Survival bias in HDSS: Effect of routine vaccinations on child survival

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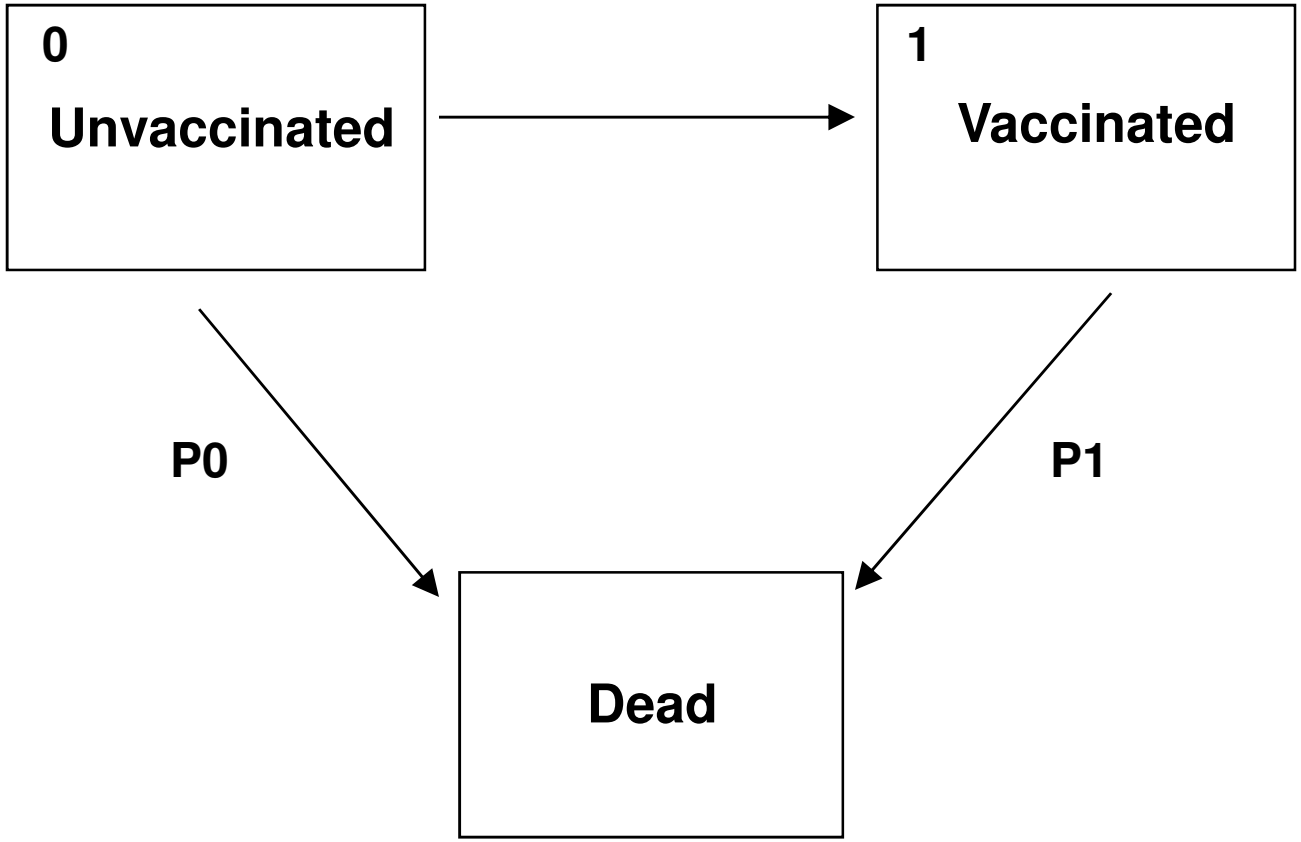
INDEPTH, AGM 2010, ACCRA

Overall objective is to study vaccine effect on overall mortality:



RR (vaccinated vs. unvaccinated) = P1/P0

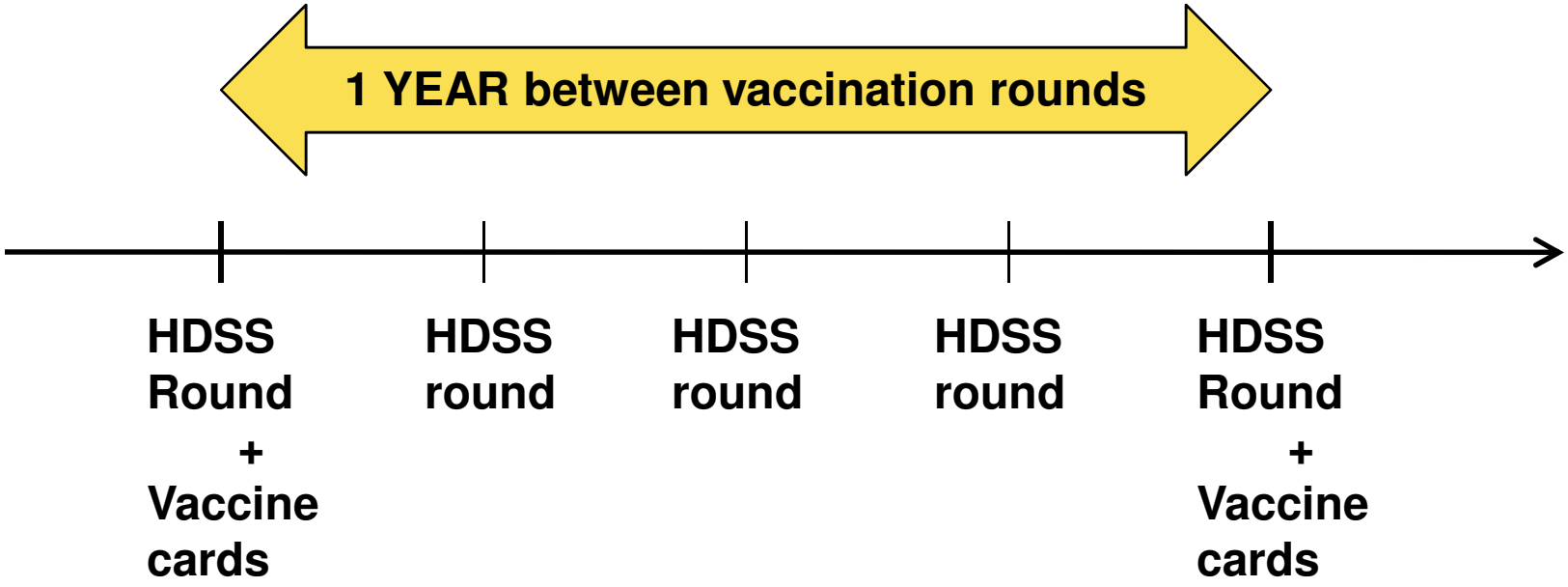
Using HDSS data

- Mortality of children is collected at HDSS rounds and sometimes by key informants

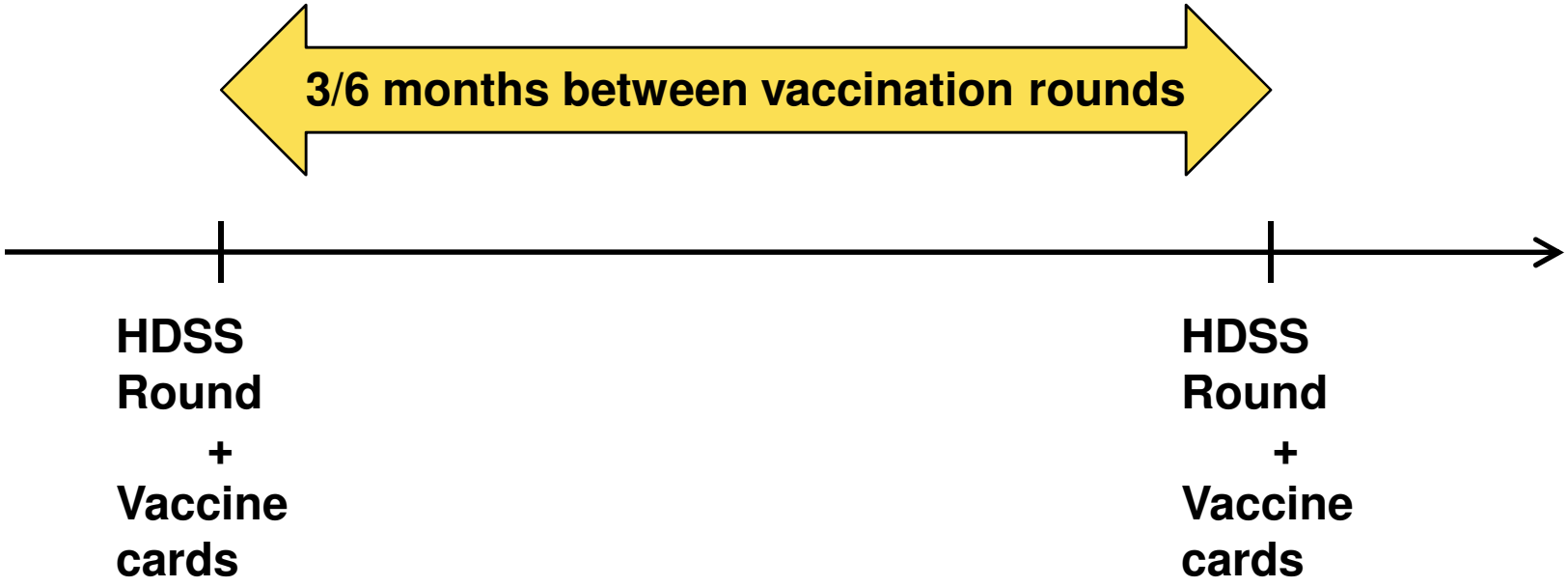
- Vaccination status: Inspect vaccination cards at HDSS rounds:
  - Card seen = vaccinated according to dates on the card
  - Card not seen = unknown vaccination status
  - Never had a card = assumed unvaccinted

- Examples: Navrongo and Bandim

Navrongo HDSS (1996-2006)



Bandim HDSS (urban/rural)



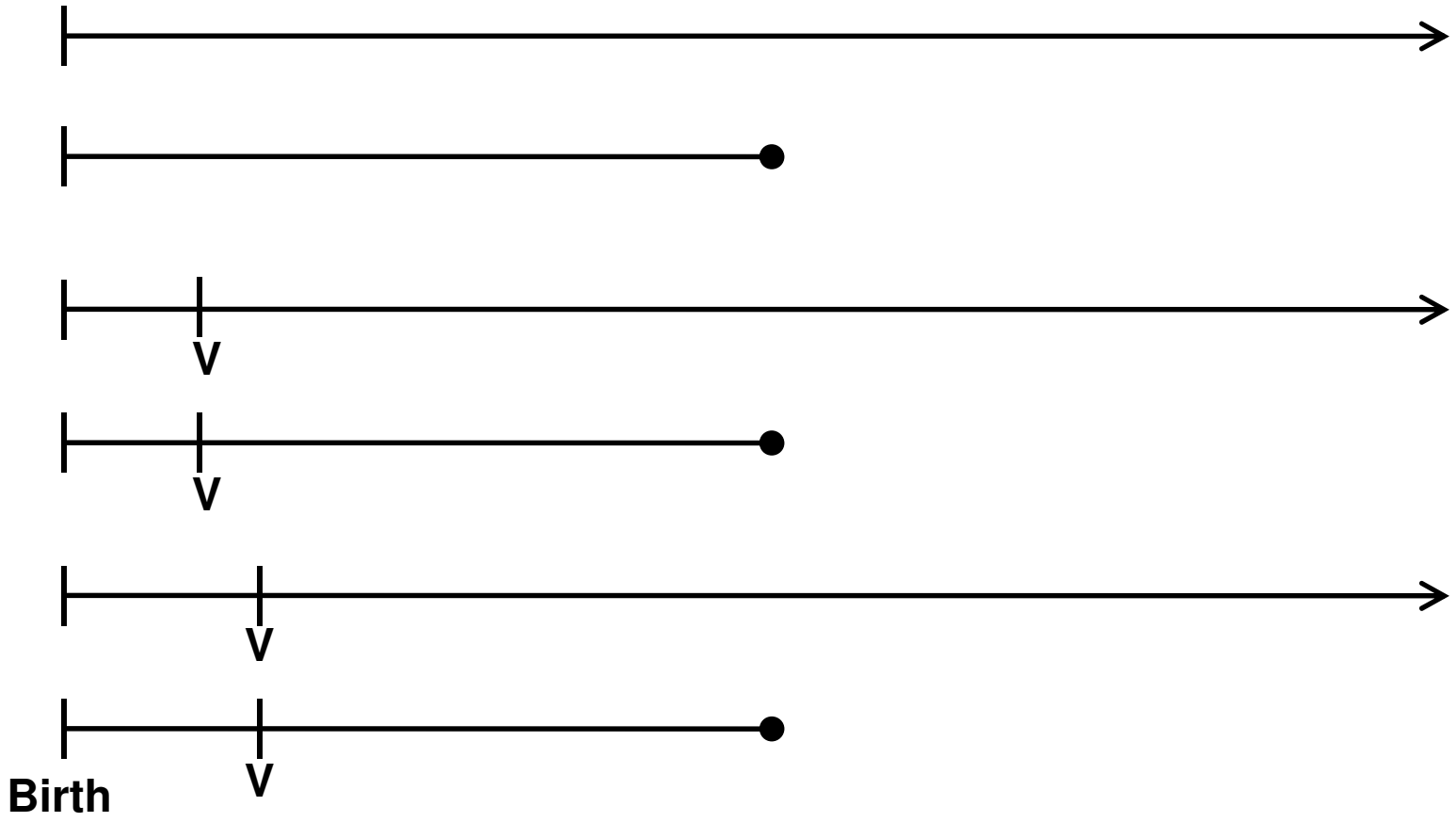
SURVIVAL BIAS

Problem: Vaccination card for children dying between visits are not inspected:

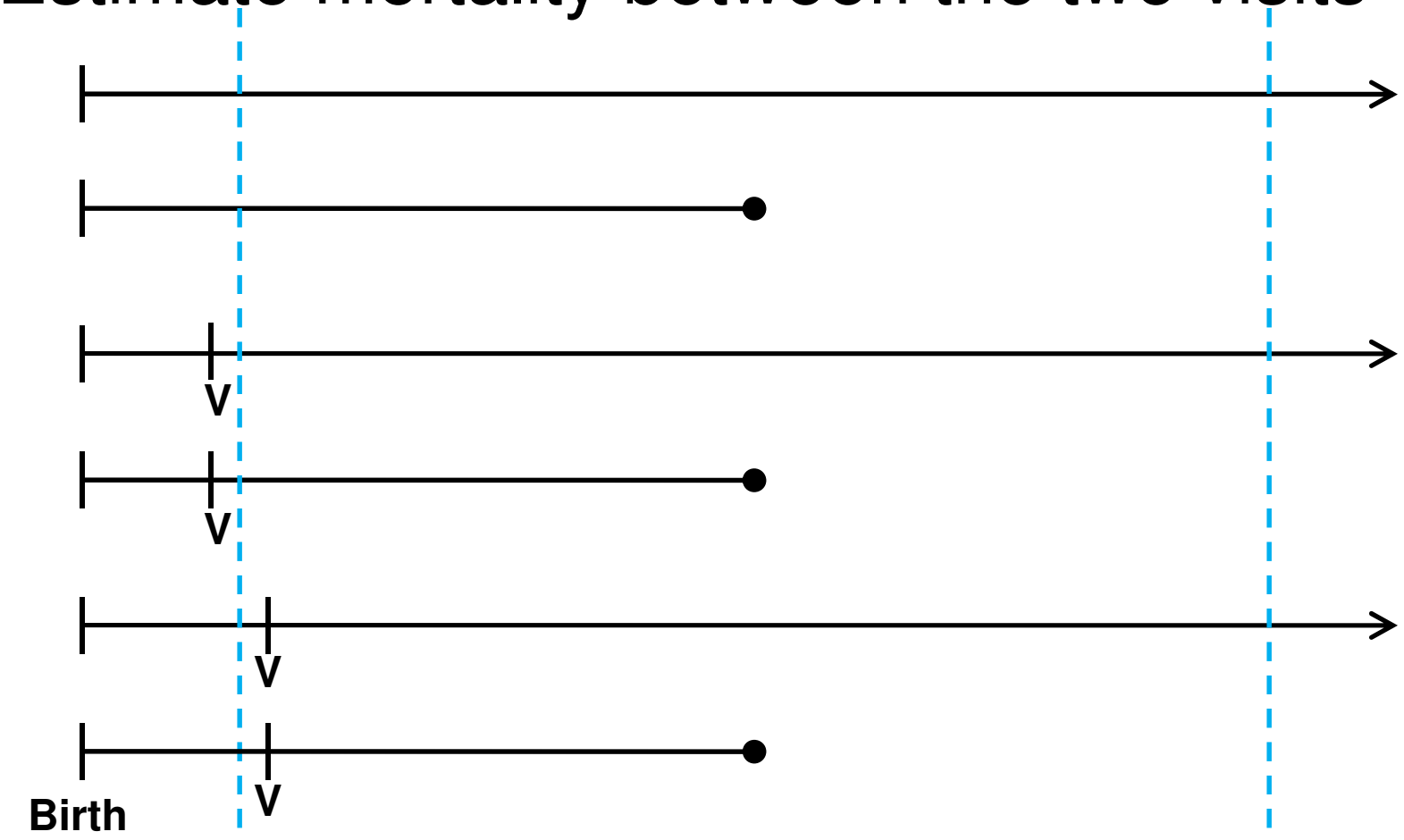
- Cards are destroyed
- Mothers are away some time after a child death
- Fieldworkes are reluctant to ask for card of dead child
- HDSS routine prints only children alive on vaccine questionnaire

- Survivors have a higher probability of getting updates of vaccine information
- Differential misclassification: vaccine status is more wrong among the deaths
- Illustrative example and Navrongo data

Illustrative example



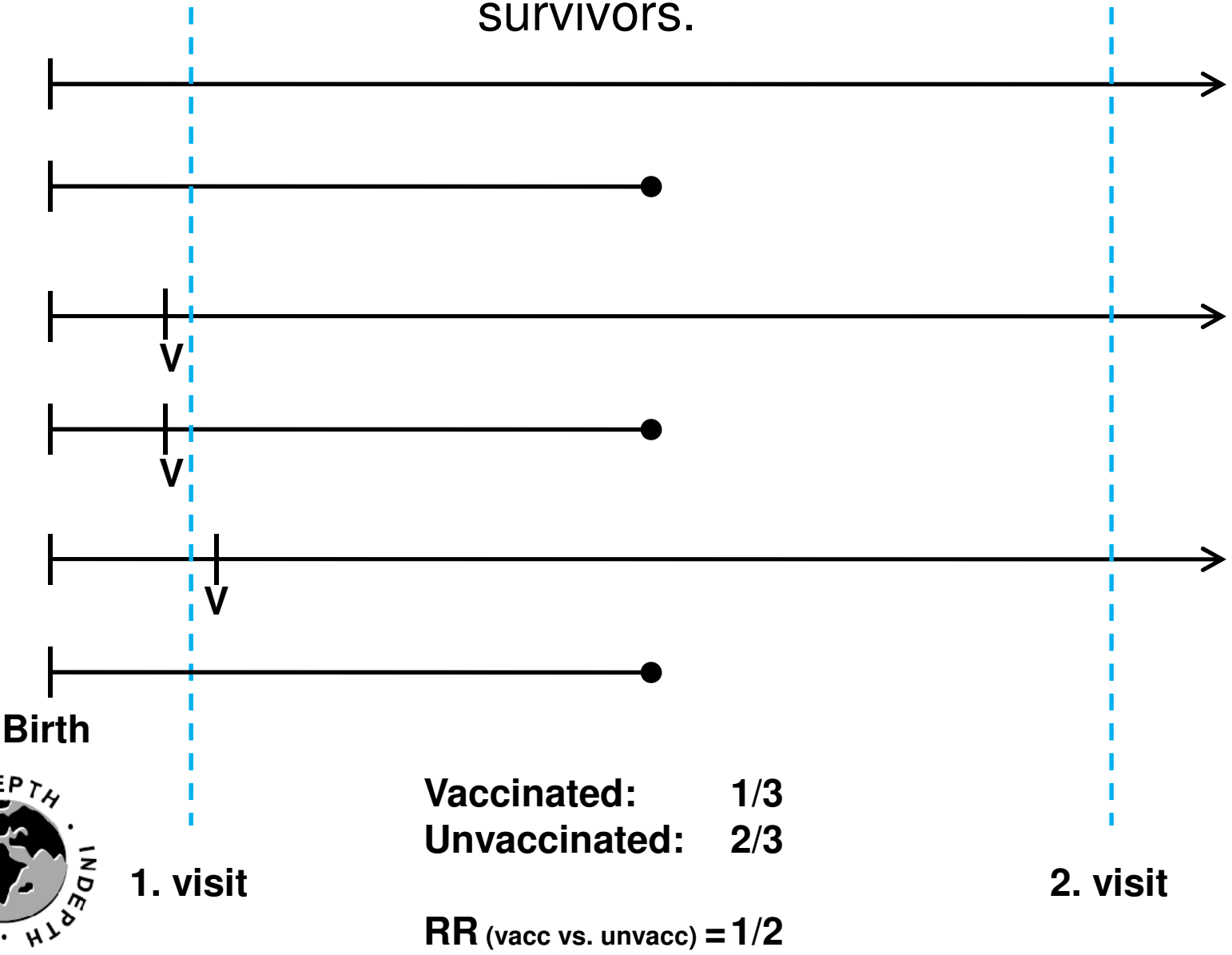
Full information:
Estimate mortality between the two visits



Vaccinated: 2/4
Unvaccinated: 1/2

RR (vacc vs. unvacc) = 1

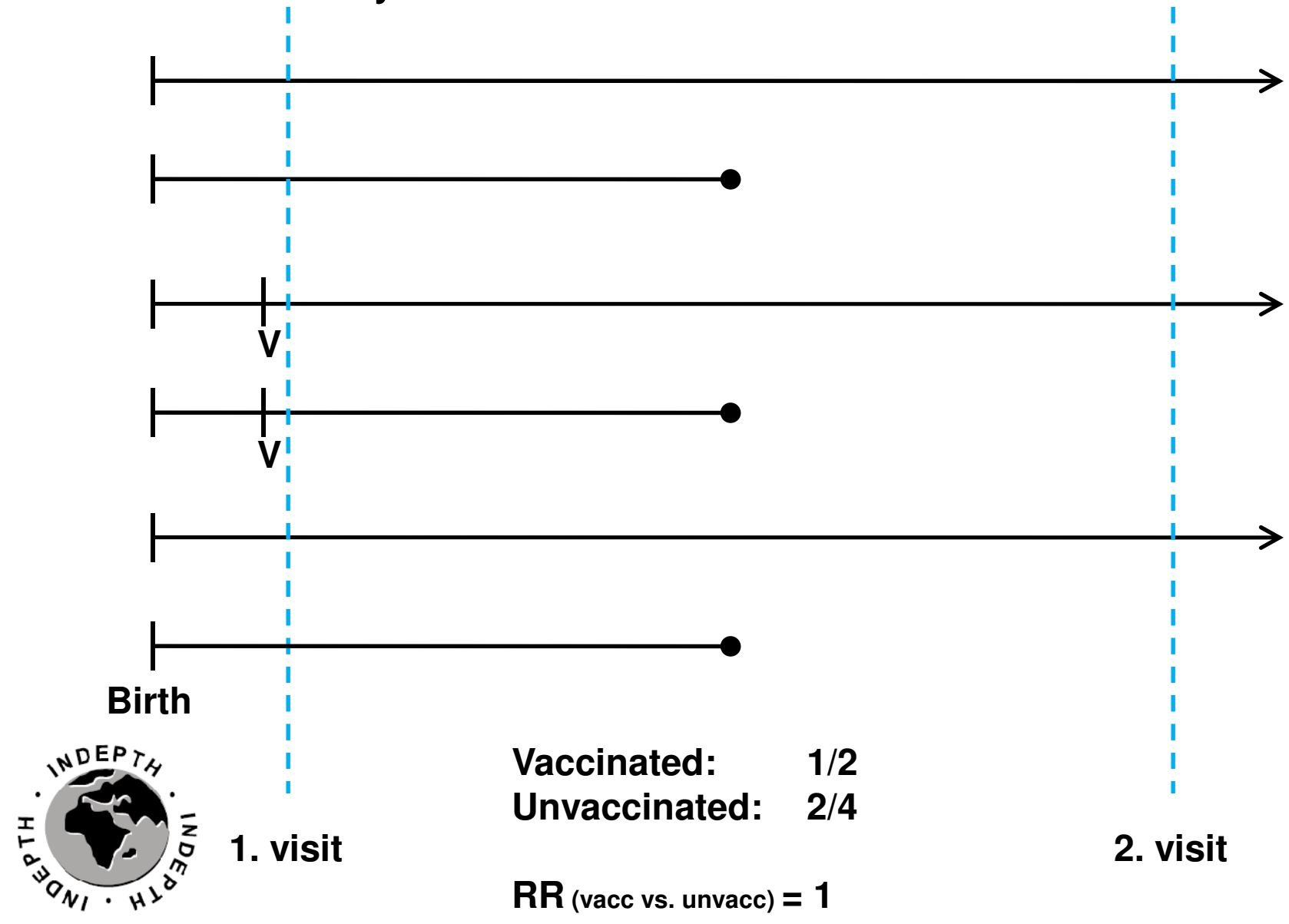
HDSS does not observe the vaccines given between visits for the deaths: **Retrospectively update** vaccinations for survivors.



Vaccinated: 1/3
Unvaccinated: 2/3

RR (vacc vs. unvacc) = 1/2

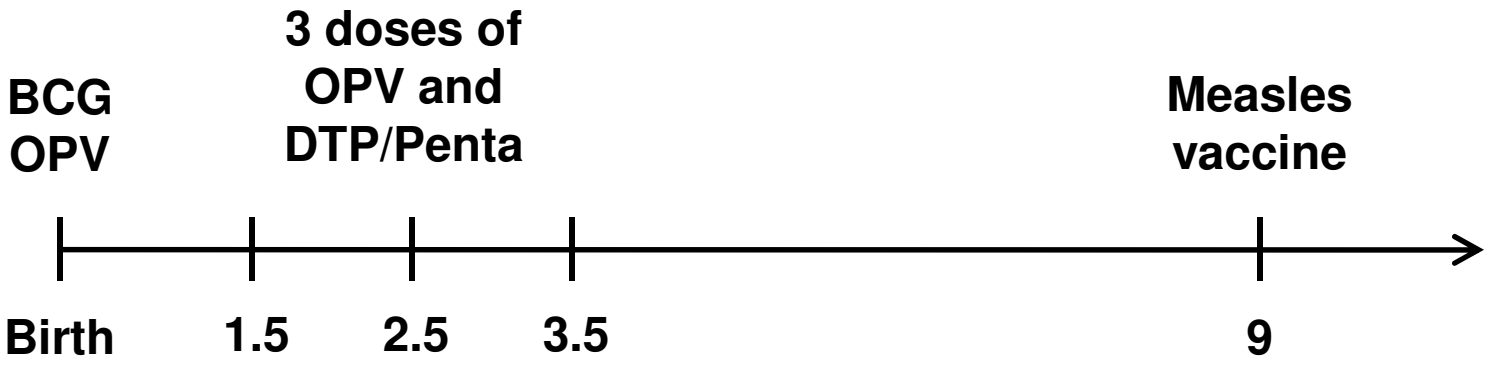
Possible solution is a **Landmark** approach: only use vaccine info from 1. visit



Vaccinated: 1/2
Unvaccinated: 2/4

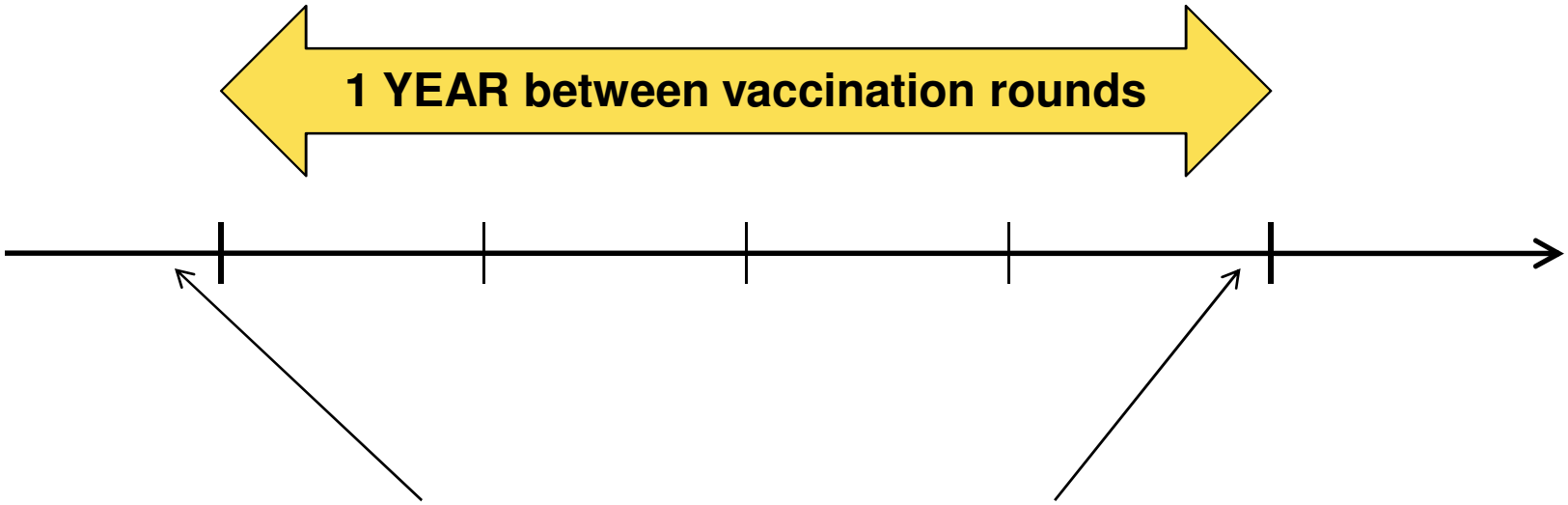
RR (vacc vs. unvacc) = 1

Vaccination schedule in infancy



Test if vaccinated children survive better using Navrongo data

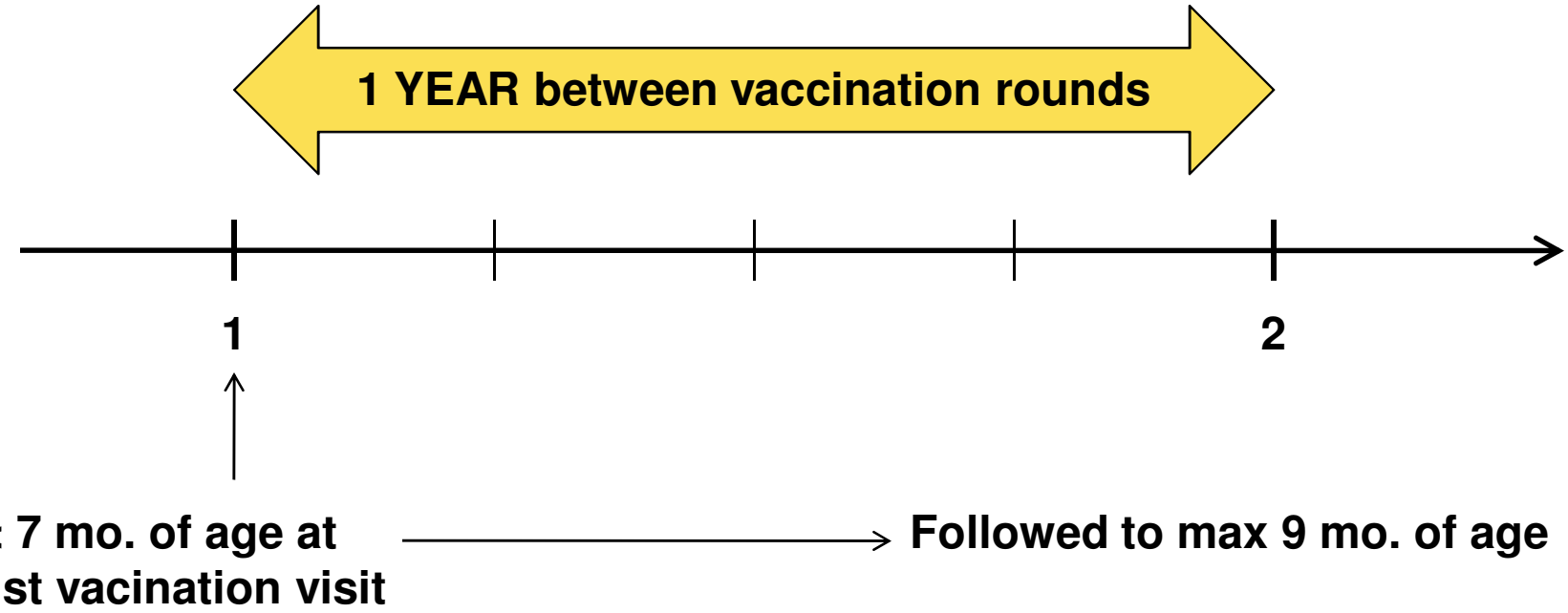
Navrongo HDSS data (1996-2006)



ONLY CHILDREN *ALIVE* AT THESE TIMES ARE PRINTED ON THE VACCINATION QUESTIONNAIRE, I.E.

ONLY UPDATES OF SURVIVING CHILDREN

Navrongo HDSS data (1996-2006)



10101 Children

Analysis approaches

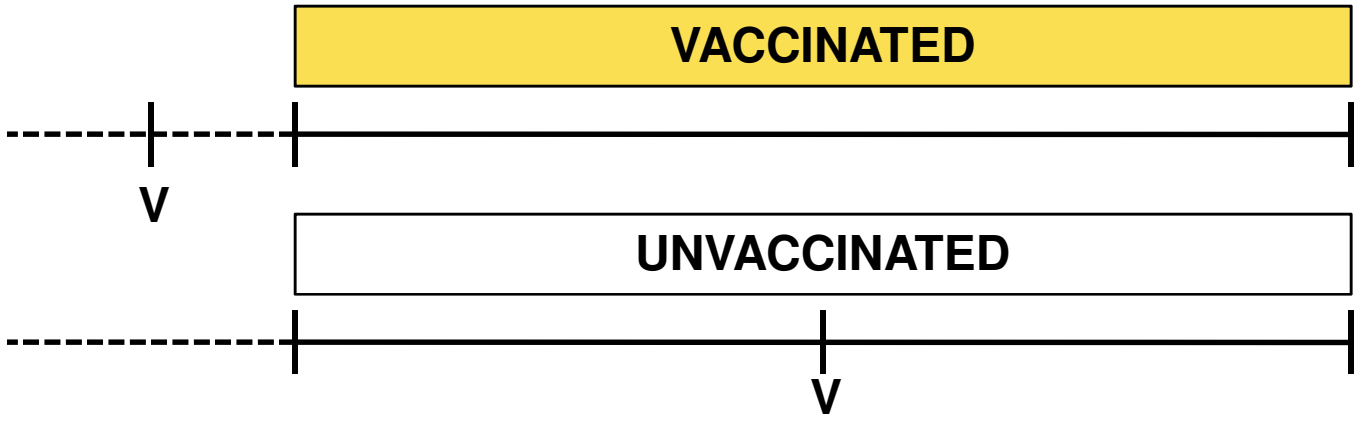
LANDMARK APPROACH	**RETROSPECTIVE UPDATING APPROACH**
Only use vaccine info from 1. visit	Use vaccine info from 1. and 2. visit
Vaccine status is a TIME-FIXED VARIABLE in the analysis	Vaccine status is a TIME-VARYING VARIABLE in the analysis

Total number of
- children
- deaths
- days of observation

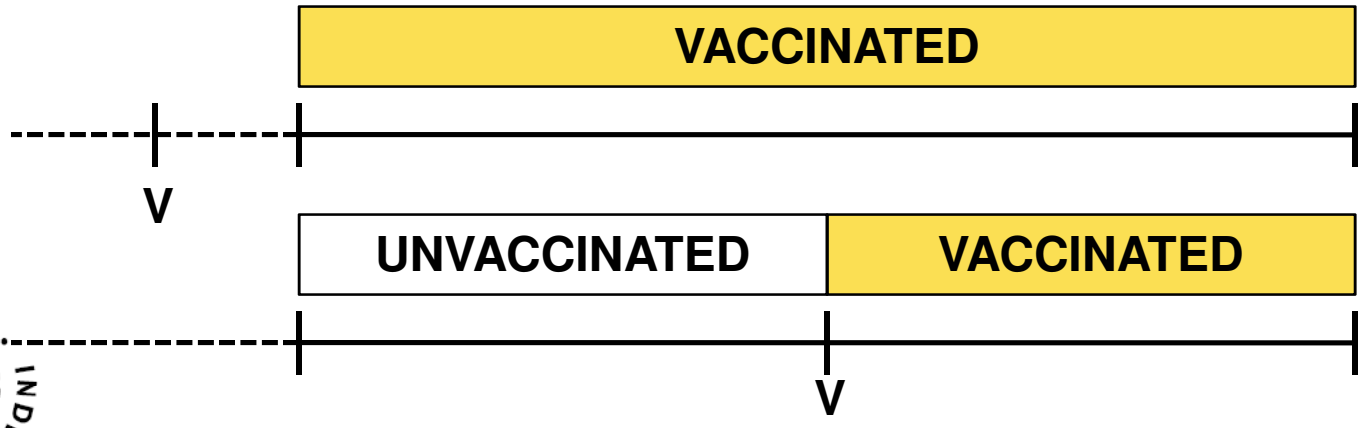
are the same in the two approaches

Contributions from children

Landmark:



Retrospective updating:



	Landmark		Retrospective updating	
	Rate (per 1000 yrs)	Deaths Days	Rate (per 1000 yrs)	Deaths Days
Vaccinated	70	202 1049826	57	203 1309993
Unvaccinated	79	119 552307	147	118 292140
Total	73	321 1602133	73	321 1602133
	Hazard ratio	(95% CI)	Hazard ratio	(95% CI)
Vaccinated vs unvaccinated	0.89	(0.77-1.03)	0.38	(0.33-0.44)
Age adjusted	0.91	(0.72-1.16)	0.44	(0.35-0.56)

Conclusions

- **Survival bias will bias hazard ratios estimates downwards (in favorite of the vaccine)**

- **The magnitude of survival bias depends on (based on simulation study)**
  - Amount of deaths not updated
  - Length between vaccine rounds
  - Vaccination coverage
  - But NOT on underlying mortality

- **Landmark will bias hazard ratios towards 1 (conservative estimates) in situations where the effect of all vaccines are assumed equal**

Conclusions

- **Landmark is not the golden solution: In situations with several different vaccines given during follow-up the bias in landmark approach is in general unpredictable**
- **Solution: minimise follow-up period with few types of vaccine given**
- **As always: Understand in detail how the HDSS data were collected before you analyse.**

Jensen *et al*. Survival bias in observational studies of the impact of routine immunizations on childhood survival. TMIH 2007

Farrington *et al*. Epidemiological studies of the non-specific effects of vaccines: II – methodological issues in the design and analysis of cohort studies. TMIH 2009