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Beyond efficacy trials: what more do we need to know about the effects of vaccines?

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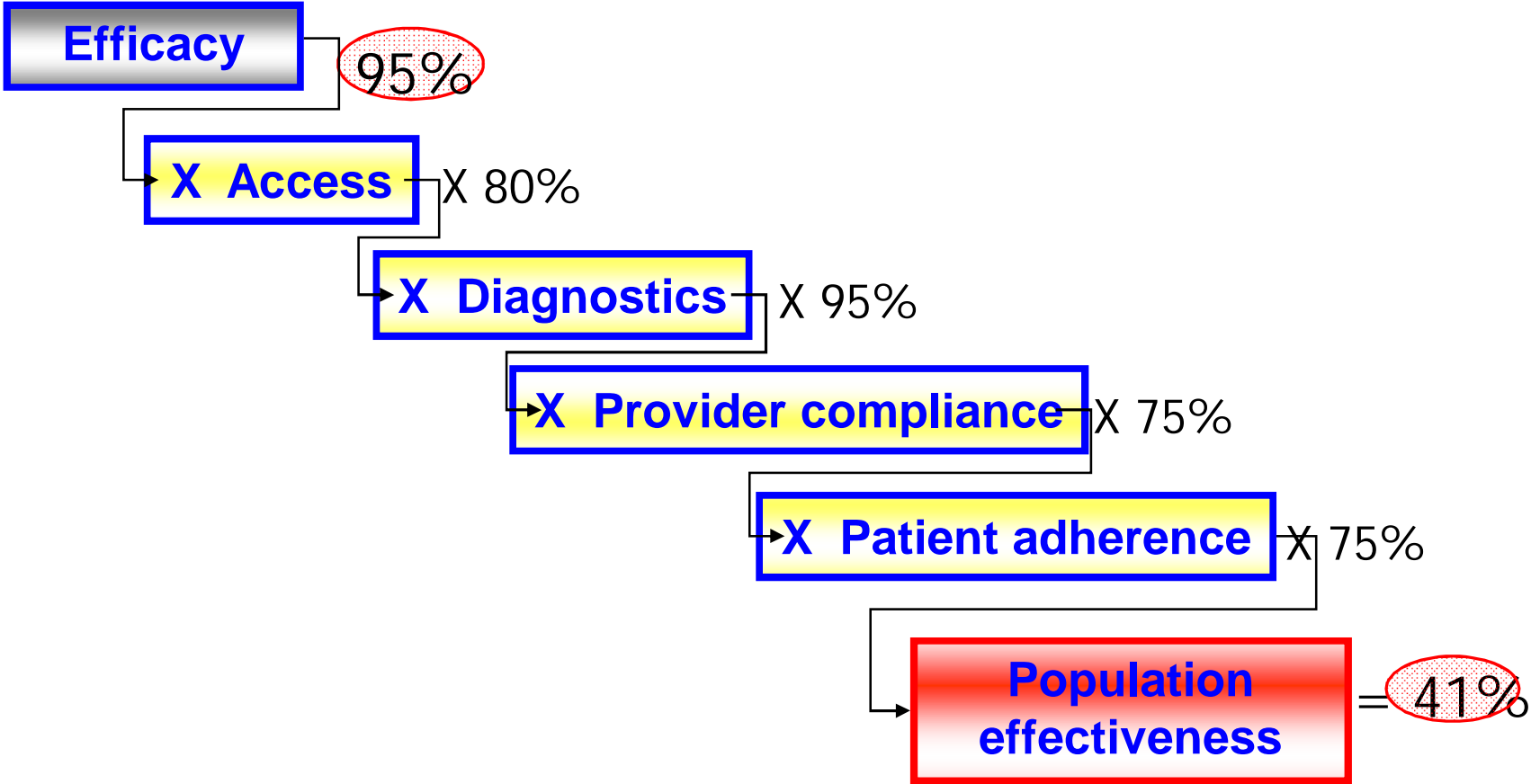
Outline

- ❖ Limitations of what can be inferred from trials
- ❖ What more do we need to know about vaccines?
 - (safety, cost, natural boosting)
 - acceptability
 - implications of incomplete coverage
 - duration of protection
 - potential effects on transmission
- ❖ How trial results combined with models can be used to infer the likely medium & long term impact of vaccination programs.

Some limitations of what can be inferred from trials

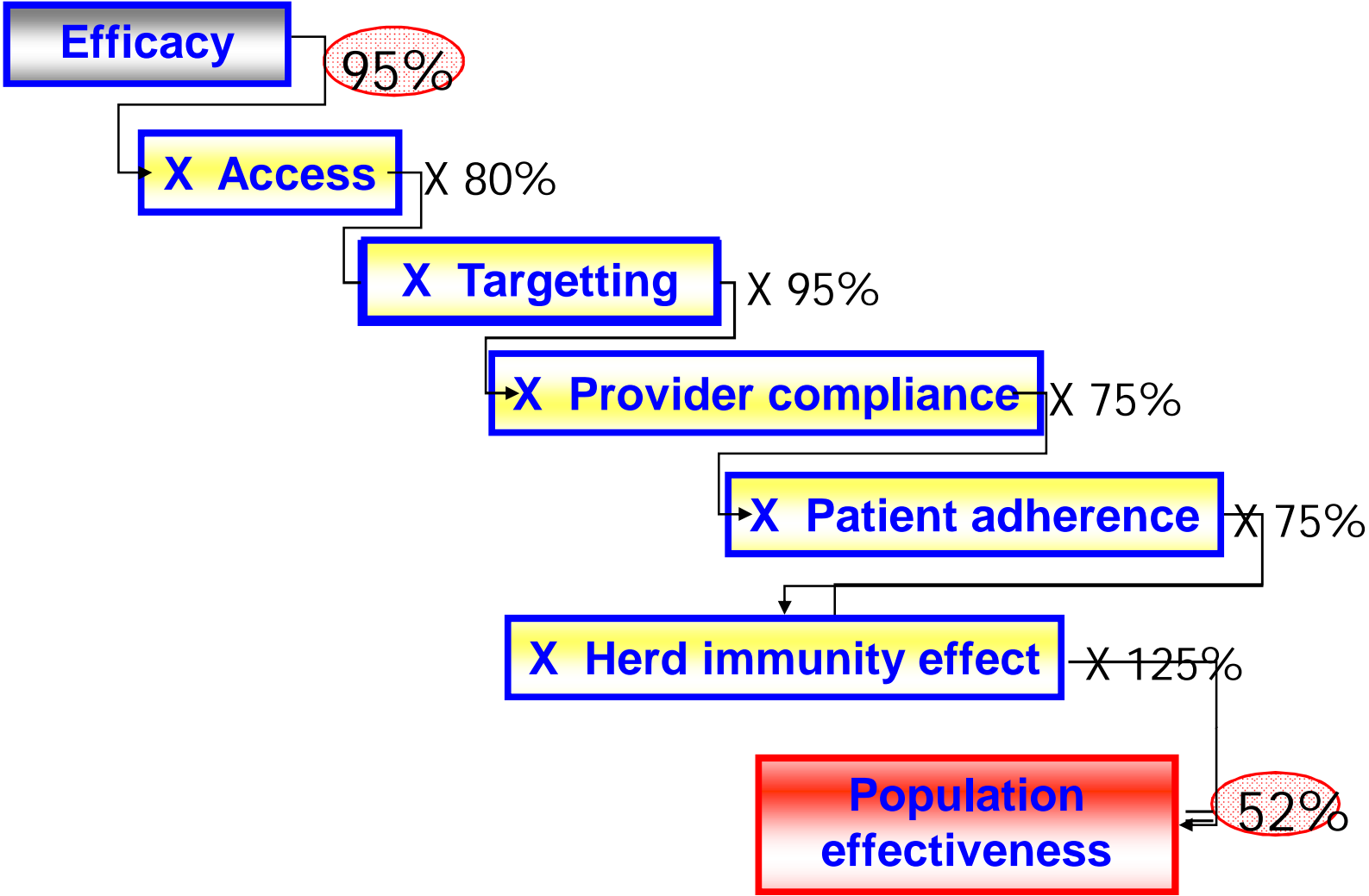
- ❖ Time-limited trials cannot assess long term effects:
 - Gradual effects on transmission
 - Interference with acquisition of natural immunity
- ❖ Trials in sub-populations do not provide measures of overall population impact
 - Herd immunity
 - Population effectiveness

From efficacy to effectiveness



Treatment

From efficacy to effectiveness



Vaccination

Acute illness

An episode of acute morbidity occurs in individual i , at time t , with probability

$$P_m(i,t) = \frac{Y_{\max}(i,t)}{Y^*(i,t) + Y_{\max}(i,t)} \quad (22)$$

where Y^* is the pyrogenic threshold and Y_{\max} is the maximum density of five daily densities sampled during the five-day time interval t . The pyrogenic threshold evolves over time via:

$$\frac{dY^*(i,t)}{dt} = \frac{\alpha Y(i,t)}{(Y_1^* + Y(i,t))(Y_2^* + Y^*(i,t))} - \varpi Y^*(i,t) \quad (23)$$

with the initial condition $Y^*(i,0) = Y_0^*$ at the birth of the host and α , ϖ , Y_1^* , and Y_2^* are constants.

Parasite densities

Each new meconium j , inhaled in individual i at time t_0 is assigned a duration of t_{\max} , sampled from

$$\ln(\tau_{\max}(i,j)) \sim \text{Normal}(5.13, 0.80) \quad (5)$$

The log density in the absence of previous exposure at each time point, $\tau = 0, 1, \dots, \tau_{\max}(i,j)$ of the infection j in host i is then normally distributed with expectation

$$\ln(y_0(i,j,\tau)) = \ln d(i) + \ln(y_G(\tau, \tau_{\max})) \quad (6)$$

where $y_G(\tau, \tau_{\max})$ is an empirical description of malariatherapy patients from the Georgia hospital and $d(i)$ represents between-host variation drawn from a log-normal distribution with variance σ_y^2 .

We measure exposure to asexual blood stages with

$$X_y(i,j,t) = \int_{t-a}^t Y(i,\tau) d\tau - \int_{t_0}^t y(i,j,\tau) d\tau \quad (7)$$

where $Y(i,\tau)$ is the total parasite density of individual i at time τ and $y(i,j,\tau)$ is the density in individual i for infection j at time τ , and

$$X_h(i,t) = \int_{t-a}^t h(i,\tau) d\tau - 1. \quad (8)$$

the expected log density for each concurrent infection is then

$$E(\ln(y(i,j,\tau))) = D_y D_h D_m \cdot \ln(y_0(i,j,\tau)) + \ln\left(\frac{D_x}{M(t)} + 1 - D_x\right)$$

where $M(t)$ is the total multiplicity of infection and

$$D_y = \frac{1}{1 + \frac{X_y(i,j,t)}{X_y^*}} \quad (10)$$

$$D_h = \frac{1}{1 + \frac{X_h(i,t)}{X_h^*}} \quad (11)$$

$$D_m = 1 - \alpha_m \exp\left(-\frac{0.693a}{a_m^*}\right) \quad (12)$$

and X_y^* , X_h^* , D_y , a_m^* , and α_m are further constants.

Variation within individual hosts is quantified by a term $\sigma_y^2(i,j,\tau)$, where

$$\sigma_y^2(i,j,\tau) = \frac{\sigma_0^2}{1 + \frac{X_y(i,t)}{X_y^*}} \quad (13)$$

and σ_0^2 and X_y^* are constants (Table 1). The simulated densities are specified using:

$$\ln(y(i,j,\tau)) \sim \text{Normal}(E(\ln(y(i,j,\tau))), \sigma_y^2(i,j,\tau)) \quad (14)$$

Infection of mosquitoes

Let

$$\Upsilon(i,t) = \beta_1 Y(i,t-2) + \beta_2 Y(i,t-3) + \beta_3 Y(i,t-4) \quad (16)$$

where t is in 5-day units, and

$$\ln(y_g(i,t)) \sim \text{Normal}(\ln(\rho \Upsilon(i,t)), \sigma_g^2) \quad (17)$$

where $\beta_1, \beta_2, \beta_3, \rho, \sigma_g^2$ are constants (Table 1). Define

$$\Pr(y_g(i,t) > y_g^*) = \Phi\left[\frac{\ln(\rho \Upsilon(i,t)) - \ln(y_g^*)}{\sigma_g}\right] = \Phi\left[\frac{\ln(\Upsilon(i,t))}{\sigma_g} + \rho^*\right] \quad (18)$$

where Φ is the cumulative normal distribution, y_g^* is the density of female gametocytes necessary for infection of the mosquito, and $\rho^* = (\ln(\rho) - \ln(y_g^*))/\sigma_g$. Then the proportion of mosquitoes that are infected feeding on individual i at time t is

$$I_m(i,t) = [\Pr(y_g(i,t) > y_g^*)]^2 \quad (19)$$

and the probability that a mosquito becomes infected at any feed is:

$$\kappa_u(t) = \eta \frac{\sum_i A(a(i,t)) I_m(i,t)}{\sum_i A(a(i,t))} \quad (20)$$

where η is a constant scale factor.

Define $\kappa_v^{(0)}(t)$ as the value of $\kappa_u(t)$ in the simulation of an equilibrium scenario to which an intervention has been applied. Let $E_{\max}^{(0)}(t + l_v)$ be the corresponding entomologic inoculation rate. $\kappa_u^{(1)}(t)$ and $E_{\max}^{(1)}(t + l_v)$ are the corresponding values for the intervention scenario. Then

$$E_{\max}^{(1)}(t + l_v) = \frac{E_{\max}^{(0)}(t + l_v) \kappa_u^{(1)}(t)}{\kappa_u^{(0)}(t)} \quad (21)$$

where l_v corresponds to the duration of the sporogonic cycle in the vector, which we approximate with two time steps (10 days). ($E_{\max}^{(0)}(t + l_v) \kappa_u^{(0)}(t)$ is the total vectorial capacity).

Infection of humans

$E_a(i,t)$, the age-adjusted entomologic inoculation rate (EIR) for individual i at time t , is given by

$$E_a(i,t) = E_{\max}(t) \frac{A(a(i,t))}{A_{\max}} \quad (1)$$

where, $A(a(i,t))$ is the average body surface area estimated for an individual of age $a(i,t)$ and A_{\max} is the average surface area of people ≥ 20 years of age in the same population. $E_{\max}(t)$ refers to the usual measure of the EIR computed from human bait collections. The force of infection is then

$$\lambda(i,t) = E_a(i,t) \left(S_u + \frac{1 - S_u}{1 + \frac{E_a(i,t)}{E^*}} \right) \left(S_{imm} + \frac{1 - S_{imm}}{1 + \left(\frac{X_p(i,t)}{X_p^*}\right)^{\gamma_p}} \right) \quad (2)$$

where S_{imm} , X_p^* , E^* , γ_p , S_u are constants (Table 1) and:

$$X_p(i,t) = \int_{t-a(i,t)}^t E_a(i,\tau) d\tau. \quad (3)$$

The number of infections $h(i,t)$ introduced in time step t , is distributed as

$$h(i,t) \sim \text{Poisson}(\lambda(i,t)) \quad (4)$$

Severe disease

We consider two different classes of severe episodes, B_1 and B_2 . $P_{B_1}(i,t)$ is the probability that an acute episode (A) is a class B_1 severe episode and is specified using

$$P_{B_1}(i,t) = \Pr(H(i,t) \in B_1 | H(i,t) \in A) = \frac{Y_{B_1}^{\max}(i,t)}{Y_{B_1}^{\max}(i,t) + Y_{\max}(i,t)} \quad (24)$$

where $Y_{B_1}^{\max}$ is a constant and $H(i,t)$ is the clinical status.

The second subset of severe malaria episodes (B_2) occur when an otherwise uncomplicated malaria episode happens to coincide with some other insult, which occurs with risk

$$F(a(i,t)) = \frac{F_0}{1 + \left(\frac{a(i,t)}{a_{\frac{1}{2}}^*}\right)} \quad (25)$$

where F_0 is the limiting value of $F(a(i,t))$ at birth, and $a_{\frac{1}{2}}^*$ is the age at which it is halved.

The probability that an episode belonging to class B_2 occurs at time t , conditional on there being a clinical episode at that time is $P_{B_2}(i,t)$ where

$$P_{B_2}(i,t) = \Pr(H(i,t) \in B_2 | H(i,t) \in A) = F(a(i,t)) \quad (26)$$

The age and time specific risk of severe malaria morbidity conditional on a clinical episode is then given by

$$P_B(i,t) = P_{B_1}(i,t) + P_{B_2}(i,t) - P_{B_1}(i,t)P_{B_2}(i,t), \quad (27)$$

Mortality

Malaria deaths in hospital are a random sample of those severe malaria cases deemed to be admitted, with age-dependent sampling fraction $Q_h(a)$, the hospital case fatality rate, derived from the data of Rebyburn and others.⁸⁶

We estimate the severe malaria case fatality in the community, $Q_c(a)$ for age group a with

$$Q_c(a) = \frac{Q_h(a)\varphi_1}{1 - Q_h(a) + Q_h(a)\varphi_1}, \quad (28)$$

where φ_1 , the estimated odds ratio for death in the community compared to death in in-patients, is an age-independent constant and $Q_h(a)$ is the hospital case fatality rate. Malaria mortality is the sum of the hospital and community malaria deaths.

The risk of neonatal mortality attributable to malaria (death in class D_1) in first pregnancies is set equal to $0.3\mu_{PG}$ where μ_{PG} is given by

$$\mu_{PG} = \mu_{\max} \left[1 - \exp\left(-\frac{x_{PG}}{x_{PG}^*}\right) \right], \quad (29)$$

where x_{PG} is related to x_{MG} , the prevalence in simulated individuals 20–24 years of age via

$$x_{PG} = 1 - \frac{1}{1 + \left(\frac{x_{MG}}{x_{MG}^*}\right)} \quad (30)$$

and x_{MG}^* and x_{PG}^* are constants (Table 1).

An indirect death in class D_2 is provoked at time t , conditional on there being a clinical episode at that time, with probability $P_{D_2}(i,t)$ where

$$P_{D_1}(i,t) = \Pr(H(i,t) \in D_2 | H(i,t) \in A) \text{ and} \quad (31)$$

$$P_{D_2}(i,t) = \frac{Q_D}{1 + \left(\frac{a(i,t)}{a_{\frac{1}{2}}^*}\right)}$$

where Q_D is limiting value of $P_{D_2}(i,t)$ at birth and $a_{\frac{1}{2}}^*$ is a constant. Deaths in class D_2 occur 30 days (six time steps) after the provoking episodes.

Datasets used for fitting models

Objective	Sources of data	Number of scenarios	Number of data points
Parasite densities in primary infections by age of infection	Collins and Jeffery (1999)	n.a.	47 patients
Infectivity of humans to mosquitoes by history of parasite density	Collins and Jeffery (2003)	n.a.	730 feeding experiments
Incidence of new infection in previously treated children	Beier <i>et al.</i> (1994)	21	62
Age pattern of incidence of new infection in treated individuals	Molineaux and Gramiccia G. (1980)	1	12
Age- and seasonal patterns of prevalence of infection	Molineaux and Gramiccia G. (1980)	6	563
Age- and seasonal patterns of parasite density	Molineaux and Gramiccia G. (1980)	6	563
Age pattern of number of concurrent infections	Maire <i>et al.</i> (2006); Owusu-Agyei <i>et al.</i> (2002)	1	12
Age pattern of incidence of clinical malaria	Trape and Rogier (1996); Kitua <i>et al.</i> (1996)	3	31
Age pattern of threshold parasite density for clinical attacks	Rogier <i>et al.</i> (1996)	1	13
Hospitalisation rate in relation to prevalence in children	See Ross <i>et al.</i> (2006)	26	10
Age pattern of hospitalisation	Marsh and Snow (1999)	4	12
Malaria specific mortality in children	Snow <i>et al.</i> (1997)	9	9
Infant mortality rate	See Ross <i>et al.</i> (2006b).	11	11

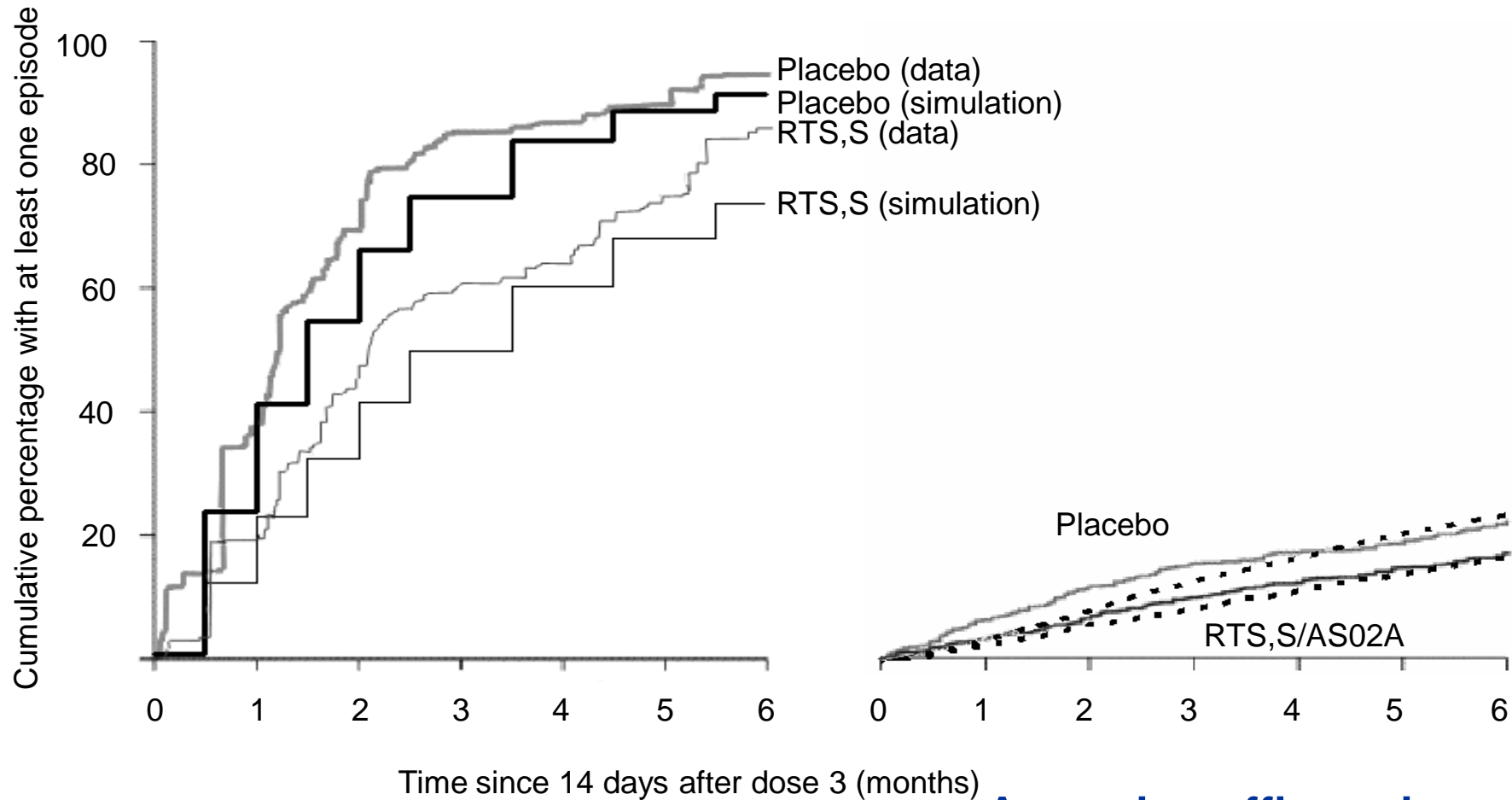
Inference of primary efficacy from trial data

- ❖ Measured efficacy in a trial often reflects only indirectly the underlying vaccine effect
- ❖ Example: **Pre-erythrocytic vaccine**
 - Define primary efficacy as % of infections (broods, clones) that are blocked
 - Measured directly in a challenge trial
 - Measured by Kaplan-Meier analysis of time to first detected infection in a field trial

Simulation of the Manhiça RTS,S trial (6 month follow-up)

Incidence of patent infection

Incidence of first recorded clinical episode after vaccination



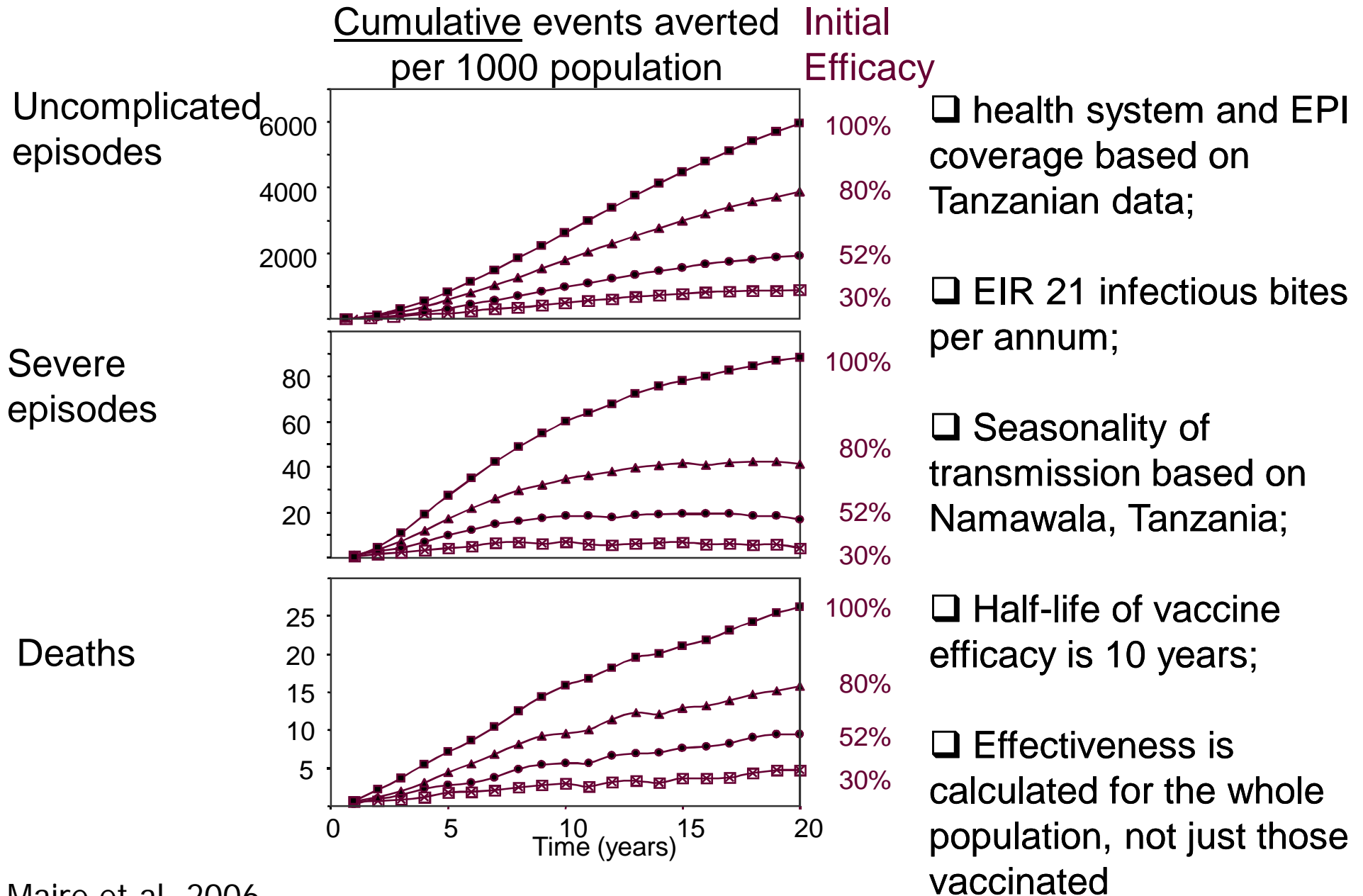
Assuming efficacy in preventing infections is 52%

Simulation of the Manhiça RTS,S trial (6 month follow-up)

Outcome	Manhiça trial	Simulation
Prevention of infection	0.45 (0.31,0.56)	0.45 (0.42,0.48)
Prevention of clinical episodes	0.30 (0.11,0.45)	0.33 (0.27,0.38)
Prevention of severe malaria	0.58 (0.16,0.81)	0.36 (0.26,0.45)

- ❖ Simulations assume 52% efficacy in preventing infections
- ❖ This corresponds to the 45% observed reduction in force of infection
- ❖ Observed clinical incidence follows from a 5% probability of effective treatment for each fever attack
- ❖ Remaining efficacy values follow from this

Predicted effect of pre-erythrocytic vaccine

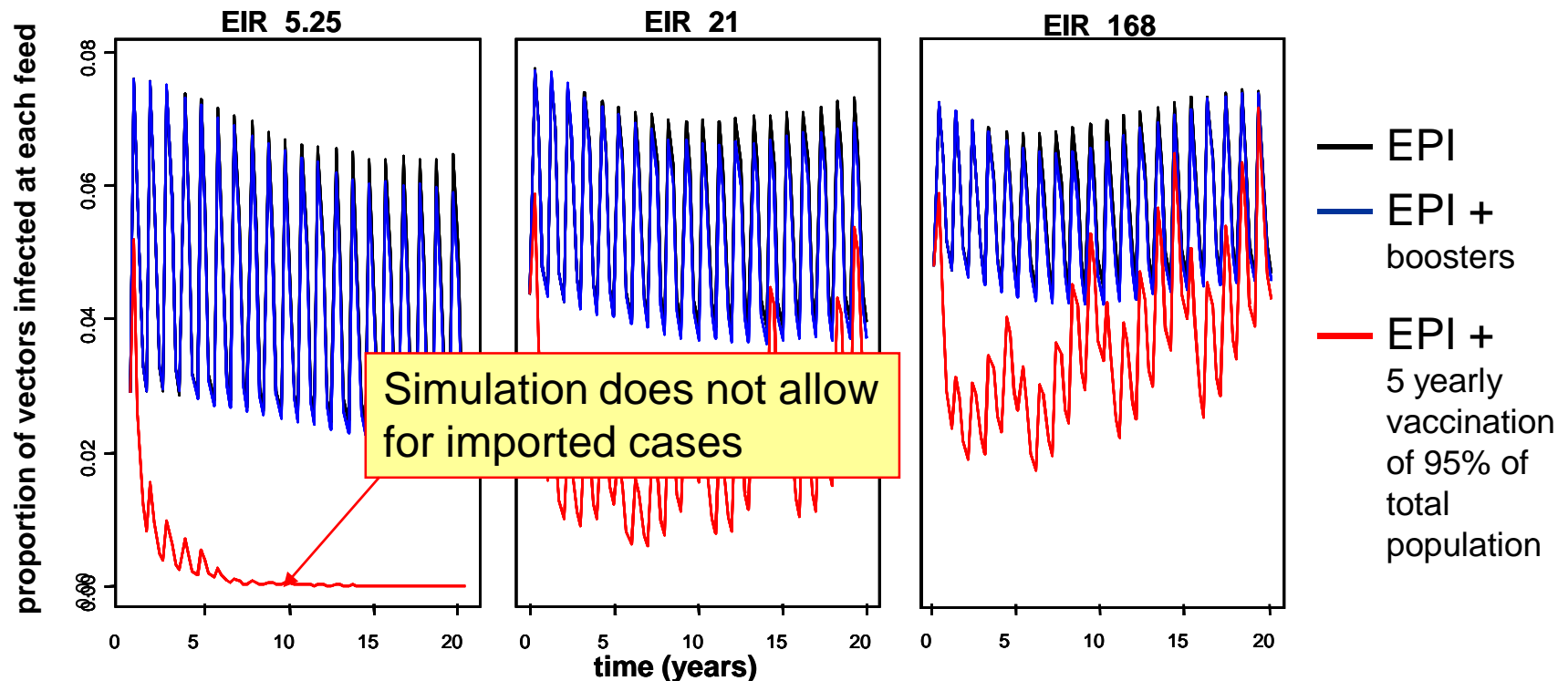


Predicted effect of pre-erythrocytic vaccine

Effect on transmission to the mosquito vector

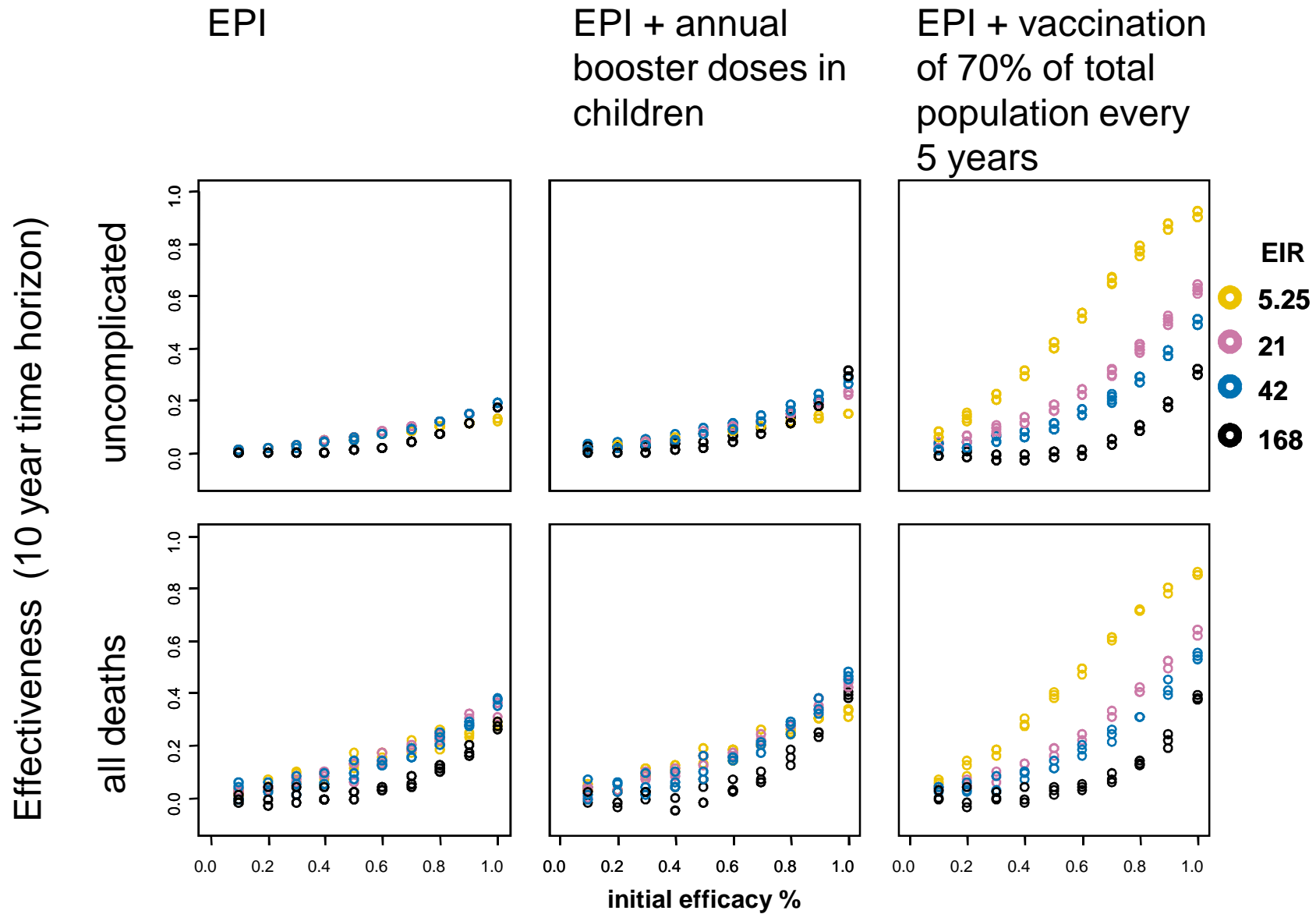
- ❖ Moderate efficacy vaccines are predicted to have little herd immunity effect if delivered only via EPI

Simulation of PEV with primary efficacy 80%, 10 year half-life



Predicted effect of pre-erythrocytic vaccine

Effect of different deployment options



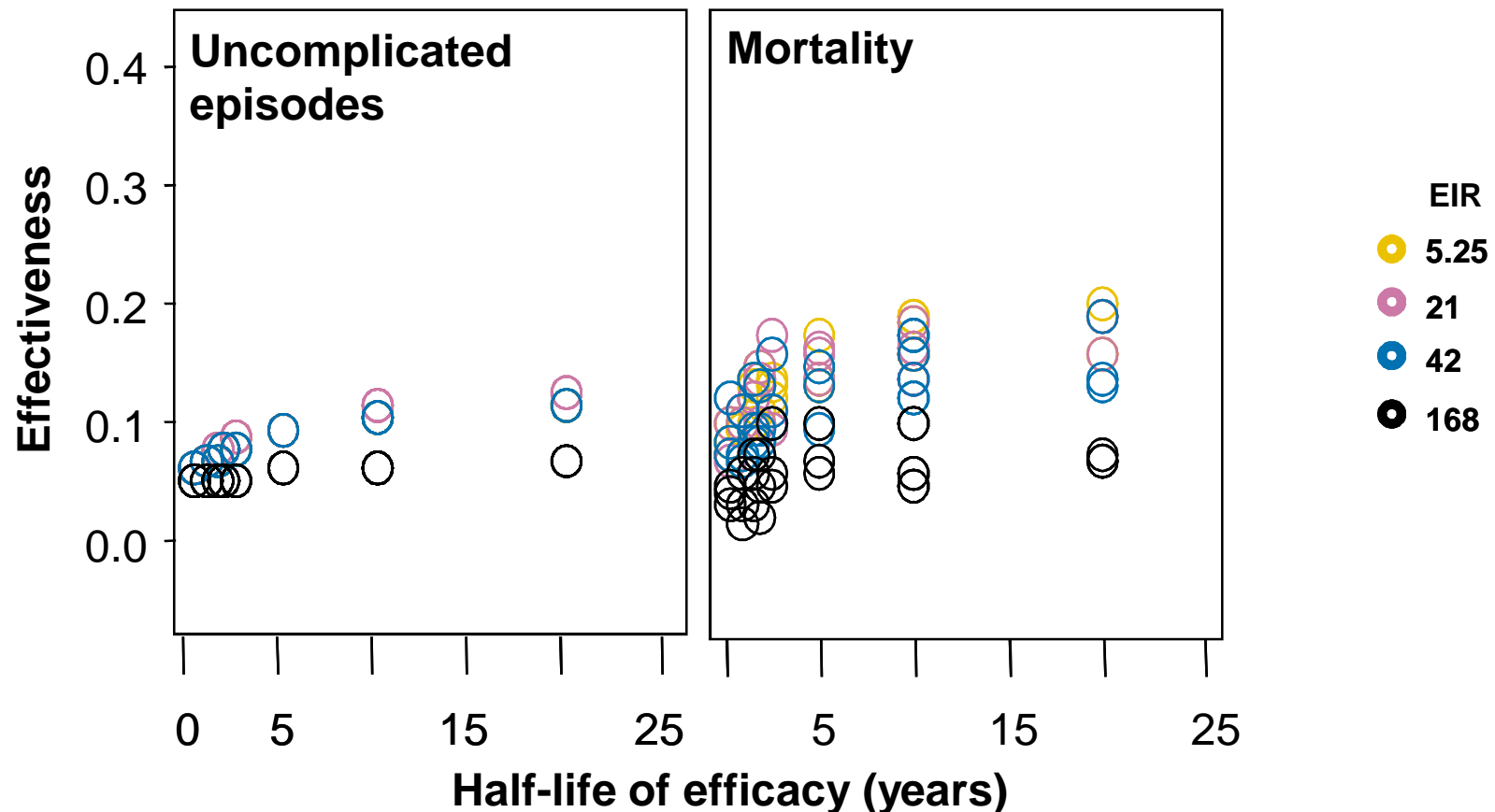
Measuring effects on transmission

- ❖ Herd immunity effects are key to realising potential advantages of vaccination compared with other interventions
- ❖ Vaccination additional to EPI is needed to achieve important effects on transmission
- ❖ Individually randomised trials cannot measure transmission directly.
 - Membrane feeding experiments (Phase 2a, probably not in small children)
 - Community randomised trials

Predicted effect of pre-erythrocytic vaccine

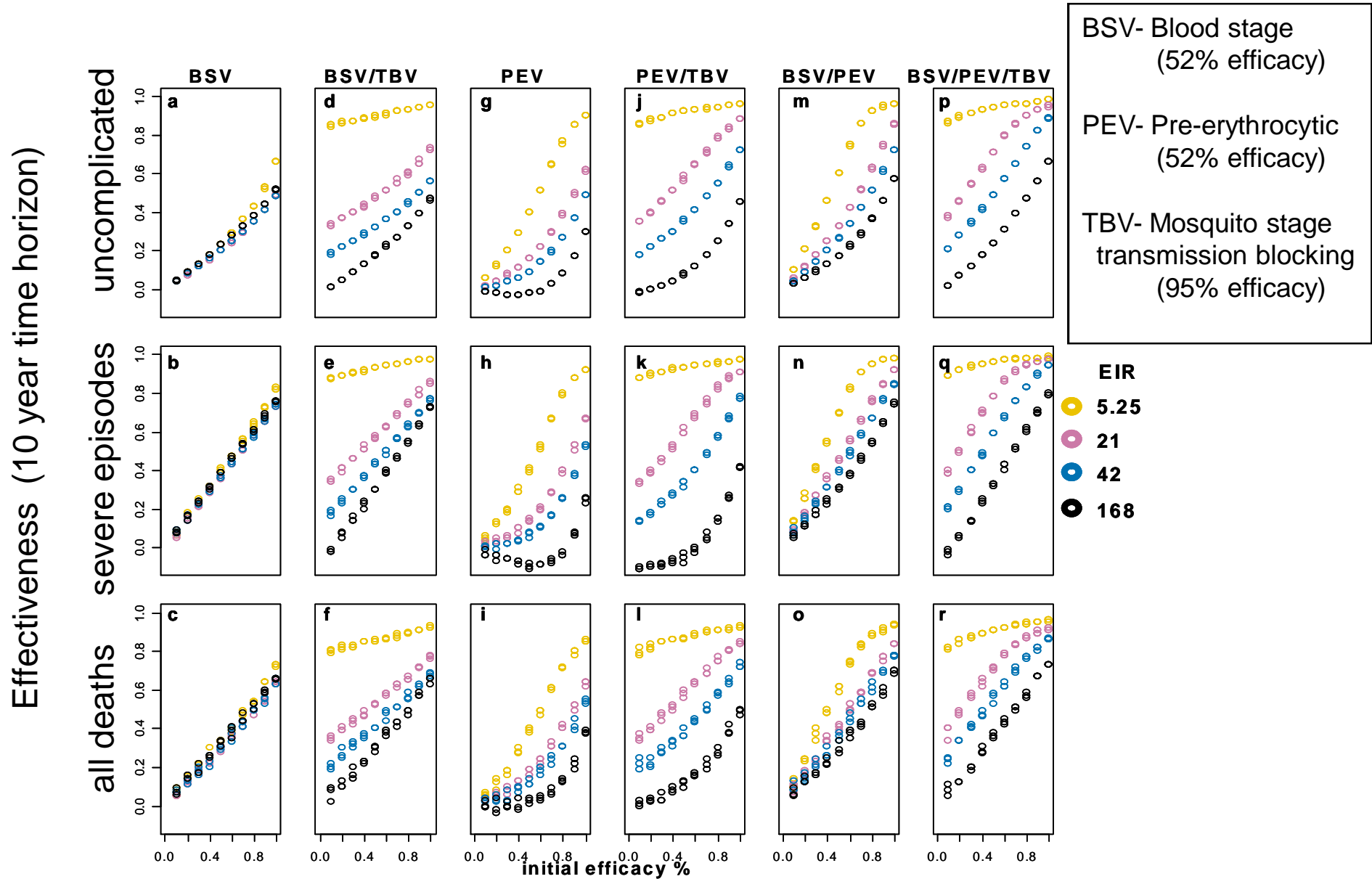
Effect of vaccine half-life

Simulation of PEV with primary efficacy 52%, delivered via EPI



Providing the half-life of the efficacy is more than about 2-3 years, there is little gained with a very long half-life

Predicted effect of different vaccine types delivered via EPI



Summary: what can simulation models add to trial results

- ❖ Prediction of long-term effects
 - Effects on acquisition of natural immunity
- ❖ Prediction of population-wide effects
 - Herd immunity
 - Health system factors (effectiveness)
 - Cost effectiveness
- ❖ Identification of data requirement
 - Duration of protection
- ❖ Suggestions for innovations
 - Things that may work well: e.g. deployment additional to EPI
 - Things that may work less well: e.g. PEV/BSV combinations

Limitations of models

❖ Data dependence

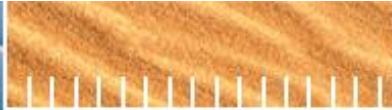
- Models can only make reasonable quantitative predictions if calibrated against/ fitted to field data

❖ Sensitivity to model assumptions

- Need to consider multiple models; do they all make similar predictions



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