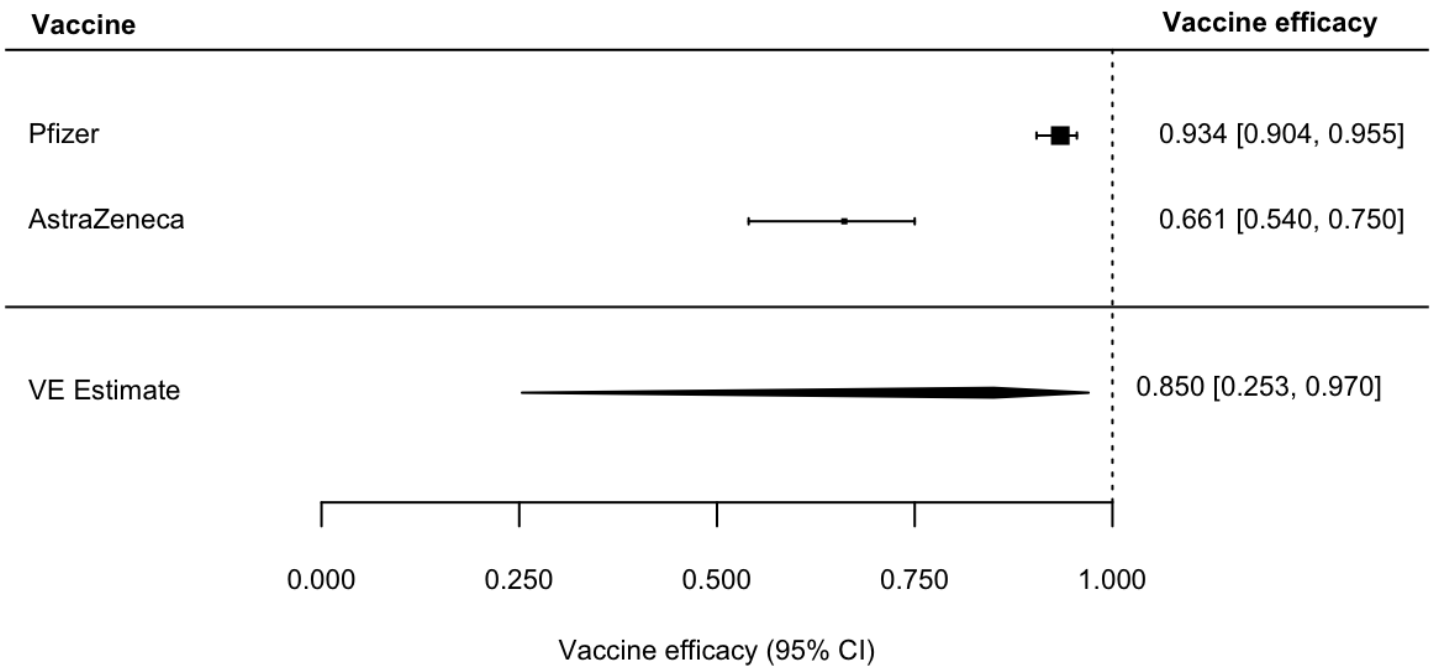

Vaccine
Vaccine efficacy
Pfizer
0.510 [0.440, 0.560]
AstraZeneca
0.470 [0.370, 0.560]
VE Estimate
0.484 [0.445, 0.521]
0.000
0.250
0.500
0.750
1.000
Vaccine efficacy (95% CI)

VE’s against the variants of concern

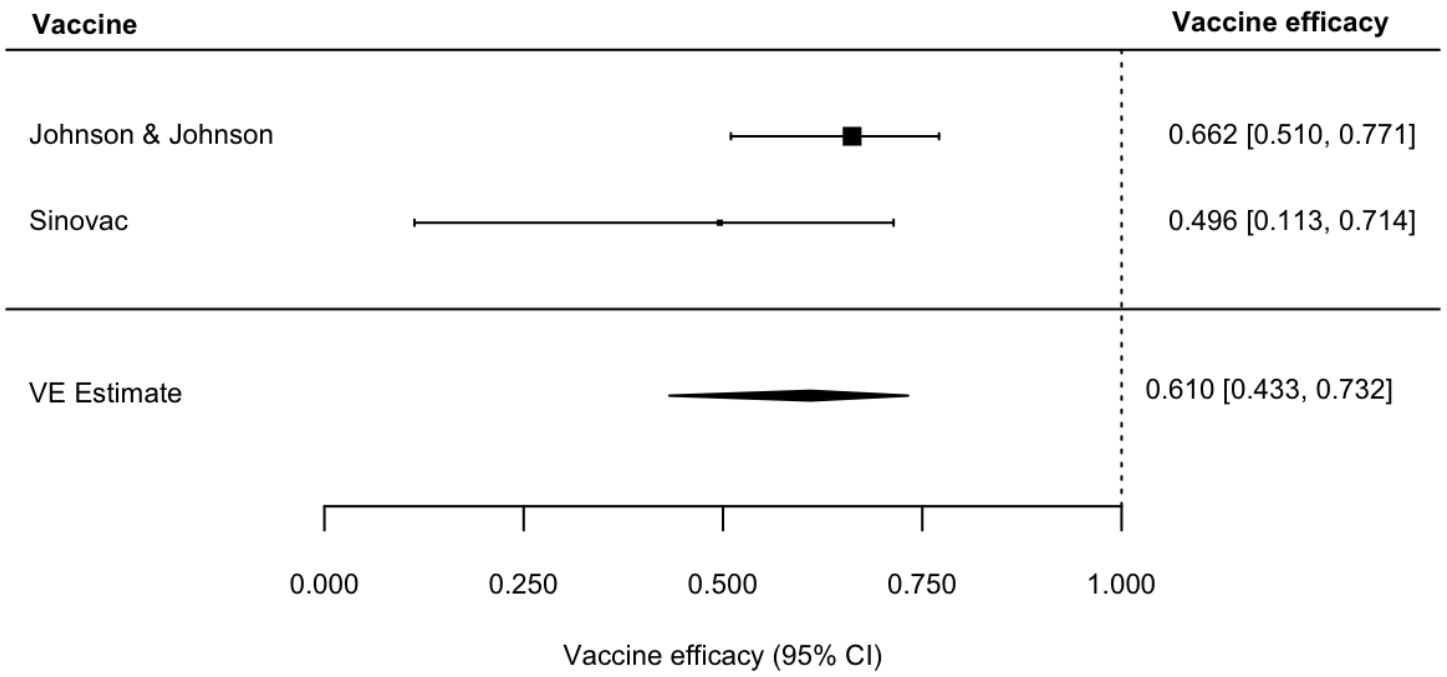
VE_{SP} against α (B.1.1.7) after dose 1



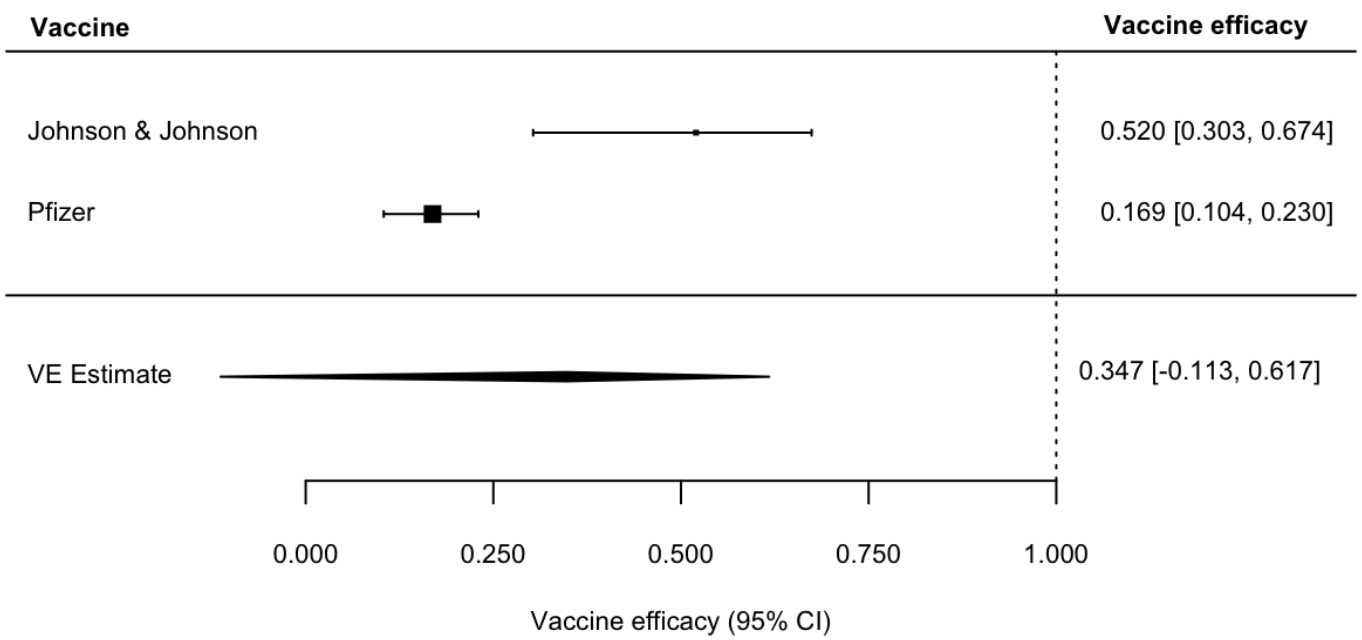
VE_{SP} against α (B.1.1.7) after dose 2



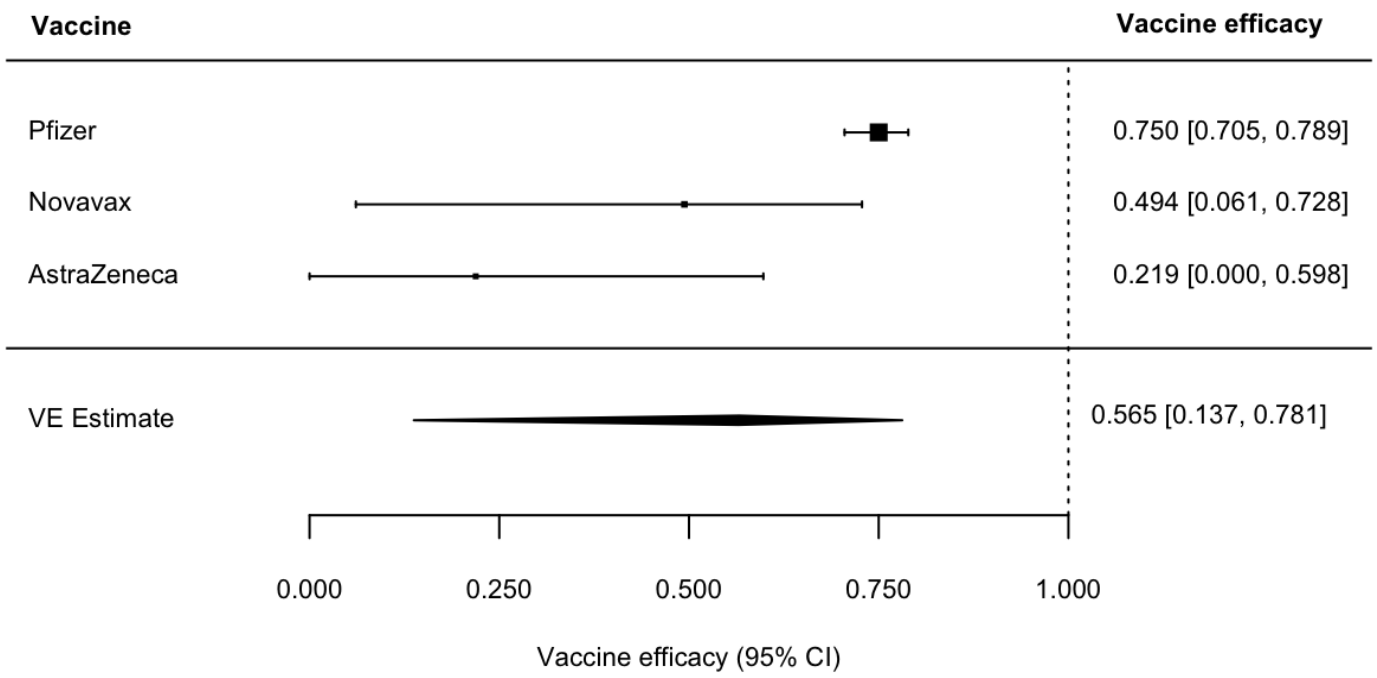
VE_{SP} against ϒ (P.1)



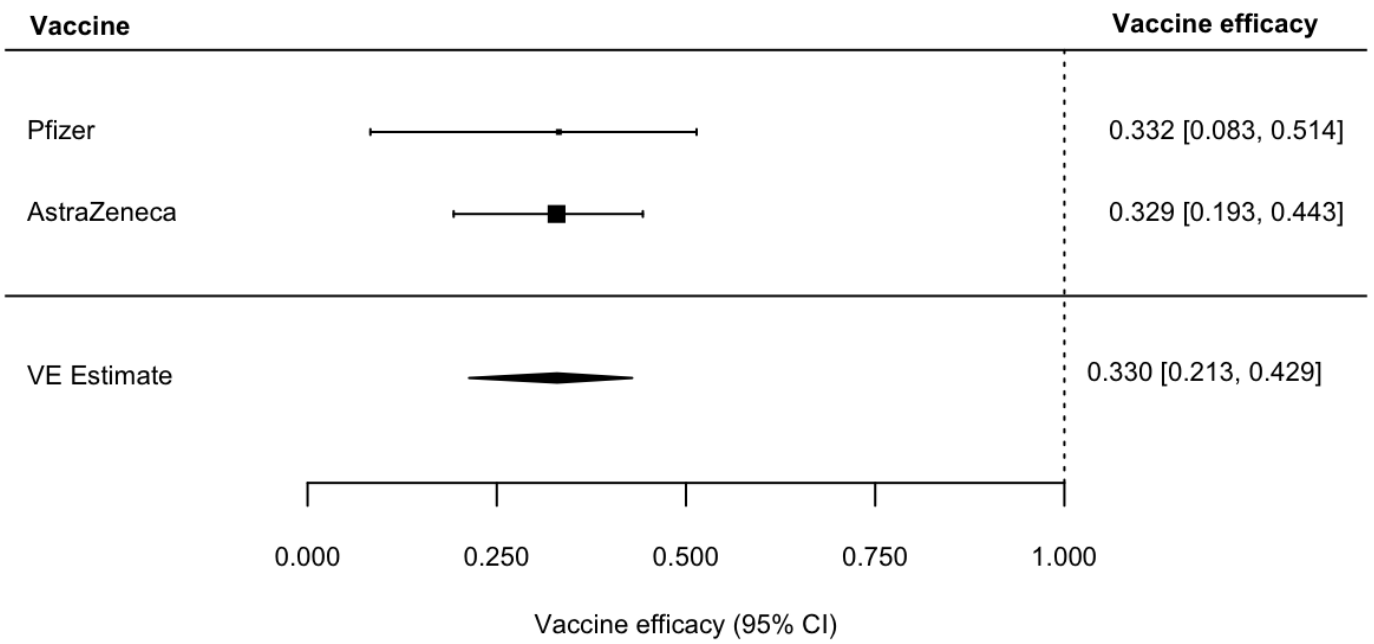
VE_{SP} against β (B.1.351) after dose 1



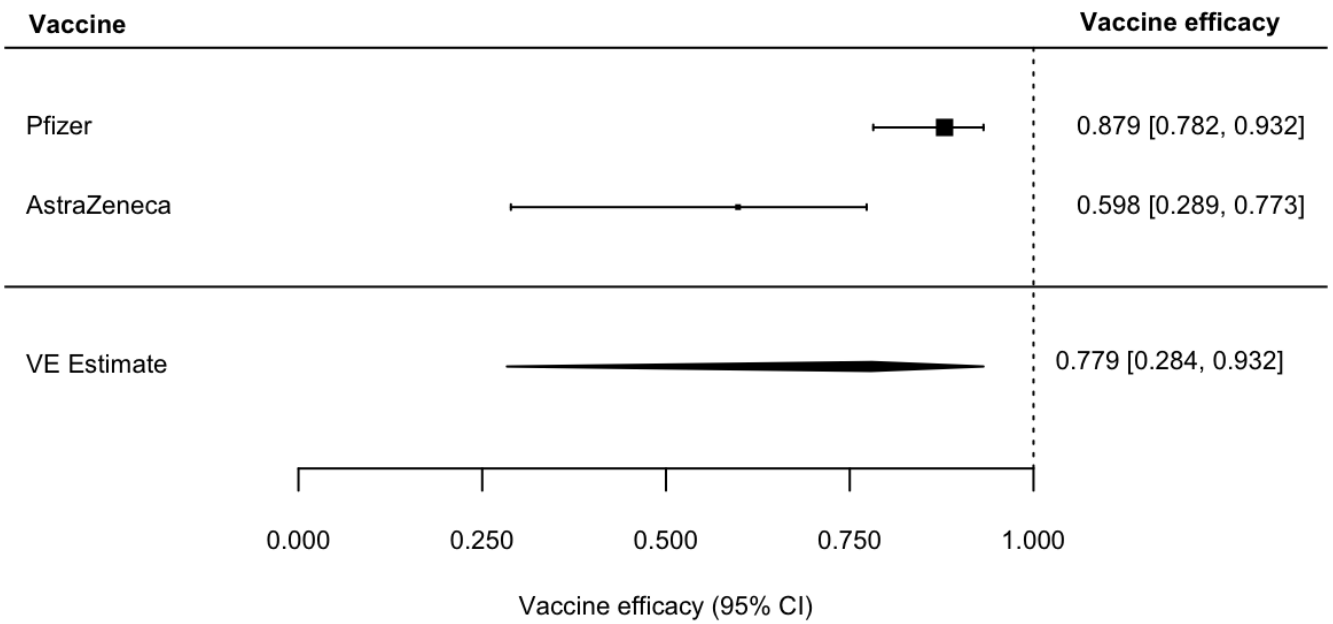
VE_{SP} against β (B.1.351) after dose 2



VE_{SP} against δ (B.1.617.2) after dose 1



VESP against δ (B.1.617.2) after dose 2



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A research and development Blueprint for action to prevent epidemics

2018 annual review of the Blueprint list of priority diseases

The second annual review of the Blueprint priority diseases was held in February 2018. WHO has developed a special tool for determining which diseases and pathogens to prioritize for research and development in public health emergency contexts. This tool seeks to identify those diseases that pose a public health risk because of their epidemic potential and for which there are no, or insufficient, countermeasures. Experts consider that given their potential to cause a public health emergency and the absence of efficacious drugs and/or vaccines, there is an urgent need for accelerated research and development for nine diseases.

List of Blueprint priority diseases

http://www.who.int/blueprint/en/

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List of Blueprint priority diseases

- Crimean-Congo haemorrhagic fever (CCHF)
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever (RVF)
- Zika
- Disease X

Additional diseases: Arenaviral hemorrhagic fevers other than Lassa Fever; Chikungunya; highly pathogenic coronaviral diseases other than MERS and SARS; emergent non-polio enteroviruses (including EV71, D68); and Severe Fever with Thrombocytopenia Syndrome (SFTS).

Core protocols for public health emergency vaccine trial design

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Creating a Framework for Conducting Randomized Clinical Trials during Disease Outbreaks

Natalie E. Dean, Ph.D., Pierre-Stéphane Gsell, Ph.D., Ron Brookmeyer, Ph.D., Forrest W. Crawford, Ph.D., Christl A. Donnelly, Sc.D., Susan S. Ellenberg, Ph.D., Thomas R. Fleming, Ph.D., M. Elizabeth Halloran, M.D., D.Sc., Peter Horby, Ph.D., Thomas Jaki, Ph.D., Philip R. Krause, M.D., Ira M. Longini, Ph.D., Sabue Mulangu, M.D., Jean-Jacques Muyembe-Tamfum, M.D., Martha C. Nason, Ph.D., Peter G. Smith, D.Sc., Rui Wang, Ph.D., Ana M. Henao-Restrepo, M.D., and Victor De Gruttola, Sc.D.

Conducting trials of novel interventions during infectious disease emergencies, such as the ongoing Covid-19 pandemic, is increasingly recognized as important for determining the efficacy of potential vaccines and therapies. Clinical trials to evaluate investigational interventions are being implemented as part of the broader efforts to control the spread of an infectious disease and to improve patient outcomes. In such circumstances, definitive evidence about the efficacy and safety of the intervention under investigation.[5,6]

At the end of an outbreak, the release of promising but inconclusive results from partially completed trials may support the belief that confirmatory trials comparing the investigational agents with the previously accepted placebo or standard-of-care comparator could no longer be conducted. This assumption can create a state of perpetual

Dean, et al. Accumulating evidence from randomized clinical trials across outbreaks. *New England Journal of Medicine* **382**, 1365-1369 (2020).

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Home / Emergencies / Diseases / Coronavirus disease 2019 / Global research on coronavirus disease (COVID-19) / WHO Solidarity Trial – Accelerating a safe and effective COVID-19 vaccine

Update on WHO Solidarity Trial – Accelerating a safe and effective COVID-19 vaccine

The availability of a safe and effective vaccine for COVID-19 is well-recognized as an additional tool to contribute to the control of the pandemic. At the same time, the challenges and efforts needed to rapidly develop, evaluate and produce this at scale are enormous. It is vital that we evaluate as many vaccines as possible as we cannot predict how many will turn out to be viable.

To increase the chances of success (given the high level of attrition during vaccine development), we must test all candidate vaccines until they fail. WHO is working to ensure that all of them have the chance of being tested at the initial stage of development.

This is a major and extraordinary global research undertaking: WHO is facilitating collaboration and accelerated efforts on a scale not seen before; it is convening vital communications across the research community and beyond.

Key links

R&D Roadmap for COVID-19

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-trial-accelerating-a-safe-and-effective-covid-19-vaccine

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WHO R&D Blueprint

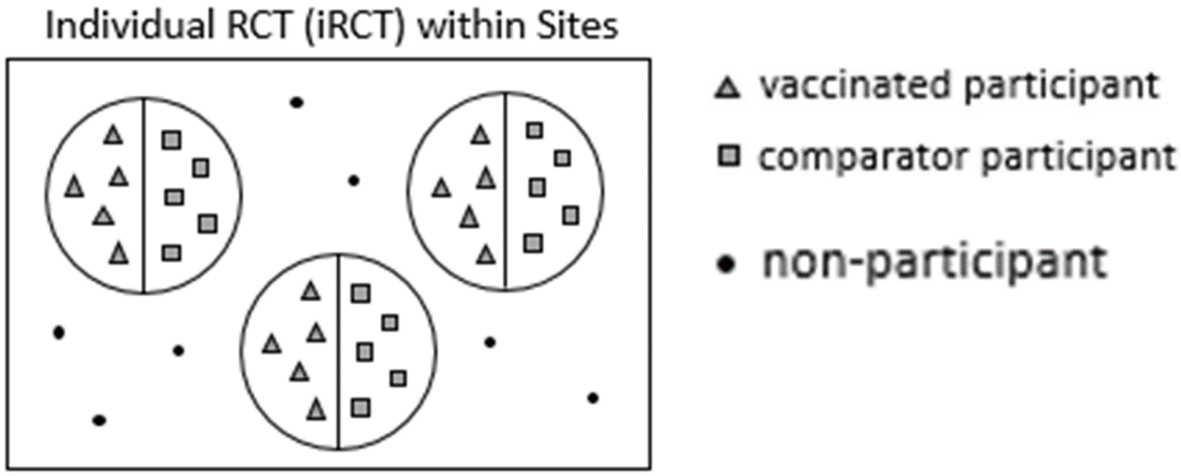
novel Coronavirus

An international randomised trial of candidate vaccines against COVID-19

- Large, international, randomized controlled clinical
- Multiple vaccines adaptively evaluated
- Different vaccines may be available or suitable to enter the trial at different times
- For each vaccine, the primary efficacy results are expected within 3-6 months of the vaccine entering the trial.

Ring vaccination randomization scheme

- Randomization within rings



Estimate direct vaccine effectiveness

Statistical analysis plan for COVID-19 vaccine trial

- Primary endpoint: Laboratory confirmed COVID-19 disease
- Primary hypothesis test:

$$H_0: VE \leqslant 30\% \quad \text{vs} \quad H_1: VE > 30\%,$$

where VE is defined as $VE = 1 - \lambda_1/\lambda_0$.

  - λ_1 is the hazard rate for COVID-DIS for vaccine recipients
  - λ_0 is the hazard rate for COVID-DIS for placebo recipients

Secondary endpoints

- Efficacy against sever disease or death
- Efficacy against disease for subgroups
- Longer term efficacy (waning, disease enhancement) with left over α
- Exploratory endpoints
  - Infection, shedding, immune correlates of risk and surrogates of protection, etc.

Randomization: K:1 vaccine to matched placebo

	Time Window #1	Time window #2	Time window #3
Vaccine arms	A	AA BB	AAA BBB CCC
Placebo arms	P_A	P_A P_B	P_A P_B P_C
Individual vaccine : matched-placebo	1:1	2:1 2:1	3:1 3:1 3:1
Individual vaccine : shared-placebo	1:1	1:1	1:1

Sample size

VE Design Alternative	Total # of post-D14 primary events	Illness attack rate		Total sample size
		Placebo	Vaccine	
60%	150	0.25%	0.1%	172,858
		0.75%	0.3%	57,417
		1.0%	0.4%	42,986
		2.0%	0.8%	21,340
70%	66	0.25%	0.075%	81,193
		0.75%	0.225%	26,970
		1.0%	0.3%	20,192
		2.0%	0.6%	10,024

About 90% power to reject the null hypothesis: VE $\leqslant$ 30%, under different VE design alternatives and 6-month incidence rates in the placebo arm, one-sided p-value of 0.025

Group sequential rules and interim analyses

- Two interim analyses for both success and futility at 1/3 and 2/3 of the statistical information (total event counts) are planned using a 1-sided O'Brien-Fleming boundary

Information Fraction (Number of Events)	Nominal one-sided significance level	Approximate HR at benefit boundary*	Approximate HR at lack-of-benefit boundary*
2/3 (100 events)	0.00071	≤ 0.333 (VE > 0.667)	≥ 0.77 (VE < 0.33)
3/3 (150 events)	0.0245	≤ 0.50 (VE > 0.50)	

Selection of vaccines: Criteria for COVID-19 vaccine prioritization

Vaccines are scored and ranked using the following criteria:

- Safety profile
- Potential for efficacy
- Vaccine stability
- Vaccine implementation
- Vaccine availability

Site selection

- Vaccine trial sites will be selected from all over the world
  - Fixed sites
  - Pop-up sites
- Criteria
  - Sustain at least a 1% COVID-19 attack rate over 6 months
    - Surveillance, serosurveys, modeling projections
  - Potential for future outbreaks
  - Infrastructure to support a large vaccine trial
- Over 200 potential sites, many countries, have shown an interest in participating

Trial is going into the field in a few days

- Up to 5 vaccines
- Starting in two countries

May the vaccines save us!

Thank You!