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

Paul Welaga, Navrongo
Henrik Ravn, Bandim

INDEPTH, AGM 2010, ACCRA
Overall objective is to study vaccine effect on overall mortality:

P0: Unvaccinated
P1: Vaccinated

Dead

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 unvaccinated

- Examples: Navrongo and Bandim
Navrongo HDSS (1996-2006)
Bandim HDSS (urban/rural)

3/6 months between vaccination rounds

HDSS Round + Vaccine cards

HDSS Round + Vaccine cards
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
- Fieldworkers 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

Birth
Full information:
Estimate mortality between the two visits

1. visit
Vaccinated: 2/4
Unvaccinated: 1/2

RR (vacc vs. unvacc) = 1

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

<table>
<thead>
<tr>
<th>Vaccination Status</th>
<th>1. visit</th>
<th>2. visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>1/3</td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td></td>
<td>2/3</td>
</tr>
</tbody>
</table>

**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

- BCG
- OPV
- 3 doses of OPV and DTP/Penta
- Measles vaccine

Birth 1.5 2.5 3.5 9

Test if vaccinated children survive better using Navrongo data
Navrongo HDSS data (1996-2006)

1 YEAR between vaccination rounds

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

ONLY UPDATES OF SURVIVING CHILDREN
Navrongo HDSS data (1996-2006)

1 YEAR between vaccination rounds

< 7 mo. of age at 1st vaccination visit

Followed to max 9 mo. of age

10101 Children
## Analysis approaches

<table>
<thead>
<tr>
<th>LANDMARK APPROACH</th>
<th>RETROSPECTIVE UPDATING APPROACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only use vaccine info from 1. visit</td>
<td>Use vaccine info from 1. and 2. visit</td>
</tr>
<tr>
<td>Vaccine status is a TIME-FIXED VARIABLE in the analysis</td>
<td>Vaccine status is a TIME-VARYING VARIABLE in the analysis</td>
</tr>
</tbody>
</table>

Total number of
- children
- deaths
- days of observation

are the same in the two approaches
Contributions from children

Landmark:

VACCINATED

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V

UNVACCINATED

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V

Retrospective updating:

VACCINATED

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V

UNVACCINATED

---------

V

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

- Survival bias will bias hazard ratios estimates downwards (in favor 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