

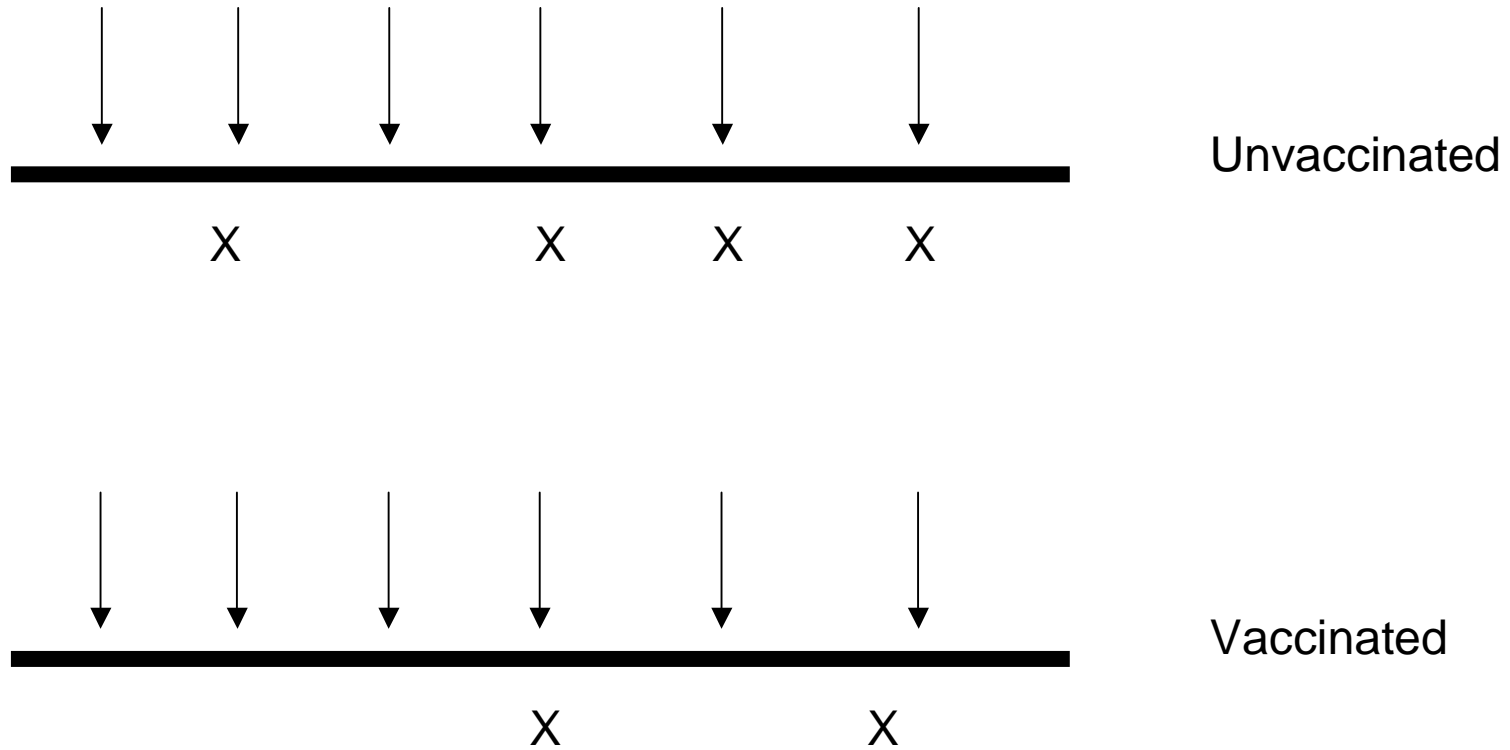
Statistical issues in estimating efficacy of malaria vaccines

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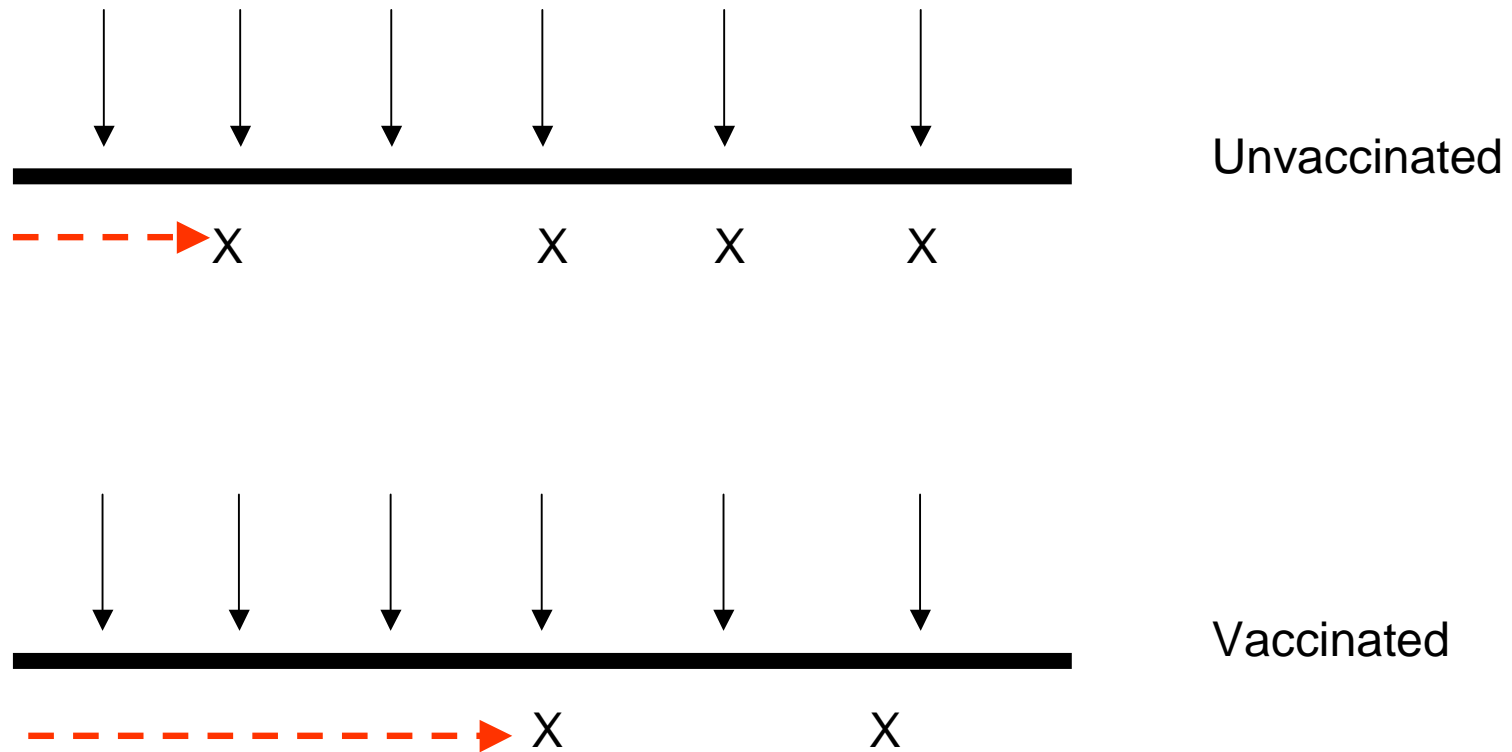
Complications

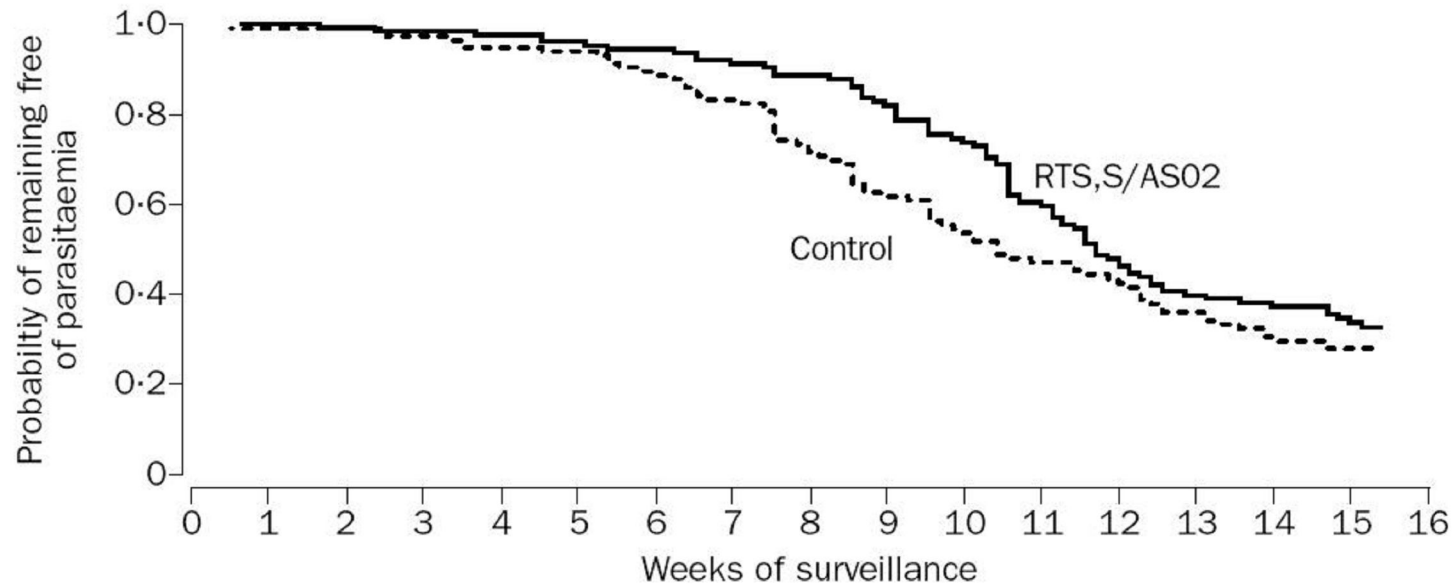
- High incidence and the variation in the degree of exposure to malaria from person to person, combine in a way that makes accurate estimation of vaccine efficacy more difficult than when the disease is rare.
- High incidence of repeated exposure forces us to be specific about the mode of action of the vaccine (partial or all-or-nothing).
“mis-specified models can give very precise estimates of the wrong answer“
-Halloran, Longini and Struchiner 1996
- The absence of immunological markers of protection makes it difficult to determine the duration of protection, we have to do this indirectly from disease incidence data.
- Malaria risk may be altered by each malaria episode, reducing the risk (treatment effects, acquired immunity) or increasing it (long term effects of the infection, relapse), complicating analysis of multiple events.

Time to first event analysis seeks to estimate the percentage reduction in malaria incidence due to vaccination



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Number at risk

RTS,S/AS02	131	129	125	118	110	90	58	45
Control	119	118	110	101	82	60	47	33

Figure 3: **Kaplan-Meier survival curves showing probability of remaining free of *P falciparum* infection during 15 weeks of surveillance in 1998**

Week 0 of surveillance began in September, 1998, 14 days after dose 3 of vaccine was administered.

- In time-to-first-event analysis, waning efficacy and heterogeneity in malaria risk from person to person, have same effect on KM curves, cannot tell the relative importance of waning and heterogeneity.
- Heterogeneity present to some degree and biases efficacy estimate downwards

Vaccine	Ref	Method	Covariates	Duration months	Extended
Spf66 Tanzania	Alonso et al 1994	First or only episode	Adjusted	12	
Spf66 Thailand	Nosten et al 1996	First or only episode	Unadjusted	15	
Spf66 Gambia	D'Alessandro 1995	First or only episode	Adjusted	3.75	15.75
RTSS Gambia	Bojang et al 2001	First or only episode	Adjusted	3.6	-
RTSS Mozambique	Alonso et al 2004	First or only episode	Adjusted	6	18.5
DNA METRAP Gamb	Moorthy et al 2004	First or only episode	Adjusted	2.75	-
FP9 METRAP Kenya	Bejon et al 2006	First or only episode	Adjusted	9	18

- Efficacy was estimated directly from the simple rate ratio:

$$1 - RR \quad \text{where } RR = \frac{\text{no. of cases in vaccine group}}{\text{time at risk in vaccine group}} \div \frac{\text{no. of cases in control group}}{\text{time at risk in control group}}$$

- or from the rate ratio from Poisson regression or the hazard ratio from Cox regression.
- This provides an average efficacy **over the period of follow-up**.
- The estimate will tend to be **conservative** because of the effects of heterogeneity.
- In covariate-adjusted analysis, there is some partial accounting for the effects of heterogeneity. Covariates should be pre-specified.
- If incidence is high, the efficacy estimate will tend to be conservative because of unexplained heterogeneity.
- Heterogeneity can be modelled but the interpretation is difficult.

Duration of protection

- In time-to-first-event analysis it is impossible to distinguish effects of heterogeneity from those of waning.
- In the absence of clear immunological indicator of vaccine-induced protection, best approach is to divide the follow-up into distinct time intervals and analyse time to next event in the complete vaccine and placebo cohorts starting at the beginning of each interval, but...

...loss to follow up, and differences in prior malaria and treatment experience, means groups may not be as comparable as at baseline.

...precision may be low, a trial powered to detect first-or-only events will be underpowered to look at effects on waning of efficacy even if the follow-up is extended for a long period.

Multiple episodes

- Data on the multiple episodes of malaria in a person reflect real disease burden, and potentially carry more information about changes in efficacy over time.
- A difficulty is that events within each person are not independent.
- If each event is treated as independent, we overstate the amount of information each observation provides, leading to P values that are too small.
- Two factors to be taken into account: variation in exposure, (some people are more likely to have more episodes than others), and the effect of one malaria episode on the risk of a subsequent one.
- Different models may give different results. For this reason analysis of multiple events has tended to be considered as a secondary rather than a primary analysis. Further research is needed.

Conclusion

- Time to first or only event preferred method for primary analysis, tends to be conservative, trials should be powered taking this into account.
- Estimates apply to the period of follow-up. Tests of waning underpowered. Caution needed inferring longer term efficacy.
- Need to fit several types of model to get good understanding of the data.
- Statistical research needed to find best approach for multiple episode data.