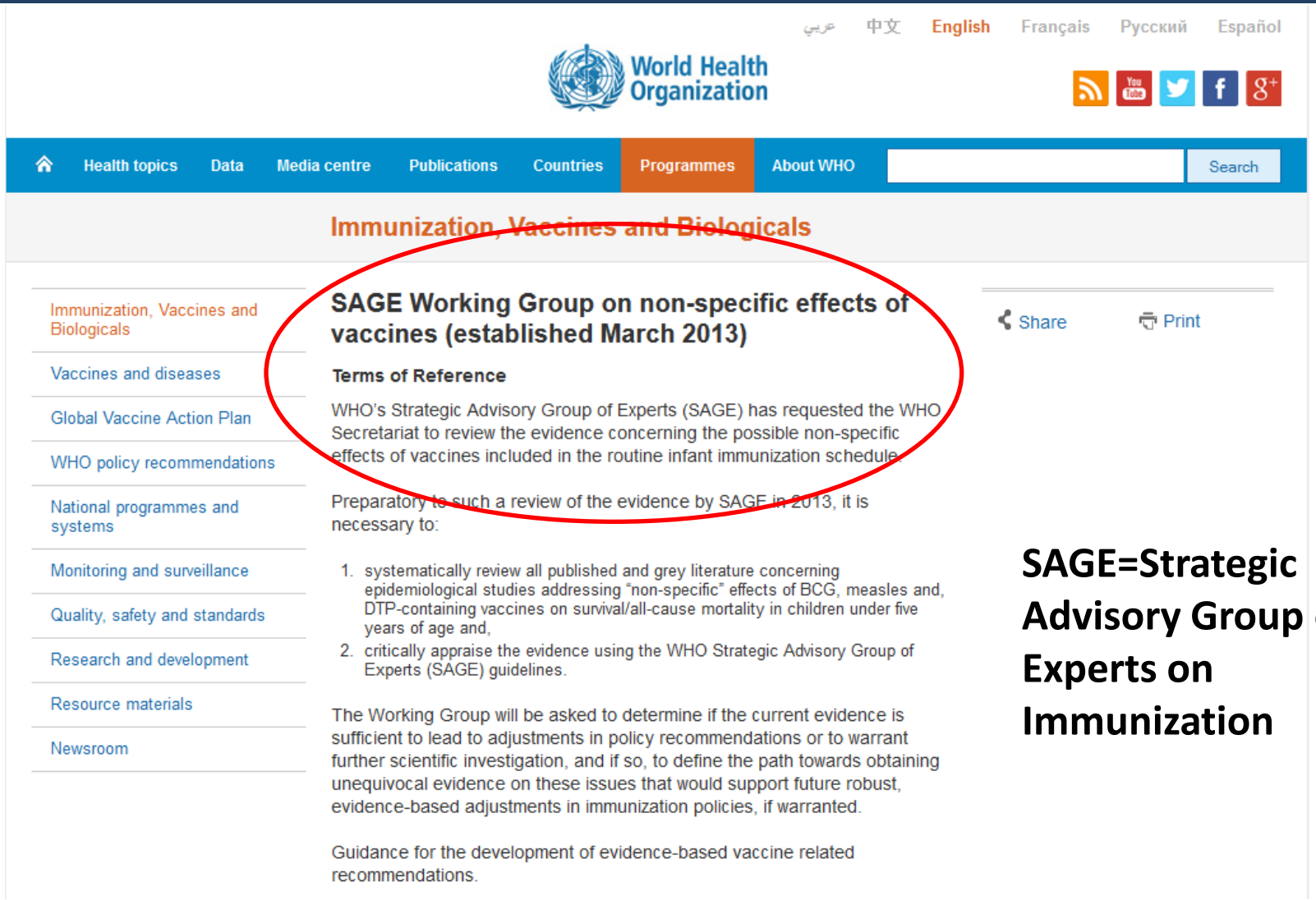
The WHO review of the possible non-specific effects of diphtheria-tetanus-pertussis (DTP)



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SAGE Working Group on non-specific effects of vaccines (established March 2013)

Terms of Reference

WHO's Strategic Advisory Group of Experts (SAGE) has requested the WHO Secretariat to review the evidence concerning the possible non-specific effects of vaccines included in the routine infant immunization schedule.

Preparatory to such a review of the evidence by SAGE in 2013, it is necessary to:

1. systematically review all published and grey literature concerning epidemiological studies addressing "non-specific" effects of BCG, measles and, DTP-containing vaccines on survival/all-cause mortality in children under five years of age and,
2. critically appraise the evidence using the WHO Strategic Advisory Group of Experts (SAGE) guidelines.

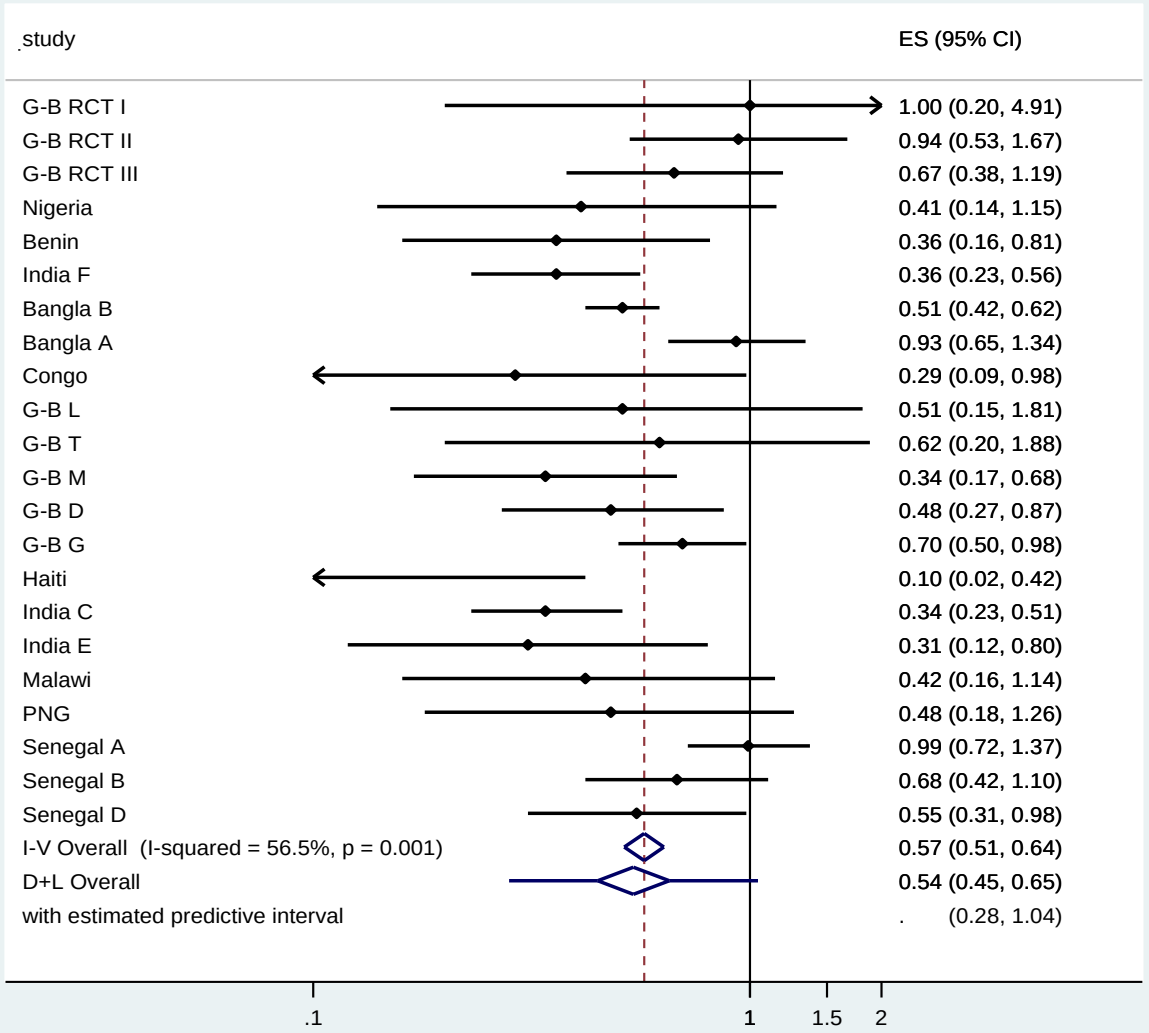
The Working Group will be asked to determine if the current evidence is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation, and if so, to define the path towards obtaining unequivocal evidence on these issues that would support future robust, evidence-based adjustments in immunization policies, if warranted.

Guidance for the development of evidence-based vaccine related recommendations.

Share Print

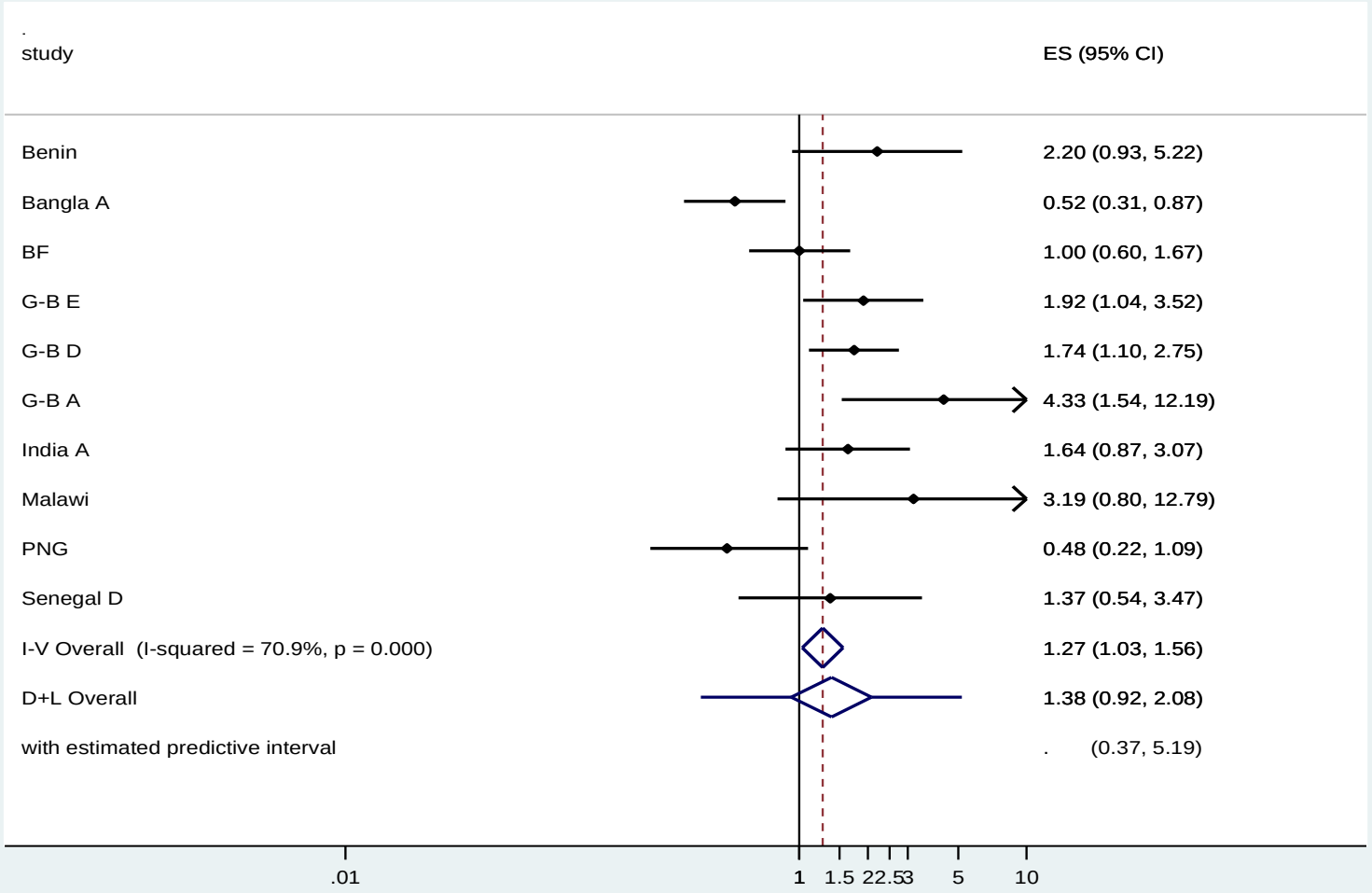
SAGE=Strategic Advisory Group of Experts on Immunization

WHO-SAGE Review of Measles vaccine (MV)



MV reduced mortality by 46% (35-55%); effect stronger for girls
BCG reduced mortality by 47% (28-60%)

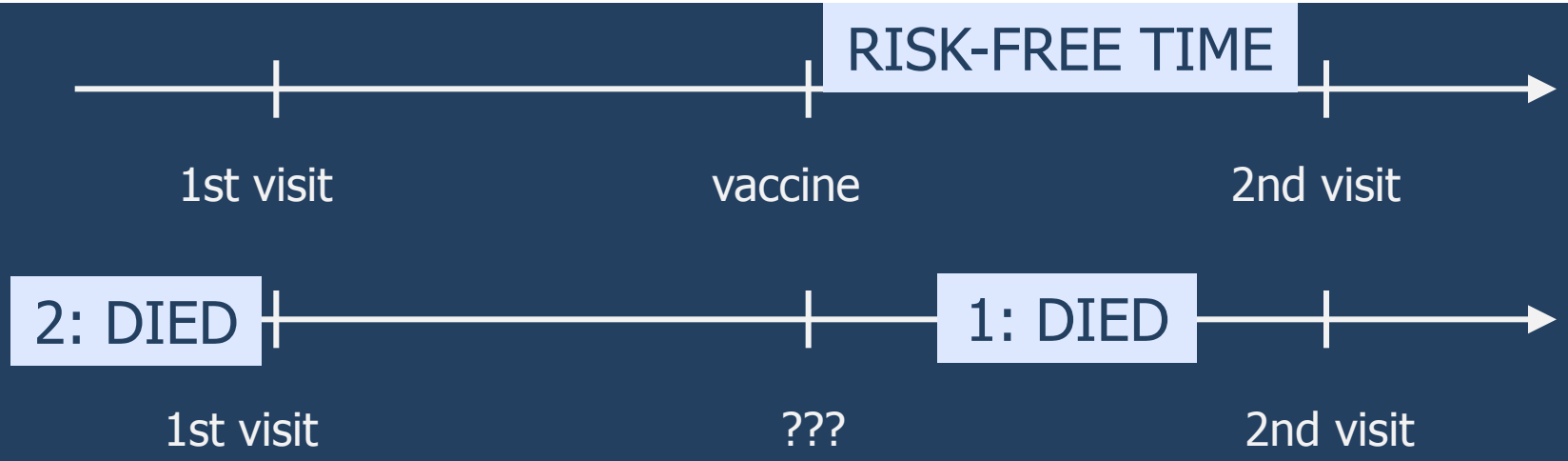
SAGE-review: DTP associated with 38% higher mortality



SAGE review 2014: The findings were inconsistent, with a majority of the studies indicating a detrimental effect of DTP, and two studies indicating a beneficial effect. Difficult to separate the effects of OPV and DTP

WHO: No DTP problem or sex-differential effect (WER 2004)

WHO-sponsored studies had survival bias (Fine&Smith TMIH 2007)



1:Retrospective updating - dead children have no vaccine information

2:Children with no vaccine information assumed to be unvaccinated

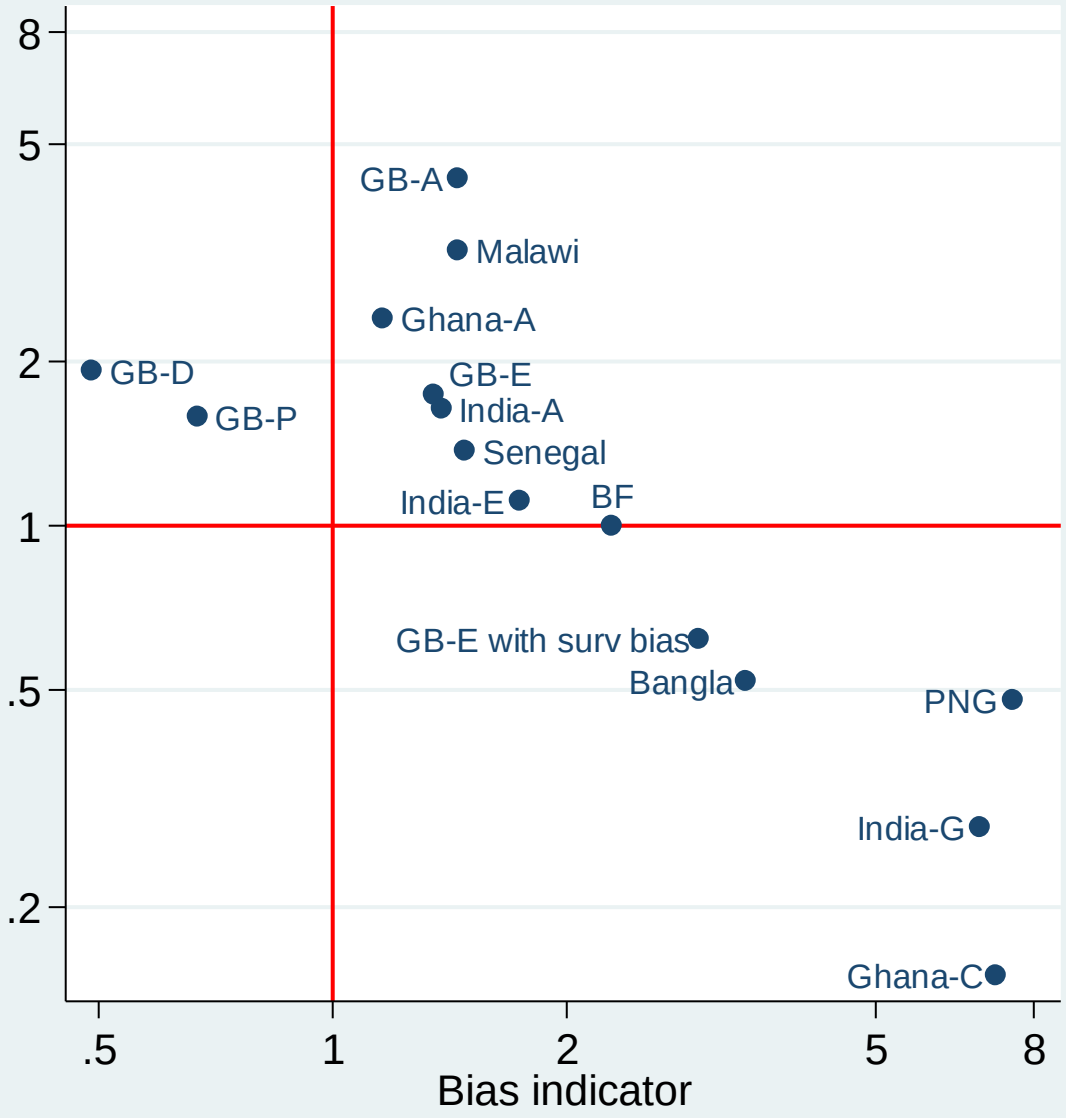
⇒ **Time after vaccination to vaccinated group; no-information deaths to unvaccinated group => too high mortality rate in "unvaccinated" and too low in "vaccinated" children**

⇒ **Hazard ratio for unvaccinated versus vaccinated children is an indicator of likely bias => "Bias indicator"**

WHO-SAGE-review: Studies of DTP

Bias indicator <2.0
DTP had 100% Higher mortality

Bias indicator =>2.0
DTP has 61% lower mortality



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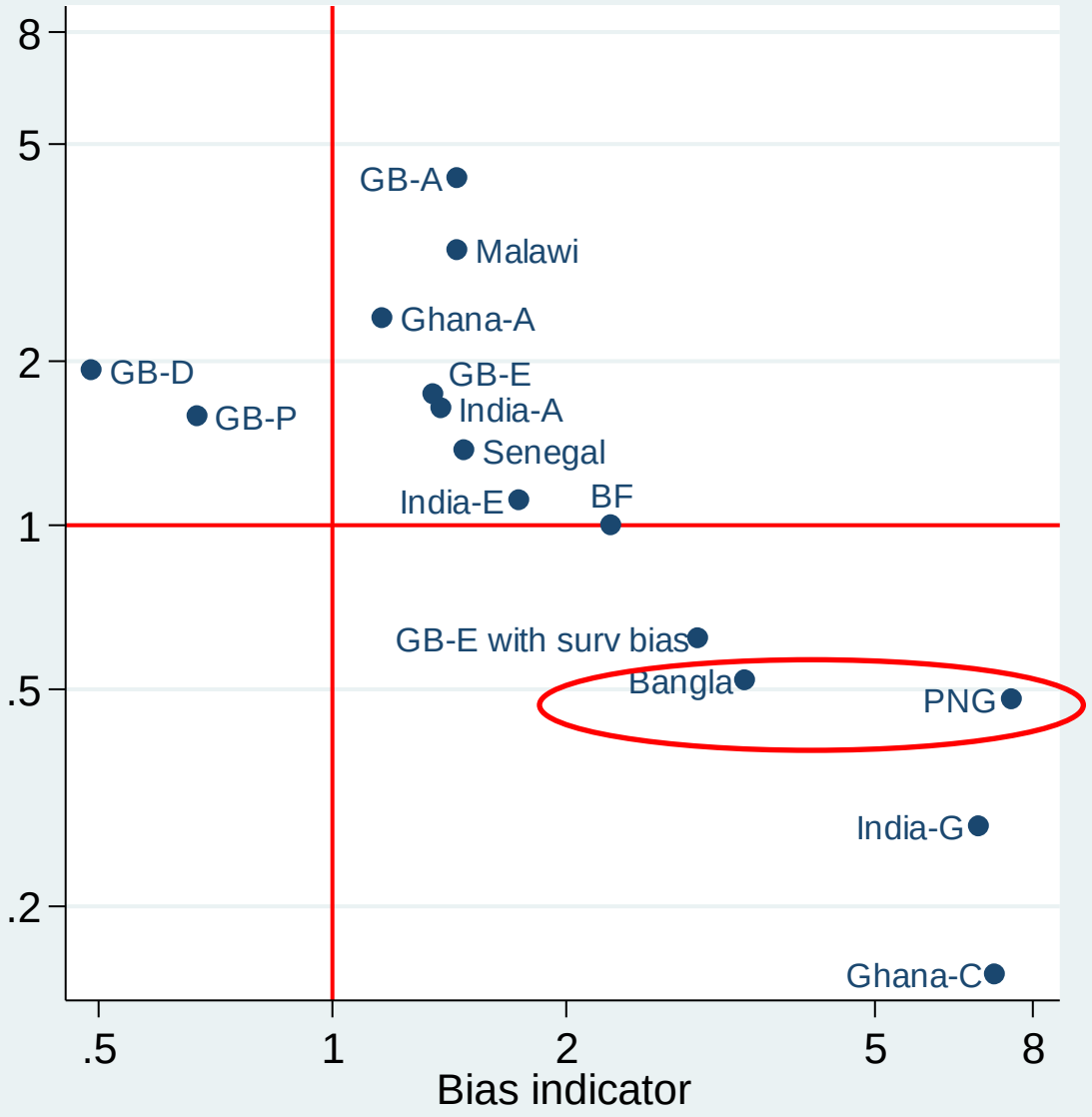

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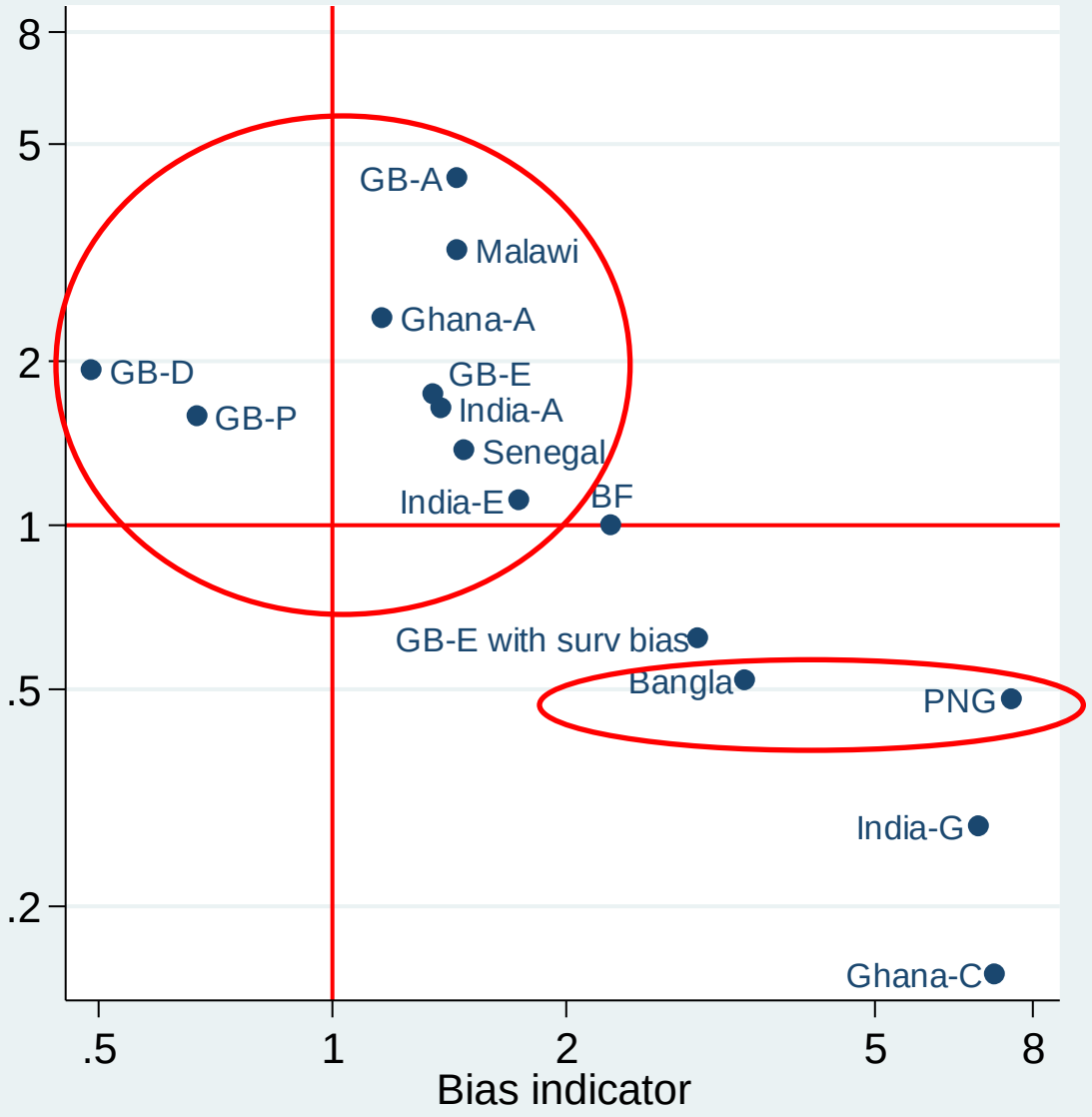
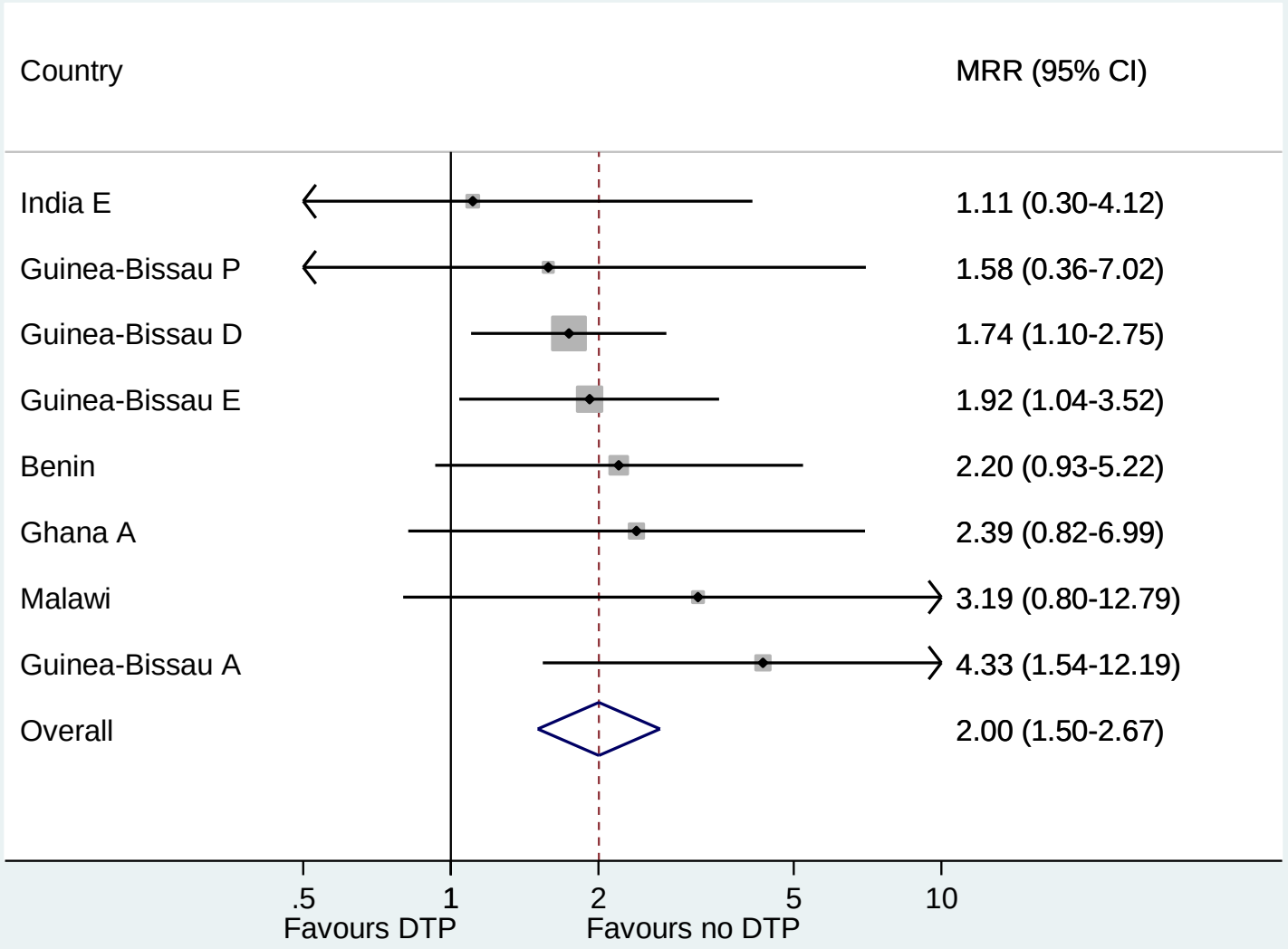
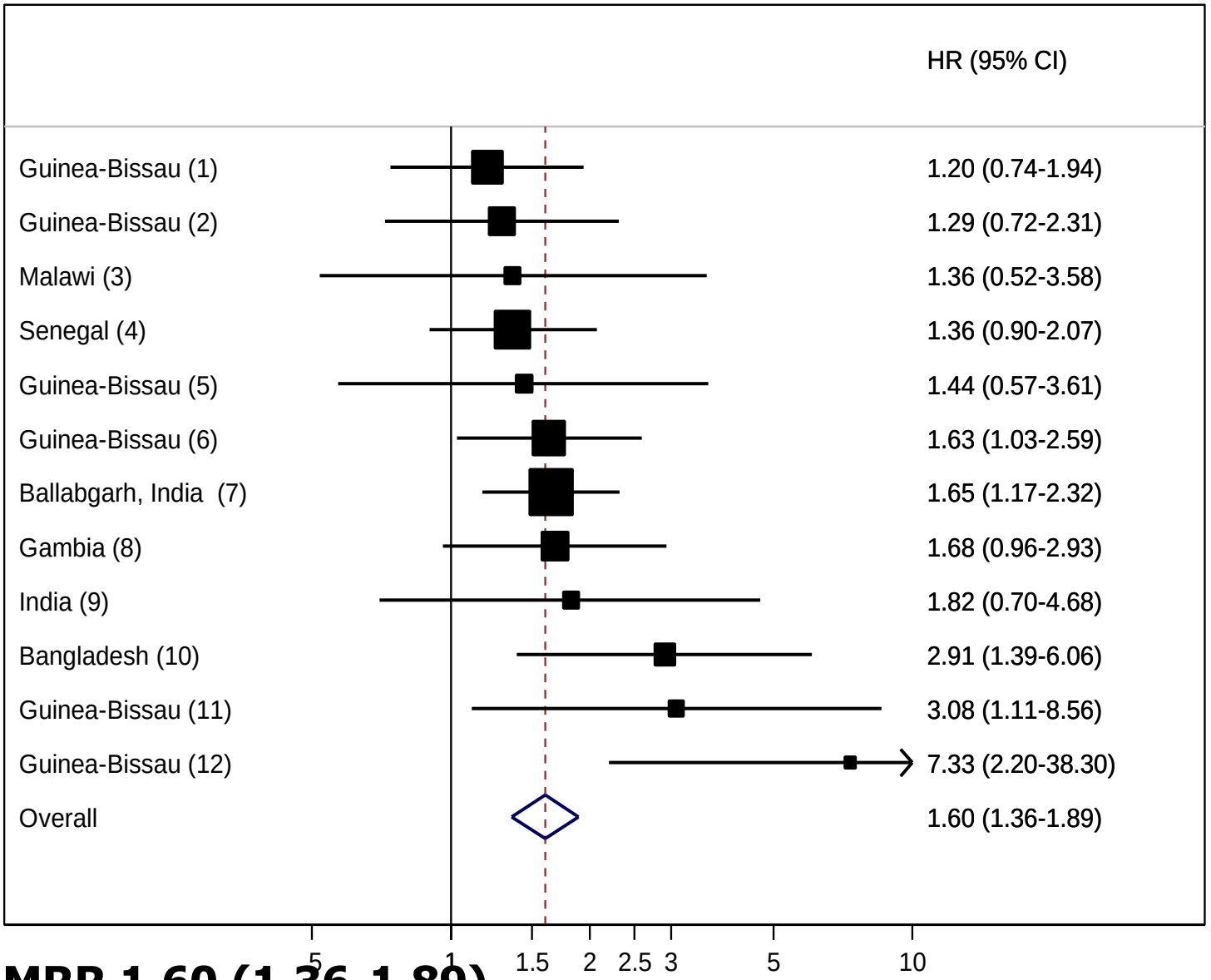


Impact of DTP in studies with no survival bias



SAGE-review: ”The findings were inconsistent with a majority of studies indicating a detrimental effect of DTP and two studies indicating a beneficial effect” => No inconsistent results – only inconsistent methodologies

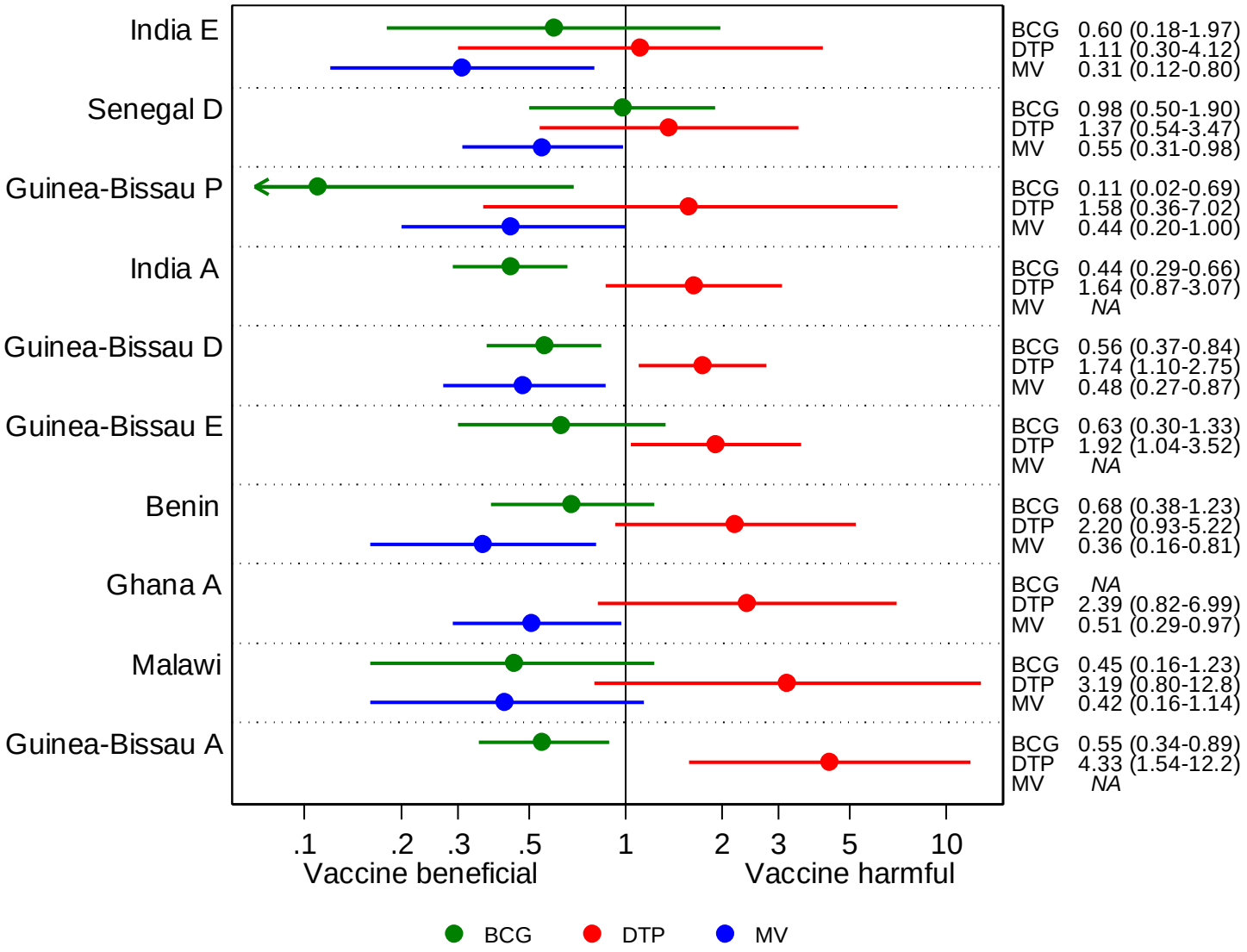
Female-male mortality rate ratio for DTP as most recent vaccine



F/M MRR 1.60 (1.36-1.89)

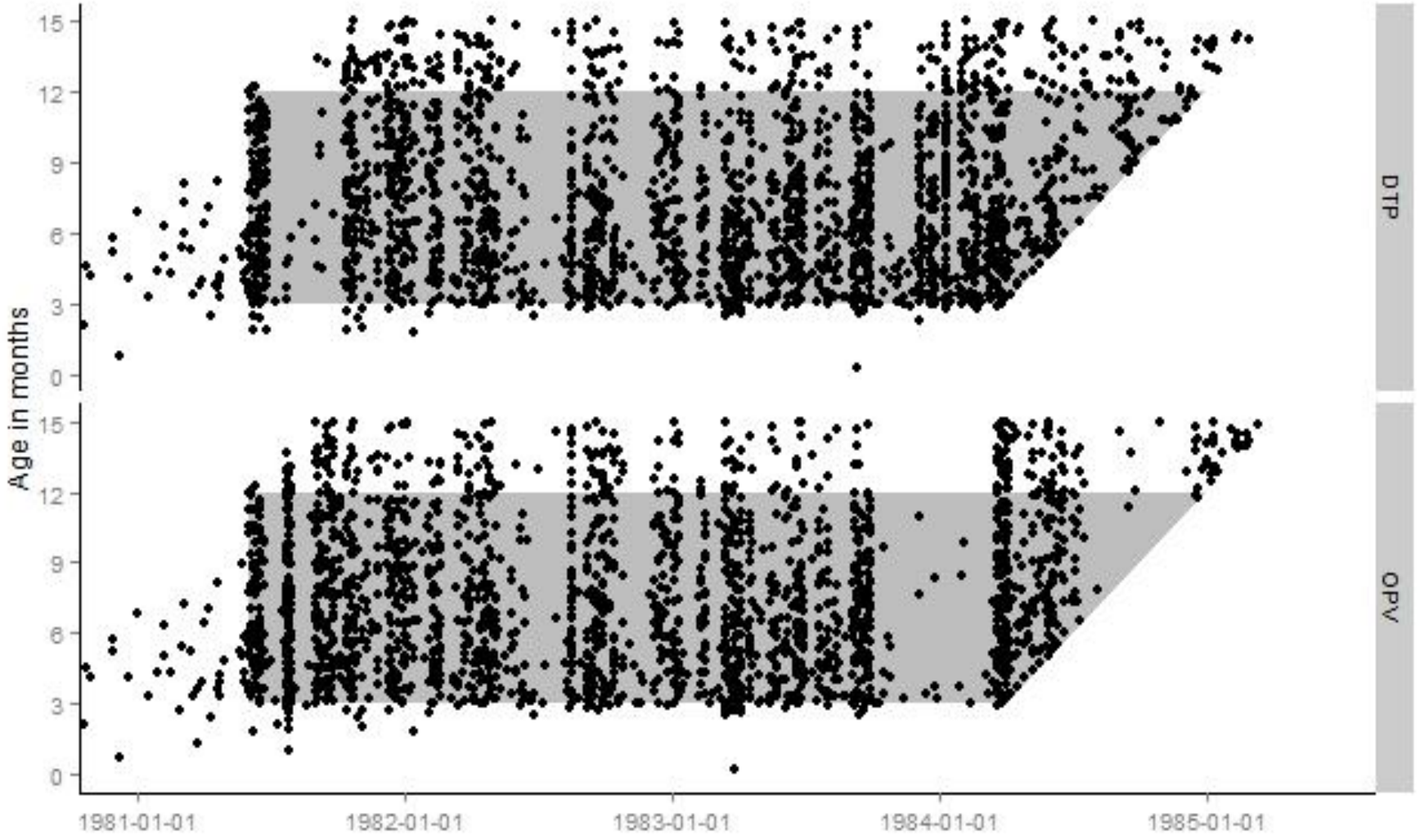
Excluded BCG=DTP1 and studies with MV during follow-up

Differential effects of BCG, DTP and MV
Studies with a bias indicator of <2.0

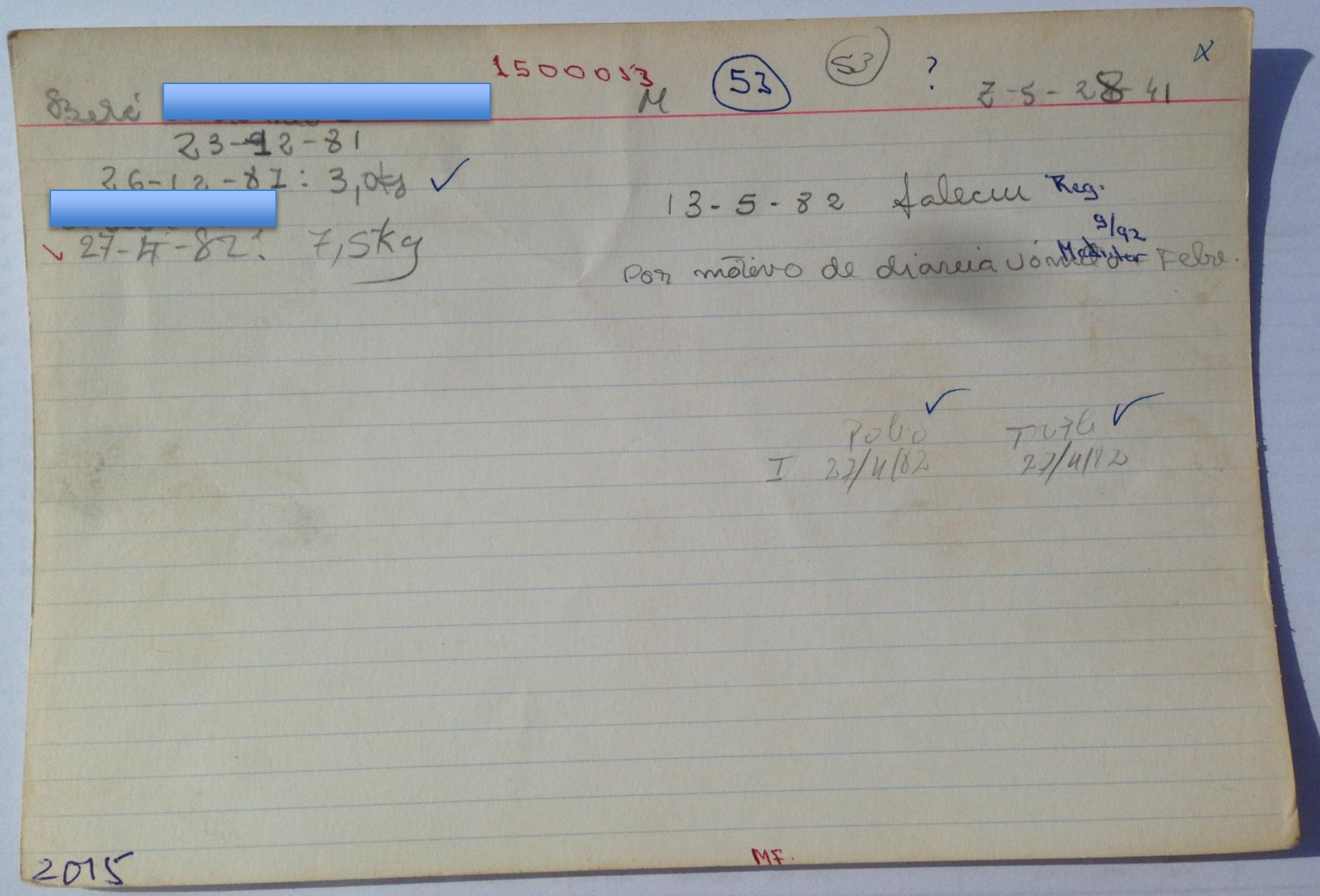


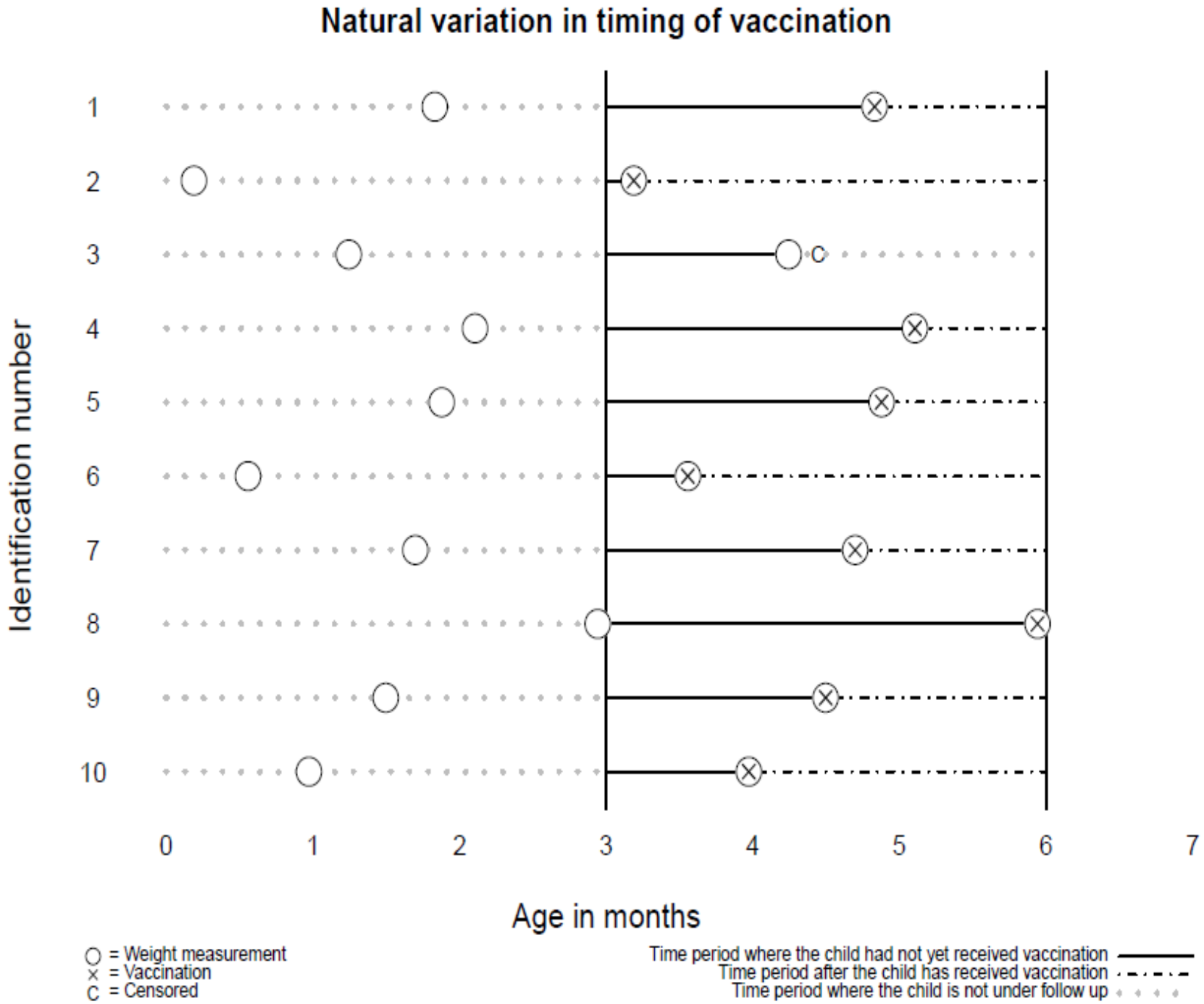
SAGE:DTP difficult to evaluate: herd immunity+administration with OPV

Introduction of DTP and OPV in Bissau in 1981



Community weighing every 3 months from 1980




Natural variation in timing of vaccination
Identification number
1
2
3
4
5
6
7
8
9
10
C
0
1
2
3
4
5
6
7
Age in months
○ = Weight measurement
× = Vaccination
C = Censored
Time period where the child had not yet received vaccination
Time period after the child has received vaccination
Time period where the child is not under follow up

Introduction of DTP and OPV in Bissau 1981-1983

Before herd immunity

Age group (months)	Rate (deaths/pyrs) No Vaccine	Rate (deaths/pyrs) Any DTP	HR DTP vs no Vaccine
3-5 (DTP+/-OPV)	4.5 (5/111.4)	17.4 (11/63.1)	5.00 (1.5-16.3)
DTP-only		35.2 (5/14.2)	10.0 (2.6-39)
DTP+OPV		12.3 (6/49)	3.52 (1.0-12.9)

Introduction of DTP and OPV in Bissau 1981-1983

Before herd immunity

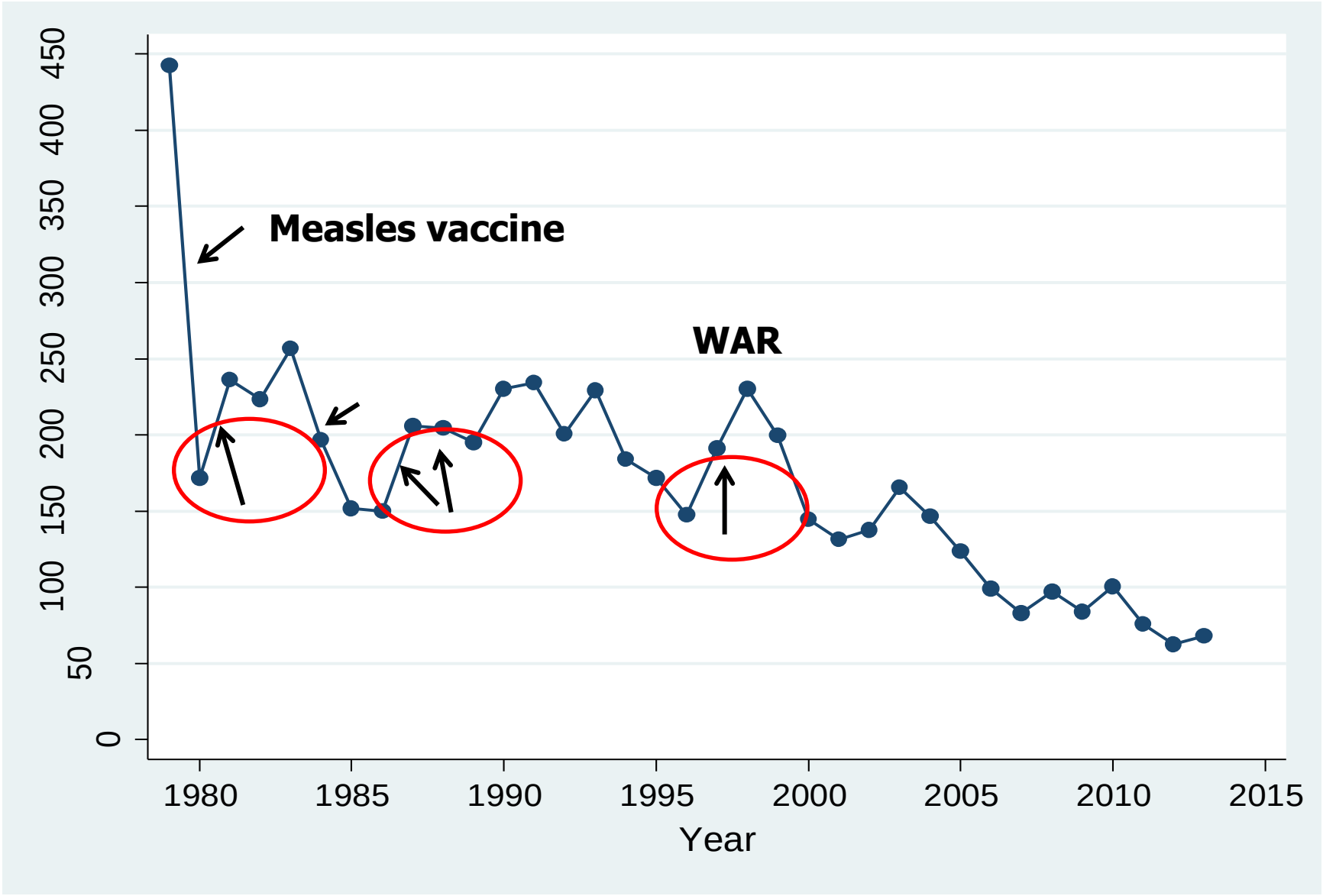
Age (months)	Rate (deaths/pyrs) DTP only	Rate (deaths/pyrs) OPV-only	HR DTP-only vs OPV-only
3-5	34.5 (6/17.4)	0 (0/8.6)	P=0.10
6-11	13.4 (9/67.1)	2.1 (1/48.4)	0.61 (0.8-52)
3-11	17.8 (15/84.5)	1.8 (1/57.0)	10.4 (1.4-79)

WHO-SAGE review used inconsistent methodology by including studies with survival or frailty bias;

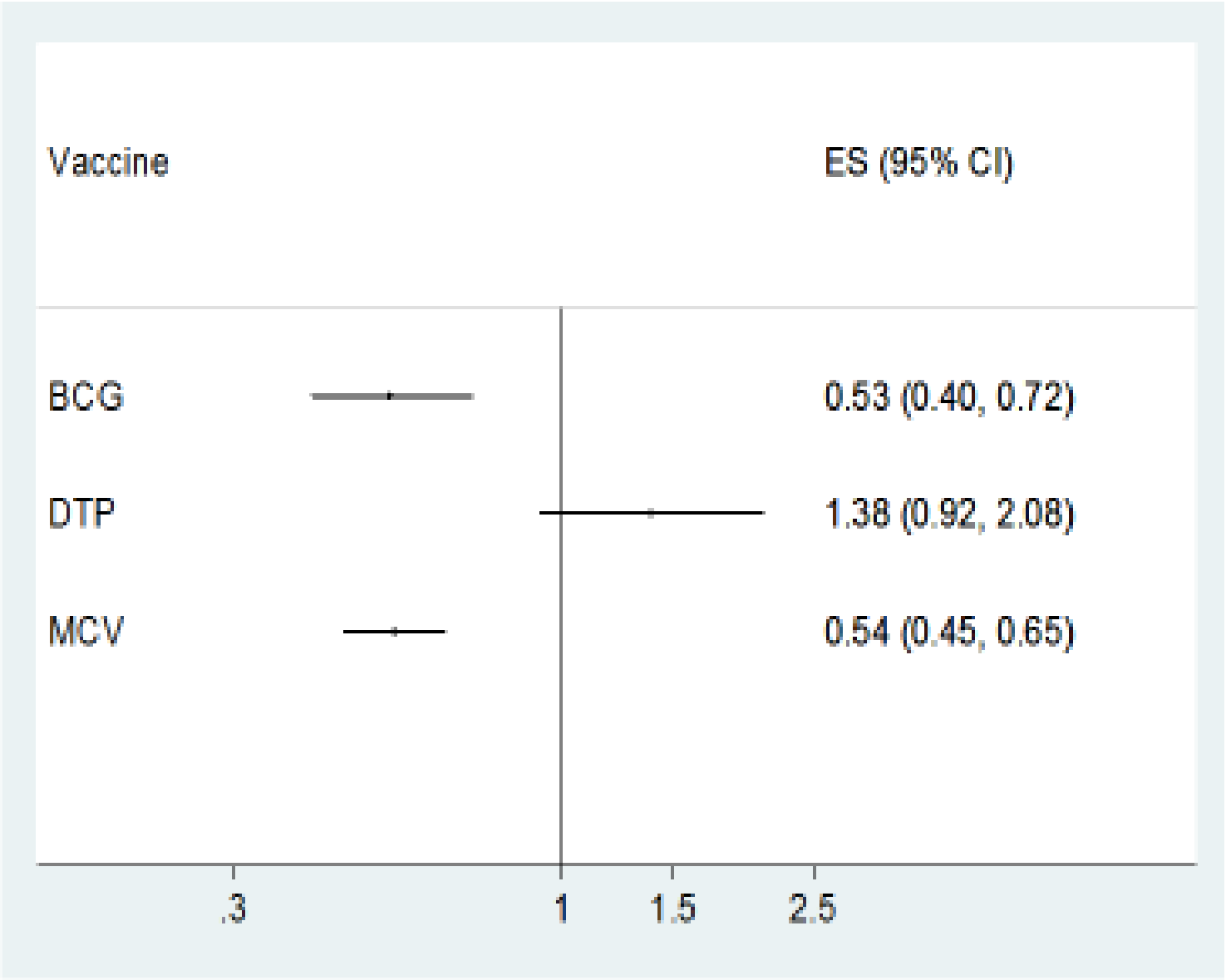
- **Herd immunity does not explain the negative effect**
- **Lack of separation of DTP and OPV is not the explanation**

DTP before MV at least 2-fold higher mortality
DTP after MV higher mortality – e.g. Welaga's Navrongo data and the high-titre measles vaccine story
These negative effects are strongest for girls
OPV has reduced the negative effects of DTP
Other inactivated vaccines have also negative effects: IPV, HBV, H1N1 and RTSS malaria vaccine

Under-five mortality in Bissau: Introduction of inactivated vaccines



Completely different effects of different vaccines

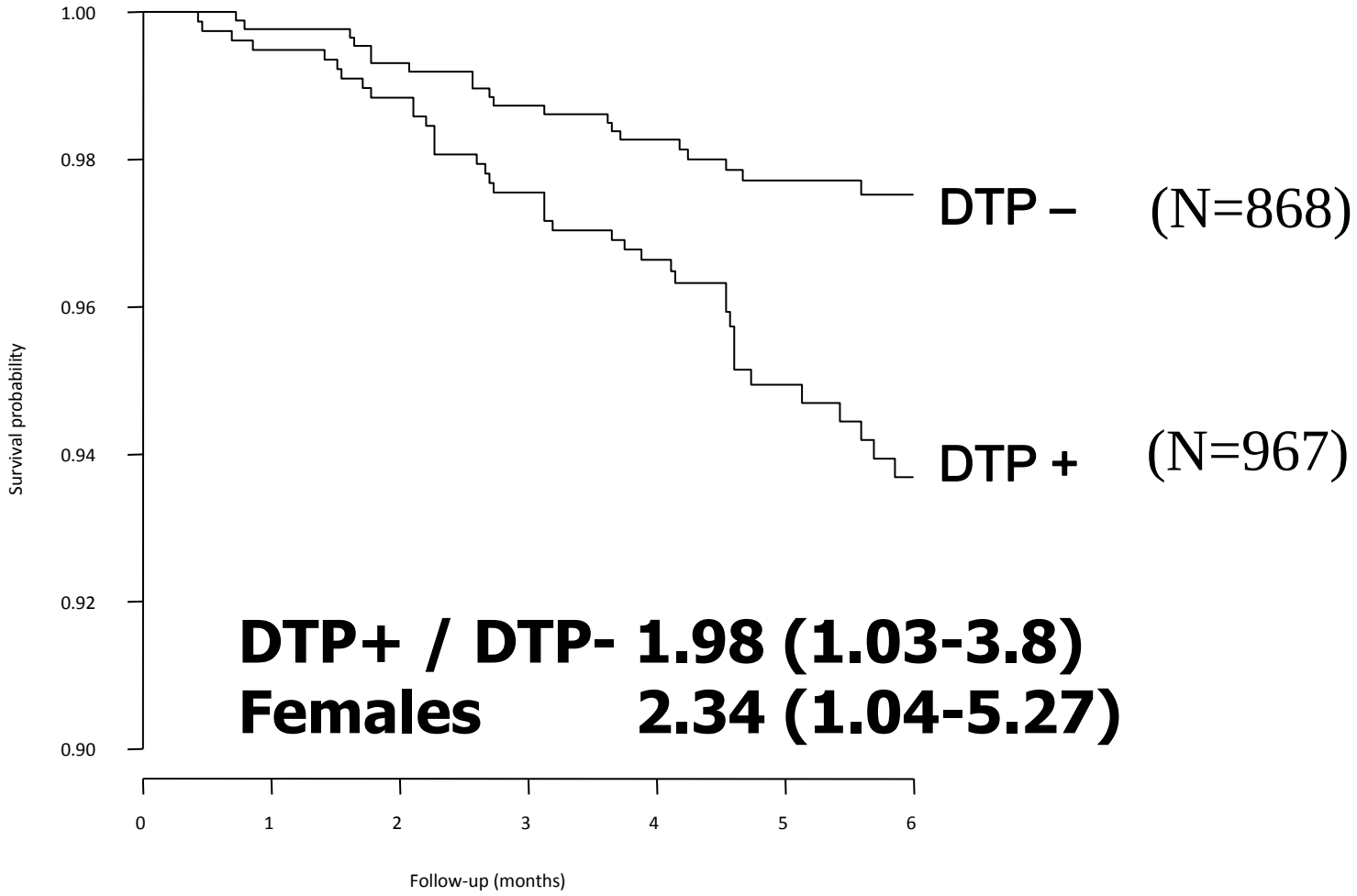


Introduction of DTP

Rural areas of Guinea-Bissau 1984-87

Children aged 2-8 mo

Unvaccinated: travelling; sick; days without vaccines



The only study of the introduction of DTP in the global literature

Aaby et al, Int J Epidemiol 2004

Introduction of DTP in Bissau 1981-1983

Before herd immunity

Age group (months)	Rate (deaths/pyrs) No Vaccine	Rate (deaths/pyrs) Any DTP	HR DTP vs no vaccine
3-5	4.5 (6/134)	15.8 (12/76)	4.34 (1.5-12.8)
6-11	10.0 (15/150)	12.3 (39/318)	1.17 (0.6-2.1)
3-11	7.9 (21/284)	12.9 (51/395)	1.66 (0.96-2.9)
Females 3-5			10.6 (1.2-96)
Males 3-5			3.1 (0.9-10.6)