World Health Organization

Non-specific effects of BCG, DTP and MV vaccines on child mortality

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Scientific Advisory Group of Experts (SAGE)

and University of Melbourne

The University of Melbourne | Melbourne School of Population & Global Health

Non-specific Effects of Vaccines

Vaccines may have effects other than against targeted diseases

Several hypotheses have been proposed:

- BCG and measles vaccines may reduce, and DT_wP vaccines may increase all-cause mortality in some populations and,

- that these effects may reflect the order in which vaccines are given.

Controversial as evidence available remains inconclusive

Long history of audit and review

Initially prompted by the studies of Peter Aaby in Guinea Bissau

2000
WHO consultants conduct research site audit Guinea Bissau. No definitive conclusions, additional data needed.

2001
WHO's Global Advisory Committee on Vaccine Safety (GACVS) finds no association between DTP and increased mortality.

2003-10
Several workshops and reviews (Danish National Research Foundation, GACVS) find conclusive evidence unlikely to be obtained from observational studies

SAGE asked the WG to determine

- if the current evidence on non-specific effects of BCG, DTP and measles containing vaccines on **all-cause mortality** in children **under 5 years** of age is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation, and

- if so, to define the **path towards obtaining unequivocal evidence** on these issues that would support future robust, evidence-based adjustments in immunization policies, if warranted.

Working Group Membership

Terry Nolan (Australia, **SAGE**, Chair)
Christine Stabell Benn (Denmark)
Zulfiqar Bhutta (Pakistan/Canada, **SAGE**)
Mike Brennan (USA)
Stephen Evans (UK)
Paul Fine (UK)
Brad Gessner (France)
Dianne Griffin (USA)
Martin Mermikwu (Nigeria)
Kate O'Brien (USA, **SAGE**)
Walt Orenstein (USA)
Jaleela Sayed (Bahrain)
Dipika Sur (India)

WHO Commissioned Reviews

Immunologic human studies systematic overview

- **Andrew Pollard**, Rama Kandasamy, Merryn Voysey (all from Univ of Oxford)

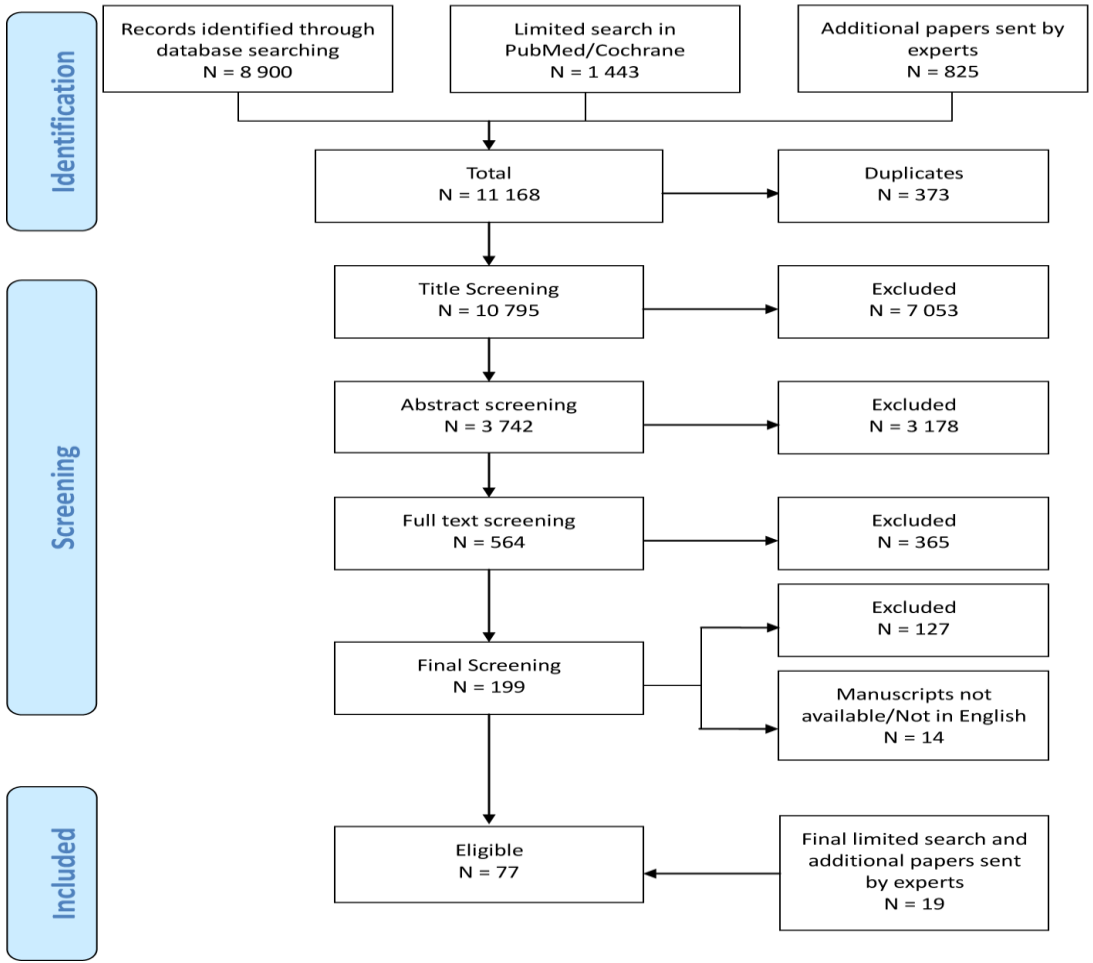
Epidemiologic studies systematic overview

- **Julian Higgins** (Univ Bristol); Art Reingold (School of Public Health, UC Berkeley); Carla Soares (Israel)

1. Systematic Review of Non-Specific Immunological Effects of Vaccination

Andrew J Pollard, Rama Kandasamy, Merryn Voysey

http://www.who.int/immunization/sage/meetings/2014/april/2_SAGE_April_NSE_Kandasamy_Immunology.pdf?ua=1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Additional papers sent by experts N = 825
Total N = 11 168
Duplicates N = 373
Title Screening N = 10 795
Excluded N = 7 053
Abstract screening N = 3 742
Excluded N = 3 178
Full text screening N = 564
Excluded N = 365
Final Screening N = 199
Excluded N = 127
Manuscripts not available/Not in English N = 14
Eligible N = 77
Final limited search and additional papers sent by experts N = 19

Overview

- 77 studies
- 3 to 2345 study participants involved across the studies.
- 48% of studies utilised BCG
- 68% were exclusively conducted in a paediatric population.
- The final time-point of outcome measurement was primarily performed (70%) between one and 12 months after vaccination

Methodological Attributes

- Not one study was rated as having low risk of bias for all criteria.
- NSIEs do not feature as a primary outcome parameter in any of the RCTs.
- Only 55% of the included studies actually reported data in a usable format for this review.
- A diverse array of immunological assays were utilised in conjunction with differences in measurement parameters and statistical analysis.

Methodological Attributes

- Consistently low level of evidence
- Lack of any high quality (low risk of bias) randomised controlled trial with focussed primary endpoints designed around non-specific immunological outcomes.
- Datasets were not reported according to effect on sex

Confounder		**N**
Co-administration with Vitamin A?		
	Yes	3
	No/Not reported	74
Presence of attribute that may affect response?		
	Yes	22
	No	55

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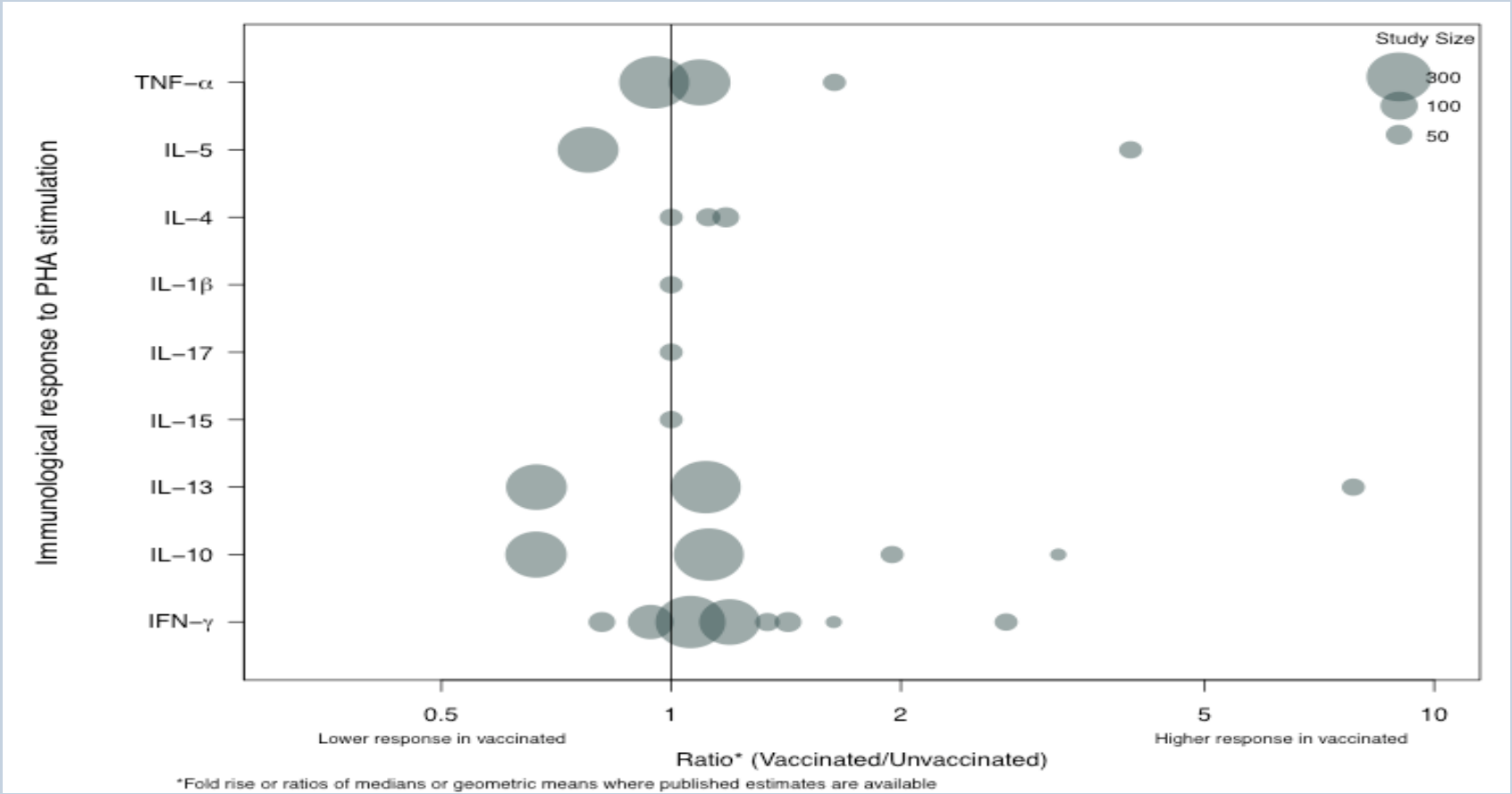
PHA stimulated responses to BCG vaccination



Conclusions

- Results inconclusive

- Heterogeneous data and inadequate high quality evidence to describe the non-specific immunological effects of current childhood vaccine programmes.
    - Data available not presented in a suitable fashion for particular analyses e.g. sex and Vitamin A

- Some evidence that in some study designs, with some vaccines, administered in some settings, where samples are taken at some time-points, and some in vitro assays are undertaken that NSIE may be detected in response to some in vitro stimuli but difficult to identify consistent findings

The Future

- Technology now makes it possible to make detailed, statistically robust, analysis of multiple parameters from small samples
  - Flow cytometry
  - Transcriptomics
  - Systems immunology
- Need high quality data on routine schedules with immunological endpoints
  - feasible and necessary to advance understanding of biology
- To address big picture questions need careful trial design and consensus about immunological endpoints (what, when)
  - Currently questionable feasibility but will be possible in the future

2. Systematic Review of Epidemiological Evidence

Julian Higgins, Karla Soares-Weiser, Arthur Reingold

http://www.who.int/immunization/sage/meetings/2014/april/4_SAGE_April_NSE_Higgins_Epidemiology.pdf?ua=1

Epidemiologic studies: 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. mort… causes other th… conditions that the vacc… designed to prevent …

  ii. on **all-cause mortality** in children under five years of age.

- to appraise the evidence critically

Criteria for inclusion (PICO)

Participants: children up to 5 years

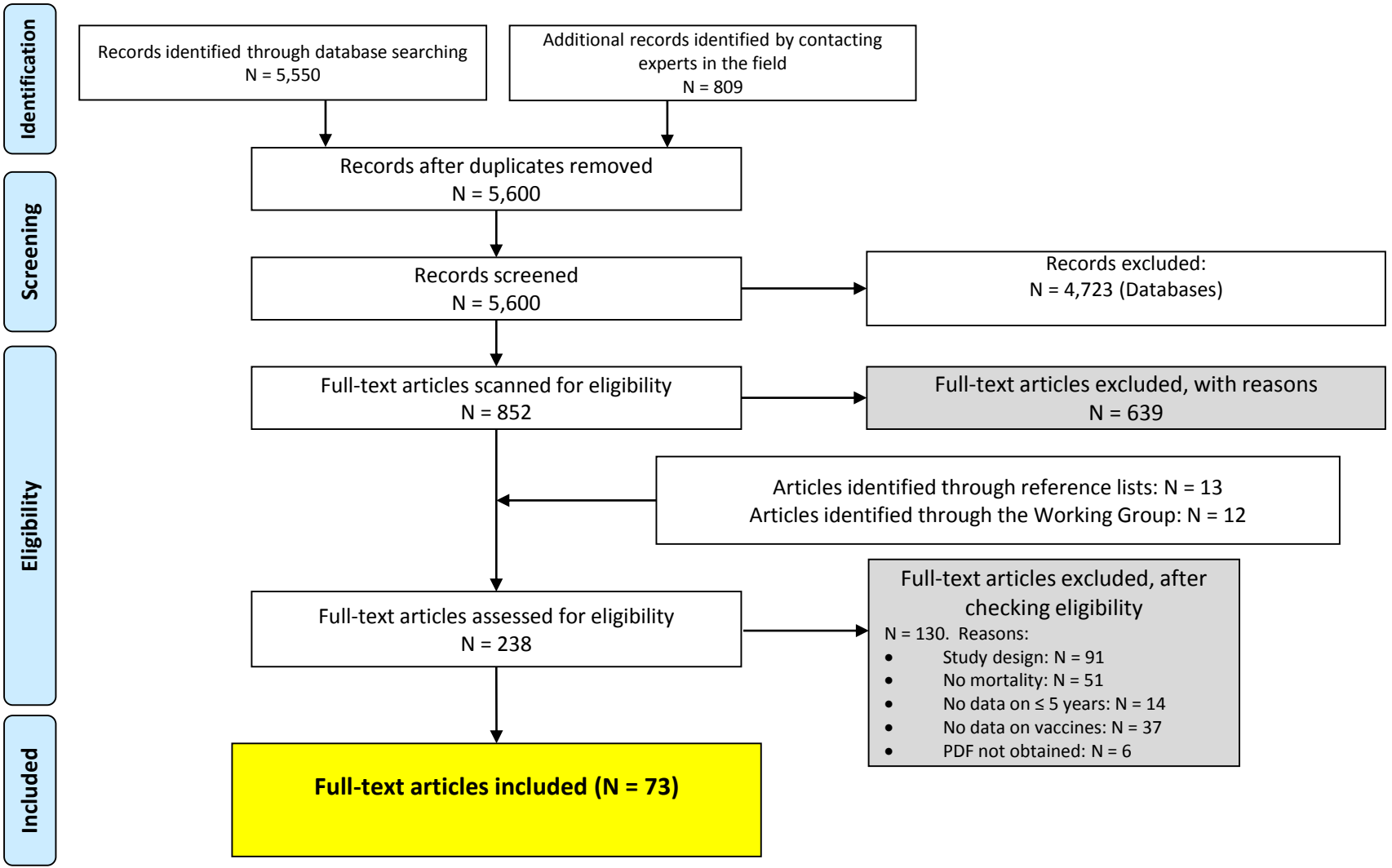
Intervention: vaccination (BCG, DTP or measles)

Comparators: no vaccination (BCG, DTP or measles respectively) or simultaneous administration of another vaccine

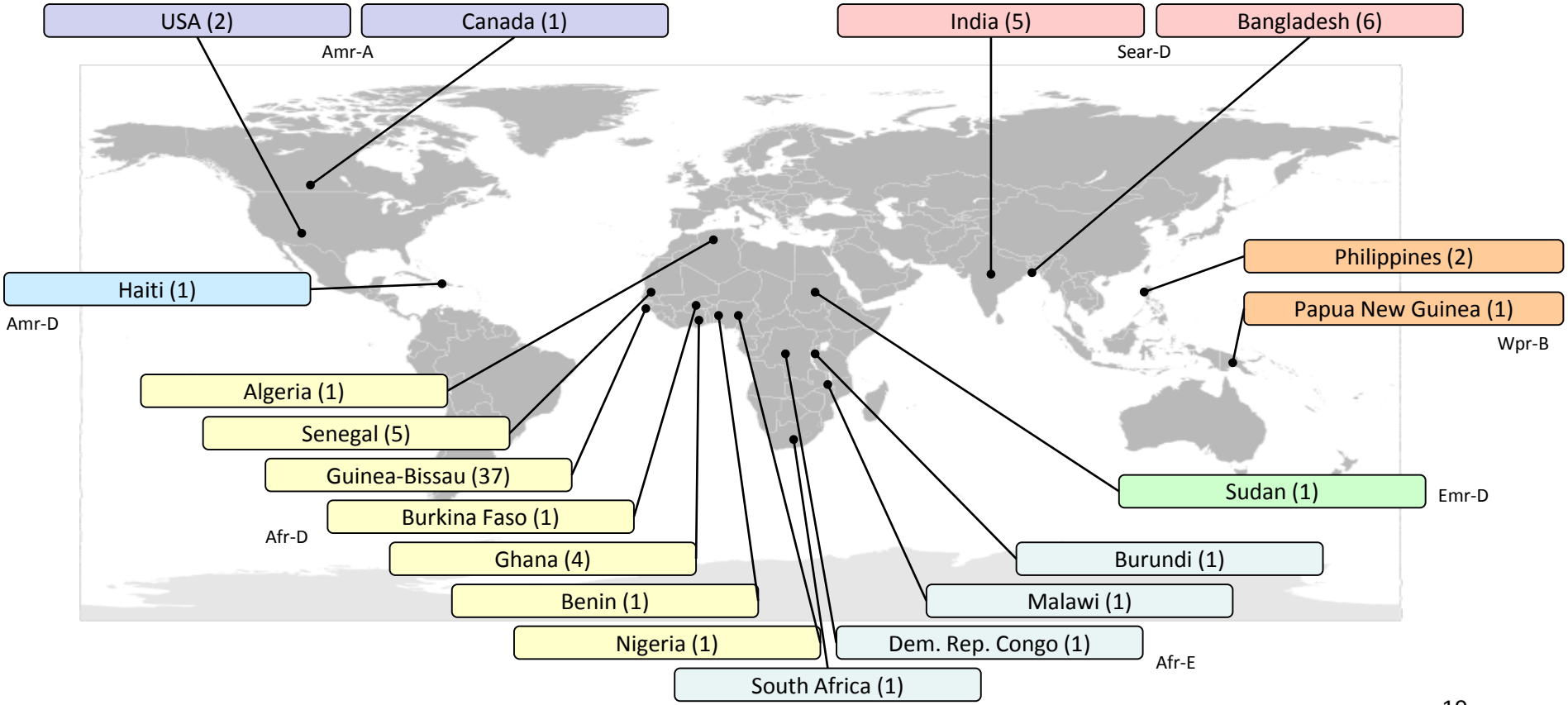
Outcome: mortality

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
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
Records excluded:
N = 4,723 (Databases)
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)

Locations of studies (73 articles)



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

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

Confounding: frailty and age

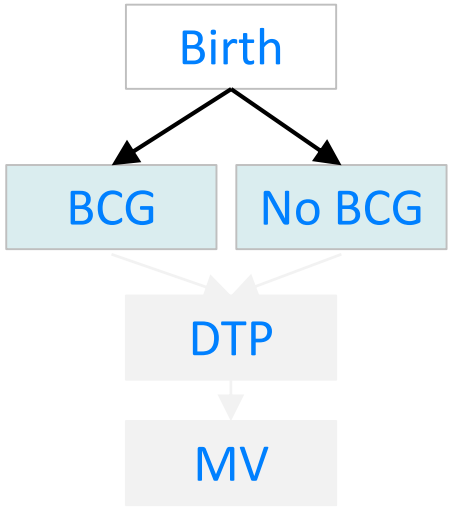
- **Frail children** believed less likely to be vaccinated
  - So those vaccinated inherently less likely to die
  - even if vaccine has no effect
  - Naive comparison of vaccinated *vs* not vaccinated likely to be **biased in favour of vaccine**
  - Lack of comprehensive adjustment for frailty
- **Confounding by age**
  - e.g. India 2006-2011 (excluded from analysis)
  - Can compute unadjusted comparison of DTP vs no DTP (i.e. BCG only), but children are at very different ages
  - **Confounding depends on mortality patterns over time**

Misclassification bias in 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)

Other biases

- **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
- Bias arising from **selection** of participants long after vaccines were given
  - A randomized trial would start follow-up at intervention
- **Co-interventions**
  - Vaccines are highly correlated so effect for BCG includes effects of DTP and measles vaccine



Results

1. BCG vs NO BCG

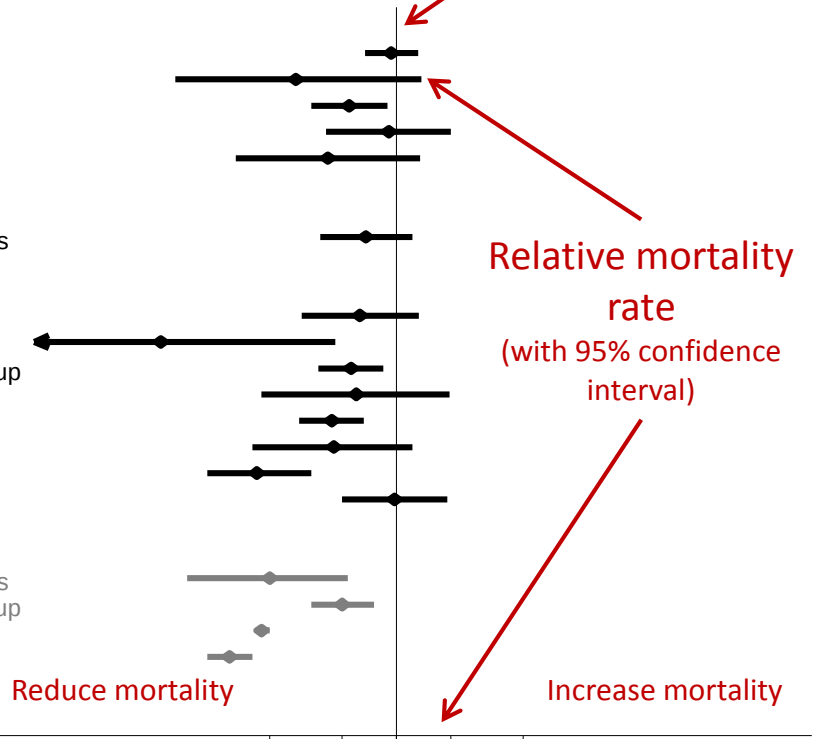
BCG and all-cause mortality

Studies

Birth cohort	*Age at first dose*	*Observation period*
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

Results

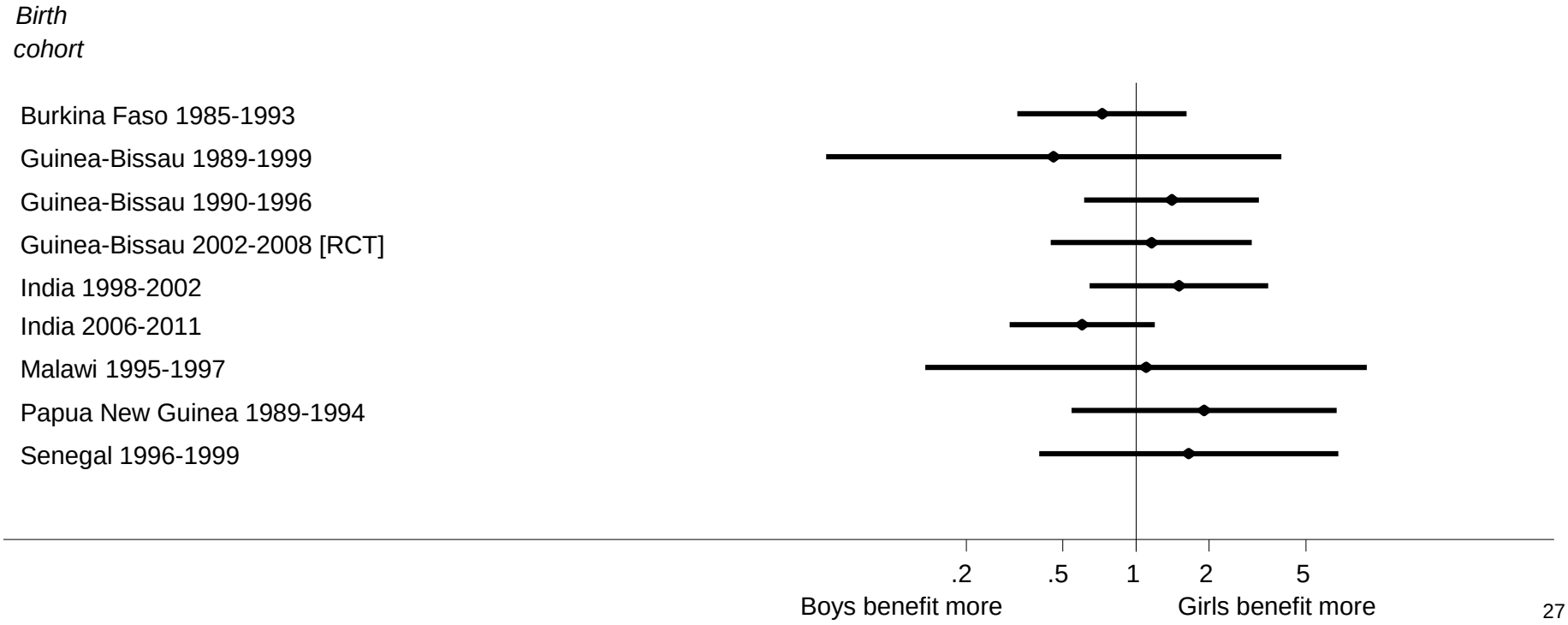
Relative mortality rate (with 95% confidence interval)

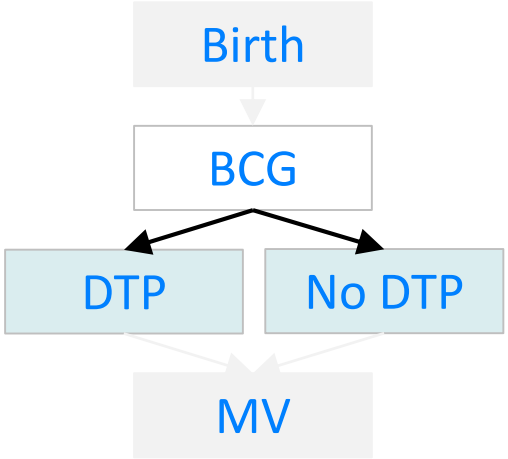


Further details

Is there a difference in the effect of BCG by gender?

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





Results

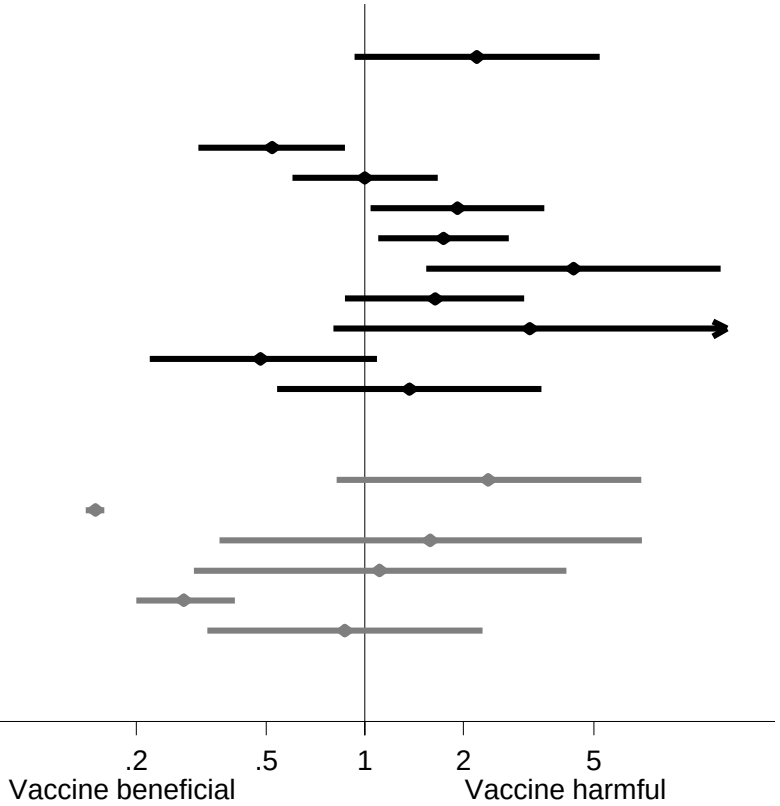
2. DTP vs NO DTP

DTP and all-cause mortality

- 16 independent birth cohorts of children, all observational (i.e. no RCTs)
  - 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 approximately 28,000 children
  - range 132 to 9,085
- Follow-up ranges from 6 to 36 months of age

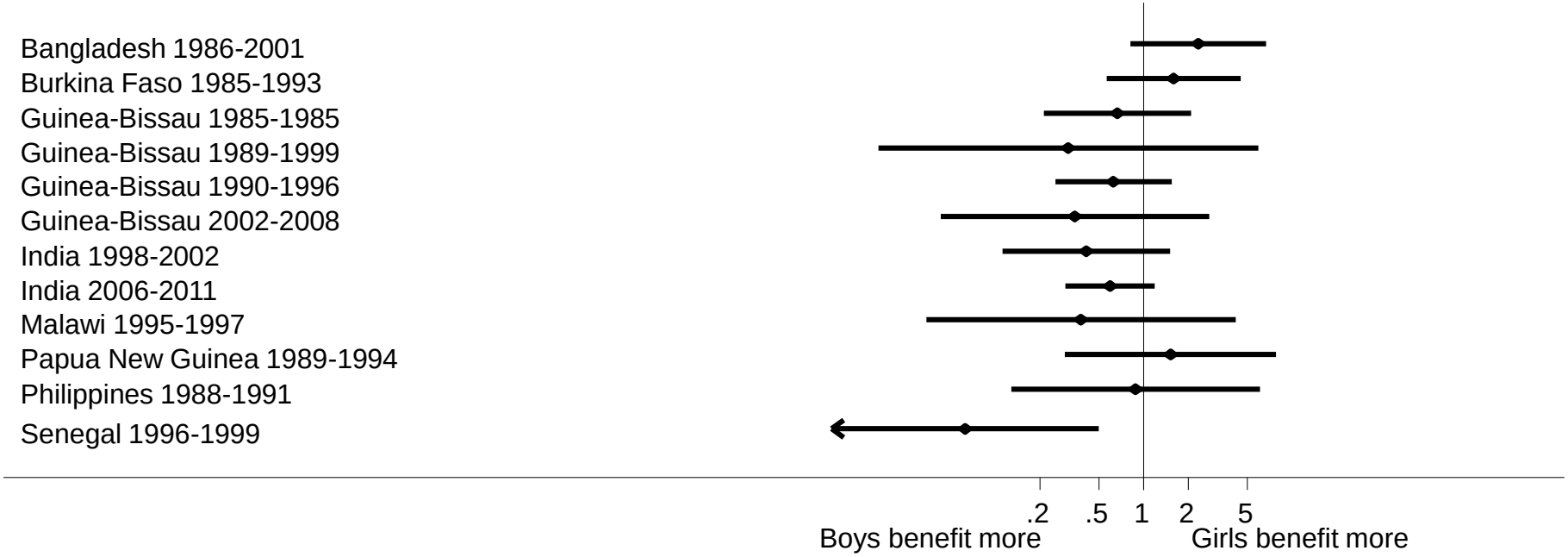
DTP and all-cause mortality

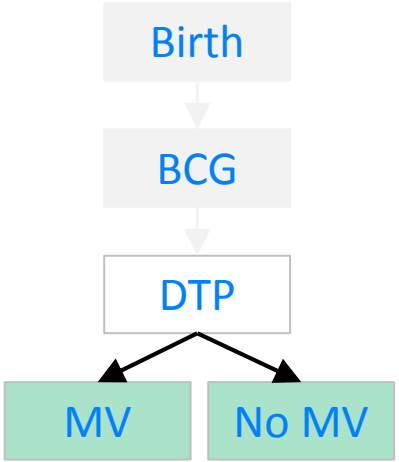
	Age at first dose	*Observation period*
1. Case-control studies		
Benin 1983-1987	NR	age 4-36 months
2. Cohort studies		
Bangladesh 1986-2001	Median 2.8 months	1.5-9 mo
Burkina Faso 1985-1993	Mean 6.3 months	6 months follow-up
Guinea-Bissau 1984-1985	NR (3-8 months)	age 8 months
Guinea-Bissau 1990-1996	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 gender?

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





Results

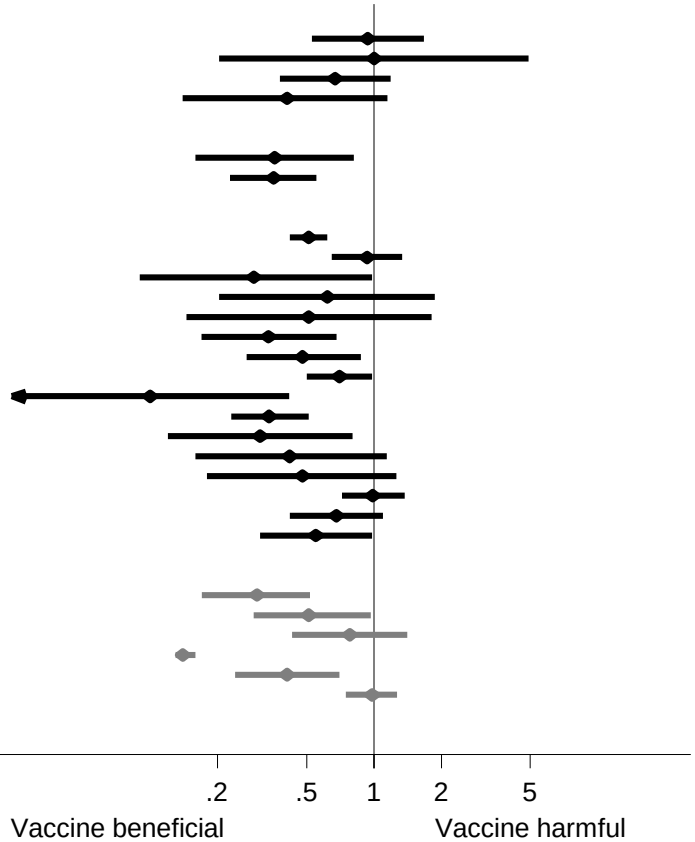
5. MEASLES VACCINE vs NO MEASLES VACCINE

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

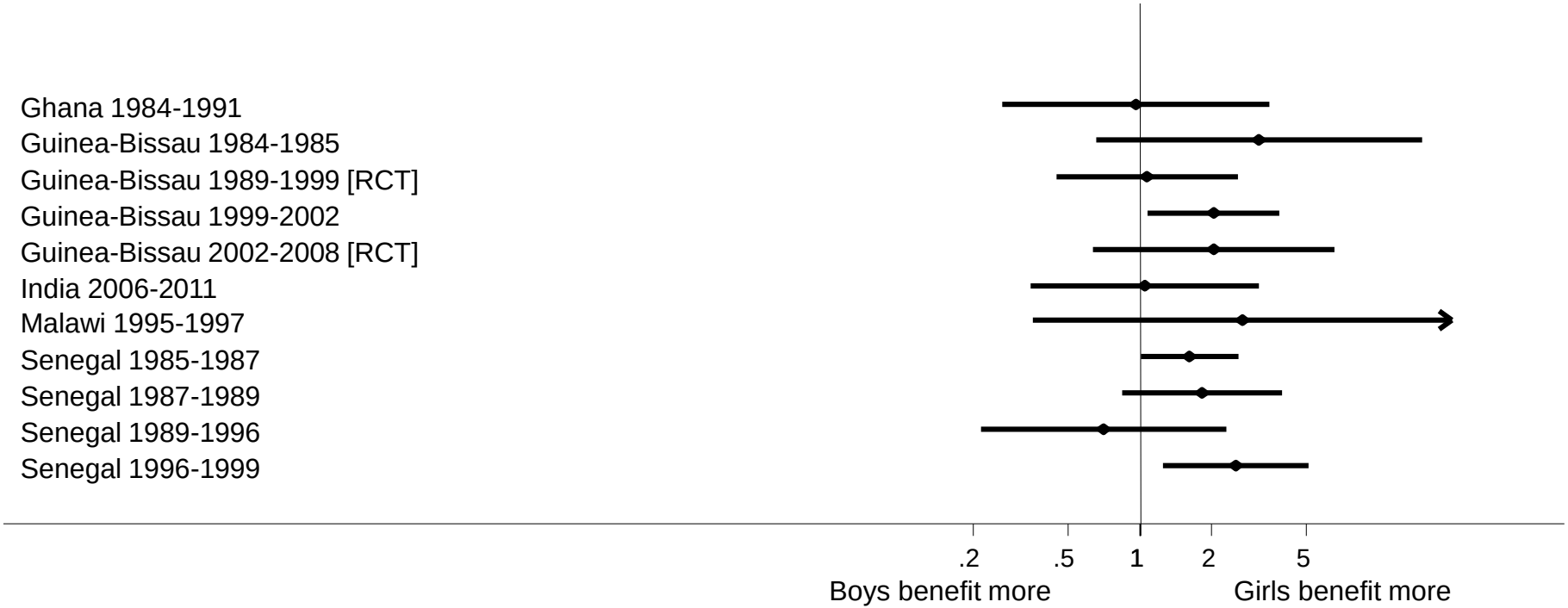
Measles vaccine and all-cause mortality

	Age at first dose	*Observation period*
1. Randomized trials		
Guinea-Bissau 1989-1999	6 months	age 6-9 months
Guinea-Bissau 1989-1999	6 months	age 6-9 months
Guinea-Bissau 2002-2008	4.5 months	age 4.5-9 months
Nigeria c.1961	6-24 months	6-20 months follow-up
2. Case-control studies		
Benin 1983-1987	NR	age 4-36 months
India 1991-1998	NR (before 12 months)	age 12-60 months
3. Cohort studies		
Bangladesh 1977-1985	NR (from 9 months)	age 9-60 months
Bangladesh 1986-2001	NR (from 9 months)	age 9-60 months
DR Congo 1973-1975	Mean 8.8 months	age 7-21 months
Guinea-Bissau 1978-1983	NR (6-35 months)	13 months follow-up
Guinea-Bissau 1978-1983	NR (6-35 months)	12 months follow-up
Guinea-Bissau 1984-1985	Median 11.1; 15 months	age 17.5 months or more
Guinea-Bissau 1990-1996	Median 10.6 months	age 7-19 months
Guinea-Bissau 1999-2002	NR (by 12 mo in 55%)	age 9-24 months
Haiti 1981-1982	Median 9 months	age 9-39 months
India 1986-1991	NR (at 6-8 [8-11] mo in 85% [15%])	age 12-60 months
India 1987-1989	Median 9.4 months	age 12-60 months
Malawi 1995-1997	Median 10.8 months	age 9-18 months
Papua New Guinea 1989-1994	NR (by 12 months in 74%)	age 6-11 months
Senegal 1985-1987	Mean 15.8 months	age 9-24 months
Senegal 1987-1989	Mean 11.6 months	age 9-24 months
Senegal 1996-1999	NR (by 12 [24] mo in 9% [20%])	age 24 months
Excluded (Very high risk of bias)		
Burundi 1984-1988	NR (at 9-11 months in 59%)	6 months follow-up
Ghana 1984-1991	NR (6-35 months)	4 months follow-up
Ghana 1994-1999	Median 9.1 months	age 9-11 months
Ghana 1998-2004	NR (by 12 [24] mo in 5% [64%])	age 60 months
India 2006-2011	Mean 9.4 months	age 9-15 months
Senegal 1989-1996	Median 9.7 months	age up to 24 months



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

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



WG CONCLUSIONS

BCG: Data from randomized studies and observational studies are suggestive of a beneficial effect of BCG in reducing all-cause mortality within the first 6-12 months of life in countries with high childhood mortality. There is no evidence of a deleterious effect of BCG on all-cause mortality.

DTP: Mortality data related to DTP only from observational studies, and only when given in combination with other vaccines. These studies had significant methodological limitations. Because of these limitations, the overall effects of DTP vaccines under different epidemiological conditions remain unclear, in particular under circumstances where the target diseases have been reduced to very low levels. The Working Group concluded that the evidence does not support a change in policy for DTP.

MV: There was evidence that measles vaccine reduced the risk of all-cause mortality independent of its effect on confirmed measles mortality (an effect that appears to be stronger in girls than boys).

Working Group conclusions 2

Sub-questions

Each 3–5 studies, all observational, all judged at high risk of bias:

Results suggest …

DTP+BCG vs BCG before DTP

… simultaneous administration may be associated with lower mortality (one study had 95% CIs that excluded no difference).

DTP before BCG compared with BCG before DTP

… no clear differences are apparent.

Co-administration of DTP and measles vaccine

… simultaneous administration may be associated with higher mortality.

Order of DTP and measles vaccine affect all-cause mortality:

… simultaneous administration may be associated with higher mortality**.**

Research Priorities
RANDOMIZED CONTROLLED TRIALS

- Need more **high quality randomised controlled trials**, wherever feasible.There are ethical and methodologic challenges.

- **RCTs of any DTP versus no DTP**, even with narrow time windows for outcome evaluation, and even in settings where endemic pertussis is low, may not be able to be conducted. The widespread use of pentavalent vaccine further complicates examination of NSEV.

- If RCTs were to be conducted, it may be appropriate to **aim for several large studies across a number of countries using the same protocol**.

- **RCTs of EPI schedule variants designed to minimise post-vaccination DTP person-time exposure before MCV vaccine** could be considered.

Research Agenda
OBSERVATIONAL STUDIES

- Further observational studies with inherent and substantial risk of bias would be **unlikely to provide conclusive evidence** about putative non-specific mortality effects.

- If observational studies are to be contemplated, their design and analysis should mimic what would be undertaken if it were to be a randomised controlled trial.

- Future studies should draw upon a **broad investigator pool and from a wide range of geographic locations and burden of disease settings**.

- The development of **standardized protocols** for both RCTs and observational studies of mortality effects, that address now well-recognised bias issues, should be considered.

Broad Research Agenda

- Any future studies should be designed and powered to **examine gender effects**. In addition, **immunological analysis should become a specific objective** of future studies based on formulating specific research questions that the study could answer.

- This could include assays that cover a breadth of immunological responses including antibodies, T-cell responses, cytokines, etc. However, the Working Group **argued against a shotgun approach** given that it would make interpretation of occasionally significant results among hundreds of comparisons difficult.

- **Systems biology approaches** may be particularly informative in providing a profile of host immune response.

SAGE determinations – April 2014

- Accepted WG conclusions and recommendations
- No change to existing policy for BCG, DTP and MV. Emphasized importance of strengthening delivery of all in EPI.
- Referred research agenda next steps to WHO's Immunization and Vaccine Related Implementation Research Advisory Committee (IVIR-AC)

http://www.who.int/wer/2014/wer8921.pdf?ua=1

Acknowledgements

- Oxford University: Andrew Pollard, Karlijn de Nie, Rama Kandasamy, Merryn Voysey, Fiona McQuaid, Rebecca Ryan, Olivia Orr, Ulrike Uhlig, Daniel O'Connor
- Julian Higgins, Professor of Evidence Synthesis, University of Bristol; Karla Soares-Weiser, Enhance Reviews Ltd; Art Reingold, Professor of Epidemiology, School of Public Health, UC Berkeley
- Ana Maria Henao Restrepo, Ximena Riveros Balta, WHO SAGE secretariat, Library staff.