

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

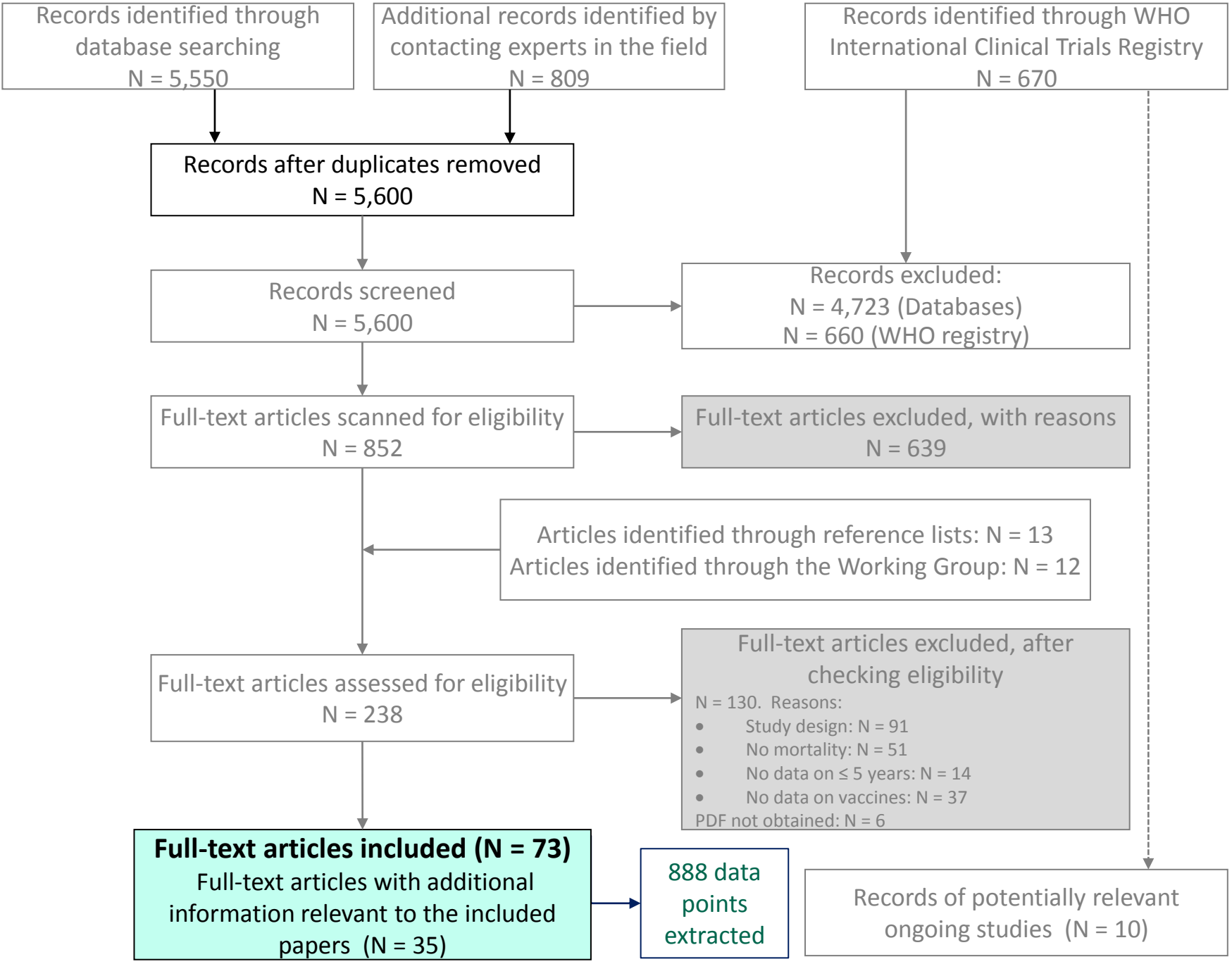
- *Participants*: children up to 5 years
- *Intervention*: vaccination (BCG, DTP or measles)
- *Comparators*: no vaccination (BCG, DTP or measles respectively) or simultaneous administration of another vaccine
 - Comparisons of different sequences of vaccine also included
 - Excluding high-titre and medium-titre 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primary research papers; or re-analyses of primary studies with full articles describing methodology (published or unpublished, any language)

Identification

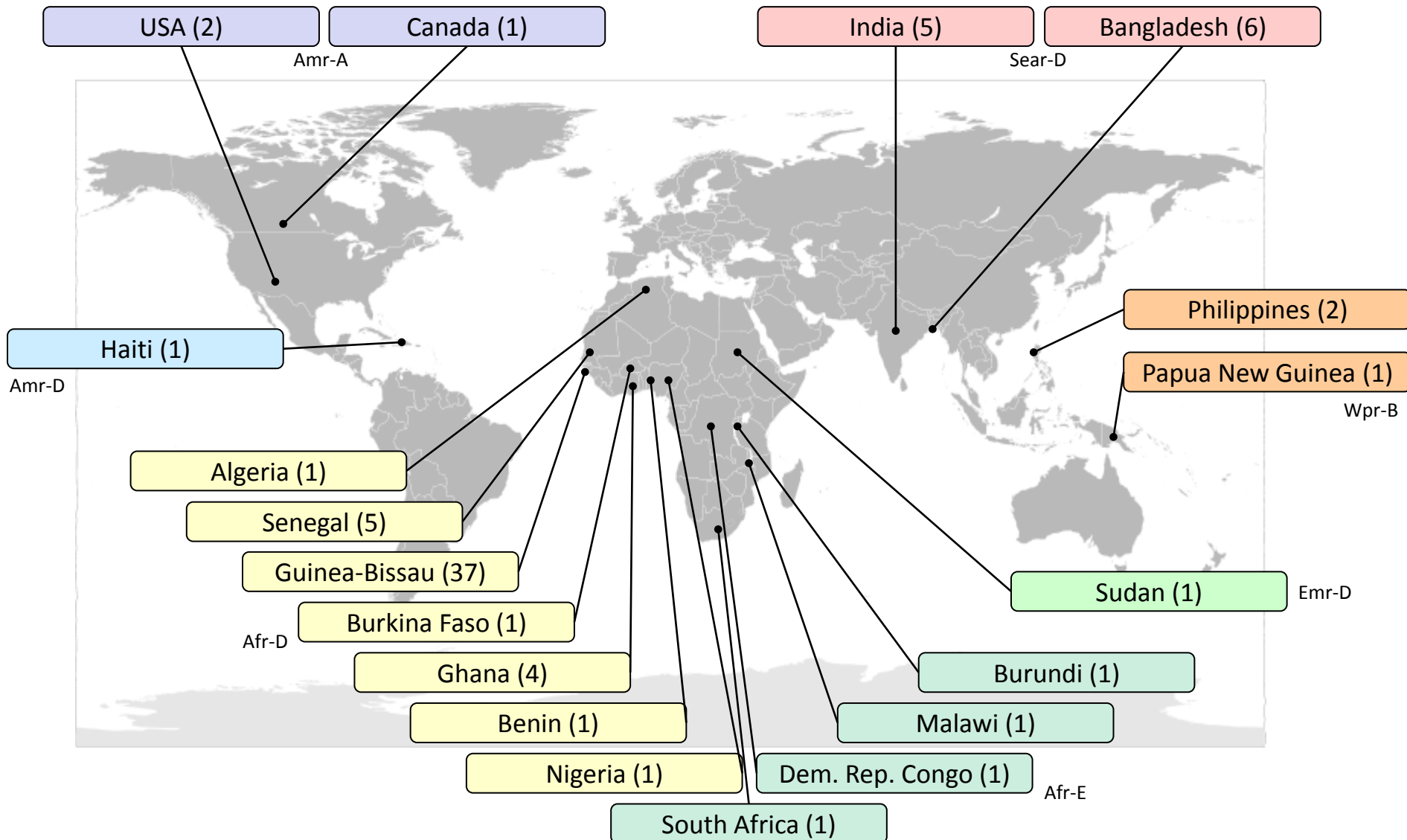
Screening

Eligibility

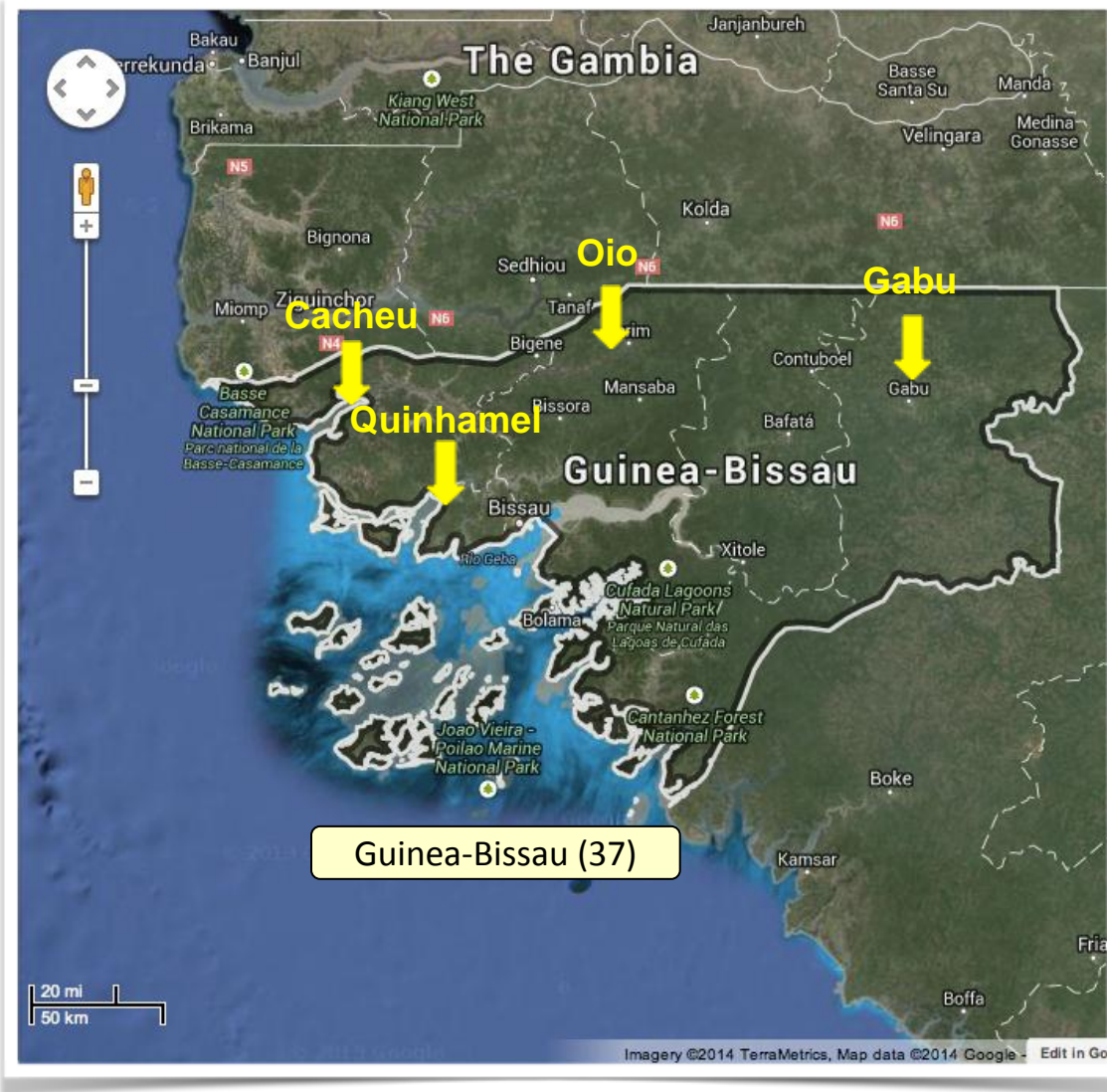
Included



Locations of studies (73 articles)

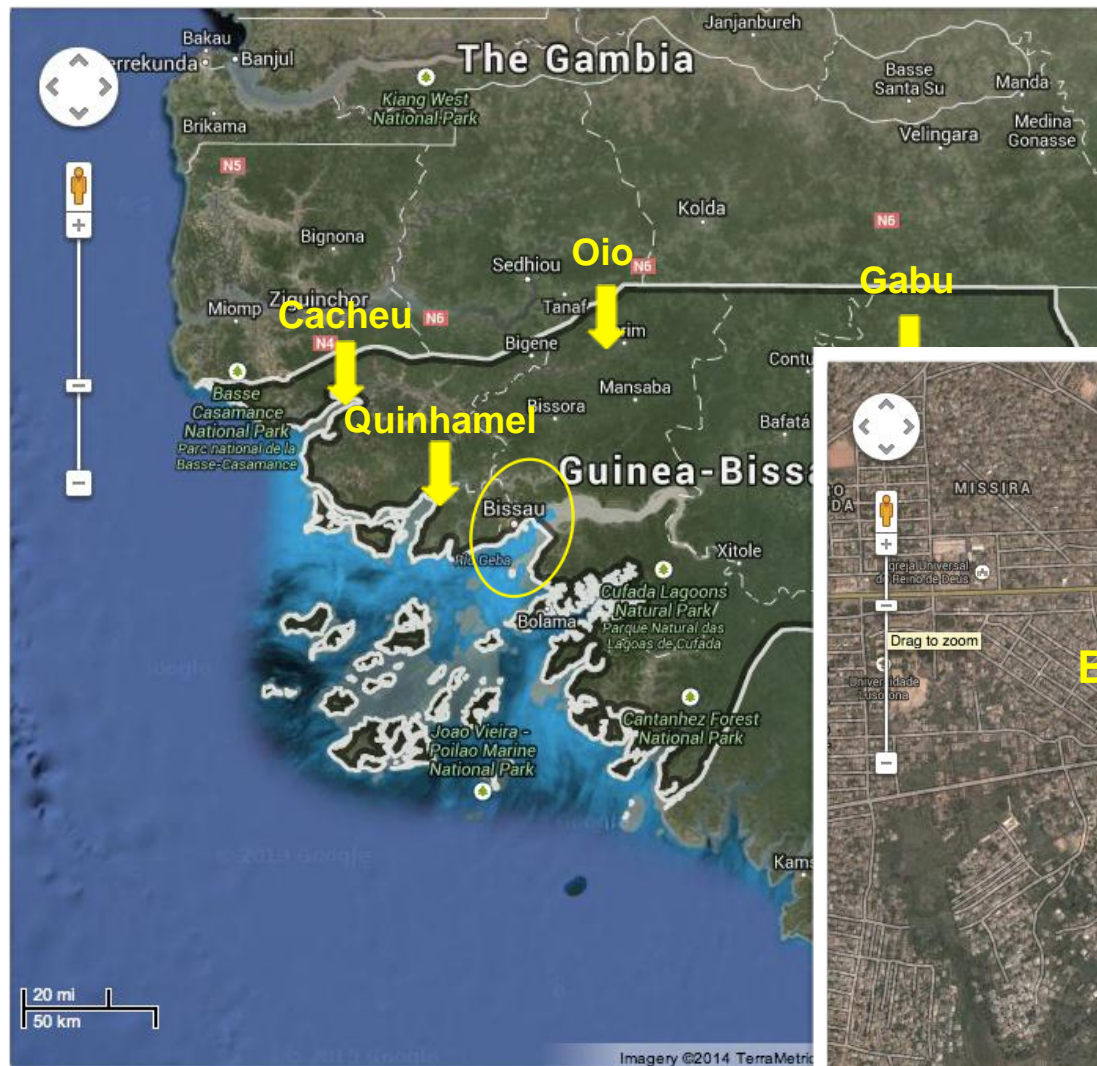


37 articles from Guinea-Bissau



- **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

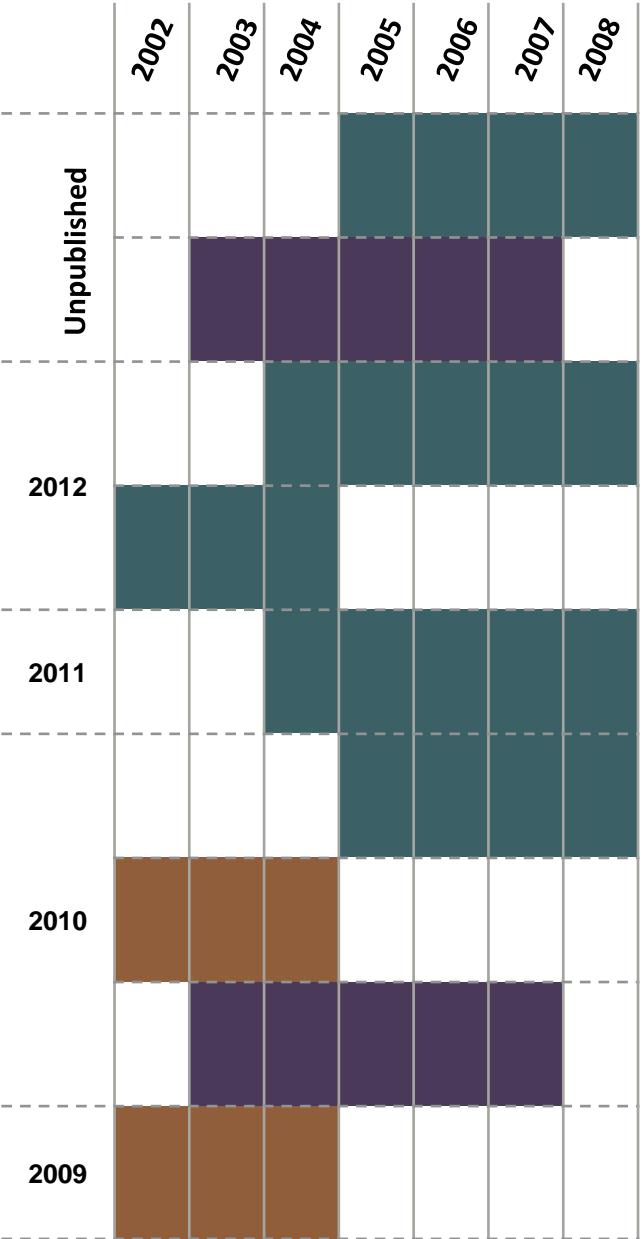


Overlap of children (1/4)

- 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



	GOAL	VACCINES	SAMPLE SIZE	FOLLOW UP (MO)
#9436	Re-analysis of 3 RCTs of VAS	BCG, MV	1,717	≤ 35
#9434	Re-analysis of 2 RCTs of 2 vs 1 MV doses	MV	1,698	≤ 60
#25	RCT of BCG and VAS in LBW	BCG, DTP	2,343	≤ 6
#61	RCT of BCG in LBW	BCG	105	≤ 12
#166	RCT of BCG and VAS in LBW	BCG, DTP1	2,343	≤ 12
#339	RCT of BCG and VAS in LBW	BCG	1,737	≤ 12
#324	RCT of BCG revaccination	BCG, DTP	2,873	≤ 12
#1731	RCT of 2 vs 1 MV doses	MV	6,648	≤ 36
#1986	Observational study of children 6-17 months received VAS	BCG, DTP, MV	1,520	≤ 18

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)

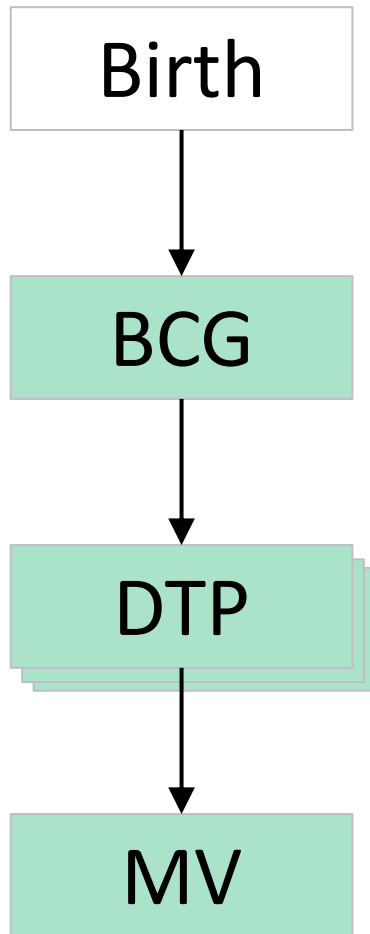
SO...

- 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

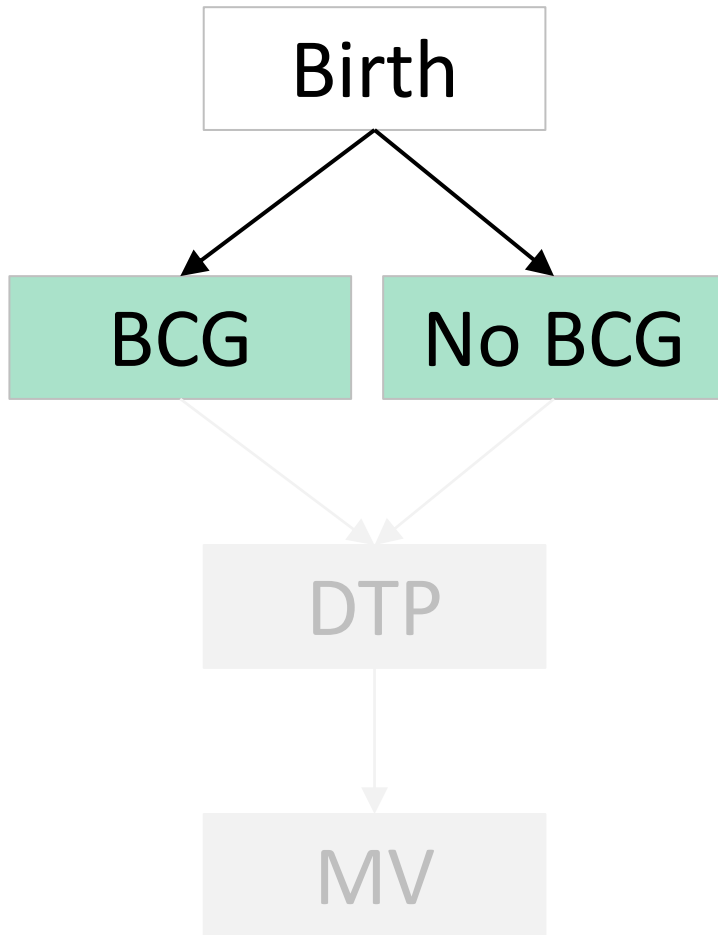
- For RCTs: Cochrane tool for risk of bias in randomized trials
- Observational studies: In-development Cochrane tool for risk of bias in non-randomized studies
 - project led from University of Bristol
 - with international methodologists from (among others) universities of Harvard, Leiden, Liverpool, 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



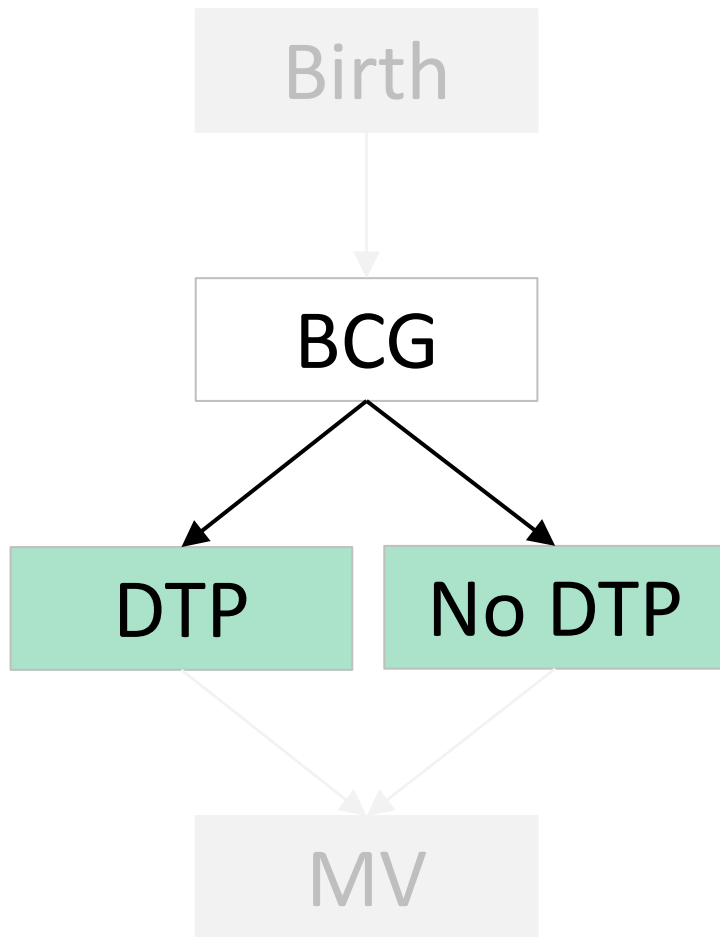
Comparison 1

- 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

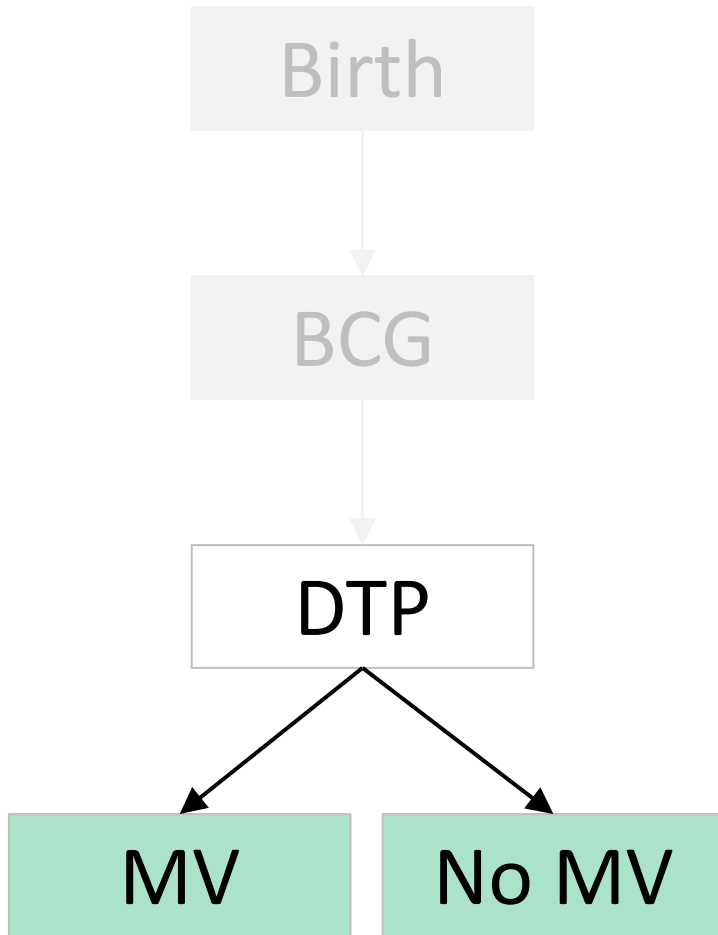
Organization of results



Comparison 2

- DTP vs No DTP
- Impact of age, gender, vitamin A status

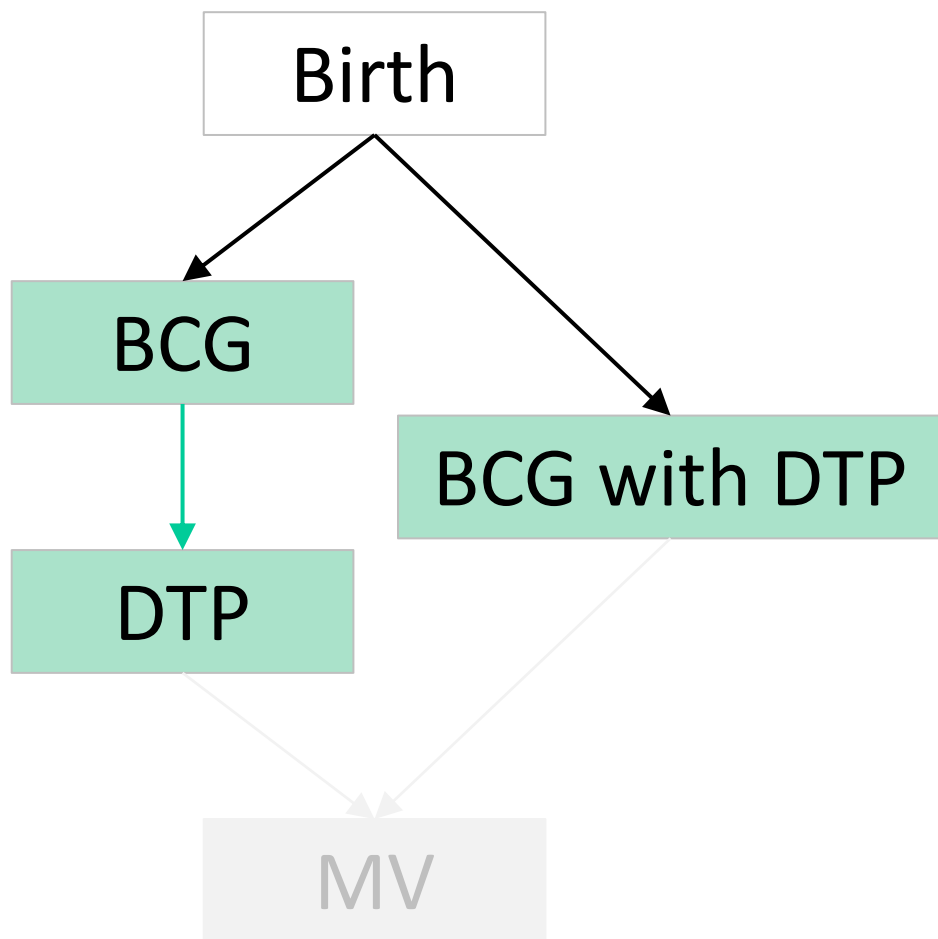
Organization of results



Comparison 5

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

Organization of results



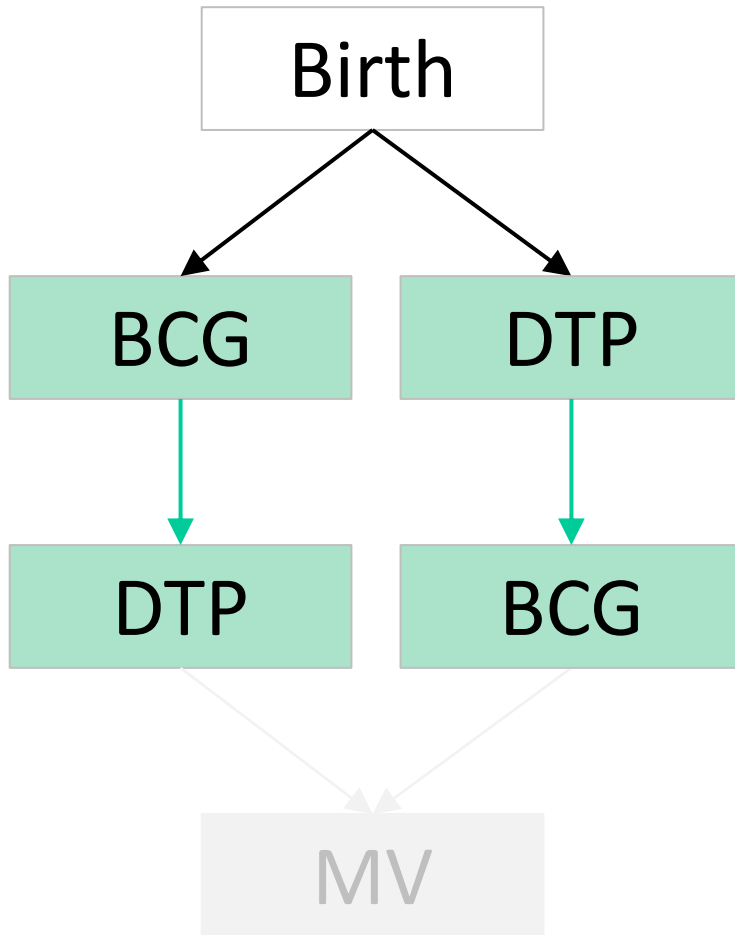
Comparison 3

- Reference schedule for BCG and DTP

vs

- Simultaneous administration

Organization of results



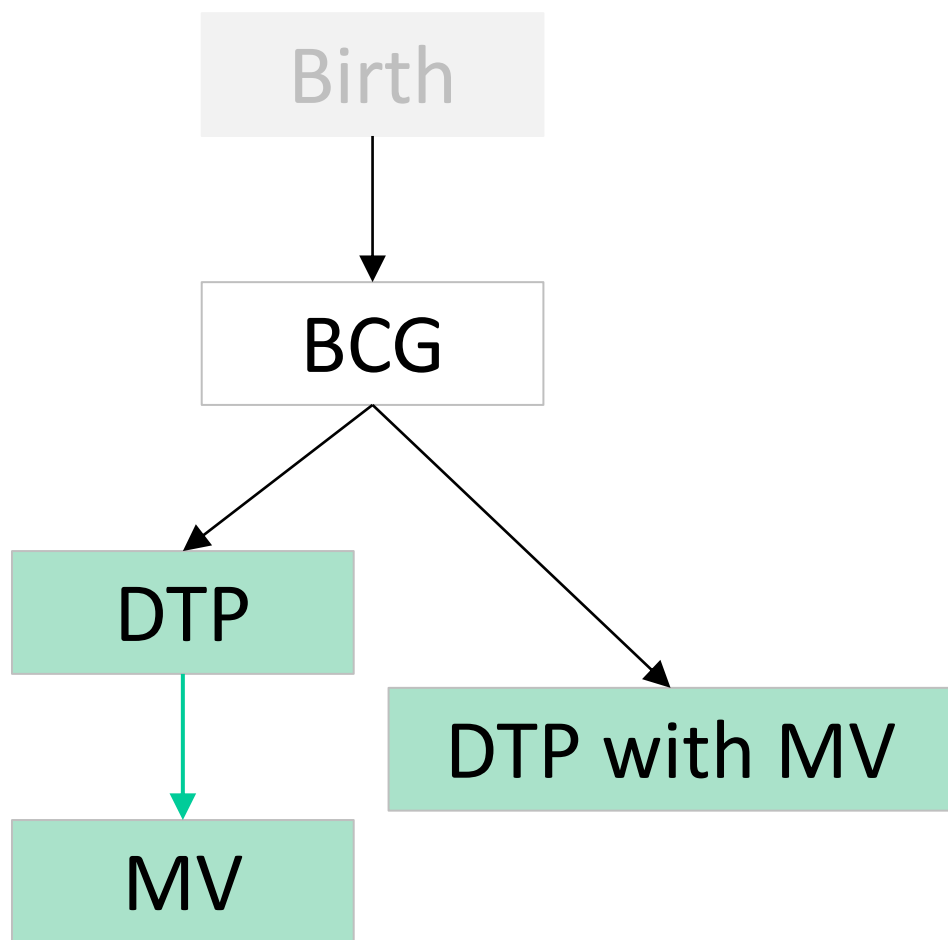
Comparison 4

- Reference schedule for BCG and DTP

vs

- DTP before BCG

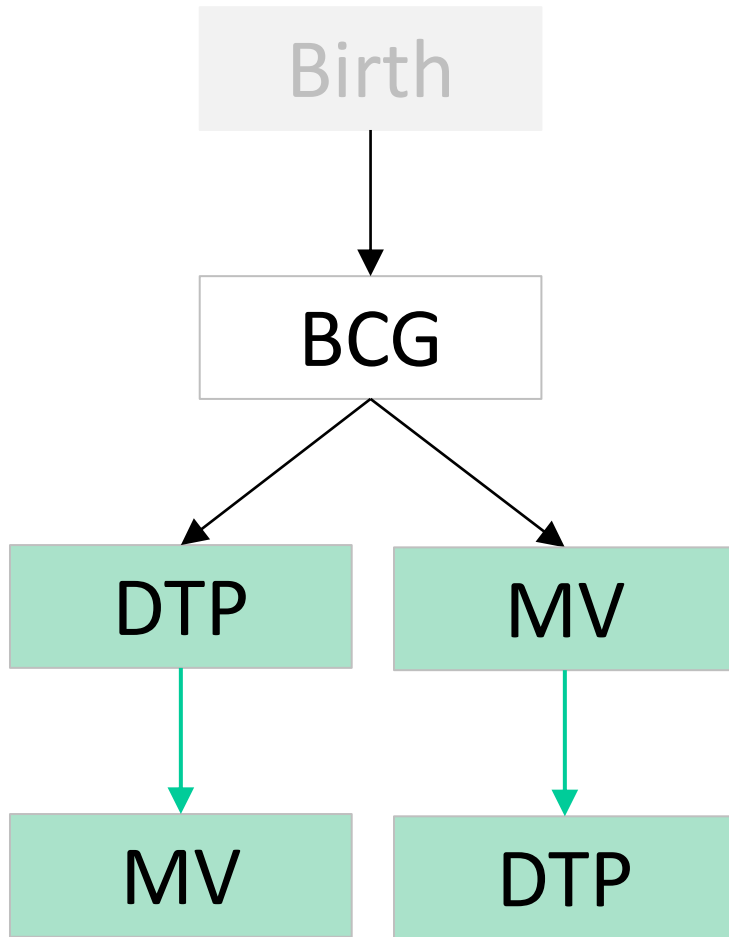
Organization of results



Comparison 6

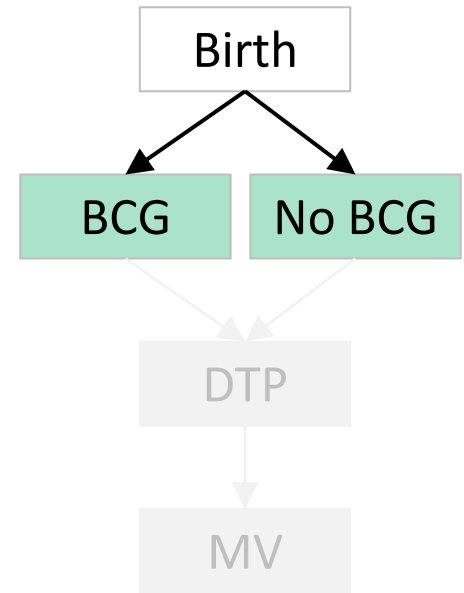
- Reference schedule for DTP and measles
- vs
- Simultaneous administration

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

Results

Birth cohort

Age at first dose

Observation period

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

age 60 months
age 1 month
age 1 month
age 48 months
age 60 months

2. Case-control studies

Benin 1983-1987	NR
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age 4-36 months

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%)

age 8 months
age 6 months
6 months follow-up
age 12 months
age 6 months
age 8 months
age 1-6 months
age 24 months

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

age 0-60 months
6 months follow-up
age 60 months
age 1.2 months

Reduce mortality

Increase mortality

Relative mortality rate (with 95% confidence interval)

Further details

Vaccine beneficial

Vaccine harmful

No effect

BCG and all-cause mortality

Birth
cohort

Age at first dose

Observation
period

1. Randomized and quasi-randomized trials

Canada 1933-1945	10 days	age 60 months
<u>Guinea-Bissau 2002-2008 (early)</u>	2 days	age 1 month
<u>Guinea-Bissau 2002-2008 (main)</u>	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

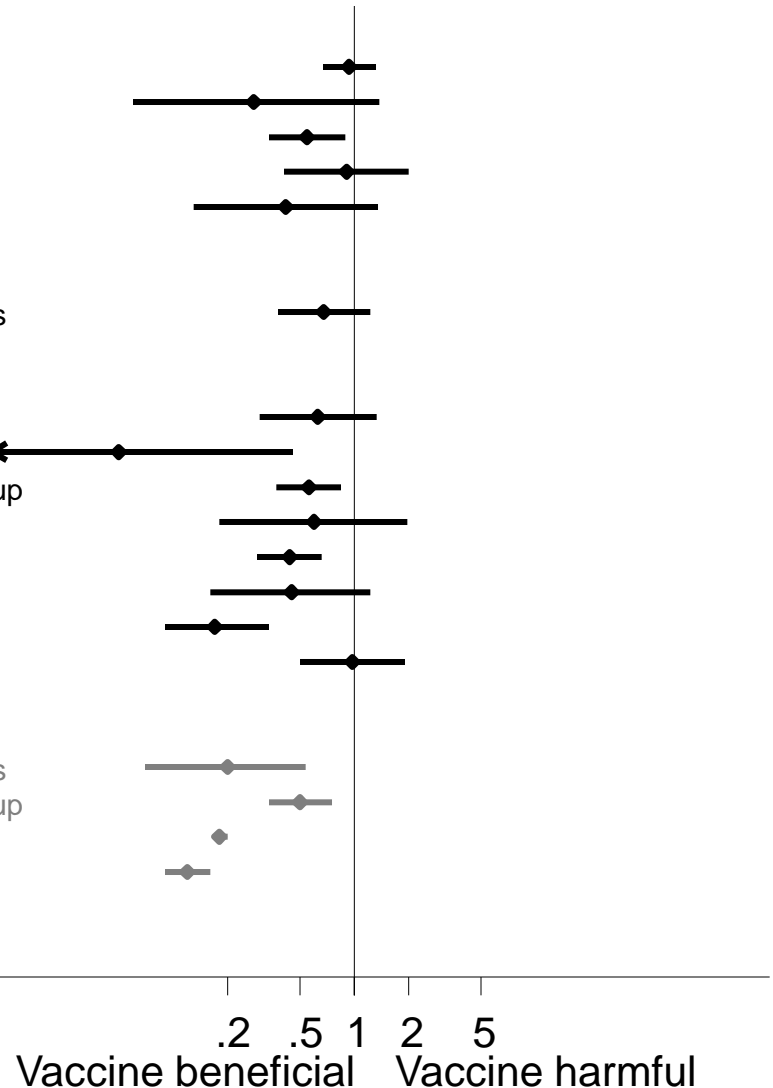
Benin 1983-1987	NR	age 4-36 months
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3. Cohort studies

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?

Birth cohort

Age of vaccination

Follow-up

Different ages at vaccination



Supported by evidence from trials of early vs delayed BCG

.2 .5 1 2 5
Vaccine beneficial Vaccine harmful

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]

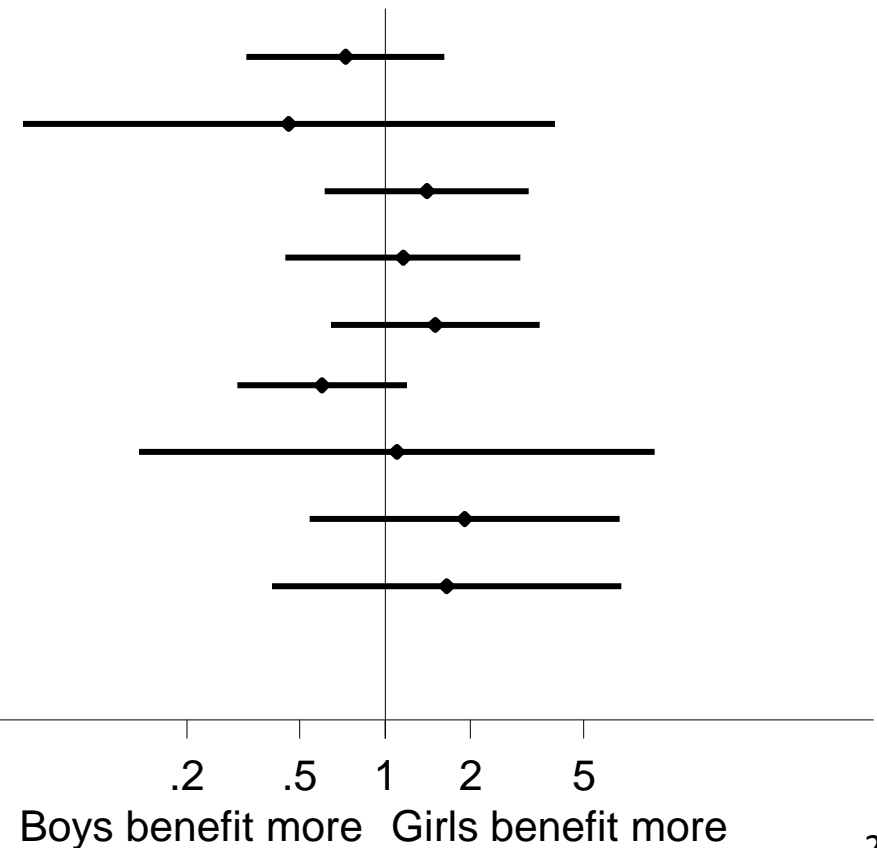
India 1998-2002

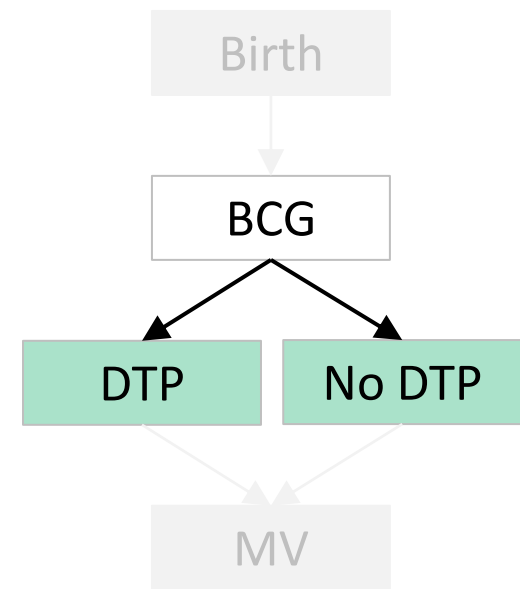
India 2006-2011

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

Age at first dose
Observation period

1. Case-control studies

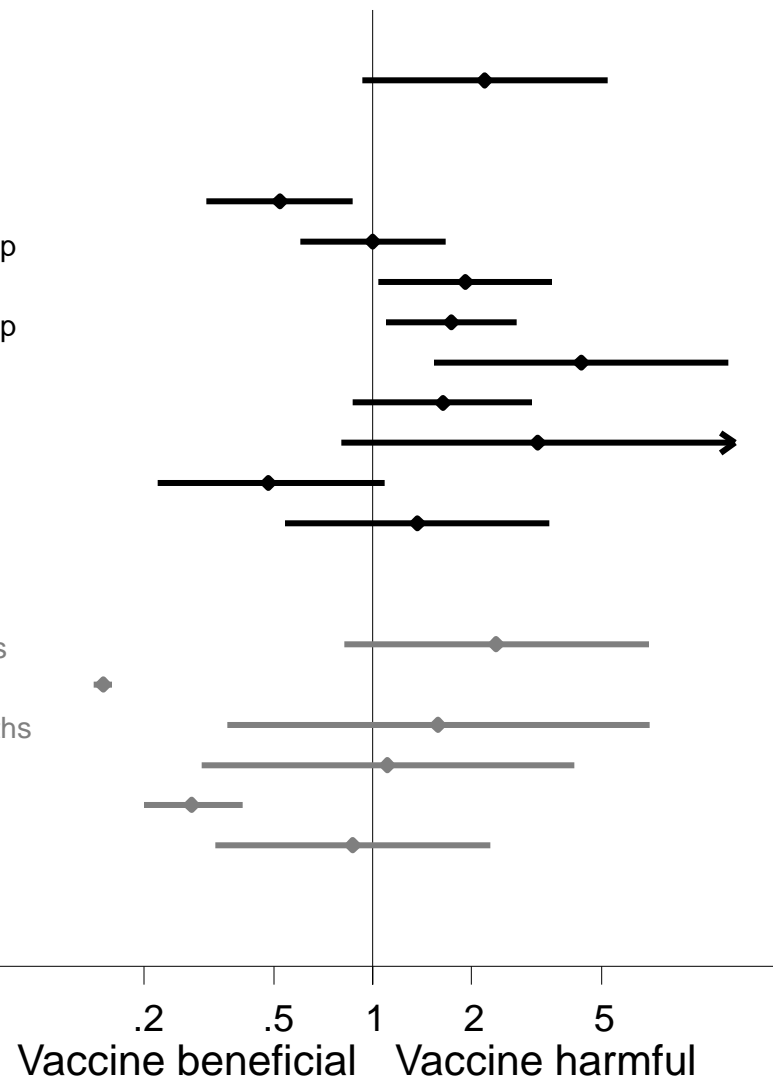
Benin 1983-1987 NR age 4-36 months

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



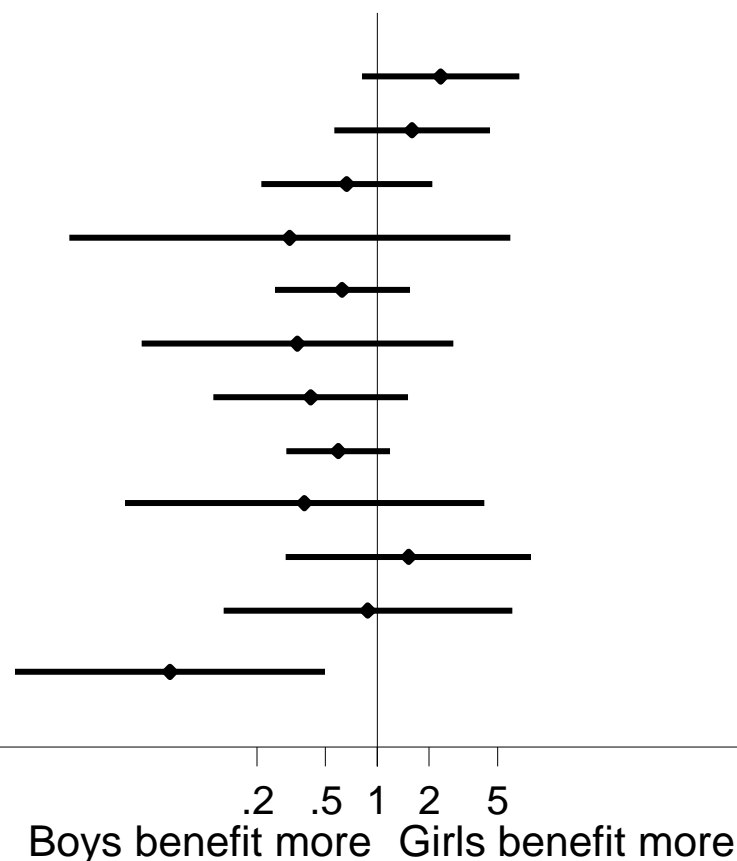
Is there a difference in the effect of DTP by age?

- 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
Philippines 1988-1991
Senegal 1996-1999



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)

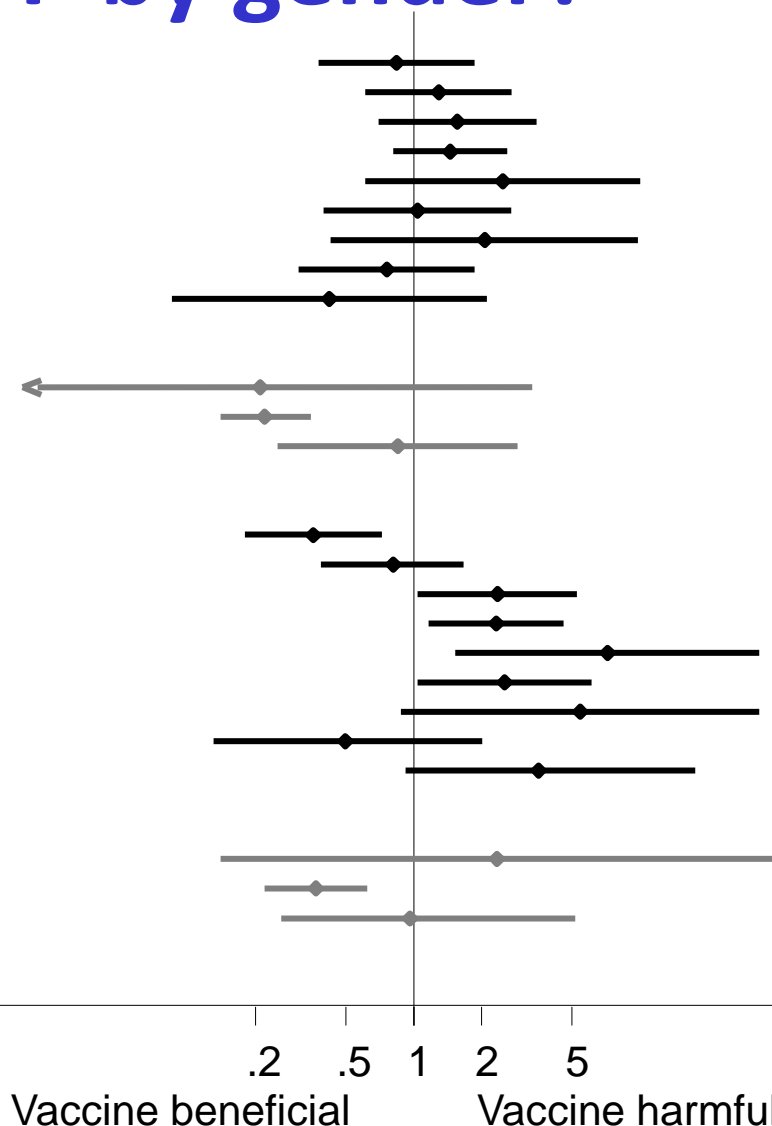
Guinea-Bissau 1989-1999
India 2006-2011
Philippines 1988-1991

Girls

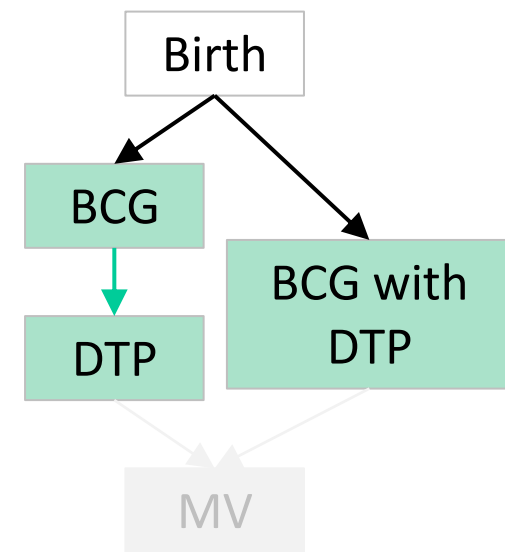
Bangladesh 1986-2001
Burkina Faso 1985-1993
Guinea-Bissau 1985-1985
Guinea-Bissau 1990-1996
Guinea-Bissau 2002-2008
India 1998-2002
Malawi 1995-1997
Papua New Guinea 1989-1994
Senegal 1996-1999

Girls (Very high risk of bias)

Guinea-Bissau 1989-1999
India 2006-2011
Philippines 1988-1991



3. BCG AND DTP GIVEN SIMULTANEOUSLY



*Observation
period*

Bangladesh 1986-2001

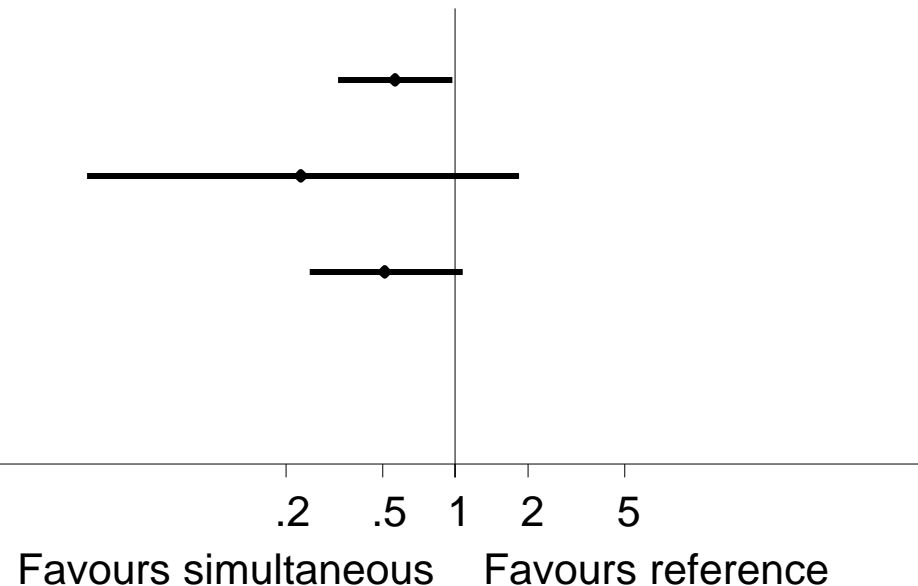
1.5-9 mo

India 1987-1989

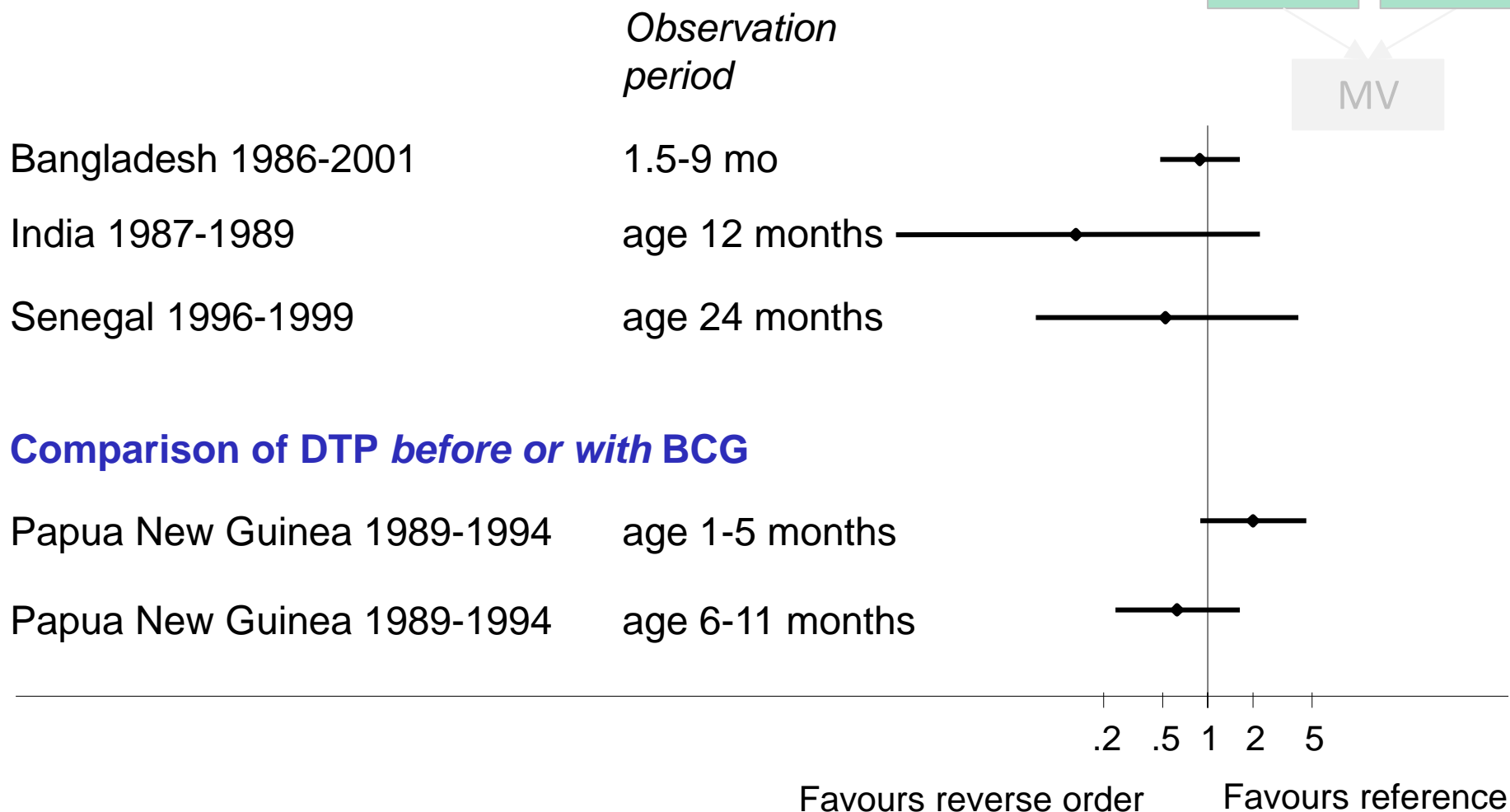
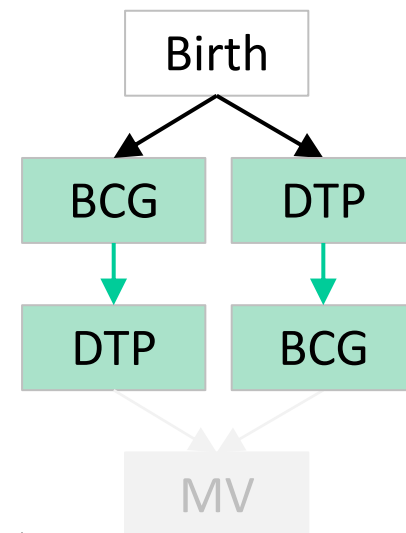
age 12 months

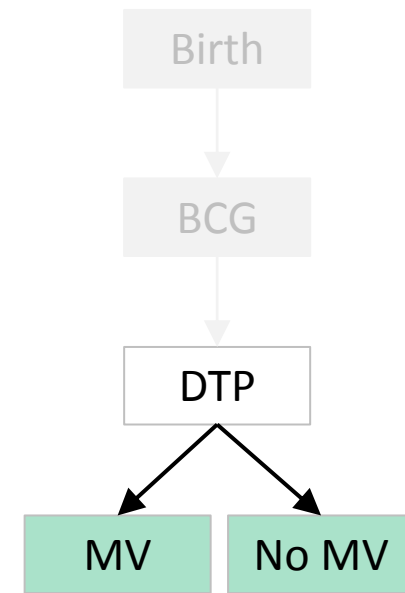
Senegal 1996-1999

age 24 months



4. DTP BEFORE BCG





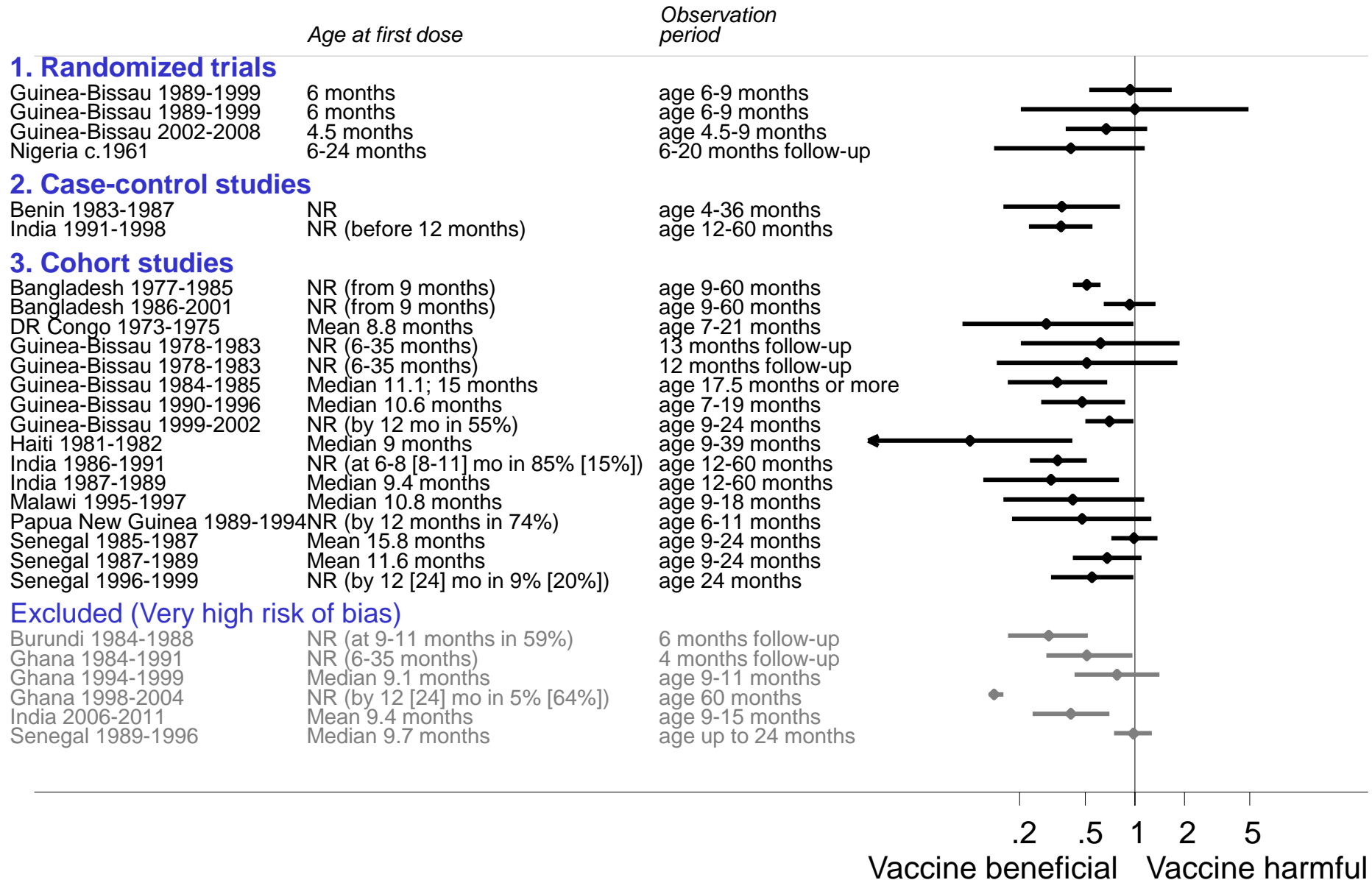
Results

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



Is there a difference in the effect of measles vaccine by age?

Age of vaccination

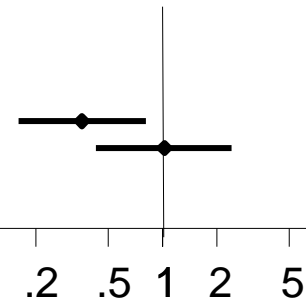
Follow-up

Different ages at vaccination

Benin 1983-1987 [CC]

up to 12 months
after 12 months

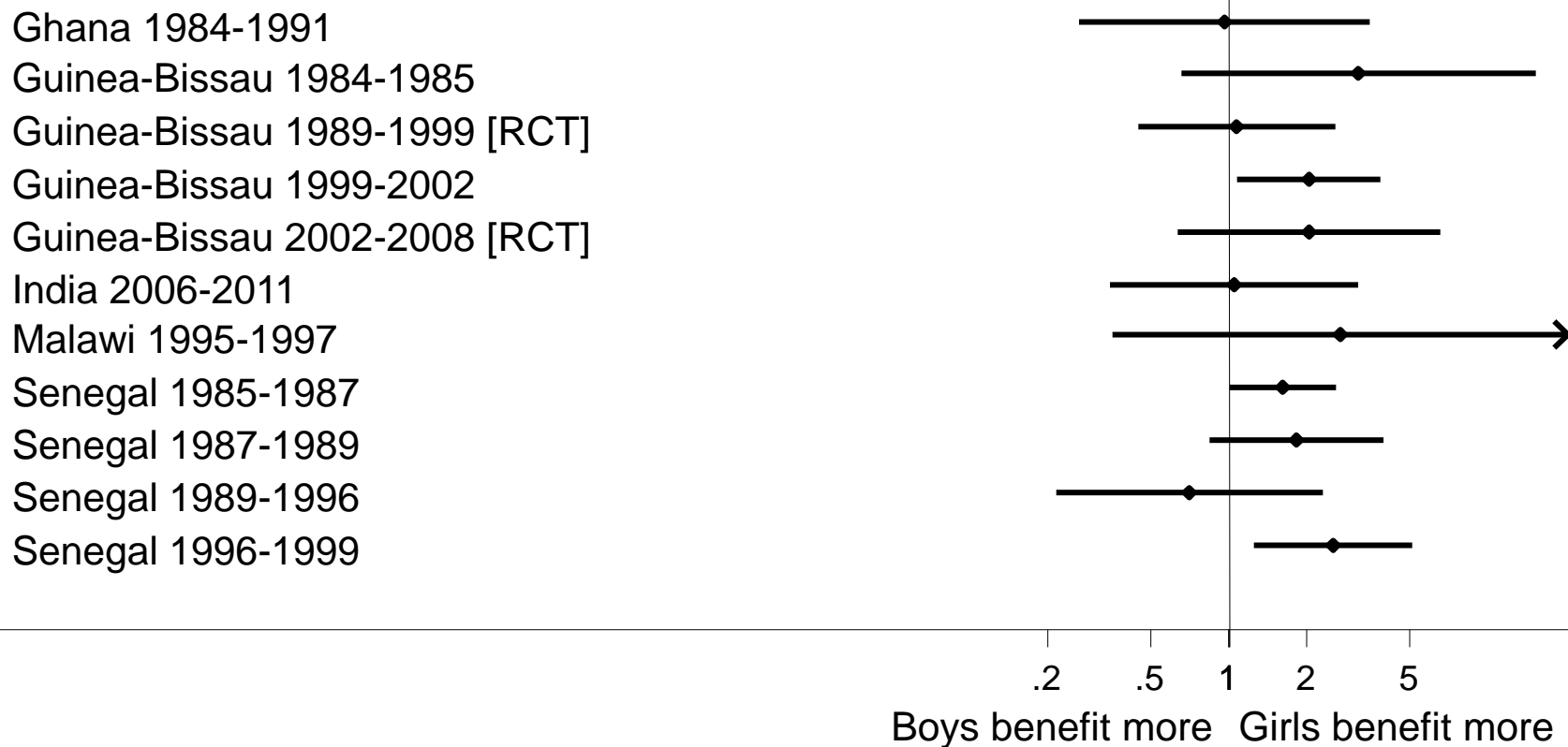
age up to 35 months



Vaccine beneficial Vaccine harmful

Is there a difference in the effect of measles vaccine by gender?

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



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)

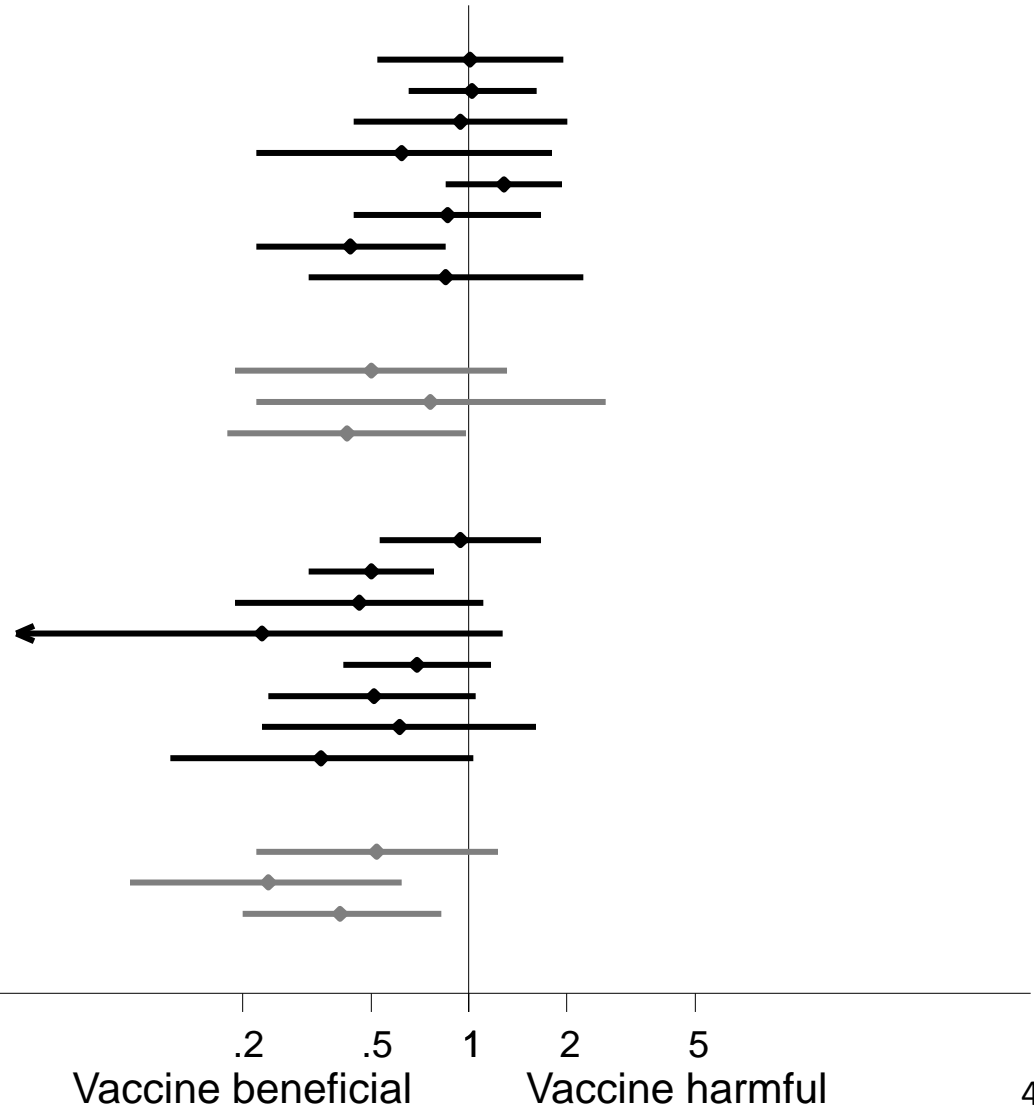
Ghana 1984-1991
Guinea-Bissau 1984-1985
India 2006-2011

Girls

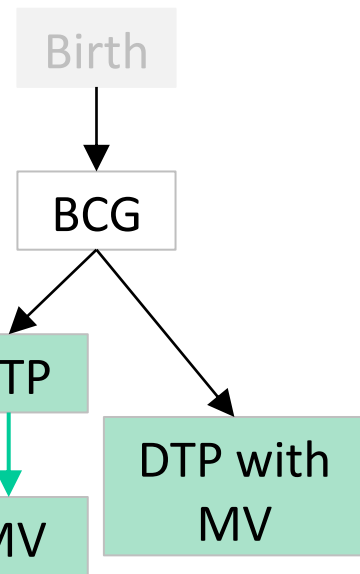
Guinea-Bissau 1989-1999 [RCT]
Guinea-Bissau 1999-2002
Guinea-Bissau 2002-2008 [RCT]
Malawi 1995-1997
Senegal 1985-1987
Senegal 1987-1989
Senegal 1989-1996
Senegal 1996-1999

Girls (Very high risk of bias)

Ghana 1984-1991
Guinea-Bissau 1984-1985
India 2006-2011



6. DTP AND MEASLES VACCINE GIVEN SIMULTANEOUSLY



Guinea-Bissau 1990-1996 & 1999-2002

Guinea-Bissau 1999-2002

India 1987-1989

Malawi 1995-1997

Senegal 1996-1999

*Observation
period*

age 6-17 months

age 9-24 months

age 12-60 months

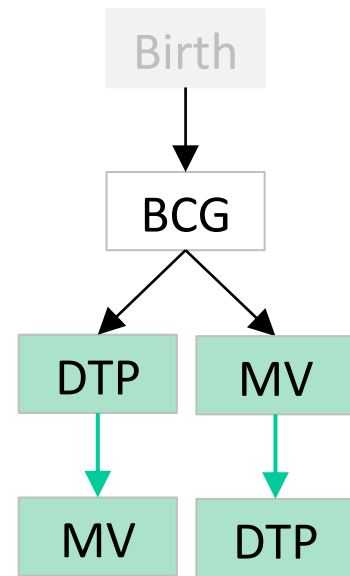
age 9-18 months

age 24 months

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Favours simultaneous Favours reference

7. DTP AFTER MEASLES VACCINE



*Observation
period*

Guinea-Bissau 1990-1996 & 1999-2002

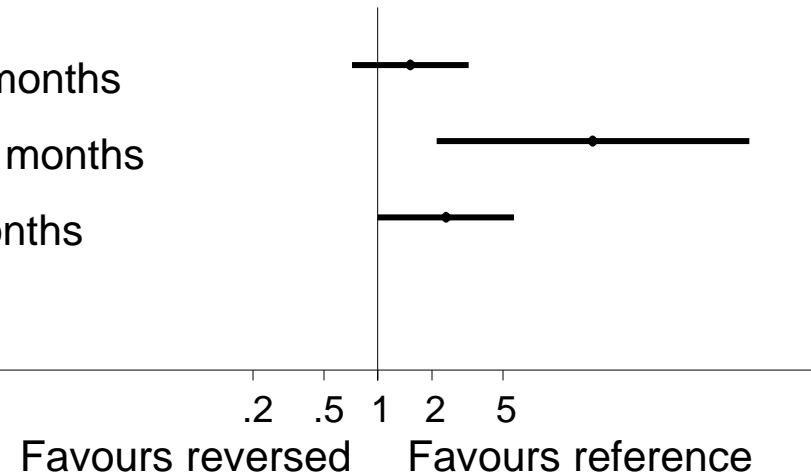
age 6-17 months

India 1987-1989

age 12-60 months

Senegal 1996-1999

age 24 months



Comment

RISK OF BIAS

Risk of bias is not the same as

Bias

- characteristics that raise risk of bias

Imprecision

- reflected in the confidence interval

Quality

- bias can occur in well-conducted studies

Reporting

- good methods may have been used but not well reported

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)

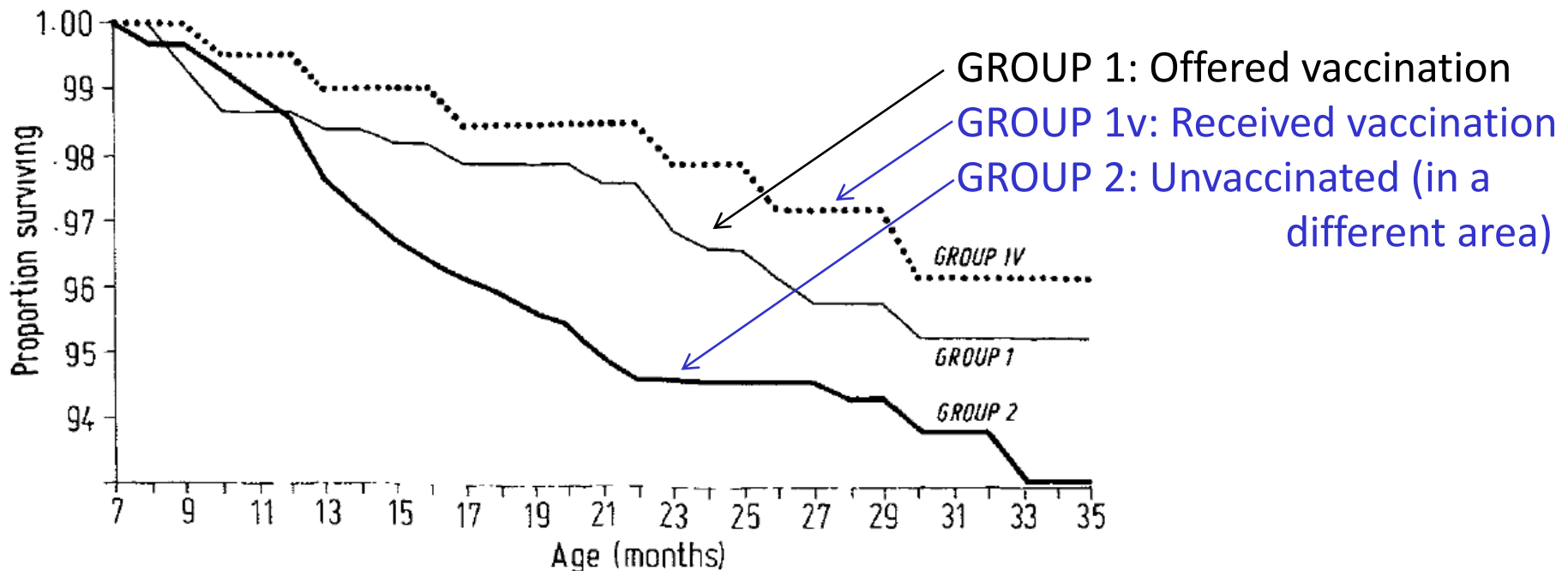


Fig. 2—Survival, by age, of the different groups.

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

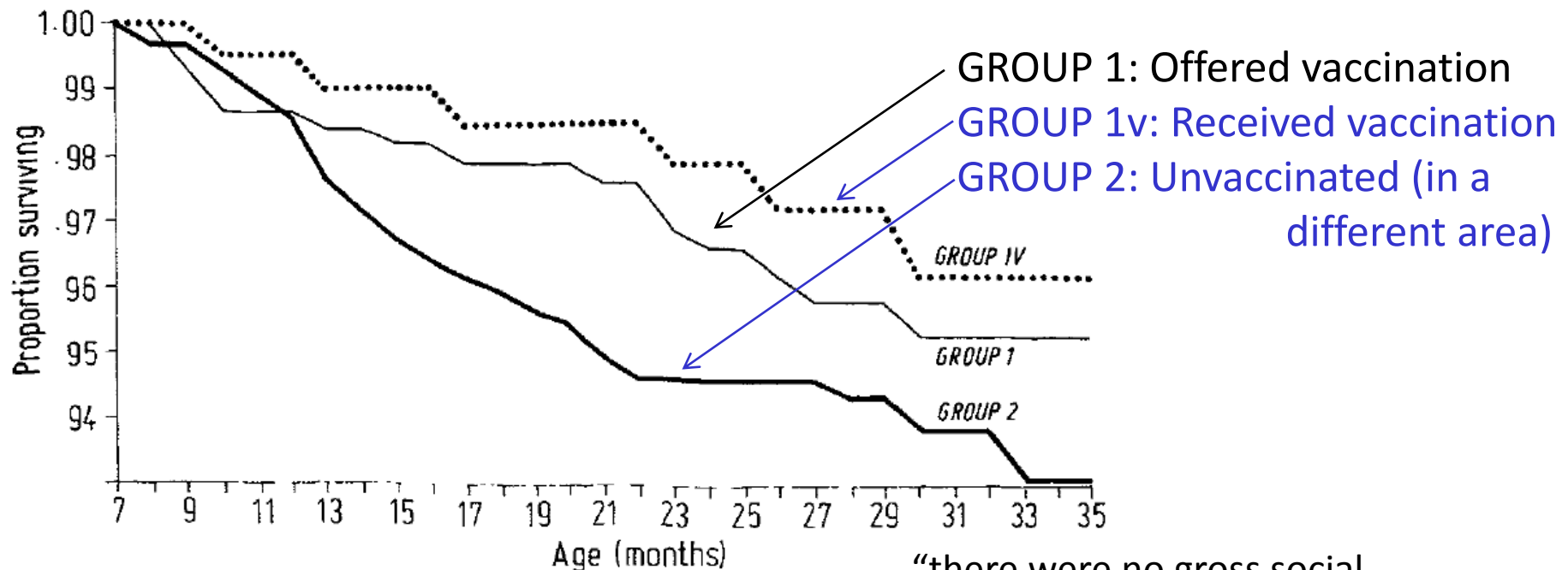


Fig. 2—Survival, by age, of the different groups.

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

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

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

Confounding: age

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

Time frames	Indicators	BCG exposed group		DTPp exposed group	
		Boy	Girl	Boy	Girl
0–5 Weeks	Child months	4878	4039	57	37
	Deaths	18	27	0	0
	Mortality rate	3.7	6.7	NA	NA
6 weeks–8 months	Child months	3273	2936	37 572	30 275
	Deaths	25	19	63	73
	Mortality rate				

- 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

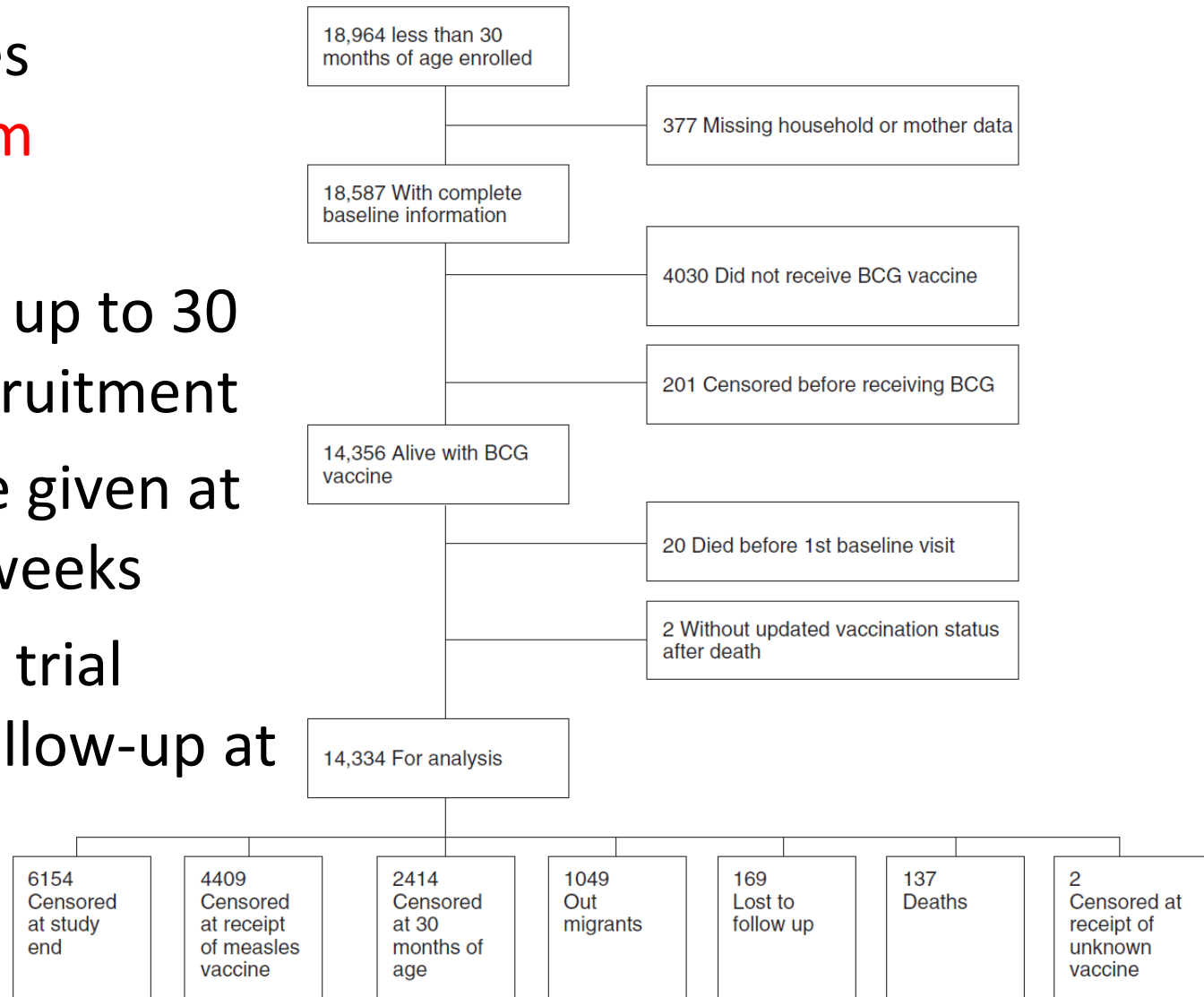


Figure 1 Flowchart detailing the selection of the study population

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.

Vaccine	Hazard ratio (confidence intervals)
BCG	0.18 (0.17–0.20)***
Polio1	0.16 (0.15–0.18)***
Polio2	0.15 (0.13–0.16)***
Polio3	0.15 (0.14–0.17)***
DPT1	0.15 (0.14–0.16)***
DPT 2	0.14 (0.13–0.16)***
DPT 3	0.15 (0.13–0.16)***
Measles	0.14 (0.13–0.16)***

***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