Lecture 10: Design and analysis of randomized vaccine trials for emerging infectious disease epidemics: From Cholera to Ebola to COVID 19

Ira Longini

University of Florida

UF UNIVERSITY of FLORIDA

WHO R&D Blueprint to combat global pandemics

World Health Organization

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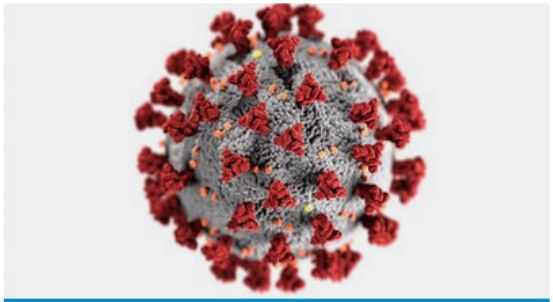
R&D Blueprint

The R&D Blueprint is a global strategy and preparedness plan that allows the rapid activation of research and development activities during epidemics. Its aim is to fast-track the availability of effective tests, vaccines and medicines that can be used to save lives and avert large scale crises. With WHO as convener, the broad global coalition of experts who have contributed to the Blueprint come from medical, scientific and regulatory backgrounds. WHO Member States welcomed the development of the Blueprint at the World Health Assembly in May 2016.

About us >

Key actions by disease



R&D Blueprint and COVID-19
R&D Blueprint and the Pandemic Response

- R&D Blueprint and Ebola/Marburg >
- R&D Blueprint and Lassa Fever >
- R&D Blueprint and MERS-CoV >
- R&D Blueprint and Nipah Virus >
- R&D Blueprint and Zika >

https://www.who.int/teams/blueprint/

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Blueprint priority diseases

- At present, the priority diseases are:
- **COVID-19**
- Crimean-Congo haemorrhagic fever
- **Ebola virus disease** and Marburg virus disease (last **Sudan and Marburg virus**)
- **Lassa fever**
- Middle East respiratory syndrome coronavirus (**MERS-CoV**) and Severe Acute Respiratory Syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever
- Zika
- "**Disease X**"*

**Disease X represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease. The R&D Blueprint explicitly seeks to enable early cross-cutting R&D preparedness that is also relevant for an unknown "Disease X".*

https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts

Literature leading up to this point

- Longini, I.M., Sagatelian, K., Rida, W.N. and Halloran, M.E.: Optimal vaccine trial design when estimating vaccine efficacy for susceptibility and infectiousness from multiple populations. *Statistics in Medicine* **17**, 1121-1136 (1998).

- Longini, I.M., Nizam, A., Ali, M., Yunus, M., Shenvi, N. and Clemens, J.D.: Controlling endemic cholera with oral vaccines. *Public Library of Science (PloS), Medicine* **4** (11) 2007: e336 doi:10.1371/journal.pmed.0040336.

- Henao-Restrepo A-M, Longini IM, Egger M, Dean NE, *et al*: Efficacy of a recombinant live VSV-vectored vaccine expressing Ebola surface glycoprotein: Interim results from the Guinea ring vaccination cluster-randomized trial. *The Lancet*, **38**, 857–866 (2015).

- Dean N, Gsell PS, Brookmeyer R, De Gruttola V, Donnelly CA, Halloran ME, Jasseh M, Nason M, Riveros X, Watson C, Henao-Restrepo AM, Longini IM: Considerations for the design of vaccine efficacy trials during public health emergencies. *Science Translational Medicine* 2019: Vol. 11, Issue 499, eaat0360, DOI: 10.1126/scitranslmed.aat0360

- Dean NE, Gsell P, Brookmeyer R, Crawford F, *et al*. Creating a framework for conducting randomized clinical trials during disease outbreaks. *New England Journal of Medicine* **382,** 1366-1369 (2020). DOI: 10.1056/NEJMsb1905390

- Longini IM, Yang Y, Fleming TR, Muñoz-Fontela C, *et al.* A platform trial design for preventive vaccines against Marburg virus and other emerging infectious disease threats. *Clinical Trials* **19**, 647–654 (2022). doi: 10.1177/17407745221110880

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Design

CLINICAL TRIALS

Clinical Trials
1–8

DOI: 10.1177/17407745221110880
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A platform trial design for preventive vaccines against Marburg virus and other emerging infectious disease threats

Ira M Longini[1], Yang Yang[1], Thomas R Fleming[2], César Muñoz-Fontela[3,4], Rui Wang[5,6], Susan S Ellenberg[7], George Qian[8], M Elizabeth Halloran[2,9], Martha Nason[10], Victor De Gruttola[6], Sabue Mulangu[11], Yunda Huang[8], Christl A Donnelly[12,13] and Ana-Maria Henao Restrepo[14]

Abstract

Background: The threat of a possible Marburg virus disease outbreak in Central and Western Africa is growing. While no Marburg virus vaccines are currently available for use, several candidates are in the pipeline. Building on knowledge and experiences in the designs of vaccine efficacy trials against other pathogens, including SARS-CoV-2, we develop designs of randomized Phase 3 vaccine efficacy trials for Marburg virus vaccines.

Methods: A core protocol approach will be used, allowing multiple vaccine candidates to be tested against controls. The primary objective of the trial will be to evaluate the effect of each vaccine on the rate of virologically confirmed Marburg virus disease, although Marburg infection assessed via seroconversion could be the primary objective in some cases. The overall trial design will be a mixture of individually and cluster-randomized designs, with individual randomization done whenever possible. Clusters will consist of either contacts and contacts of contacts of index cases, that is, ring vaccination, or other transmission units.

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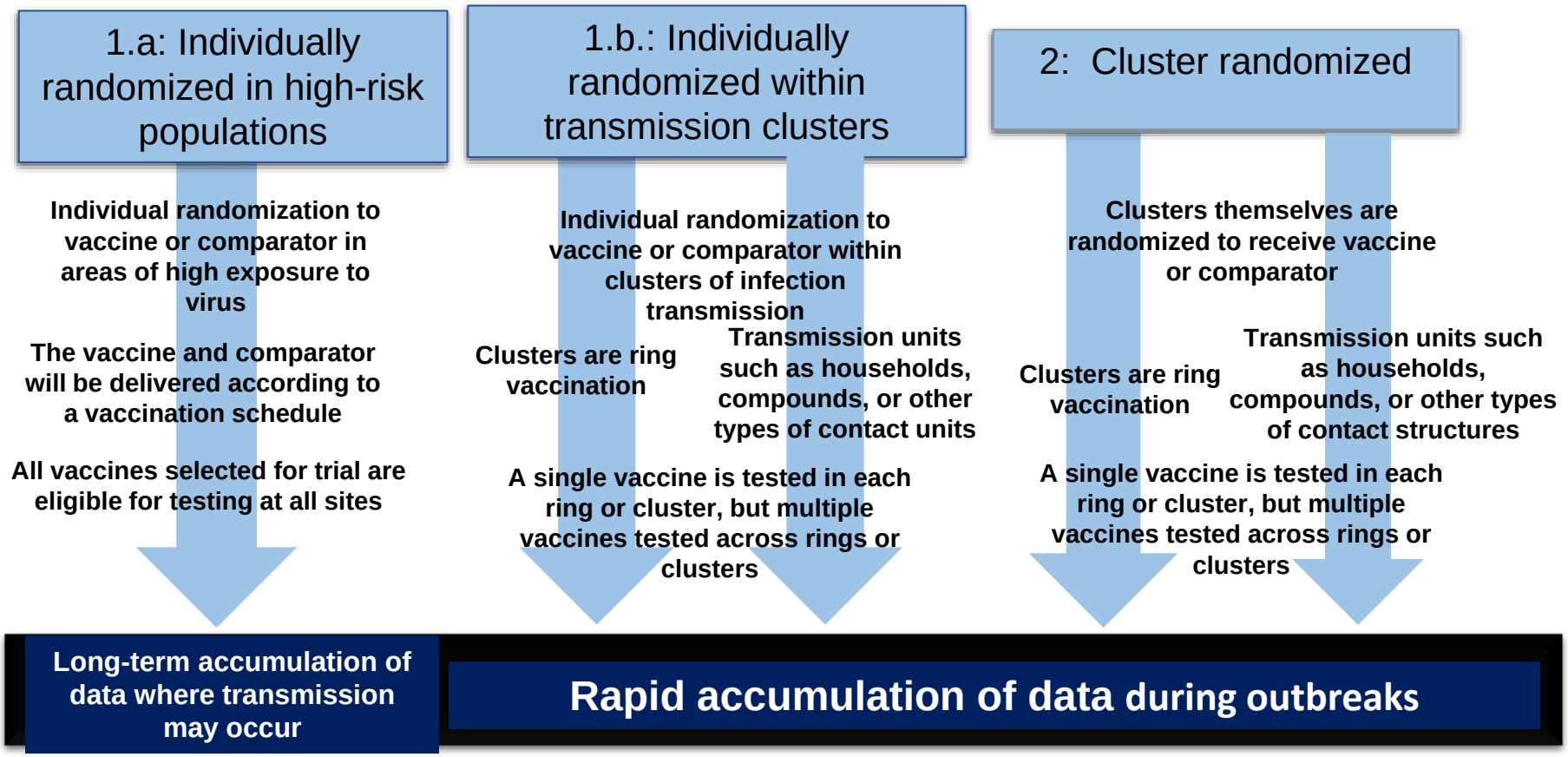
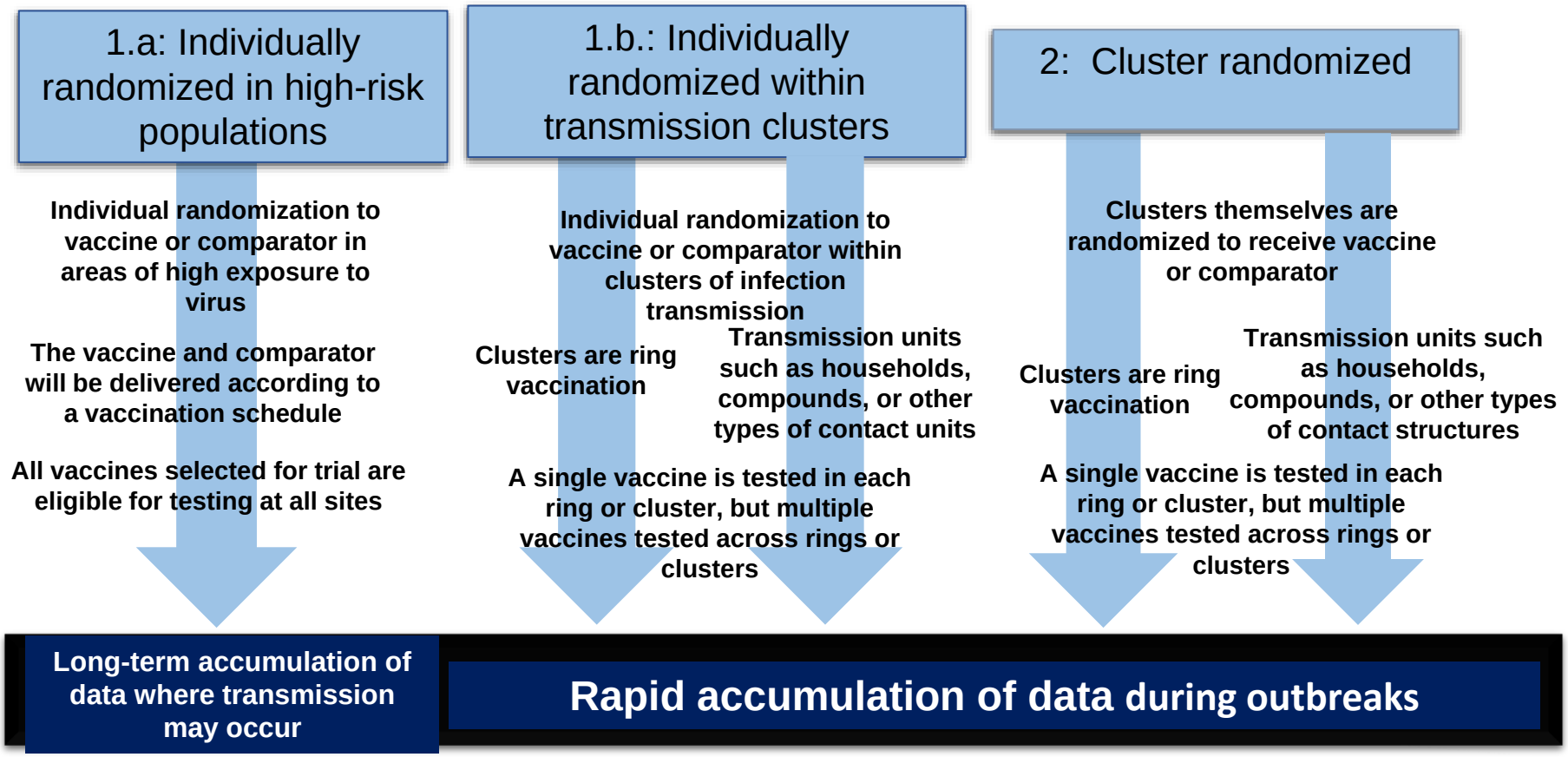
Vaccine trial designs



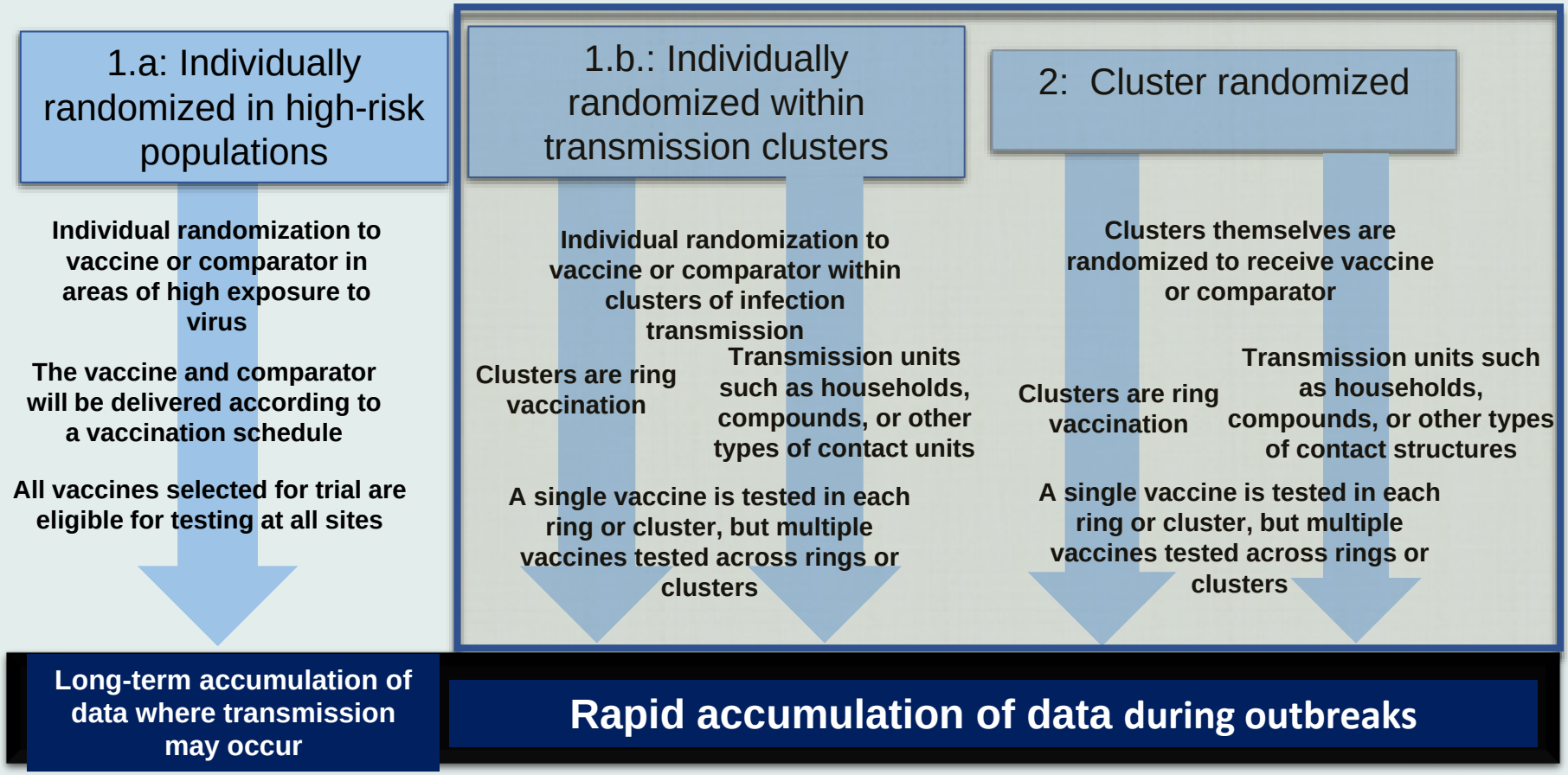
Example 1: Cholera vaccine trial in Bangladesh

Longini, I.M., Nizam, A., Ali, M., Yunus, M., Shenvi, N. and Clemens, J.D.: Controlling endemic cholera with oral vaccines. *PloS Medicine* 4 (2007)

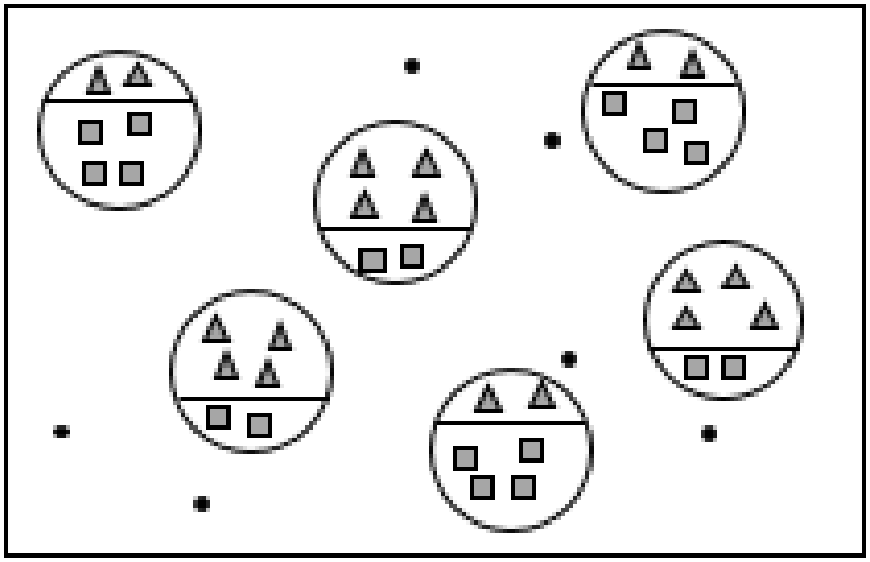
Vaccine trial designs



Vaccine trial designs



Two-Stage Randomization



△ vaccinated participant

□ comparator participant

• non-participant

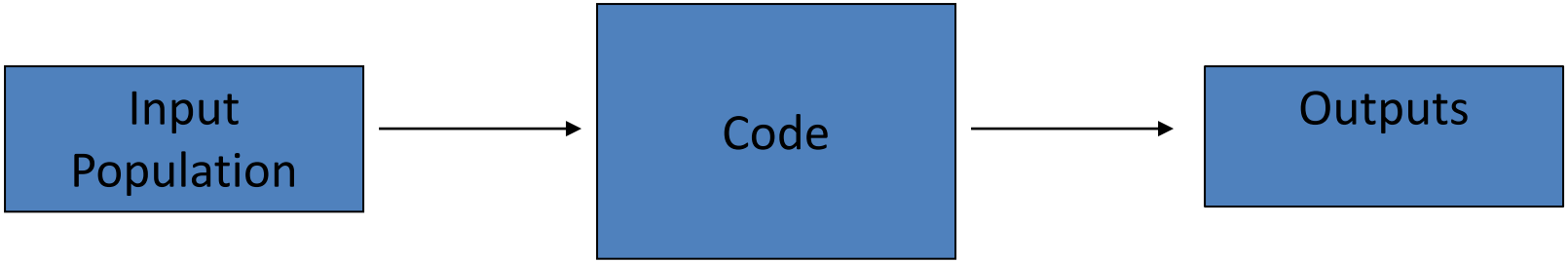
Estimate direct, overall, indirect and total effectiveness

Goals of Simulation Model

- Calibrate to historical attack rate and vaccine effectiveness data

- Simulate use of cholera vaccine at various coverage levels, study effectiveness measures

Simulator Overview



- Population of Matlab in 1985

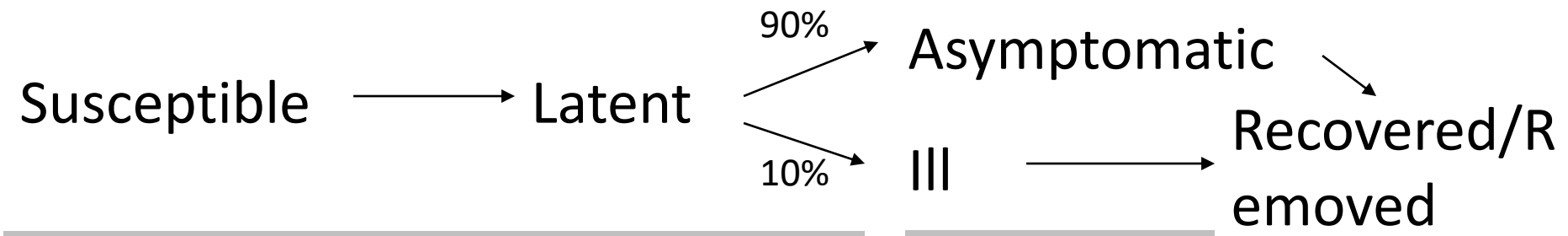
- ANSI c code models cholera natural history and community level transmission
- Developed on unix. Portable
- 1000 runs per simulation

- Illness attack rates
- Effectiveness measures
- Spatial distribution of cholera cases

Simulator Elements

- Disease natural history model and parameters
- Community-level transmission of cholera infection
- Matlab population demographics (age, gender, location, travel within Matlab)
- Historical illness attack rate data for model calibration

Cholera Natural History



In each subpopulation, on any given day of the epidemic, there is a probability of infection, determined by an infection function (next slide)

1 day: 40%

2 days: 40%

3-5 days: 20%

Uniform distribution 7-14 days

Additional assumptions:

- **Ill shed at 10 times the rate of asymptomatics**
- **Working males:**
  - **circulate >= 1 day**
  - **Pr(withdrawal after ill)= 0.75**

Infection Function

The probability that a susceptible person will be infected in a particular location on day t is:

$$f = \left[1-(1-\theta^{x}bp)^{n_{uv}(t)}(1-\theta^{x}\phi bp)^{n_{v}(t)}\right]$$

Where

- p = transmission probability
- Θ = 1 – vaccine efficacy against susceptibility (VE_S)
- x = 1 if susceptible is vaccinated, 0 if unvaccinated
- b = seasonal boost factor for first month
- $n_{uv}(t)$ = # unvacc. infectious people
- $n_v(t)$ = # vacc. infectious people
- Φ = 1 – vaccine efficacy against infectiousness (VE_I)

Model Calibration

Model input parameters

p: 0.000009

b: 10

VE_S: 0.7

VE_I: 0.5

Number of initial infectives: 5

Probability of withdrawal given ill: 0.75

Probability asymptomatic: 0.9

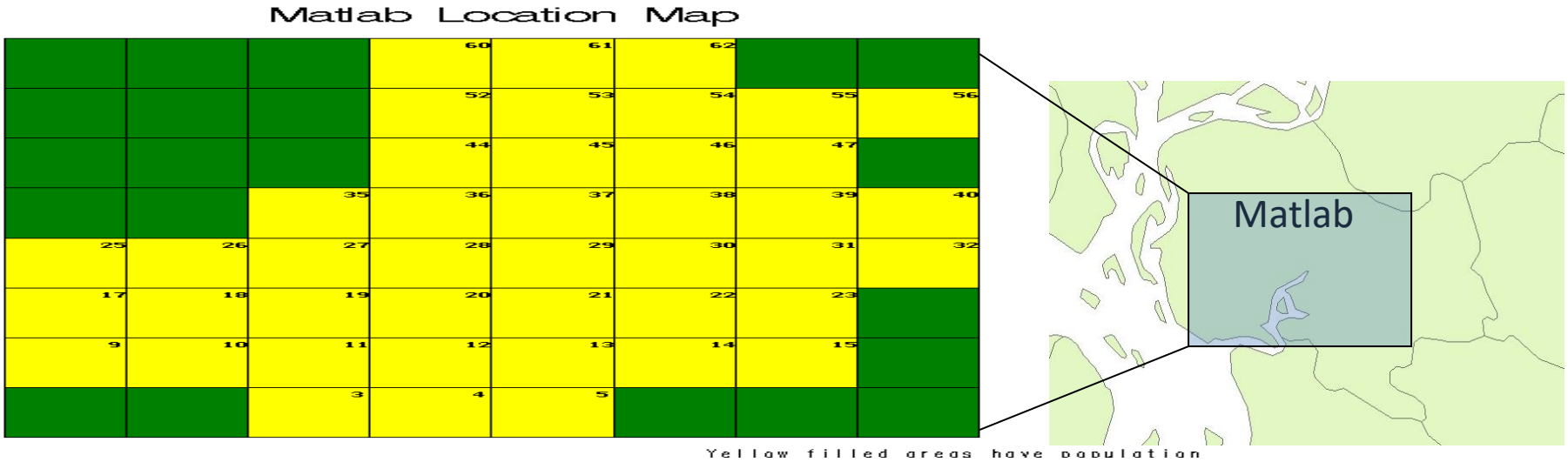
Population Characteristics

- 183,826 subjects from Matlab
- 50.5% Female 49.5% Males
- Geographic map
  - Bari code
  - X,Y coordinates
  - Age on 1/1/1985
- Vaccinated where children 2 – 15 years old and women > 15 years old.

Population Characteristics

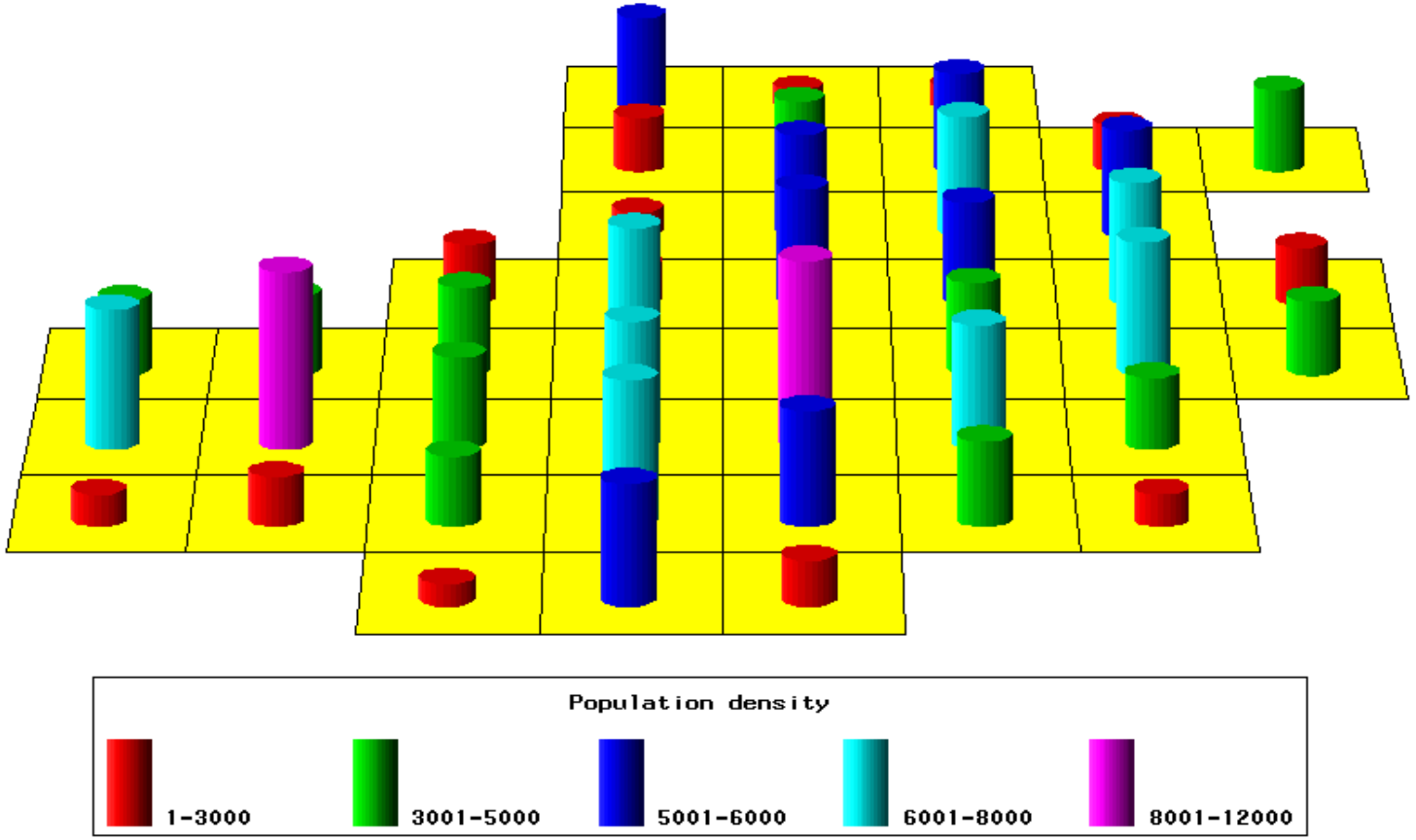
Matlab “Grid”

- Matlab area mapped to 64 ‘sub-regions’
- Each subject mapped to one of the sub-regions based on the GIS location



Population Characteristics

Distribution of Population Across the Grid



Population Characteristics

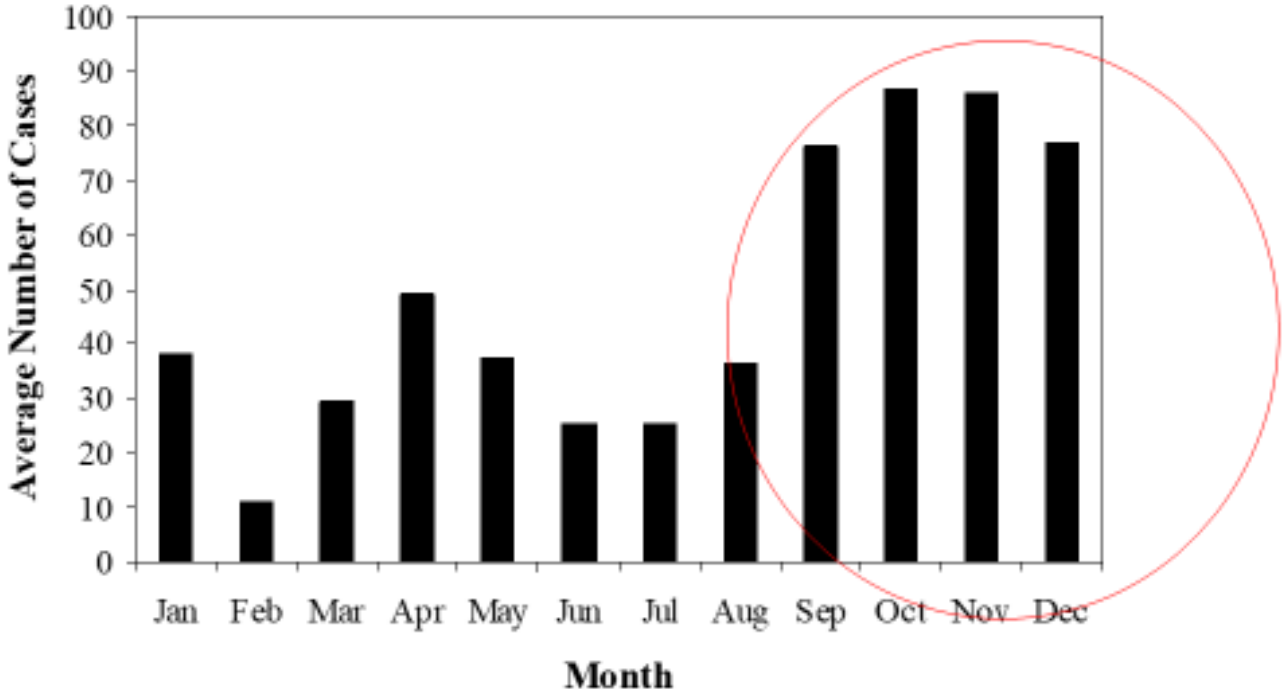
Connectivity Between Sub-regions

- Males over 16 years old, and 50% of males between 14 -16 years old were randomly assigned a work sub-region according to the following distance function:
  - 55% work and reside in same sub-region
  - 35% work 4-10km away from residence sub-region
  - 10% work >10km away[4]

4. Distance function derived from time traveled to school reported in Matlab Health and Socioeconomic Survey dataset, 1996. http://www.icpsr.umich.edu/

Model Calibration

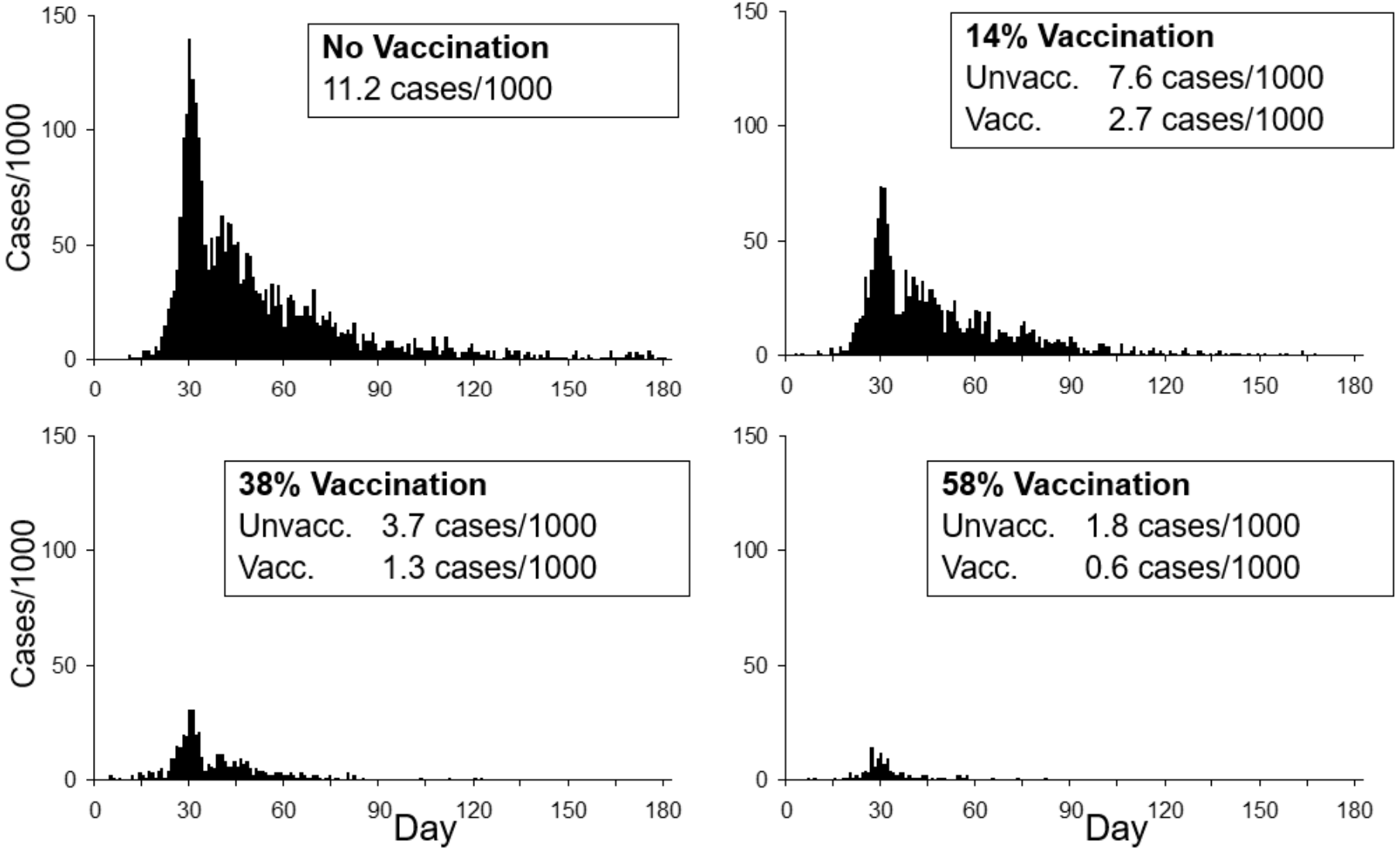
- Annual autumn/winter outbreaks in Matlab



Vaccination Coverages, Average Incidence Rates and Direct Effectiveness (Calibration Runs)

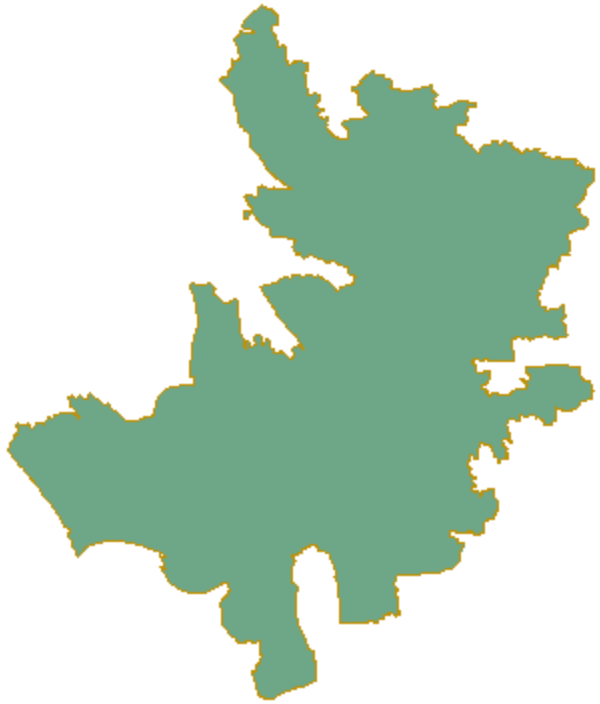
Vaccination Coverage (%)		Mean Cases/1000 (95% CI)				Mean Direct Effectiveness (%) (95% CI)	
		Placebo		Vaccinated			
Target Population	Overall Population	Observed	Simulated	Observed	Simulated	Observed	Simulated
14	9	7.0 (6.5, 7.5)	7.8 (1.9, 14.8)	2.7 (1.9, 3.5)	2.8 (0.5, 6.1)	62	65 (52, 77)
31	20	5.9 (5.4, 6.4)	4.7 (0.9, 10.2)	2.5 (2.0, 3.0)	1.7 (0.3, 3.8)	58	65 (55, 76)
38	25	4.7 (4.2, 5.2)	3.8 (0.8, 8.6)	1.6 (1.2, 2.0)	1.3 (0.2, 3.4)	67	65 (54, 77)
46	30	4.7 (4.2, 5.2)	2.8 (0.5, 6.8)	2.3 (1.9, 2.7)	1.0 (0.1, 2.5)	52	66 (54, 79)
58	38	1.5 (1.2, 1.8)	1.8 (0.3, 4.8)	1.3 (1.0, 1.6)	0.6 (0.1, 1.8)	14	66 (51, 80)

χ^2 goodness-of-fit test for frequency data p = 0.84


No Vaccination
11.2 cases/1000
14% Vaccination
Unvacc. 7.6 cases/1000
Vacc. 2.7 cases/1000
38% Vaccination
Unvacc. 3.7 cases/1000
Vacc. 1.3 cases/1000
58% Vaccination
Unvacc. 1.8 cases/1000
Vacc. 0.6 cases/1000
Cases/1000
Day
0
50
100
150
0
30
60
90
120
150
180

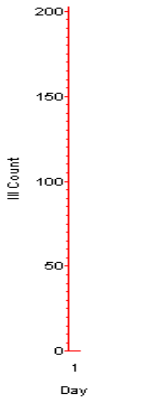
Mass Vaccination: 0 % Day 1

Red: Ill Yellow:Recovered



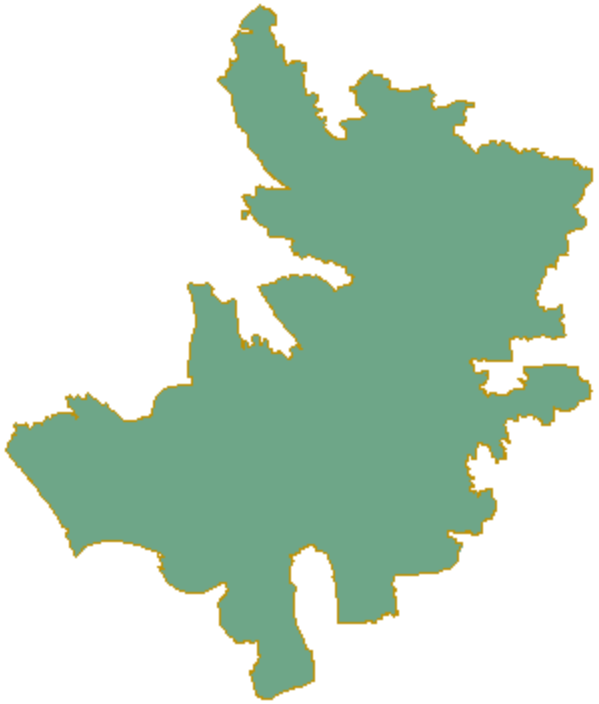
Epidemic curve: Day 1

Mass Vaccination:0 %



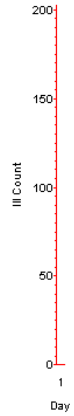
Mass Vaccination: 58 % Day 1

Red: Ill Yellow:Recovered



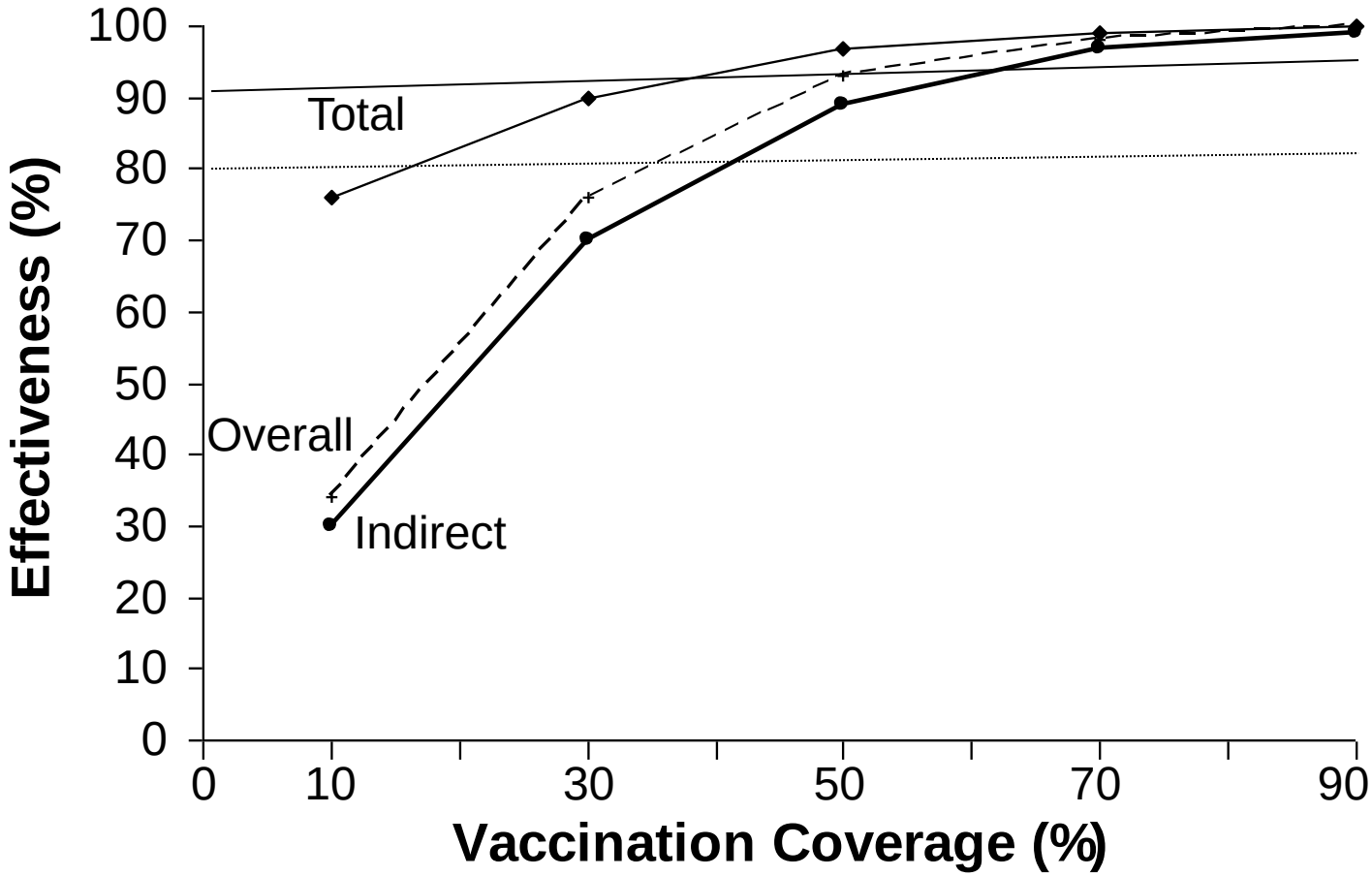
Epidemic curve: Day 1

Mass Vaccination:58 %



Average Indirect, Total and Overall Effectiveness of Vaccination, and Cases Prevented 10,000 Per Doses

Vaccination Coverage (%)	Mean Effectiveness (%) (95%CI)			Mean # Cases Prevented per 10,000 Doses
	Indirect	Total	Overall	
10	30 (-39, 83)	76 (47, 95)	34 (-30, 84)	50
30	70 (31, 93)	90 (76, 98)	76 (44, 95)	40
50	89 (72, 98)	97 (91, 99)	93 (82, 99)	30
70	97 (91, 99)	99 (97, 100)	98 (95, 100)	20
90	99 (98, 100)	100 (99, 100)	100 (99, 100)	20


Effectiveness (%)
100
90
80
70
60
50
40
30
20
10
0
Total
Overall
Indirect
0
10
30
50
70
90
Vaccination Coverage (%)

Underlying statistical model
Some notation

- Partition *K* randomized studies into K_1 IRT and *K*- K_1 CRT
- X_{ij}^k is the treatment indicator for individual *j* in cluster *i* for study *k*.
- Then the fraction vaccinated in a particular cluster is $\overline{X}_{i,-j}^k = (n_i^k - 1)^{-1} \sum_{\ell=1,\ell\neq j}^{n_i^k} X_{i\ell}^k$, where n_i^k is the number of individuals in cluster *i* for study *k*.
- Let *p* be the (randomized) vaccine coverage in a cluster, and we have $\overline{X}_{i,-j} \approx p_0$ for IRTs and $\overline{X}_{i,-j} = 0$,or 1 for CRTs.

Effectiveness measures

- Direct: $$\mathrm{VE}(t)_{D,p} = 1 - \frac{\lambda(t \mid X_{ij} = 1, \overline{X}^k_{i,-j} = p)}{\lambda(t \mid X_{ij} = 0, \overline{X}^k_{i,-j} = p)},$$
- Indirect: $$\mathrm{VE}(t)_{I,p} = 1 - \frac{\lambda(t \mid X_{ij} = 0, \overline{X}^k_{i,-j} = p)}{\lambda(t \mid X_{ij} = 0, \overline{X}^k_{i,-j} = 0)}$$
- Total: $$\mathrm{VE}(t)_{T,p} = 1 - \frac{\lambda(t \mid X_{ij} = 1, \overline{X}^k_{i,-j} = p)}{\lambda(t \mid X_{ij} = 0, \overline{X}^k_{i,-j} = 0)}$$
- Overall: $$\mathrm{VE}(t)_{O,p} = 1 - \frac{\lambda(t \mid X_{ij} \in \{0,1\}, \overline{X}^k_{i,-j} = p)}{\lambda(t \mid X_{ij} = 0, \overline{X}^k_{i,-j} = 0)}.$$

Estimating equations

We assume a Cox model:

(1) $$\lambda_{ij}^{k}(t \mid X_{ij}^{k}, \overline{X}_{i,-j}^{k}) = \lambda_0(t)\exp\{\beta_1 X_{ij}^{k} + \beta_2 \overline{X}_{i,-j}^{k}\}$$

where $\lambda_0(t)$ is an unspecified study-specific baseline hazard function.

An estimator of (β_1, β_2) can be obtained based on the working assumption that the individuals within each cluster are independent of one another. That is, they can be estimated by solving the following estimating equations:

(2) $$\boldsymbol{\Phi}(\boldsymbol{\beta}) = \sum_{i,j,k} \Delta_{ij}^{k}\{\boldsymbol{X}_{ij}^{k} - \frac{\boldsymbol{S}_1(\boldsymbol{\beta}, U_{ij}^{k})}{S_0(\boldsymbol{\beta}, U_{ij}^{k})}\} = \mathbf{0}$$

where $S_0(\boldsymbol{\beta}, t) = \sum_{i',j',k'} Y_{i'j'}^{k'}(t) exp(\boldsymbol{\beta}^T \boldsymbol{X}_{i'j'}^{k'})$, $\boldsymbol{S}_1(\boldsymbol{\beta}, t) = \sum_{i',j',k'} Y_{i'j'}^{k'}(t) exp(\boldsymbol{\beta}^T \boldsymbol{X}_{i'j'}^{k'}) \boldsymbol{X}_{i'j'}^{k'}$, with $\boldsymbol{X}_{ij}^{k} = (X_{ij}^{k}, \overline{X}_{i,-j}^{k})^T$ and $Y_{ij}^{k}(t) = I\{U_{ij}^{k} \geq t\}$. Equation (2) corresponds to the partial likelihood score function for the marginal Cox model (1).

Estimating variance

It has been shown that, under mild conditions, $\hat{\boldsymbol{\beta}} = (\hat{\beta}_1, \hat{\beta}_2)^T$ is consistent for the true parameter values $(\beta_{1,0}, \beta_{2,0})^T$ and as number of clusters $I = \sum_{k=1}^{K} I_k$ goes to infinity, the asymptotic distribution of $(\hat{\beta}_1, \hat{\beta}_2)^T$ can be approximated by a normal distribution with mean 0 and covariance matrix Γ in a sandwich form.[6] The variance of $\hat{\boldsymbol{\beta}}$ can be estimated by (implemented in the coxph function in R):

$$\hat{\boldsymbol{\Gamma}}(\hat{\boldsymbol{\beta}}) = \boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}}) \left[\sum_{i,k} \left(\sum_{j} \boldsymbol{M}_{ij}^{k}(\hat{\boldsymbol{\beta}}) \right) \left(\sum_{j} \boldsymbol{M}_{ij}^{k}(\hat{\boldsymbol{\beta}}) \right)^T \right] \boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}}),$$

where $\boldsymbol{I}(\boldsymbol{\beta}) = -\partial \boldsymbol{\Phi}(\boldsymbol{\beta}) / \partial \boldsymbol{\beta}$, and

$$\boldsymbol{M}_{ij}^{k}(\boldsymbol{\beta}) = \delta_{ij}^{k} \{ \boldsymbol{X}_{ij}^{k} - \frac{\boldsymbol{S}_1(\boldsymbol{\beta}, U_{ij}^{k})}{S_0(\boldsymbol{\beta}, U_{ij}^{k})} \} - \sum_{i',j',k'} \frac{\Delta_{i'j'}^{k'} Y_{ij}^{k}(U_{i'j'}^{k'}) exp(\boldsymbol{\beta}^T \boldsymbol{X}_{ij}^{k})}{S_0(\boldsymbol{\beta}, U_{i'j'}^{k'})} \times \{ \boldsymbol{X}_{ij}^{k} - \frac{\boldsymbol{S}_1(\boldsymbol{\beta}, U_{i'j'}^{k'})}{S_0(\boldsymbol{\beta}, U_{i'j'}^{k'})} \}.$$

Under the assumption of Model (1),

Effectives measures from Cox model

Under the assumption of Model (1),

$$\mathrm{VE}_{D,p} = 1 - exp(\beta_1)$$
$$\mathrm{VE}_{I,p} = 1 - exp(p\beta_2)$$
$$\mathrm{VE}_{T,p} = 1 - exp(\beta_1 + p\beta_2)$$
$$\mathrm{VE}_{O,p} = 1 - \{pexp(\beta_1 + p\beta_2) + (1-p)exp(p\beta_2)\}.$$

Where β_1 measures the direct effect and β_2 the indirect effect in a Cox model, and *p* is the vaccination coverage.

Estimating variance of VE estimators

Estimates for $VE_{D,p}$, $VE_{I,p}$, $VE_{T,p}$, and $VE_{O,p}$ can be obtained by plugging in estimates for β_1 and β_2 along with the corresponding coverage level p. Confidence intervals for $VE_{D,p}$, $VE_{I,p}$, and $VE_{T,p}$ can be obtained by transforming the confidence intervals for β_1, β_2, and $\beta_1+p\beta_2$. Confidence intervals for $VE_{O,p}$ can be obtained by first calculating a standard error estimate using the Delta method, then forming a Wald-type confidence interval. More specifically, we write the estimated variance-covariance matrix for $(\hat{\beta}_1, \hat{\beta}_2)$, $\hat{\Gamma} = \begin{bmatrix} \hat{V}_{\beta_1,\beta_1} & \hat{V}_{\beta_1,\beta_2} \\ \hat{V}_{\beta_2,\beta_1} & \hat{V}_{\beta_2,\beta_2} \end{bmatrix}$. Then the Wald-type $100(1-\alpha)\%$ confidence interval for β_1, β_2, and $\beta_1 + p\beta_2$ are:

$$(L_{\beta_1} = \hat{\beta}_1 - Z_{\alpha/2}\sqrt{\hat{V}_{\beta_1,\beta_1}}\ ,\ U_{\beta_1} = \hat{\beta}_1 + Z_{\alpha/2}\sqrt{\hat{V}_{\beta_1,\beta_1}}),$$

$$(L_{\beta_2} = \hat{\beta}_2 - Z_{\alpha/2}\sqrt{\hat{V}_{\beta_2,\beta_2}}\ ,\ U_{\beta_2} = \hat{\beta}_2 + Z_{\alpha/2}\sqrt{\hat{V}_{\beta_2,\beta_2}}),$$

and

$$(L_{\beta_1+p\beta_2} = \hat{\beta}_1 + p\hat{\beta}_2 - Z_{\alpha/2}\sqrt{\hat{V}(\hat{\beta}_1 + p\hat{\beta}_2)}\ ,\ U_{\beta_1+p\beta_2} = \hat{\beta}_1 + p\hat{\beta}_2 + Z_{\alpha/2}\sqrt{\hat{V}(\hat{\beta}_1 + p\hat{\beta}_2)}),$$

where $\hat{V}(\hat{\beta}_1 + p\hat{\beta}_2) = \hat{V}_{\beta_1,\beta_1} + p^2\hat{V}_{\beta_2,\beta_2} + 2p\hat{V}_{\beta_1,\beta_2}$.

The resulting $100(1-\alpha)\%$ CIs for the direct effect VE_d, VE_i, and $VE_{t,p}$ are given by:

$$(1 - \exp(U_{\beta_1}), 1 - \exp(L_{\beta_1})),$$

$$(1 - \exp(U_{\beta_2}), 1 - \exp(L_{\beta_2})),$$

and

$$(1 - \exp(U_{\beta_1+p\beta_2}), 1 - \exp(L_{\beta_1+p\beta_2})),$$

respectively.

For the overall effect, we calculate the variance for $\widehat{\mathrm{VE}}_{O,p}$ directly using the Delta method:

$$\begin{aligned}\widehat{\mathrm{Var}}(\widehat{\mathrm{VE}}_{O,p}) = {} & p^2 exp(2\hat{\beta}_1 + 2p\hat{\beta}_2)\hat{V}_{\beta_1,\beta_1} + p^4 exp(2\hat{\beta}_1 + 2p\hat{\beta}_2)\hat{V}_{\beta_2,\beta_2} \\ & + 2p^3(1-p)exp(\hat{\beta}_1 + 2p\hat{\beta}_2)\hat{V}_{\beta_2,\beta_2} + p^2(1-p)^2 exp(2p\hat{\beta}_2)\hat{V}_{\beta_2,\beta_2} \\ & + 2p^3 exp(2\hat{\beta}_1 + 2p\hat{\beta}_2)\hat{V}_{\beta_1,\beta_2} + 2p^2(1-p)exp(\hat{\beta}_1 + 2p\hat{\beta}_2)\hat{V}_{\beta_1,\beta_2}.\end{aligned}$$

Then the corresponding CI of $\mathrm{VE}_{O,p}$ is

$$(\widehat{\mathrm{VE}}_{O,p} - Z_{\alpha/2}\sqrt{\widehat{\mathrm{Var}}(\widehat{\mathrm{VE}}_{O,p})}\ ,\ \widehat{\mathrm{VE}}_{O,p} + Z_{\alpha/2}\sqrt{\widehat{\mathrm{Var}}(\widehat{\mathrm{VE}}_{O,p})}).$$

We note that the resulting Wald-type intervals may not be range-preserving. Alternatively, we can sample $(\hat{\beta}_1, \hat{\beta}_2)$ from their asymptotic distribution, calculate the corresponding VE measures, then form a confidence interval using the percentile method.

When there is dependence

- The case where $VE_{D,p}$ could depend on the coverage level

(3) $$\lambda_{ij}^{k}(t \mid X_{ij}^{k}, \overline{X}_{i,-j}^{k}) = \lambda_0(t)\exp\{\beta_1 X_{ij}^{k} + \beta_2 \overline{X}_{i,-j}^{k} + \beta_3 X_{ij}^{k} * \overline{X}_{i,-j}^{k}\}$$

Under Model (3), we have:

$$\mathrm{VE}_{D,p} = 1 - exp(\beta_1 + p\beta_3)$$

$$\mathrm{VE}_{I,p} = 1 - exp(p\beta_2)$$

$$\mathrm{VE}_{T,p} = 1 - exp(\beta_1 + p\beta_2 + p\beta_3)$$

$$\mathrm{VE}_{O,p} = 1 - \{pexp(\beta_1 + p\beta_2 + p\beta_3) + (1-p)exp(p\beta_2)\}.$$

Estimation and inference can proceed similarly as before.

Properties of estimators from simulations

TABLE 1

Estimation of model parameters using data from Trial 1, Trial 2, and both trials. Sample average: average of estimates across simulated datasets; ESE: empirical standard errors; ASE: average of estimated standard errors; Coverage: empirical coverage rate for 95% confidence intervals. Results are based on 5000 simulated datasets

	Data	Sample Average	ESE	ASE	Coverage
$I^{(1)} = I^{(2)} = 200$					
$\beta_1 = -0.5$	Trial 1 only	-0.5021	0.0249	0.0244	94.18%
	Both Trials	-0.5009	0.0218	0.0216	94.42%
$\beta_2 = -0.5$	Trial 1 only	-0.5186	0.4670	0.4587	94.26%
	Both Trials	-0.5010	0.0701	0.0698	94.84%
$\beta_1 + \beta_2 = -1$	Trial 2 only	-1.0025	0.0703	0.0701	95.08%

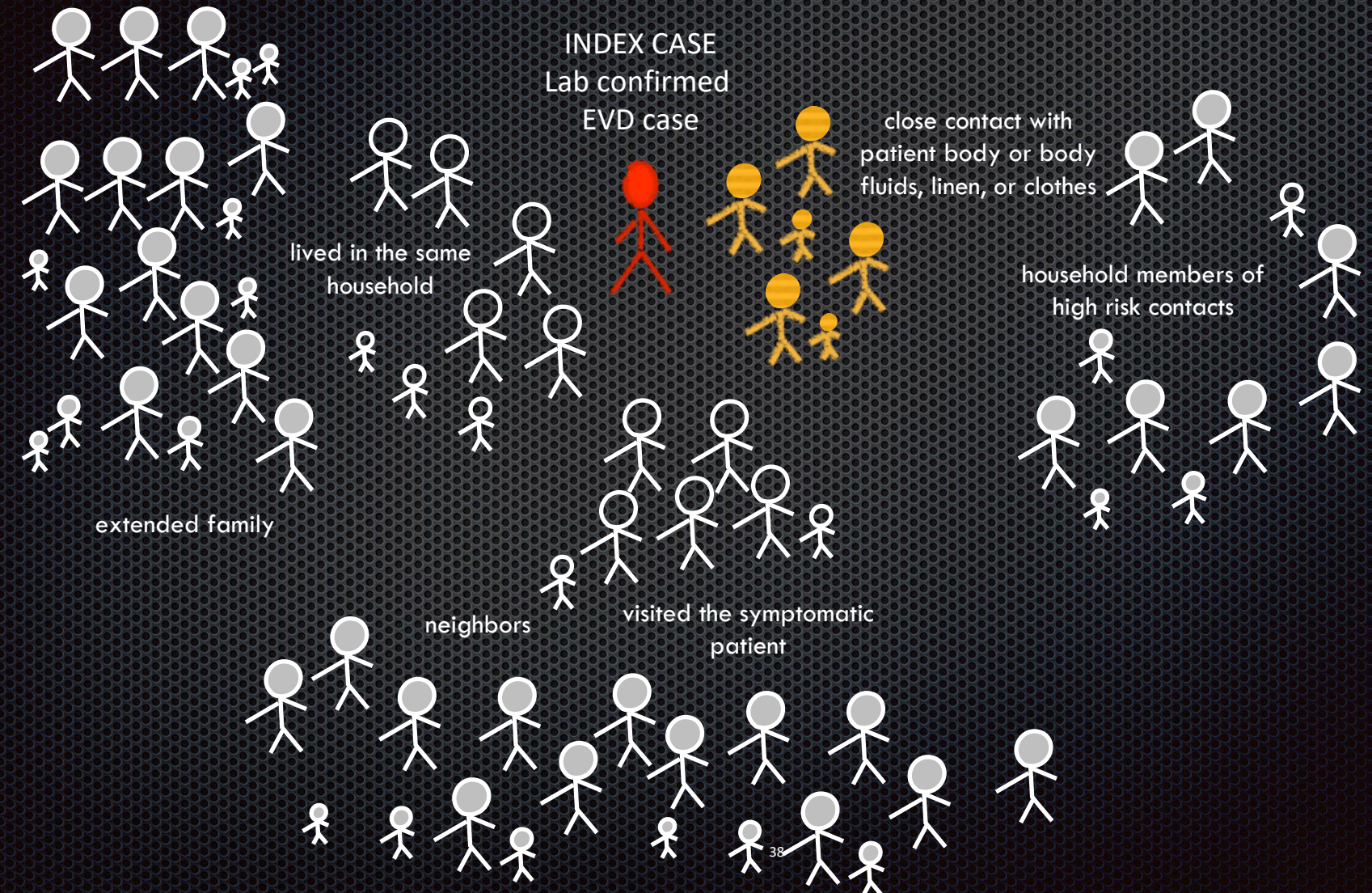
Table 4 Estimation of direct, indirect, total and overall effects using data from Trial 1, Trial 2, Trial 3, all IRTs and all trials. Sample average: average of estimates across simulated datasets; ESE: empirical standard errors; ASE: average of estimated standard errors; Coverage: empirical coverage rate for 95% confidence intervals. Results are based on 5000 simulated datasets

	Data	Average	ESE	Coverage[†]
$VE_D = 0.6200$	Trial 1 only	0.6178	0.0556	95.02%
	Trial 2 only	0.6185	0.0773	94.94%
	IRTs	0.6194	0.0452	94.98%
	All Trials	0.6193	0.0451	94.86%
$VE_{I,0.25} = 0.6683$	Trial 1 only	0.6577	0.0836	94.10%
	Trial 2 only	0.6502	0.1227	94.24%
	IRTs	0.6674	0.0342	94.50%
	All Trials	0.6680	0.0182	95.04%
$VE_{I,0.5} = 0.8900$	Trial 1 only	0.8758	0.0636	94.10%
	Trial 2 only	0.8626	0.1064	94.24%
	IRTs	0.8882	0.0230	94.50%
	All Trials	0.8895	0.0122	95.04%
$VE_{T,0.25} = 0.8740$	Trial 1 only	0.8690	0.0380	94.48%
	Trial 2 only	0.8663	0.0558	94.40%
	IRTs	0.8736	0.0185	94.84%
	All Trials	0.8739	0.0145	94.82%
$VE_{T,0.5} = 0.9582$	Trial 1 only	0.9524	0.0259	94.30%
	Trial 2 only	0.9473	0.0435	94.20%
	IRTs	0.9576	0.0095	94.70%
	All Trials	0.9581	0.0057	94.66%
$VE_{O,0.25} = 0.7197$	Trial 1 only	0.7105	0.0710	93.96%
	Trial 2 only	0.7042	0.1042	92.26%
	IRTs	0.7190	0.0286	94.58%
	All Trials	0.7195	0.0147	95.06%
$VE_{O,0.5} = 0.9241$	Trial 1 only	0.9141	0.0443	91.82%
	Trial 2 only	0.9050	0.0743	88.08%
	IRTs	0.9229	0.0157	94.12%
	All Trials	0.9238	0.0080	94.96%

Example 2: Ebola and ring vaccination

What is a vaccination ring?

Contacts and contacts of contacts



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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See Online/Editorial
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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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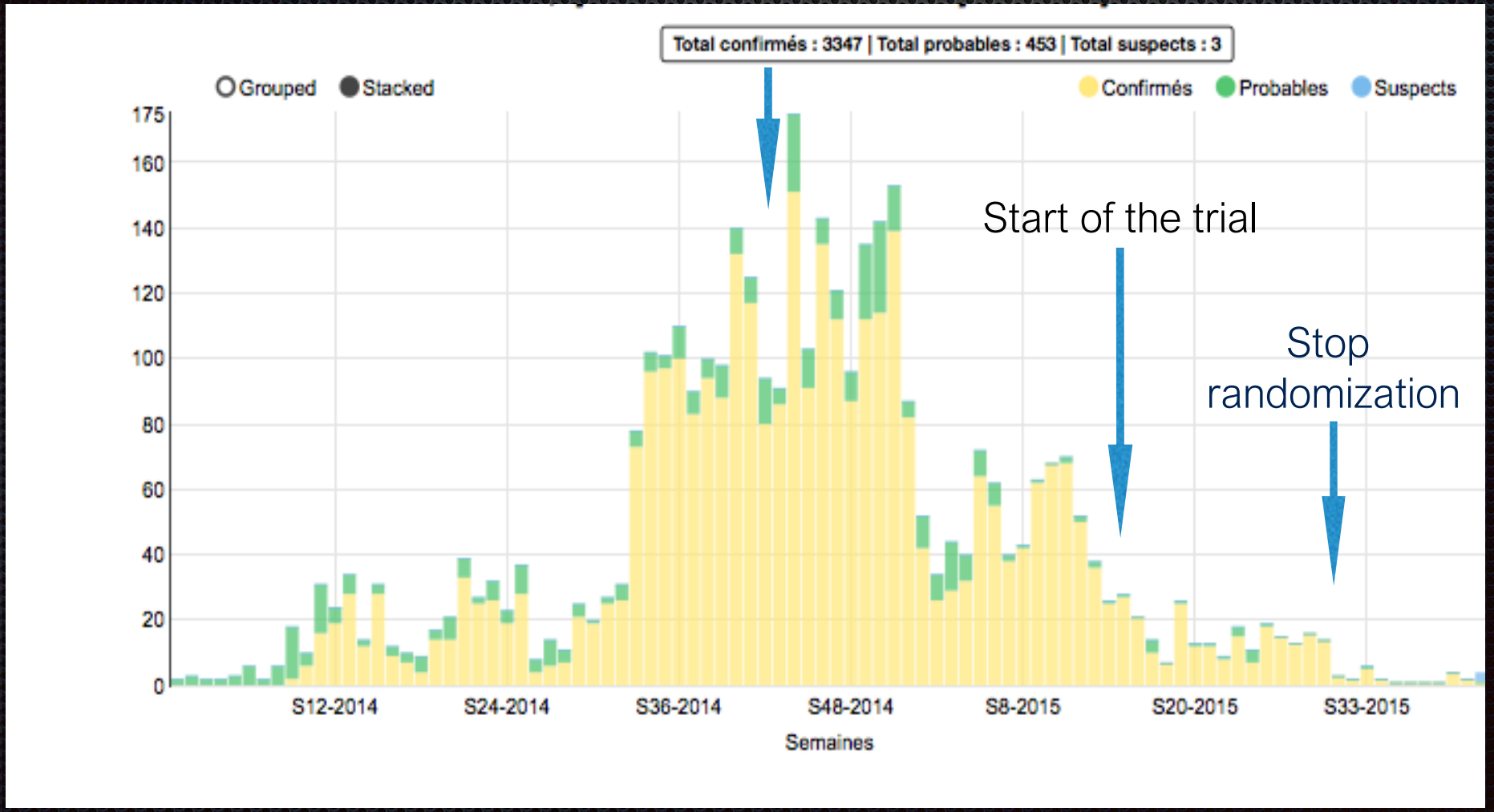
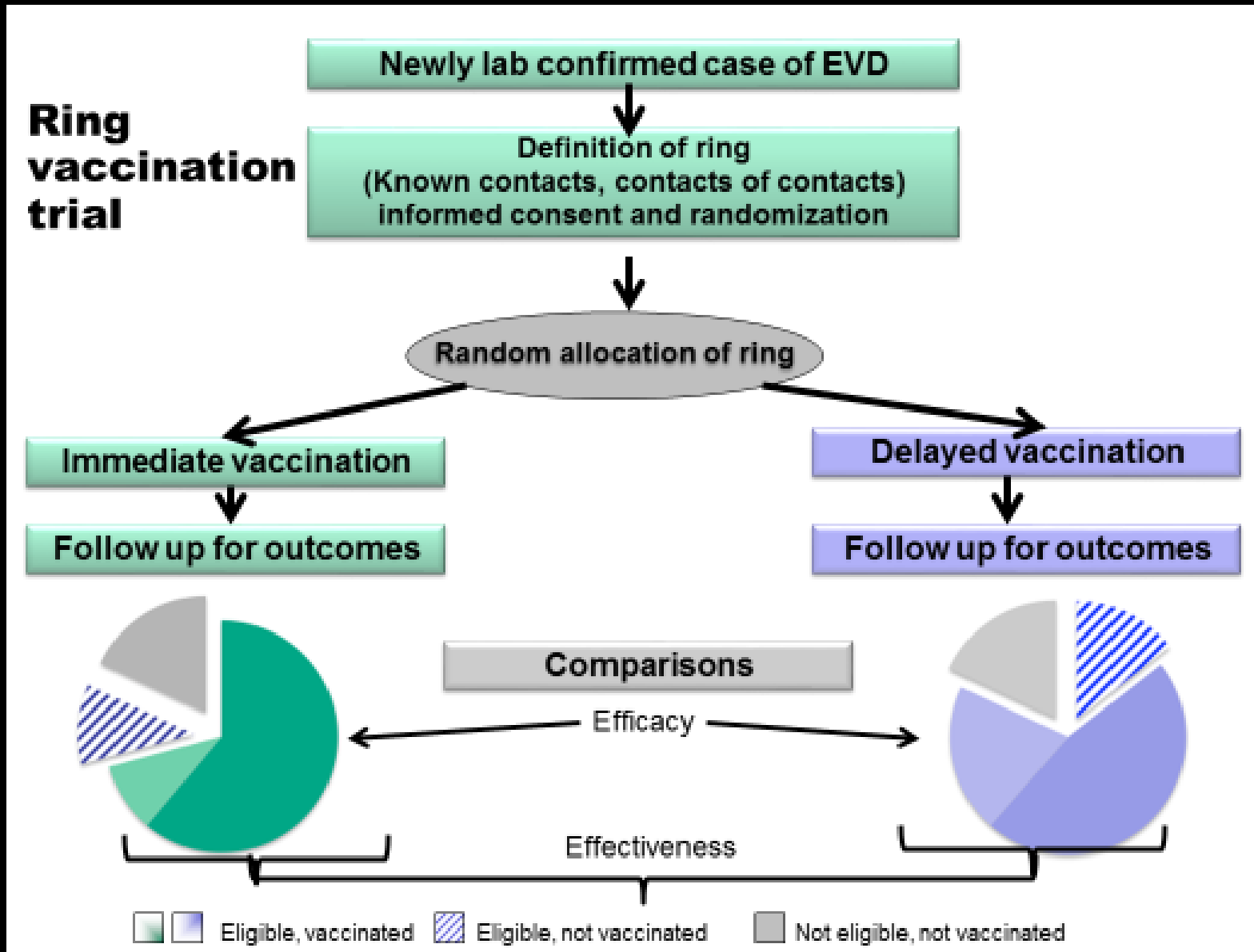
*Contributed equally

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

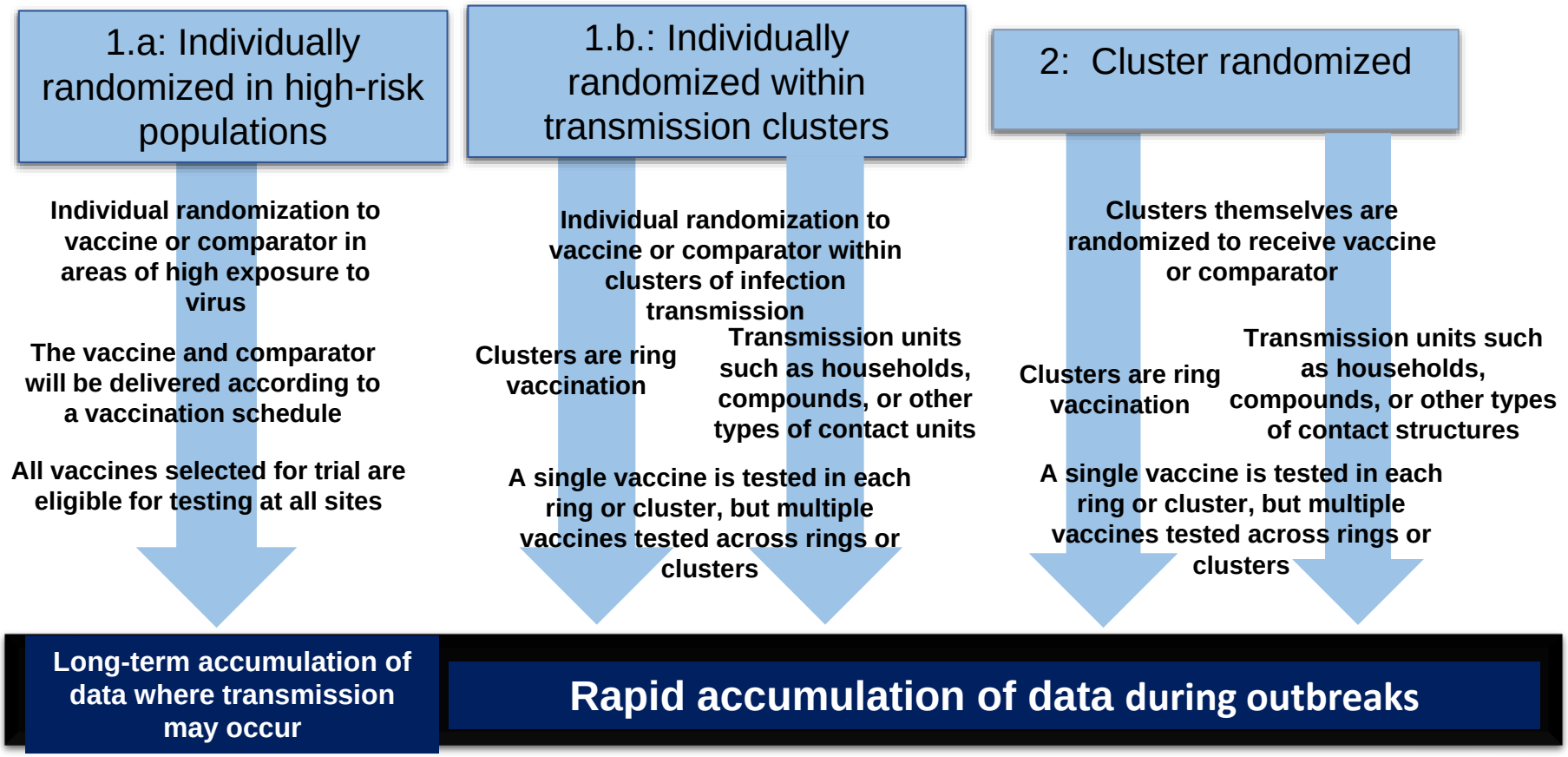
Cases of Ebola by week of notification of cases, Guinea 2014-15

Decision to conduct trial

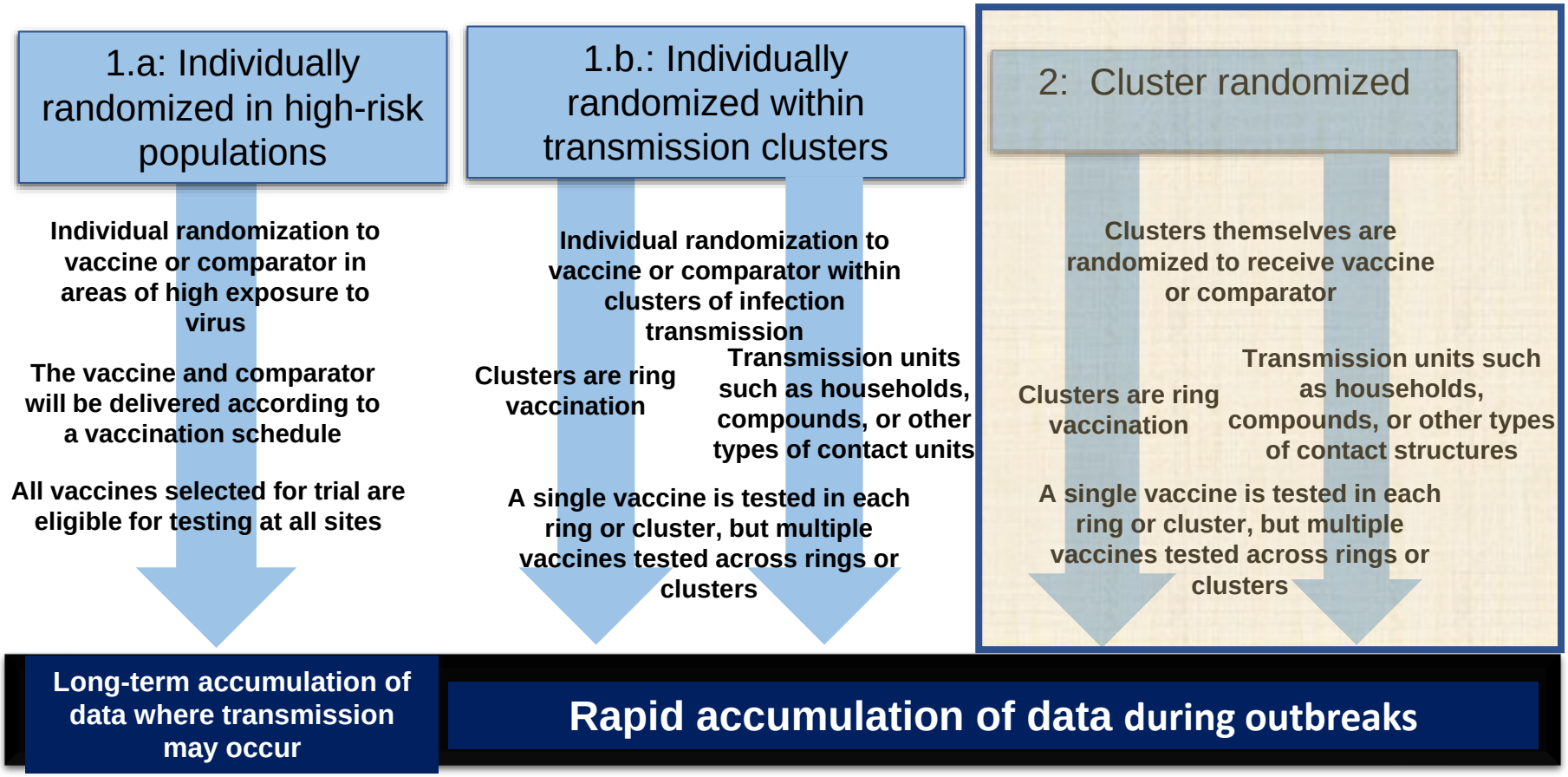



Ring vaccination trial
Newly lab confirmed case of EVD
Definition of ring
(Known contacts, contacts of contacts)
informed consent and randomization
Random allocation of ring
Immediate vaccination
Delayed vaccination
Follow up for outcomes
Follow up for outcomes
Comparisons
Efficacy
Effectiveness
Eligible,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

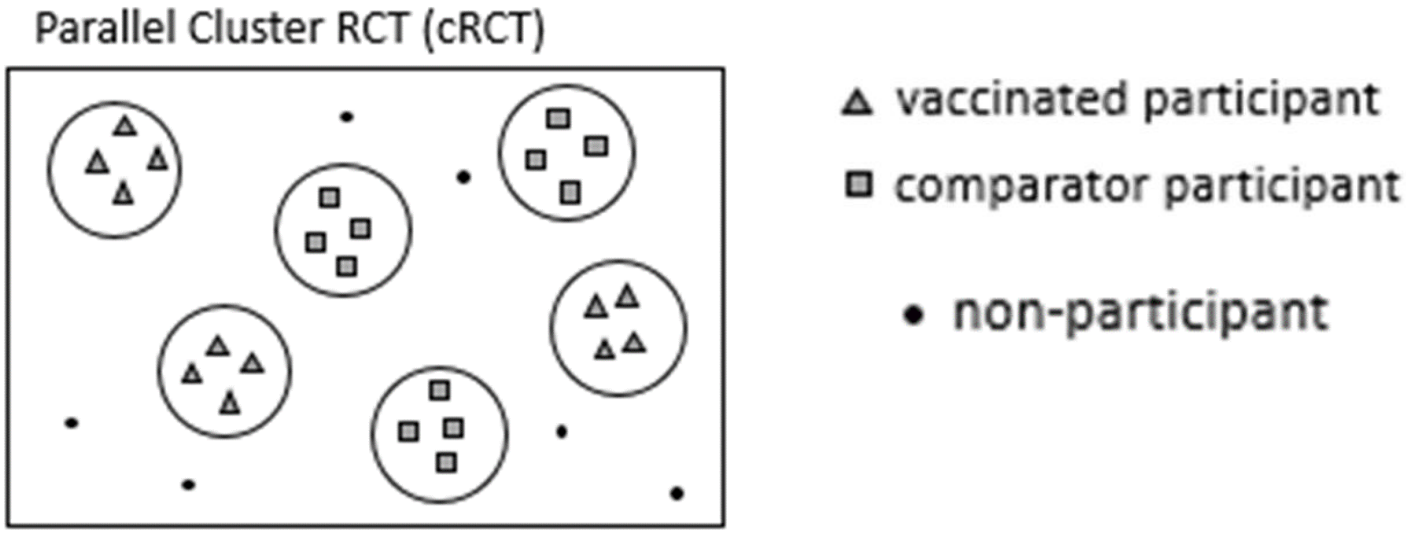
Vaccine trial designs



Vaccine trial designs



Cluster randomized



Estimate total and overall effectiveness

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)

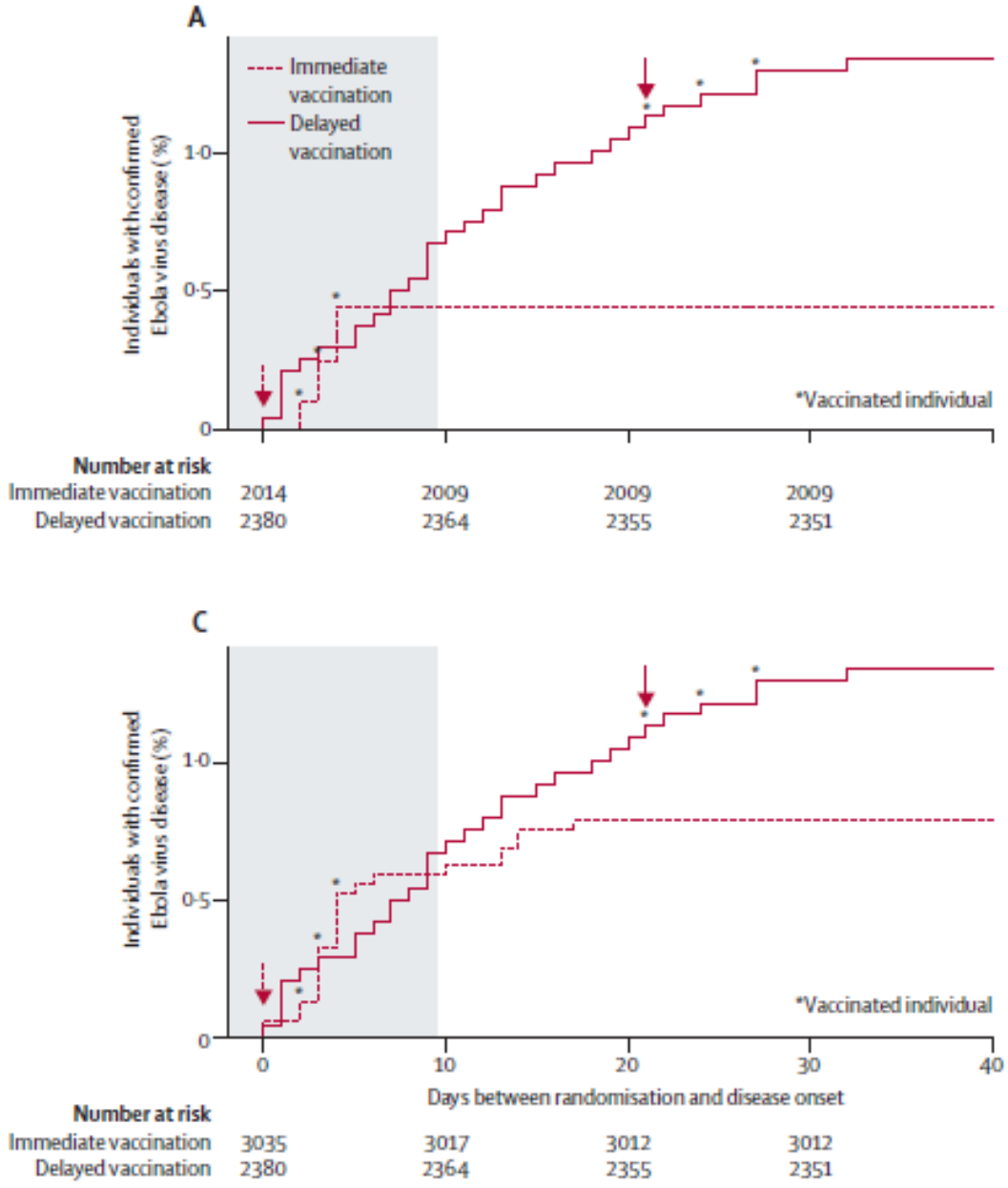
How was the ring vaccination trial implemented?

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

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

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

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

Over 450,000 people have been vaccinated in the 2019 - 2022 outbreaks of Ebola in the DRC

Current filovirus outbreaks

Global Regions Select language

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Equatorial Guinea confirms first-ever Marburg virus disease outbreak

13 February 2023

Brazzaville/Malabo – Equatorial Guinea today confirmed its first-ever outbreak of Marburg virus disease. Preliminary tests carried out following the deaths of at least nine people in the country's eastern Kie Ntem Province turned out positive on one of the samples for the viral haemorrhagic fever.*

Equatorial Guinean health authorities sent samples to the Institut Pasteur reference laboratory in Senegal with support from World Health Organization (WHO) to determine the cause of the disease after an alert by a district health official on 7 February. Of the eight samples tested at Institut Pasteur, one turned out positive for the virus. So far nine deaths and 16 suspected cases with symptoms including fever, fatigue and blood-stained vomit and diarrhoea have been reported.

Further investigations are ongoing. Advance teams have been deployed in the affected districts to trace contacts, isolate and provide medical care to people showing symptoms of the disease. Efforts are also underway to rapidly mount emergency response, with WHO deploying health emergency experts in epidemiology, case management, infection prevention, laboratory and risk communication to support the national response efforts and

Click image to enlarge

WHO Africa / Countries / News

Tanzania confirms first-ever outbreak of Marburg Virus Disease

21 March 2023

Brazzaville/Dar es Salaam – Tanzania today confirmed its first-ever cases of Marburg Virus Disease after laboratory tests were carried out following reports of cases and deaths in the country's north-west Kagera region.

Tanzania's National Public Health Laboratory analysed samples to determine the cause of illness after eight people developed symptoms including fever, vomiting, bleeding and renal failure. Five of the eight cases, including a health worker, have died and the remaining three are receiving treatment. A total of 161 contacts have been identified and being monitored.

"The efforts by Tanzania's health authorities to establish the cause of the disease is a clear indication of the determination to effectively respond to the outbreak. We are working with the government to rapidly scale up control measures to halt the spread of the virus and end the outbreak as soon as possible," said Dr Matshidiso Moeti, World Health Organization (WHO) Regional Director for Africa.

Click image to enlarge

COVID-19 Vaccine Trials

World Health Organization

Health Topics | Countries | Newsroom | Emergencies | Data | About WHO

Home / Diseases / Coronavirus disease (COVID-19) / Global research on coronavirus disease (COVID-19) / Solidarity Trial Vaccines

The **Solidarity Trial Vaccines** (STV) is an international, multi center, multi vaccine, adaptive, shared placebo, event driven, individually randomized controlled clinical trial that aims to evaluate the efficacy and safety of promising new COVID-19 vaccines.

The primary objective is to evaluate the effect of each vaccine on reducing the rate of virologically confirmed COVID-19 disease, regardless of severity.

Key features of the trial include:

- mobile trial sites to enable reaching people in remote areas and achieve more equitable recruitment
- interim analyses to identify better performing candidates and to eliminate those that are performing poorly against pre-specified statistical thresholds
- long-term follow-up to increase the rigour of results and enable formal evaluation of efficacy vs. severe disease and duration of efficacy

26 October 2021 | Statement

WHO statement on Solidarity Trial Vaccines

Key resources

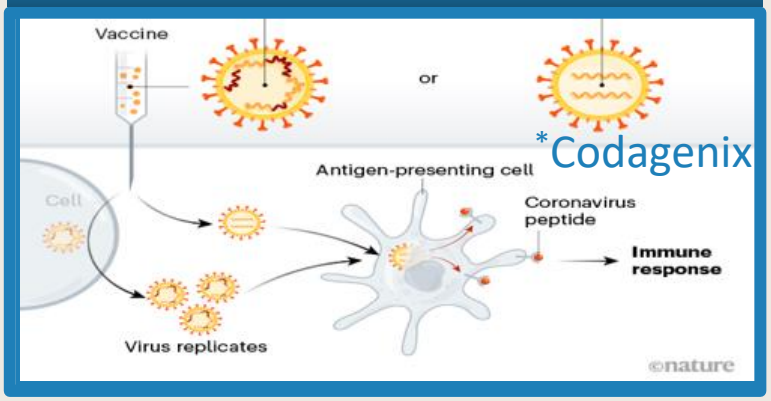
WHO statement on Solidarity Trial Vaccines >

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-trial-of-covid-19-vaccines

Types of COVID-19 candidate vaccines

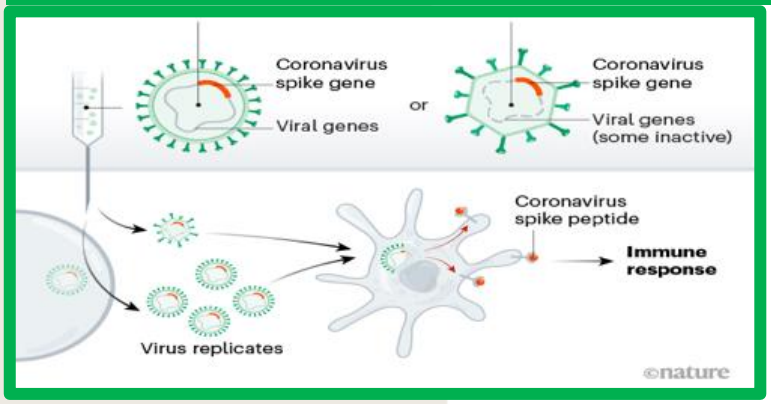
VIRUS VACCINES

Live-attenuated virus | Inactivated virus



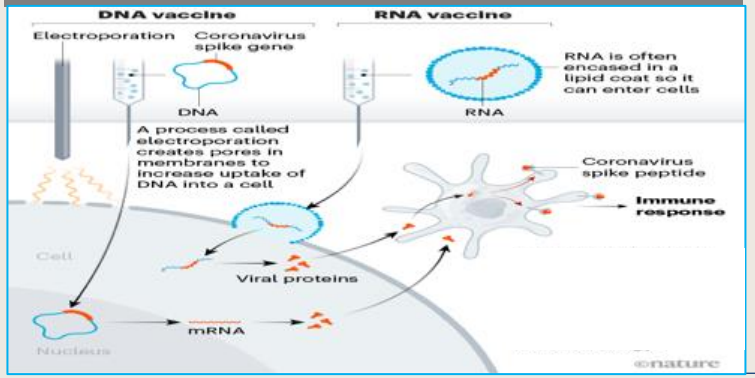
VIRAL VECTOR VACCINES

Replicating viral vector | Non-replicating viral vector



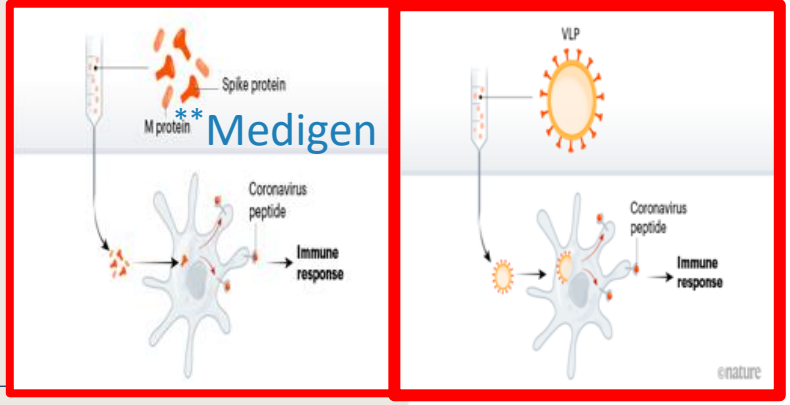
NUCLEIC ACID VACCINES

DNA and RNA vaccines



PROTEIN-BASED VACCINES

Protein subunits | Virus-like particles



World Health Organization

R&DBlueprint
Powering research to prevent epidemics

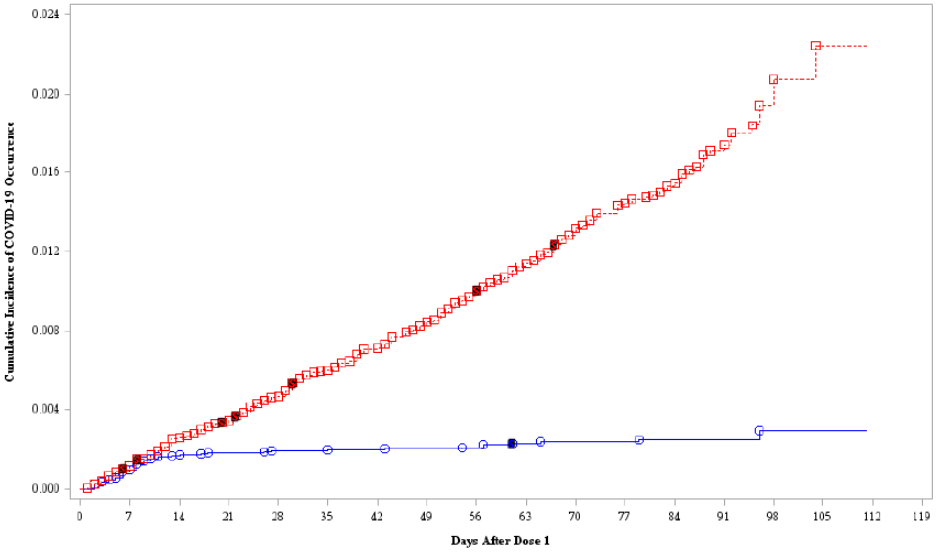
Effectiveness of current COVID vaccines

- Most licensed vaccines started with VE > 90% against any COVID disease for the original strain, but are not protecting well against the Omicron variants, VE < 40%.
- Most started with VE > 95% against severe disease and have slipped a bit against the Omicron variants, VE ≈ 80%.
- We need an Omicron vaccine for primary series and boosters, or a live attenuated vaccine that stimulates mucosal immunity

For example, phase III vaccine trail

- Sponsor Name: Pfizer
- Vaccine: BNT162b2 RNA vaccine
- **Final analysis carried out at 196 events**
  - **VE = 94.6% (95% CI 89.9 to 97.3)**
    - **Apparent VE severe disease and older adults**
    - **Safe so far, but more severe reaction in those with allergies**
    - **Licensed**

Figure 13 Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population



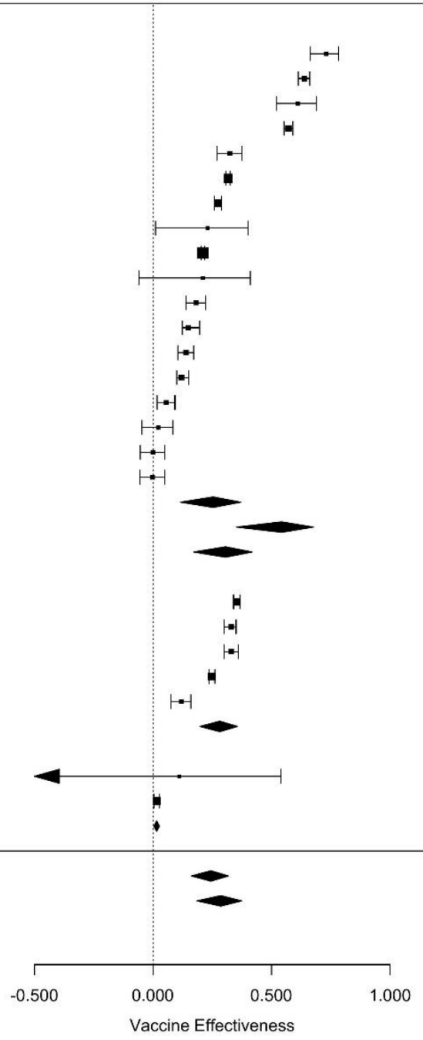
https://www.fda.gov/media/144246/download

CENTER FOR INFERENCE & DYNAMICS OF INFECTIOUS DISEASES

UF UNIVERSITY of FLORIDA

Recent meta-analysis against omicron:
Overall vaccine effectiveness of full dose doses against infection or symptomatic infection

Author(s) and Year	Region	Vaccine	Case Event	Age Group (years)	Test Timing (days)	Estimate [95% CI]
Pure mRNA Vaccines, full doses						
Powell, et al. (2021)	UK	BNT162b2/BNT162b2	SI	12-15	≥14	0.730 [0.664, 0.783]
Florentino, et al. (2022)	Scotland	BNT162b2/BNT162b2	SI	12-17	≥14	0.638 [0.613, 0.661]
Carazo, et al. (2022)	Canada	Mixed (BNT162b2/mRNA-1273)	SI	≥18	≥7	0.610 [0.520, 0.690]
Powell, et al. (2021)	UK	BNT162b2/BNT162b2	SI	16-17	≥14	0.572 [0.553, 0.590]
Buchan, et al. (2022b)	Canada	BNT162b2/BNT162b2	SI	12-17	≥7	0.324 [0.269, 0.375]
Florentino, et al. (2022)	Brazil	BNT162b2/BNT162b2	SI	12-17	≥14	0.316 [0.307, 0.325]
Andrews, et al. (2022)	UK	mRNA-1273/mRNA-1273	SI	≥18	≥14	0.274 [0.260, 0.288]
Grewal, et al. (2022a)	Canada	Mixed (BNT162b2/mRNA-1273)	SI	≥60	NR	0.230 [0.010, 0.400]
Andrews, et al. (2022)	UK	BNT162b2/BNT162b2	SI	≥18	≥14	0.210 [0.204, 0.217]
Kim, et al. (2022)	USA	Mixed (BNT162b2/mRNA-1273)	SI	≥18	≥14	0.210 [-0.060, 0.410]
Lind, et al. (2022)	Brazil	Mixed (BNT162b2/mRNA-1273)	AI	≥5	≥14	0.181 [0.139, 0.222]
Chin, et al. (2022)	USA	Mixed (BNT162b2/mRNA-1273)	AI	≥18	≥7	0.149 [0.123, 0.197]
Tseng, et al. (2022a)	USA	mRNA-1273/mRNA-1273	AI	≥18	≥14	0.139 [0.105, 0.171]
Young-Xu, et al. (2022)	USA	Mixed (BNT162b2/mRNA-1273)	AI	≥18	≥14	0.120 [0.100, 0.150]
Chemaitelly, et al. (2022)	Qatar	BNT162b2/BNT162b2	SI	all ages	≥30	0.056 [0.018, 0.092]
Altarawneh, et al. (2022)	Qatar	mRNA-1273/mRNA-1273	SI	all ages	14-300	0.022 [-0.046, 0.085]
Chemaitelly, et al. (2022)	Qatar	mRNA-1273/mRNA-1273	SI	all ages	≥30	-0.000 [-0.053, 0.050]
Altarawneh, et al. (2022)	Qatar	BNT162b2/BNT162b2	SI	all ages	14-300	-0.002 [-0.055, 0.049]
Pooled VE in adults: (Q = 198.83, df = 7, p < .01; I^2 = 99.6%, τ^2 = 5.52e-02)						0.254 [0.115, 0.371]
Pooled VE in children and adolescents: (Q = 758.63, df = 4, p < .01; I^2 = 99.6%, τ^2 = 1.55e-01)						0.542 [0.352, 0.677]
Pooled VE in all age groups: (Q = 2179.16, df = 17, p < .01; I^2 = 99.8%, τ^2 = 1.43e-01)						0.306 [0.171, 0.418]
Partial mRNA Vaccines, full doses						
Kirsebom, et al. (2022a) BA2	UK	Mixed (BNT162b2/mRNA-1273/ChAdOx1)	SI	≥18	≥14	0.353 [0.340, 0.366]
Andeweg, et al. (2022) BA1	Netherlands	Mixed (BNT162b2/mRNA-1273/ChAdOx1)	SI	≥18	≥14	0.330 [0.300, 0.350]
Andeweg, et al. (2022) BA2	Netherlands	Mixed (BNT162b2/mRNA-1273/ChAdOx1)	SI	≥18	≥14	0.330 [0.300, 0.360]
Kirsebom, et al. (2022a) BA1	UK	Mixed (BNT162b2/mRNA-1273/ChAdOx1)	SI	≥18	≥14	0.249 [0.236, 0.261]
Buchan, et al. (2022a)	Canada	Mixed (≥1 mRNA Vaccine)	SI	≥18	≥7	0.119 [0.076, 0.160]
Pooled VE in adults: (Q = 221.71, df = 4, p < .01; I^2 = 98.7%, τ^2 = 1.55e-02)						0.281 [0.198, 0.356]
Non-mRNA Vaccines, full doses						
Nunes, et al. (2022)	South Africa	Janssen	SI	≥18	≥14	0.110 [-0.720, 0.540]
Andrews, et al. (2022)	UK	ChAdOx1/ChAdOx1	SI	≥18	≥14	0.015 [0.004, 0.027]
Pooled VE in adults: (Q = 0.09, df = 1, p = 0.76; I^2 = 0.0%, τ^2 = 0.00e+00)						0.015 [0.004, 0.027]
Pooled VE in adults across all vaccine types: (Q = 2062.13, df = 14, p < .01; I^2 = 99.6%, τ^2 = 3.64e-02)						0.244 [0.162, 0.318]
Pooled VE in all age groups across all vaccine types: (Q = 4240.63, df = 24, p < .01; I^2 = 99.8%, τ^2 = 1.09e-01)						0.286 [0.185, 0.374]
Test for VE Difference in All across Vaccine Types: Q_M = 1.21, df = 2, p = 0.55						



Song S, Madewell Z, Liu M, Longini I, Yang Y. Effectiveness of SARS-CoV-2 vaccines against Omicron infection and severe events: A Systematic review and meta-analysis of test-negative design studies. *Frontiers in Public Health* **11** (2023) https://www.frontiersin.org/articles/10.3389/fpubh.2023.1195908

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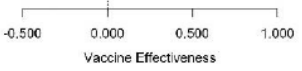
Overall vaccine effectiveness of second booster dose against Infection or symptomatic infection and against severe events

Author(s) and Year	Region	Variant Type	Vaccine	Case Event	Age Group (years)	Test Timing Median (IQR) or Mean (SD) (days)	Estimate [95% CI]
Infection, short term, 2nd booster							
Intawong, et al. (2022)	Thailand	Omicron	Mixed (BNT162b2/mRNA-1273/ChAdOx1)	AI	≥18	40 (26, 57)	0.750 [0.710, 0.800]
Chariyalertsak, et al. (2022)	Thailand	Omicron	ChAdOx1	AI	≥18	≥14 40 (26-57)	0.730 [0.480, 0.890]
Nittayasoot, et al. (2022)	Thailand	Omicron (BA.1/BA.2)	Mixed (BNT162b2/mRNA-1273/ChAdOx1/CoronaVac)	AI	Majority is 18-59	68.49 (28.2)	0.711 [0.708, 0.717]
Chariyalertsak, et al. (2022)	Thailand	Omicron	BNT162b2	AI	≥18	≥14 40 (26-57)	0.710 [0.600, 0.790]
Chariyalertsak, et al. (2022)	Thailand	Omicron	mRNA-1273	AI	≥18	≥14 40 (26-57)	0.710 [0.590, 0.790]
Grewal, et al. (2022a)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	SI	≥60	≥7 40 (30)	0.690 [0.610, 0.760]
Grewal, et al. (2022b)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	SI	≥60	<84	0.690 [0.610, 0.750]
Tartof, et al. (2022b)	US	Omicron (BA.4/BA.5)	Mixed (BNT162b2/mRNA-1273/Janssen)	AI in hospital	≥50	<90	0.660 [0.200, 0.850]
Tartof, et al. (2022b)	US	Omicron (BA.4/BA.5)	Mixed (BNT162b2/mRNA-1273/Janssen)	AI in ED	≥50	<90	0.650 [0.350, 0.820]
Tseng, et al. (2022b)	USA	Omicron (BA.4)	mRNA-1273	AI	≥18	14-90	0.587 [0.325, 0.747]
Tseng, et al. (2022b)	USA	Omicron (BA.2)	mRNA-1273	AI	≥18	14-90	0.572 [0.472, 0.653]
Grewal, et al. (2022a)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	AI	≥60	≥7 40 (30)	0.490 [0.430, 0.540]
Grewal, et al. (2022b)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	AI	≥60	<84	0.490 [0.440, 0.540]
Tseng, et al. (2022b)	USA	Omicron (BA.2.12.1)	mRNA-1273	AI	≥18	14-90	0.472 [0.348, 0.574]
Tartof, et al. (2022b)	US	Omicron (BA.4/BA.5)	Mixed (BNT162b2/mRNA-1273/Janssen)	AI in UC	≥50	<90	0.350 [0.100, 0.540]
Tseng, et al. (2022b)	USA	Omicron (BA.5)	mRNA-1273	AI	≥18	14-90	0.349 [0.158, 0.497]
Tartof, et al. (2022b)	US	Omicron (BA.4/BA.5)	Mixed (BNT162b2/mRNA-1273/Janssen)	AI in outpatient	≥50	<90	0.280 [0.100, 0.430]
Pooled VE in adults across all vaccine types against AI or SI, short term: (Q = 373.19, df = 16, p < .01; I^2 = 94.6%, τ^2 = 1.05e-01)							0.596 [0.520, 0.661]
Infection, long term, 2nd booster							
Tartof, et al. (2022b)	US	Omicron (BA.4/BA.5)	Mixed (BNT162b2/mRNA-1273/Janssen)	AI in ED	≥50	≥90	0.780 [0.500, 0.910]
Grewal, et al. (2022b)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	SI	≥60	≥84	0.535 [0.465, 0.596]
Grewal, et al. (2022b)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	AI	≥60	≥84	0.355 [0.313, 0.394]
Tartof, et al. (2022b)	US	Omicron (BA.4/BA.5)	Mixed (BNT162b2/mRNA-1273/Janssen)	AI in hospital	≥50	≥90	0.330 [-1.120, 0.790]
Tartof, et al. (2022b)	US	Omicron (BA.4/BA.5)	Mixed (BNT162b2/mRNA-1273/Janssen)	AI in UC	≥50	≥90	0.200 [-0.230, 0.480]
Tseng, et al. (2022b)	USA	Omicron (BA.2)	mRNA-1273	AI	≥18	>90	0.173 [-0.453, 0.626]
Tseng, et al. (2022b)	USA	Omicron (BA.2.12.1)	mRNA-1273	AI	≥18	>90	0.140 [-0.484, 0.619]
Tartof, et al. (2022b)	US	Omicron (BA.4/BA.5)	Mixed (BNT162b2/mRNA-1273/Janssen)	AI in outpatient	≥50	≥90	0.110 [-0.180, 0.340]
Tseng, et al. (2022b)	USA	Omicron (BA.4)	mRNA-1273	AI	≥18	>90	0.063 [-0.663, 0.704]
Tseng, et al. (2022b)	USA	Omicron (BA.5)	mRNA-1273	AI	≥18	>90	0.050 [-0.569, 0.611]
Pooled VE in adults across all vaccine types against AI, long term: (Q = 34.37, df = 9, p < .01; I^2 = 78.8%, τ^2 = 6.81e-02)							0.327 [0.154, 0.464]
Severe outcome, short term, 2nd booster							
Nittayasoot, et al. (2022)	Thailand	Omicron (BA.1/BA.2)	Mixed (BNT162b2/mRNA-1273/ChAdOx1/CoronaVac)	INV	Majority are 18-59	42 (0)	0.996 [0.970, 0.999]
Nittayasoot, et al. (2022)	Thailand	Omicron (BA.1/BA.2)	Mixed (BNT162b2/mRNA-1273/ChAdOx1/CoronaVac)	D	Majority are 18-59	42 (0)	0.993 [0.945, 0.999]
Tseng, et al. (2022b)	USA	Omicron (BA.2)	mRNA-1273	H	≥18	≥14 Majority < 90	0.964 [0.884, 0.989]
Grewal, et al. (2022c)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	H/D	50-59	7-119	0.958 [0.901, 0.982]
Grewal, et al. (2022c)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	H/D	70-79	7-119	0.925 [0.908, 0.940]
Grewal, et al. (2022c)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	H/D	60-69	7-119	0.919 [0.892, 0.940]
Grewal, et al. (2022c)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	H/D	≥80	7-119	0.910 [0.893, 0.925]
Tseng, et al. (2022b)	USA	Omicron (BA.4/BA.5)	mRNA-1273	H	≥18	≥14 Majority < 90	0.885 [0.518, 0.972]
Grewal, et al. (2022a)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	SO	≥60	≥7 40 (30)	0.860 [0.810, 0.900]
Grewal, et al. (2022b)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	SO	≥60	<84	0.820 [0.770, 0.860]
Link-Gelles, et al. (2022)	USA	Omicron (BA.2/BA.2.12.1)	Mixed (BNT162b2/mRNA-1273)	H	≥50	≥7 27 (17-41)	0.800 [0.710, 0.850]
Ferdinands, et al. (2022b)	USA	Omicron	Mixed (BNT162b2/mRNA-1273)	H	≥65	7-60 33 (19-50)	0.760 [0.710, 0.800]
Ferdinands, et al. (2022b)	USA	Omicron	Mixed (BNT162b2/mRNA-1273)	H	50-64	≥7 33 (19-50)	0.720 [0.510, 0.830]
Adams, et al. (2022)	USA	Omicron (BA.1/BA.2/BA.4/BA.5)	Mixed (BNT162b2/mRNA-1273/Janssen)	H	≥18	≥7 28 (15-42)	0.630 [0.370, 0.780]
Pooled VE in adults across all vaccine types against severe outcomes, short term: (Q = 183.40, df = 15, p < .01; I^2 = 97.9%, τ^2 = 1.54e+00)							0.873 [0.755, 0.934]
Severe outcome, long term, 2nd booster							
Grewal, et al. (2022c)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	H/D	70-79	≥120	0.890 [0.840, 0.920]
Grewal, et al. (2022c)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	H/D	≥80	≥120	0.860 [0.850, 0.910]
Grewal, et al. (2022c)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	H/D	60-69	≥120	0.880 [0.790, 0.930]
Grewal, et al. (2022c)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	H/D	50-59	≥120	0.860 [0.440, 0.960]
Grewal, et al. (2022b)	Canada	Omicron	Mixed (BNT162b2/mRNA-1273)	SO	≥60	≥84	0.760 [0.738, 0.815]
Pooled VE in adults across all vaccine types against severe outcomes, short term: (Q = 23.09, df = 4, p < .01; I^2 = 76.9%, τ^2 = 9.28e-02)							0.859 [0.803, 0.899]



SI: symptomatic infection; AI: any infection; ED/UC: emergency department or urgent care encounter; Mixed: the study reported VEs of these vaccines combined without distinguishing between them; H: hospitalization; D: death; SO: severe outcomes; INV: invasive

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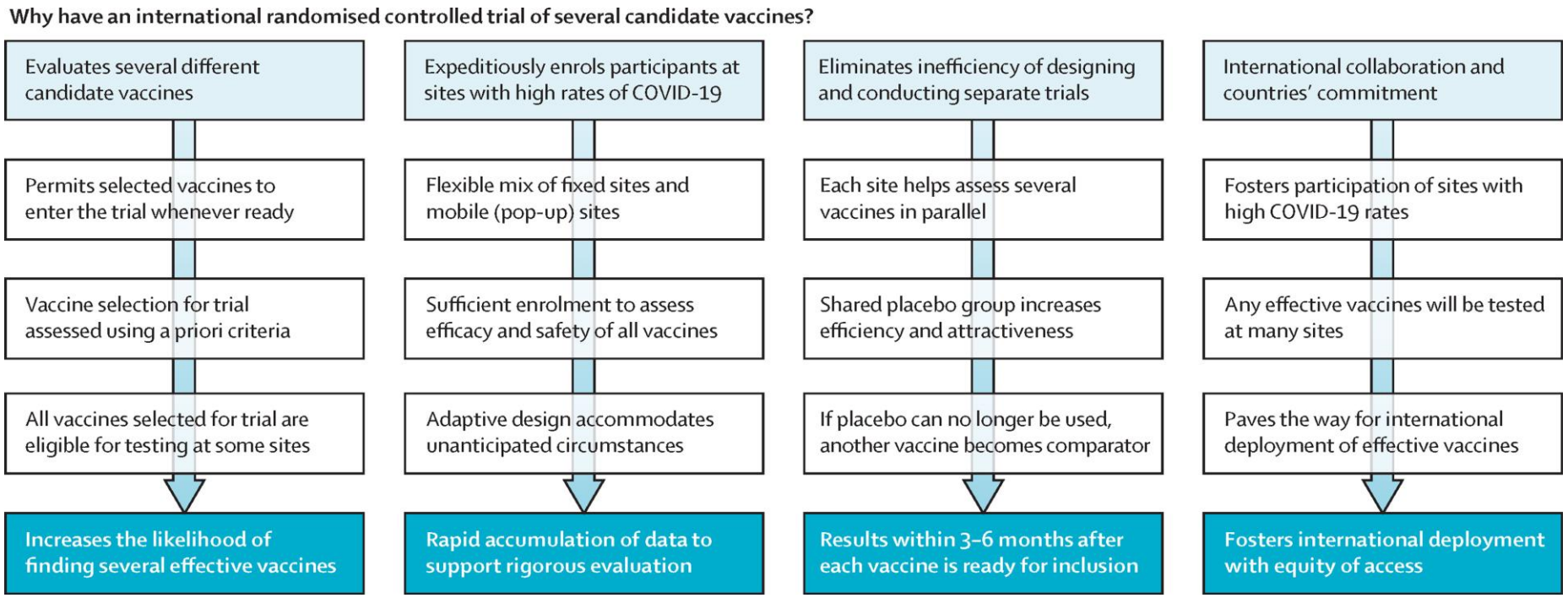
WHO Solidarity vaccines trial

An international randomised trial of several candidate vaccines

- Prompt, efficient, and reliable evaluation of the several of the candidate SARS-CoV-2 vaccines under development
- Assessment of efficacy and safety
- Identification of those appropriate for deployment

Basic design of trials

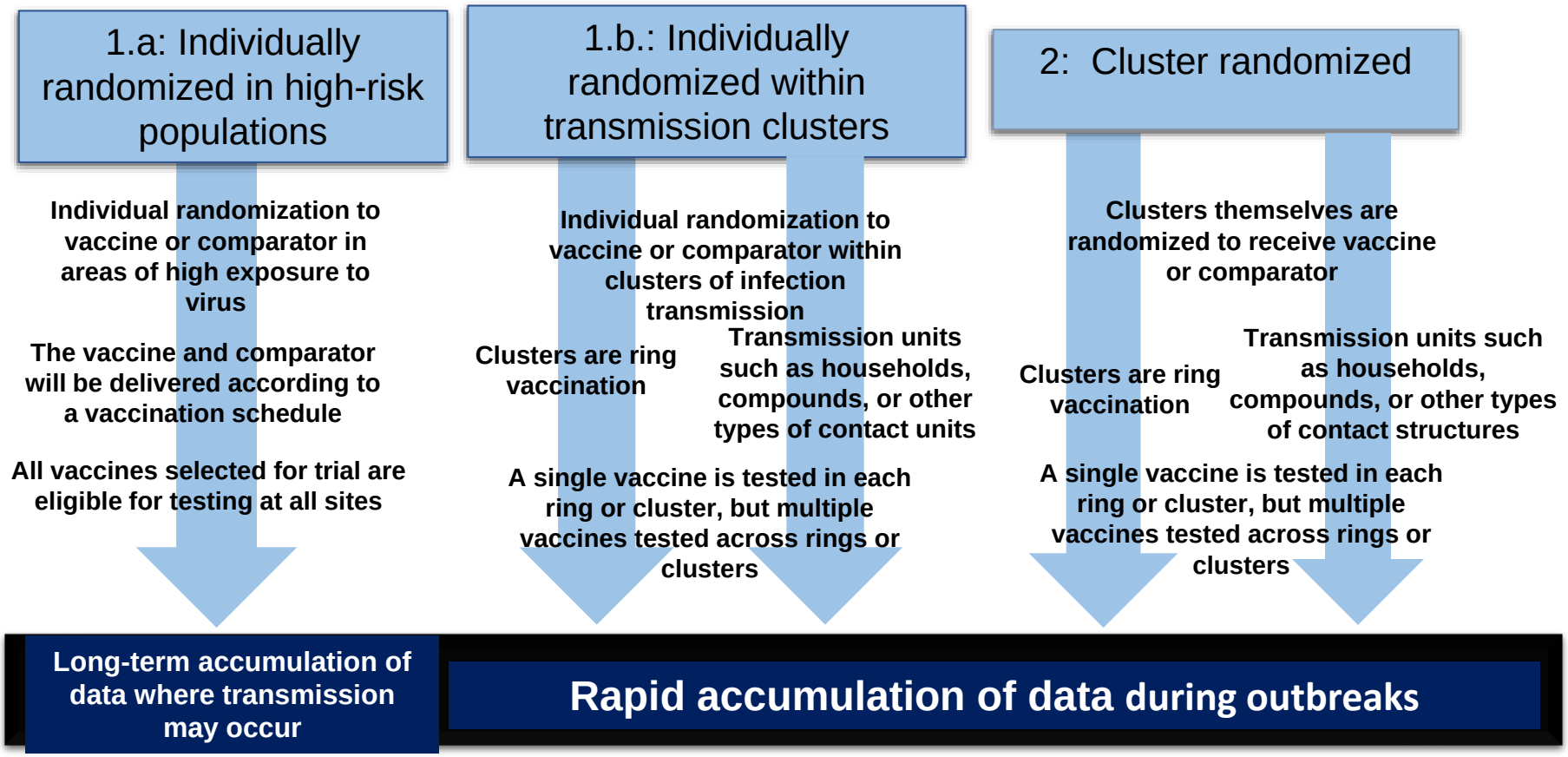


Krause P, Henao-Restrepo AM, Longini I, Peto R, Fleming TR. COVID vaccine trials should prove worthwhile efficacy, not just some efficacy. *Lancet*. DOI: https://doi.org/10.1016/S01406736(20)318213(2020)

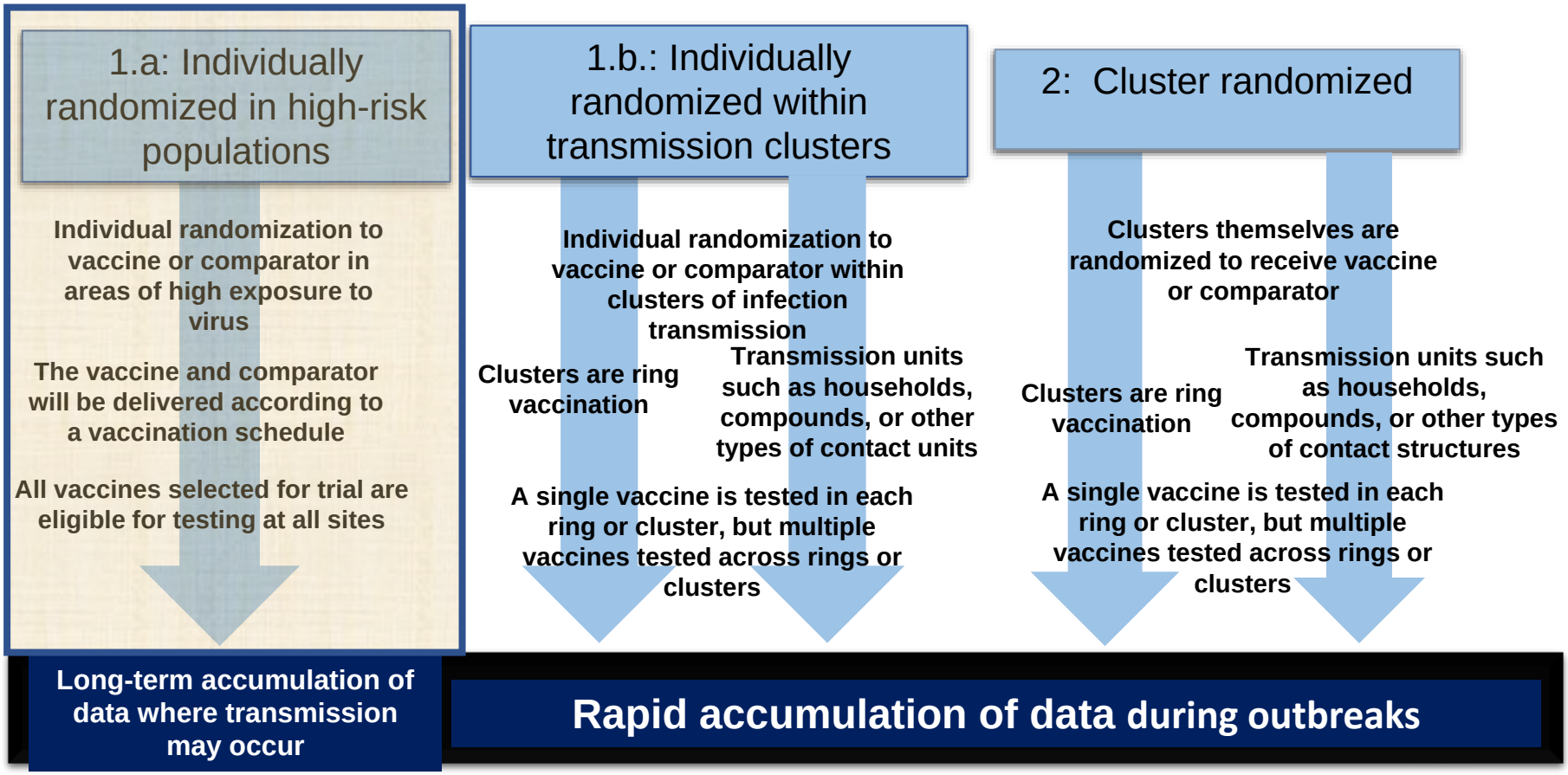
Trial operating characteristics

- Find vaccines with a VE ≥ 50% and eliminate those with a VE ≤ 30%
- Need a total of 150 events per vaccine vs placebo comparison
- One interim analysis at 100 events per vaccine vs placebo comparison
- Need about 20,000 participants per vaccine arm and 20,000 in the shared placebo arm.

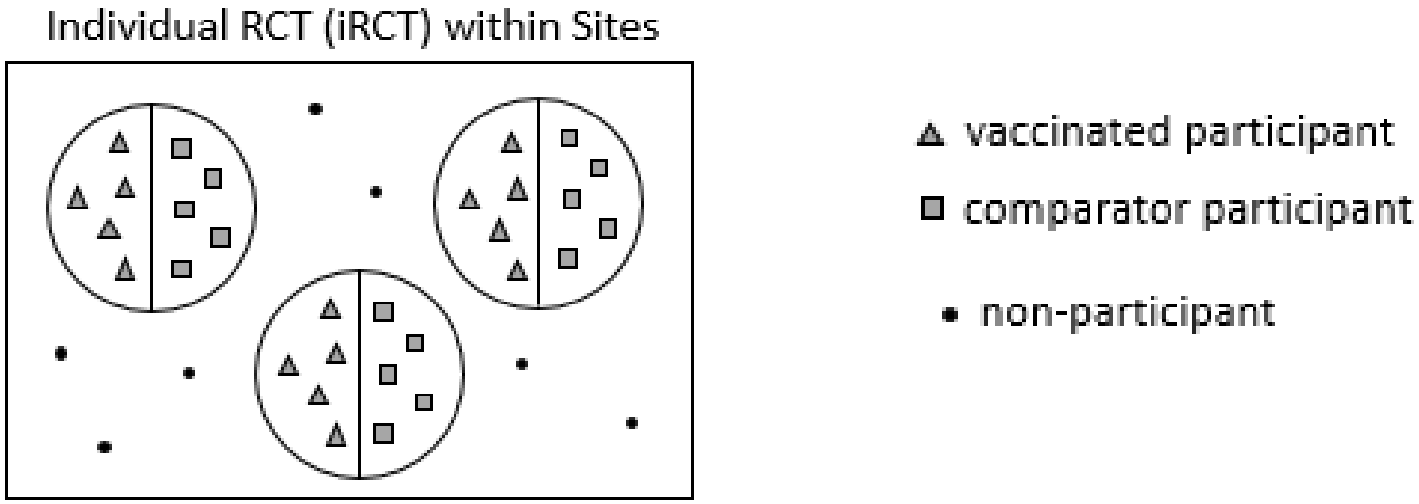
Vaccine trial designs



Vaccine trial designs



Individually randomized



Estimate direct effectiveness only

Current Solidarity Trial

- Medigen (protein-based) vaccine with adjuvant (aluminum hydroxide and CpG 1018)
  - Mali, Philippians and Colombia
  - ~ 20,000 per arm
  - Results will be available soon

- Codagenix live attenuated intranasal vaccine
  - Kenya, Mali, Sierra Leone and Colombia
  - Currently in the field

Thank You!