Non-specific effects of BCG, DTP and measles vaccines

Systematic review of epidemiological evidence

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on behalf of

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Systematic review objectives

• to review published and grey literature on epidemiological studies addressing “non-specific” effects of BCG, DTP and measles-containing vaccines on:
  i. mortality from causes other than those conditions that the vaccine is designed to prevent and,
  ii. on all-cause mortality in children under five years of age.

• to appraise the evidence critically
Research questions

• Is administration of each vaccine given in infancy associated with an effect on each mortality outcome in children up to five years of age?

• Is there a difference of the effect:
  – between boys and girls?
  – by age dose is received and number of doses?
  – by prior, or co-administration of vitamin A and/ or other vaccines?
  – by sequence/order in which vaccines are given?
Outline

• What we sought
• Articles we found
• Comments on review process
  – overlapping samples
  – risk of bias
• Results for main comparisons and comparisons of vaccine strategies
• Critical appraisal (risk of bias)
• Summary
Criteria for inclusion

- **Participants**: children up to 5 years
- **Intervention**: vaccination (BCG, DTP or measles)
- **Comparators**: no vaccination (BCG, DTP or measles respectively) or simultaneous administration of another vaccine
  - Comparisons of different sequences of vaccine also included
  - Excluding high-titre and medium-title measles vaccine
- **Outcomes**: mortality (as previous slide)

- **Study designs**: randomized (or quasi-randomized) controlled trials; cohort studies; case-control studies

- **Data sources**: primary research papers; or re-analyses of primary studies with full articles describing methodology (published or unpublished, any language)
Records identified through database searching
N = 5,550

Additional records identified by contacting experts in the field
N = 809

Records after duplicates removed
N = 5,600

Records screened
N = 5,600

Full-text articles scanned for eligibility
N = 852

Full-text articles excluded, with reasons
N = 639

Articles identified through reference lists: N = 13
Articles identified through the Working Group: N = 12

Full-text articles assessed for eligibility
N = 238

Full-text articles excluded, after checking eligibility
N = 130. Reasons:
- Study design: N = 91
- No mortality: N = 51
- No data on ≤ 5 years: N = 14
- No data on vaccines: N = 37
- PDF not obtained: N = 6

Full-text articles included (N = 73)
Full-text articles with additional information relevant to the included papers (N = 35)

888 data points extracted

Records excluded:
N = 4,723 (Databases)
N = 660 (WHO registry)

Records identified through WHO International Clinical Trials Registry
N = 670

Records of potentially relevant ongoing studies (N = 10)
Locations of studies (73 articles)

- USA (2)
- Canada (1)
- Philippines (2)
- Guinea-Bissau (37)
- Senegal (5)
- India (5)
- Bangladesh (6)
- Ghana (4)
- Burundi (1)
- Malawi (1)
- Sudan (1)
- Algeria (1)
- Burkina Faso (1)
- Benin (1)
- Nigeria (1)
- South Africa (1)
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37 articles from Guinea-Bissau

- 6 articles from rural areas: Oio, Cacheu, Gabu, Quinhamel, Biombo
- 3 articles reporting data on hospitalized children (Simao Mendes National Hospital)
- 28 articles from Bandim area
37 articles from Guinea-Bissau
Overlap of children (1/4)

• From the protocol:
  “For each study, we will use the best available comparison-level data or group-level data to derive the rate ratio (RR) for vaccinated compared with unvaccinated individuals, with 95% confidence interval (CI)”
Overlap of children (2/4)

• Grouped articles by similarity, e.g.

• e.g.1 Guinea-Bissau group A
  – papers relating to a randomized trial of BCG (early vs delayed) and vitamin A supplementation in low-birth weight infants in the Bandim area of Bissau
  – also data on measles vaccine and mortality

• e.g.2 Guinea-Bissau group C
  – papers relating to a randomized trial of two vs. one dose of measles vaccine in the same area
<table>
<thead>
<tr>
<th>Year</th>
<th>Unpublished</th>
<th>2011</th>
<th>2010</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#9436 Re-analysis of 3 RCTs of VAS</td>
<td>2012</td>
<td>#324 RCT of BCG revaccination</td>
<td>2008</td>
</tr>
<tr>
<td></td>
<td>BCG, MV</td>
<td>#9434 Re-analysis of 2 RCTs of 2 vs 1 MV doses</td>
<td>BCG, DTP1</td>
<td>#1731 RCT of 2 vs 1 MV doses</td>
</tr>
<tr>
<td></td>
<td>1,717</td>
<td>MV</td>
<td>2,343</td>
<td>MV</td>
</tr>
<tr>
<td></td>
<td>≤ 35</td>
<td>≤ 60</td>
<td>≤ 6</td>
<td>≤ 36</td>
</tr>
<tr>
<td></td>
<td>#25 RCT of BCG and VAS in LBW</td>
<td>#61 RCT of BCG in LBW</td>
<td>#339 RCT of BCG and VAS in LBW</td>
<td>#324 RCT of BCG revaccination</td>
</tr>
<tr>
<td></td>
<td>BCG, DTP</td>
<td>BCG</td>
<td>BCG</td>
<td>BCG, DTP</td>
</tr>
<tr>
<td></td>
<td>2,343</td>
<td>105</td>
<td>1,737</td>
<td>2,873</td>
</tr>
<tr>
<td></td>
<td>≤ 6</td>
<td>≤ 12</td>
<td>≤ 12</td>
<td>≤ 12</td>
</tr>
<tr>
<td></td>
<td>#166 RCT of BCG and VAS in LBW</td>
<td>#339 RCT of BCG and VAS in LBW</td>
<td>Observational study of children 6-17 months received VAS</td>
<td>#1986 Observational study of children 6-17 months received VAS</td>
</tr>
<tr>
<td></td>
<td>BCG, DTP1</td>
<td>BCG</td>
<td>BCG, DTP, MV</td>
<td>BCG, DTP, MV</td>
</tr>
<tr>
<td></td>
<td>2,343</td>
<td>1,737</td>
<td>6,648</td>
<td>1,520</td>
</tr>
</tbody>
</table>
Overlap of children (4/4)

BUT...

- likely that part of the population receiving BCG at birth (Guinea-Bissau A) later participated in the measles vaccine trial (Guinea-Bissau C)

SO...

- created ‘birth cohorts’ (which may divide up differently for different vaccines)

- We developed a detailed algorithm to select one result for each comparison (where available) to represent the children in each birth cohort
  - avoids double counting of children
Risk of bias assessment

• For RCTs: Cochrane tool for risk of bias in randomized trials
• Observational studies: In-development Cochrane tool for risk of bias in non-randomized studies
  – project led from University of Bristol
  – with international methodologists from (among others) universities of Harvard, Leiden, Liverpool, London School of Hygiene and Tropical Medicine, McGill, McMaster, Ottawa, Oxford, Paris Descartes, Toronto; and from RTI International, UK Medical Research Council, Nordic Cochrane Centre
Organization of results

- This schedule is our reference point
- All results here are for all-cause mortality
Organization of results

Comparison 1
- BCG vs No BCG
- Impact of age, gender, vitamin A status

General remark:
- Follow-up is often quite short, so as not to be affected by subsequent vaccines
Organization of results

Comparison 2
- DTP vs No DTP
- Impact of age, gender, vitamin A status
Organization of results

Comparison 5

- Measles vaccine vs No measles vaccine
- Impact of age, gender, vitamin A status
Organization of results

Comparison 3

- Reference schedule for BCG and DTP
  vs
- Simultaneous administration
Organization of results

Comparison 4

- Reference schedule for BCG and DTP vs
- DTP before BCG
Organization of results

Comparison 6

- Reference schedule for DTP and measles vs
- Simultaneous administration
Organization of results

Comparison 7

- Reference schedule for DTP and measles vs
- DTP after measles vaccine
Results

1. BCG VS NO BCG
BCG and all-cause mortality

• 18 independent birth cohorts

• 5 trials, 13 observational studies
  – 4 excluded from analysis due to very high risk of bias

• Total sample size approx. 36,000 children
  – range 105 to 10274

• Follow up ranges from 1 to 60 months of age
**Studies**

**BCG and all-cause mortality**

**1. Randomized and quasi-randomized trials**
- Canada 1933-1945: 10 days
- Guinea-Bissau 2002-2008 (early): 2 days
- Guinea-Bissau 2002-2008 (main): 2 days
- USA c.1935: 0-4 years
- USA c.1941: 7-10 days

**2. Case-control studies**
- Benin 1983-1987: NR

**3. Cohort studies**
- Guinea-Bissau 1984-1985: NR (0-8 months)
- Guinea-Bissau 1989-1999: 1-7 days
- Guinea-Bissau 1990-1996: Median 1 month
- India 1987-1989: Median 1.6 months
- India 1998-2002: Median 19 days
- Malawi 1995-1997: Median 16 days
- Papua New Guinea 1989-1994: Median 1 month
- Senegal 1996-1999: NR (by 12 months in 44%)

**Excluded (Very high risk of bias)**
- Bangladesh 1986-2001: 0-2 months
- Burkina Faso 1985-1993: Mean 4.8 months
- Ghana 1998-2004: NR (by 12 months in 57%)
- India 2006-2011: Mean 17 days

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**Results**

**Relative mortality rate** (with 95% confidence interval)

- **Reduce mortality**
  - Vaccine beneficial
  - Median 1 month
  - Age 8 months
  - Age 6 months
  - 6 months follow-up

- **Increase mortality**
  - Vaccine harmful
  - Mean 4.8 months
  - Age 0-60 months
  - 6 months follow-up

- **No effect**
  - Median 1.6 months
  - Age 12 months
  - Age 6 months
  - Age 8 months
  - Age 1-6 months

---

**Further details**
BCG and all-cause mortality

1. Randomized and quasi-randomized trials

- Canada 1933-1945: 10 days, age 60 months
- Guinea-Bissau 2002-2008 (early): 2 days, age 1 month
- Guinea-Bissau 2002-2008 (main): 2 days, age 1 month
- USA c.1935: 0-4 years, age 48 months
- USA c.1941: 7-10 days, age 60 months

2. Case-control studies

- Benin 1983-1987: NR, age 4-36 months

3. Cohort studies

- Guinea-Bissau 1984-1985: NR (0-8 months), age 8 months
- Guinea-Bissau 1989-1999: 1-7 days, age 6 months
- Guinea-Bissau 1990-1996: Median 1 month, 6 months follow-up
- India 1987-1989: Median 1.6 months, age 12 months
- India 1998-2002: Median 19 days, age 6 months
- Malawi 1995-1997: Median 16 days, age 8 months
- Papua New Guinea 1989-1994: Median 1 month, age 1-6 months
- Senegal 1996-1999: NR (by 12 months in 44%), age 24 months

Excluded (Very high risk of bias)

- Bangladesh 1986-2001: 0-2 months, age 0-60 months
- Burkina Faso 1985-1993: Mean 4.8 months, 6 months follow-up
- Ghana 1998-2004: NR (by 12 months in 57%), age 60 months
- India 2006-2011: Mean 17 days, age 1.2 months
Is there a difference in the effect of BCG by age?

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Age of vaccination</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh 1986-2001</td>
<td>vaccination at 0-2 months</td>
<td>age 0-60 months</td>
</tr>
<tr>
<td></td>
<td>vaccination at 2-6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vaccination at 6-12 months</td>
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<td>vaccination at 12-60 months</td>
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<tr>
<td>Guinea-Bissau 1989-1999</td>
<td>vaccination at first week</td>
<td>up to 6 months</td>
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<tr>
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<td>vaccination after first week</td>
<td></td>
</tr>
</tbody>
</table>

Supported by evidence from trials of early vs delayed BCG
Is there a difference in the effect of BCG by gender?

Analysis of boy/girl differences in effect (‘statistical interaction’)

Birth cohort

Burkina Faso 1985-1993
Guinea-Bissau 1989-1999
Guinea-Bissau 1990-1996
Guinea-Bissau 2002-2008 [RCT]
India 1998-2002
India 2006-2011
Malawi 1995-1997
Papua New Guinea 1989-1994
Senegal 1996-1999
Results

2. DTP VS NO DTP
DTP and all-cause mortality

• 16 independent birth cohorts of children, all observational
  – 6 excluded from analysis due to very high risk of bias

• Always given with OPV where information available (8 out of 10 studies)

• Total sample size approx. 28,000 children
  – range 132 to 9085

• Follow up ranges from 6 to 36 months of age
DTP and all-cause mortality

1. Case-control studies
Benin 1983-1987 NR age 4-36 months

2. Cohort studies
Bangladesh 1986-2001 Median 2.8 months 1.5-9 mo
Burkina Faso 1985-1993 Mean 6.3 months 6 months follow-up
Guinea-Bissau 1984-1985 NR (3-8 months) age 8 months
Guinea-Bissau 1990-1996 Median 3 months 6 months follow-up
Guinea-Bissau 2002-2008 NR (1.5-6 months) age 6 months
India 1998-2002 Median 2 months age 6 months
Malawi 1995-1997 Median 2.2 months age 8 months
Papua New Guinea 1989-1994 Before 3 months for most age 1-5 months
Senegal 1996-1999 NR (before 9 months) age 24 months

Excluded (Very high risk of bias)
Ghana 1984-1991 NR age 10-39 months
Ghana 1998-2004 NR (by 12 months in 47%) age 60 months
Guinea-Bissau 1989-1999 NR (from 1.2 months) age 1.25-20 months
India 1987-1989 Median 3.8 months age 12 months
India 2006-2011 Mean 2 months age 8 months
Philippines 1988-1991 NR (before 7 months) age 30 months
Is there a difference in the effect of DTP by age?

- No within-cohort comparisons of effects at different ages at vaccination
Is there a difference in the effect of DTP by gender?

Analysis of boy/girl differences in effect ('statistical interaction')

- Bangladesh 1986-2001
- Burkina Faso 1985-1993
- Guinea-Bissau 1985-1985
- Guinea-Bissau 1989-1999
- Guinea-Bissau 1990-1996
- Guinea-Bissau 2002-2008
- India 1998-2002
- India 2006-2011
- Malawi 1995-1997
- Papua New Guinea 1989-1994
- Senegal 1996-1999

Boys benefit more

Girls benefit more
Is there a difference in the effect of DTP by gender?

Boys
Bangladesh 1986-2001
Burkina Faso 1985-1993
Guinea-Bissau 1985-1985
Guinea-Bissau 1990-1996
Guinea-Bissau 2002-2008
India 1998-2002
Malawi 1995-1997
Papua New Guinea 1989-1994
Senegal 1996-1999

Boys (Very high risk of bias)
Guinea-Bissau 1989-1999
India 2006-2011

Girls
Bangladesh 1986-2001
Burkina Faso 1985-1993
Guinea-Bissau 1985-1985
Guinea-Bissau 1990-1996
Guinea-Bissau 2002-2008
India 1998-2002
Malawi 1995-1997
Papua New Guinea 1989-1994
Senegal 1996-1999

Girls (Very high risk of bias)
Guinea-Bissau 1989-1994
India 2006-2011
3. BCG AND DTP GIVEN SIMULTANEOUSLY

Observation period

Bangladesh 1986-2001  1.5-9 mo
India 1987-1989    age 12 months
Senegal 1996-1999  age 24 months

Favours simultaneous  Favours reference
4. DTP BEFORE BCG

Bangladesh 1986-2001 1.5-9 mo
India 1987-1989 age 12 months
Senegal 1996-1999 age 24 months

Comparison of DTP before or with BCG
Papua New Guinea 1989-1994 age 1-5 months
Papua New Guinea 1989-1994 age 6-11 months
5. MEASLES VACCINE VS NO MEASLES VACCINE
Measles vaccine and all-cause mortality

• 28 independent birth cohorts

• 4 trials, 24 observational studies
  – 6 excluded from analysis due to very high risk of bias

• Total sample size approx. 116,000 children
  – range 99 to 36,650

• Follow up ranges from 9 to 60 months of age
# Measles vaccine and all-cause mortality

## Age at first dose

<table>
<thead>
<tr>
<th>Study</th>
<th>Observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea-Bissau 1989-1999</td>
<td>age 6-9 months</td>
</tr>
<tr>
<td>Guinea-Bissau 1989-1999</td>
<td>age 6-9 months</td>
</tr>
<tr>
<td>Guinea-Bissau 2002-2008</td>
<td>age 4.5-9 months</td>
</tr>
<tr>
<td>Nigeria c.1961</td>
<td>6-20 months follow-up</td>
</tr>
<tr>
<td>Guinea-Bissau 1989-1999</td>
<td>age 4-36 months</td>
</tr>
<tr>
<td>Guinea-Bissau 1989-1999</td>
<td>age 12-60 months</td>
</tr>
<tr>
<td>Benin 1983-1987</td>
<td>age 9-60 months</td>
</tr>
<tr>
<td>Guinea-Bissau 1989-1999</td>
<td>age 9-60 months</td>
</tr>
<tr>
<td>Guinea-Bissau 1990-1996</td>
<td>age 13 months follow-up</td>
</tr>
<tr>
<td>Guinea-Bissau 1990-1996</td>
<td>age 12 months follow-up</td>
</tr>
<tr>
<td>Bangladesh 1977-1988</td>
<td>age 17.5 months or more</td>
</tr>
<tr>
<td>Bangladesh 1986-2001</td>
<td>age 7-19 months</td>
</tr>
<tr>
<td>DR Congo 1973-1975</td>
<td>age 9-24 months</td>
</tr>
<tr>
<td>Guinea-Bissau 1984-1985</td>
<td>age 9-24 months</td>
</tr>
<tr>
<td>Guinea-Bissau 1984-1985</td>
<td>age 9-39 months</td>
</tr>
<tr>
<td>Guinea-Bissau 1990-1996</td>
<td>age 12-60 months</td>
</tr>
<tr>
<td>Guinea-Bissau 1999-2002</td>
<td>age 12-60 months</td>
</tr>
<tr>
<td>Haiti 1981-1982</td>
<td>age 12-60 months</td>
</tr>
<tr>
<td>India 1986-1991</td>
<td>age 12-60 months</td>
</tr>
<tr>
<td>India 1987-1989</td>
<td>age 9-18 months</td>
</tr>
<tr>
<td>Malawi 1995-1997</td>
<td>age 6-11 months</td>
</tr>
<tr>
<td>Papua New Guinea 1989-1994</td>
<td>age 9-24 months</td>
</tr>
<tr>
<td>Senegal 1985-1987</td>
<td>age 9-24 months</td>
</tr>
<tr>
<td>Senegal 1987-1989</td>
<td>age 24 months</td>
</tr>
<tr>
<td>Senegal 1996-1999</td>
<td>age 24 months</td>
</tr>
<tr>
<td>Burundi 1984-1988</td>
<td>age 6 months follow-up</td>
</tr>
<tr>
<td>Ghana 1984-1991</td>
<td>age 6-20 months</td>
</tr>
<tr>
<td>Ghana 1994-1999</td>
<td>age 9-11 months</td>
</tr>
<tr>
<td>Ghana 1998-2004</td>
<td>age 60 months</td>
</tr>
<tr>
<td>India 2006-2011</td>
<td>age 9-15 months</td>
</tr>
<tr>
<td>Senegal 1989-1996</td>
<td>age up to 24 months</td>
</tr>
</tbody>
</table>

## Excluded (Very high risk of bias)

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine beneficial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea-Bissau 1989-1999</td>
<td>6 months follow-up</td>
</tr>
<tr>
<td>Guinea-Bissau 1990-1996</td>
<td>4 months follow-up</td>
</tr>
<tr>
<td>Guinea-Bissau 1998-1999</td>
<td>age 9-11 months</td>
</tr>
<tr>
<td>Guinea-Bissau 2002-2008</td>
<td>age 60 months</td>
</tr>
<tr>
<td>Guinea-Bissau 2006-2011</td>
<td>age 9-15 months</td>
</tr>
<tr>
<td>Guinea-Bissau 2009-2012</td>
<td>age up to 24 months</td>
</tr>
</tbody>
</table>
Is there a difference in the effect of measles vaccine by age?

**Different ages at vaccination**
- Benin 1983-1987 [CC]
  - Age of vaccination: up to 12 months after 12 months
  - Follow-up: age up to 35 months
Is there a difference in the effect of measles vaccine by gender?

Analysis of boy/girl differences in effect (‘statistical interaction’)

Ghana 1984-1991
Guinea-Bissau 1984-1985
Guinea-Bissau 1989-1999 [RCT]
Guinea-Bissau 1999-2002
Guinea-Bissau 2002-2008 [RCT]
India 2006-2011
Malawi 1995-1997
Senegal 1985-1987
Senegal 1987-1989
Senegal 1989-1996
Senegal 1996-1999
Is there a difference in the effect of measles vaccine by gender?

**Boys**
- Guinea-Bissau 1989-1999 [RCT]
- Guinea-Bissau 1999-2002
- Guinea-Bissau 2002-2008 [RCT]
- Malawi 1995-1997
- Senegal 1985-1987
- Senegal 1987-1989
- Senegal 1989-1996
- Senegal 1996-1999

**Boys (Very high risk of bias)**
- Ghana 1984-1991
- Guinea-Bissau 1984-1985
- India 2006-2011

**Girls**
- Guinea-Bissau 1989-1999 [RCT]
- Guinea-Bissau 1999-2002
- Guinea-Bissau 2002-2008 [RCT]
- Malawi 1995-1997
- Senegal 1985-1987
- Senegal 1987-1989
- Senegal 1989-1996
- Senegal 1996-1999

**Girls (Very high risk of bias)**
- Ghana 1984-1991
- Guinea-Bissau 1984-1985
- India 2006-2011

1.2
1.5
2
2.5
3
3.5
4
4.5
5

Vaccine beneficial
Vaccine harmful
6. DTP AND MEASLES VACCINE GIVEN SIMULTANEOUSLY

**Observation period**

- Guinea-Bissau 1999-2002: age 9-24 months
- India 1987-1989: age 12-60 months
- Malawi 1995-1997: age 9-18 months
- Senegal 1996-1999: age 24 months
7. DTP AFTER MEASLES VACCINE

Observation period

Guinea-Bissau 1990-1996 & 1999-2002  age 6-17 months
India 1987-1989                  age 12-60 months
Senegal 1996-1999                age 24 months

Favours reversed  Favours reference
Comment

RISK OF BIAS
Risk of bias is not the same as

<table>
<thead>
<tr>
<th>Bias</th>
<th>Imprecision</th>
</tr>
</thead>
<tbody>
<tr>
<td>• characteristics that raise risk of bias</td>
<td>• reflected in the confidence interval</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>• bias can occur in well-conducted studies</td>
<td>• good methods may have been used but not well reported</td>
</tr>
</tbody>
</table>
Main concerns about risk of bias

- Confounding
- Misclassification
- Selection bias
- Co-interventions
Confounding
(inherent differences between children vaccinated and children not vaccinated)

- Example: DR Congo (MV) (included in analysis)

Fig. 2—Survival, by age, of the different groups.
Confounding

(inherent differences between children vaccinated and children not vaccinated)

- Example: DR Congo (MV) (included in analysis)
- No allowance for possible differences between vaccinated and unvaccinated children

“there were no gross social differences between the two areas”

Fig. 2—Survival, by age, of the different groups.
Confounding: frail children

- Frail children believed less likely to be vaccinated
  - Disappointing amount of evidence about this
- So those vaccinated inherently less likely to die
  - Even if vaccine has no effect
- So naive comparison of vaccinated vs not vaccinated likely to be biased in favour of vaccine
- Lack of comprehensive adjustment for frailty

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>BCG [% (n)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5005</td>
<td>59 (2936)</td>
</tr>
<tr>
<td>Male</td>
<td>5269</td>
<td>59 (3133)</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2500</td>
<td>6880</td>
<td>60 (4155)</td>
</tr>
<tr>
<td>&lt;2500</td>
<td>3394</td>
<td>56 (1914)</td>
</tr>
<tr>
<td>Mother’s prior live births</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>8858</td>
<td>60 (5281)</td>
</tr>
<tr>
<td>≥3</td>
<td>1416</td>
<td>56 (788)</td>
</tr>
<tr>
<td><strong>Household/familial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wood fuel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9556</td>
<td>58 (5539)</td>
</tr>
<tr>
<td>No</td>
<td>718</td>
<td>74 (530)</td>
</tr>
<tr>
<td>Hard roof</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6965</td>
<td>63 (4358)</td>
</tr>
<tr>
<td>No</td>
<td>3309</td>
<td>52 (1711)</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4758</td>
<td>63 (3612)</td>
</tr>
<tr>
<td>No</td>
<td>3753</td>
<td>54 (2457)</td>
</tr>
<tr>
<td>Have electricity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5807</td>
<td>64 (3709)</td>
</tr>
<tr>
<td>No</td>
<td>4467</td>
<td>53 (2360)</td>
</tr>
<tr>
<td>Have TV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1864</td>
<td>70 (1305)</td>
</tr>
<tr>
<td>No</td>
<td>8410</td>
<td>57 (4764)</td>
</tr>
<tr>
<td>Own or lease land</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5258</td>
<td>57 (2981)</td>
</tr>
<tr>
<td>No</td>
<td>5016</td>
<td>62 (3088)</td>
</tr>
<tr>
<td>Own cattle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2854</td>
<td>53 (1506)</td>
</tr>
<tr>
<td>No</td>
<td>7420</td>
<td>62 (4563)</td>
</tr>
</tbody>
</table>

- e.g. India 1998-2002 (included in analysis)
Confounding: age

- e.g. India 2006-2011 *(excluded from analysis)*

<table>
<thead>
<tr>
<th>Time frames</th>
<th>Indicators</th>
<th>BCG exposed group</th>
<th>DTPp exposed group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Boy</td>
<td>Girl</td>
</tr>
<tr>
<td>0–5 Weeks</td>
<td>Child months</td>
<td>4878</td>
<td>4039</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Mortality rate</td>
<td>3.7</td>
<td>6.7</td>
</tr>
<tr>
<td>6 weeks–8 months</td>
<td>Child months</td>
<td>3273</td>
<td>2936</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Mortality rate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Can compute unadjusted comparison of DTP vs no DTP (i.e. BCG only), but children are at very different ages
- **Bias depends on mortality patterns over time**
Misclassification bias (determining non-vaccination)

• e.g. Burkina-Faso (included in analysis)
• Researchers visited families every 6-12 months
• Collected information from vaccination cards
• Vaccinated: Vaccination recorded on vaccination card
• Unvaccinated: “When the card was not seen, we assumed that the child had not been vaccinated”
• It’s possible these children would have been vaccinated: if so the result is biased towards no effect (towards the null)
Misclassification bias (survival bias)

• Major problem can occur if vaccination status is updated retrospectively
  – particularly if vaccination cards are destroyed when a child dies
  – particularly if there is a long period between visits to the children

• Excluded any study with potentially serious biases in this respect
Bias arising from selection of participants long after vaccines were given

- e.g. Philippines (excluded from analysis)
- Children aged up to 30 months at recruitment
- DTP should be given at 6, 10 and 14 weeks
- A randomized trial would start follow-up at intervention

Figure 1 Flowchart detailing the selection of the study population
Co-interventions

- e.g. Ghana 1998-2004 (excluded from analysis)
- Vaccines are highly correlated so effect for BCG includes effects of DTP and measles vaccine
- (Other critical problems with this study due to annual visits to children)

Table II. Univariate time-conditional hazard ratios for the impact of eight vaccines on mortality among children younger than five, Kassena-Nankana District, Ghana.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Hazard ratio (confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>0.18 (0.17–0.20)***</td>
</tr>
<tr>
<td>Polio1</td>
<td>0.16 (0.15–0.18)***</td>
</tr>
<tr>
<td>Polio2</td>
<td>0.15 (0.13–0.16)***</td>
</tr>
<tr>
<td>Polio3</td>
<td>0.15 (0.14–0.17)***</td>
</tr>
<tr>
<td>DPT1</td>
<td>0.15 (0.14–0.16)***</td>
</tr>
<tr>
<td>DPT 2</td>
<td>0.14 (0.13–0.16)***</td>
</tr>
<tr>
<td>DPT 3</td>
<td>0.15 (0.13–0.16)***</td>
</tr>
<tr>
<td>Measles</td>
<td>0.14 (0.13–0.16)***</td>
</tr>
</tbody>
</table>

***Significant at $p \leq 0.001$. 
CONCLUDING REMARKS
Summary

• There was some evidence from randomized trials, but with short follow up

• All observational studies were considered to be at high risk of bias
  – some excluded because judged to be at very high risk

• Biases due to selective reporting may also be present, but these are very difficult to detect
Summary: BCG

• Is administration of BCG vaccine given in infancy associated with an effect on all-cause mortality in children up to five years of age?

- May reduce risk of all-cause mortality
- **GRADE**: Very little confidence

• Is there a difference of the effect:
  - between boys and girls?
    - No difference apparent
  - by age dose is received?
    - Suggestion of greater benefit when given earlier
  - by prior, or co-administration of vitamin A and/or other vaccines?
    - Insufficient evidence
Summary: DTP (1/2)

• Is administration of DTP vaccine (with OPV) given in infancy associated with an effect on all-cause mortality in children up to five years of age?

  Inconsistent evidence*  
  **GRADE**: Very little confidence

• Is there a difference of the effect:
  – between boys and girls?

  Effects may be more deleterious or variable in girls

  – by age dose is received and number of doses received?

  No data available

  – by prior, or co-administration of vitamin A and/ or other vaccines?

  Insufficient evidence

*No studies reported on DTP without OPV
Summary: DTP (2/2)

• Is there a difference of the effect:
  – by sequence/order in which vaccines are given?
    • When administered simultaneously with BCG
      May reduce risk of all-cause mortality compared with BCG before DTP  
      **GRADE:** Very little confidence

    • When administered before BCG
      No difference apparent  
      **GRADE:** Very little confidence

    • When administered simultaneously with measles vaccine
      May increase risk of all-cause mortality compared with DTP before measles  
      **GRADE:** Very little confidence

    • When administered after measles vaccine
      May increase risk of all-cause mortality compared with DTP before measles  
      **GRADE:** Very little confidence
Summary: Measles vaccine

• Is administration of measles vaccine given in infancy associated with an effect on all-cause mortality in children up to five years of age?

May reduce risk of all-cause mortality  GRADE: Limited confidence

• Is there a difference of the effect:
  – between boys and girls?
    Suggestion of (greater) benefit in girls
  – by age dose is received?
    Suggestion of greater benefit when given earlier
  – by prior, or co-administration of vitamin A and/or other vaccines?
    Insufficient evidence
Concluding remarks

• There is not a single approach to design and analysis of studies in this research area
• Leaves open the possibility that investigators may have tried multiple ways to select and analyse the data
• Thereby putting the accessible literature as a whole at risk of bias