Danmarks Grundforskningsfond
Danish National Research Foundation

VIVA Research Center for Vitamins & Vaccines

Inactivated vaccines and off-targeted effects: DTP and interaction between live and inactivated vaccines (and impact of survival bias)

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Bandim Health Project
Statens Serum Institut
and
University of Southern Denmark
Denmark

Les Pensières, 9 June 2015

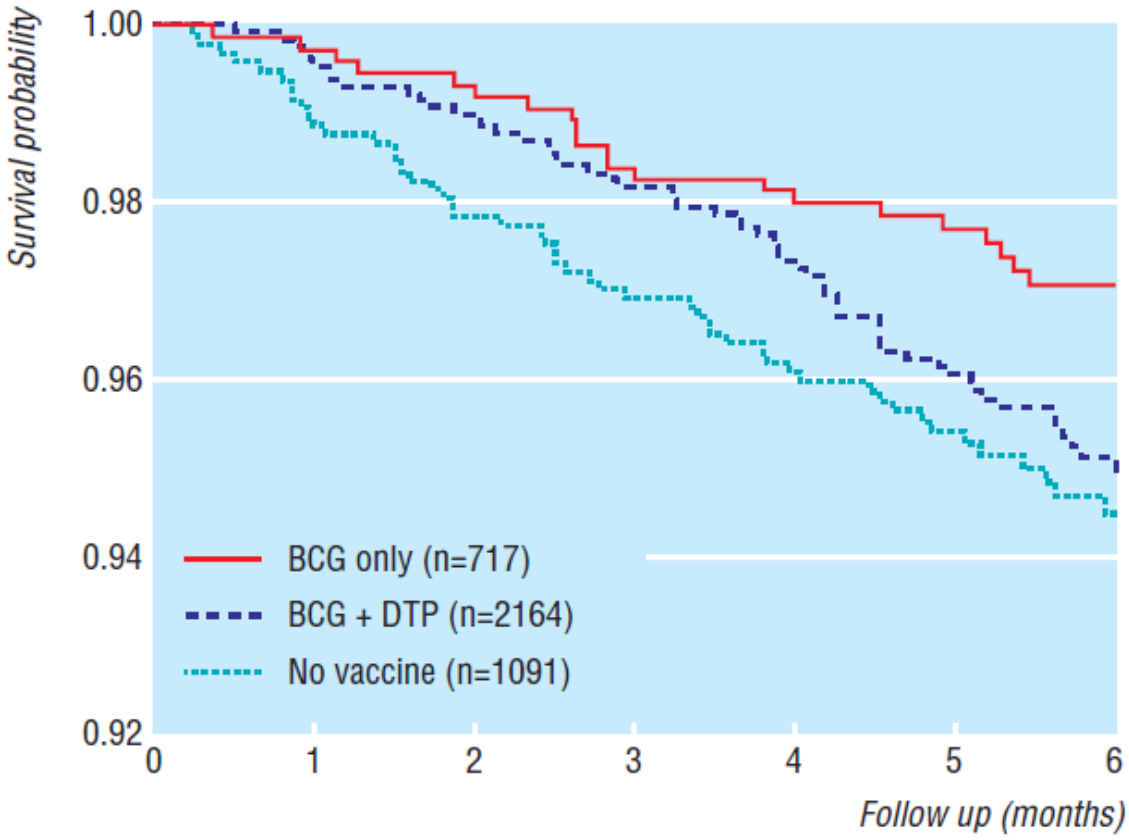
University of Southern Denmark

Projecto de Saúde BANDIM

BMJ VOLUME 321 9 DECEMBER 2000 bmj.com

Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa

Ines Kristensen, Peter Aaby, Henrik Jensen



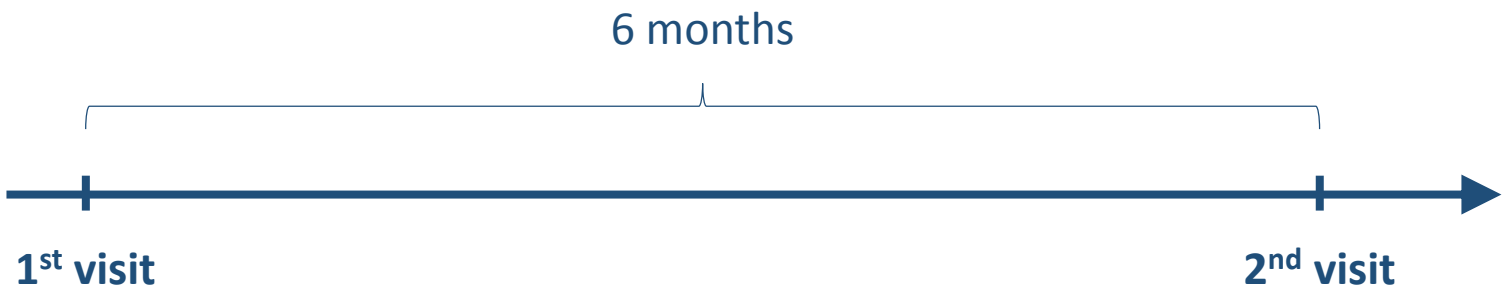
BCG **0.55 (0.36-0.85)**

DTP **1.84 (1.10-3.10)**

BMJ VOLUME 321 9 DECEMBER 2000 bmj.com

Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa

Ines Kristensen, Peter Aaby, Henrik Jensen



Analysis: Vaccine status at 1st visit and subsequent mortality

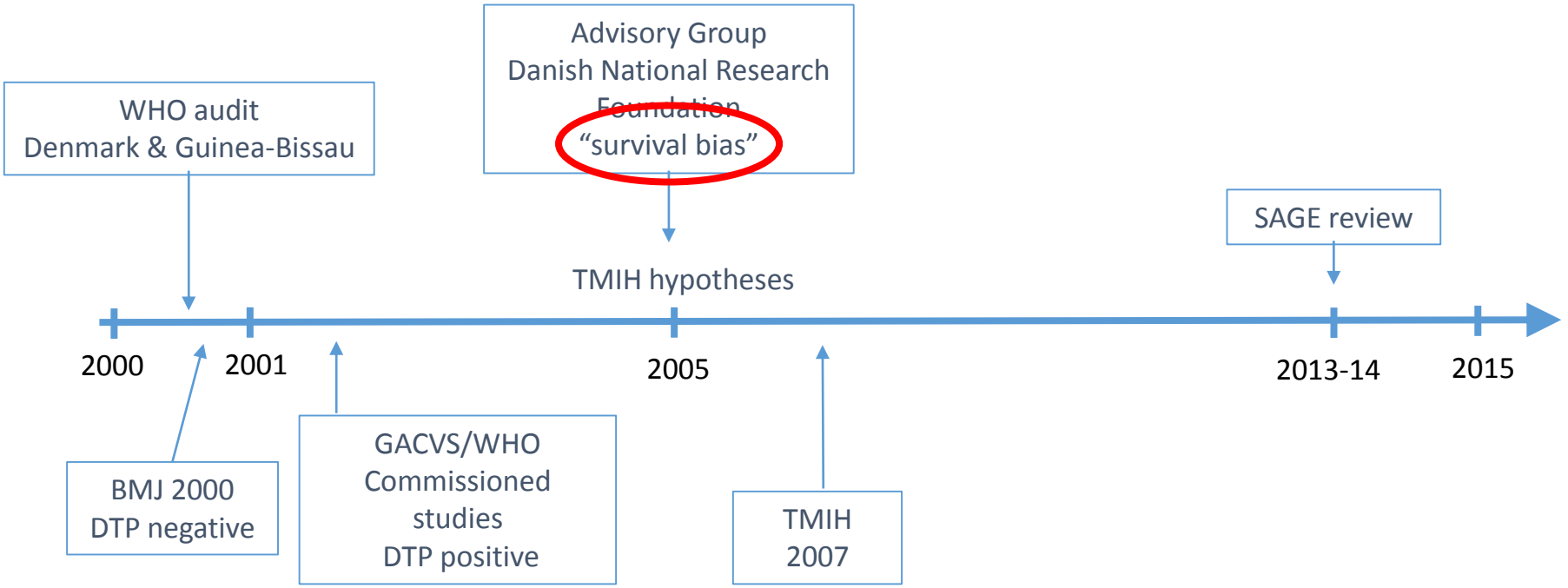
BMJ VOLUME 311 19 AUGUST 1995

Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries

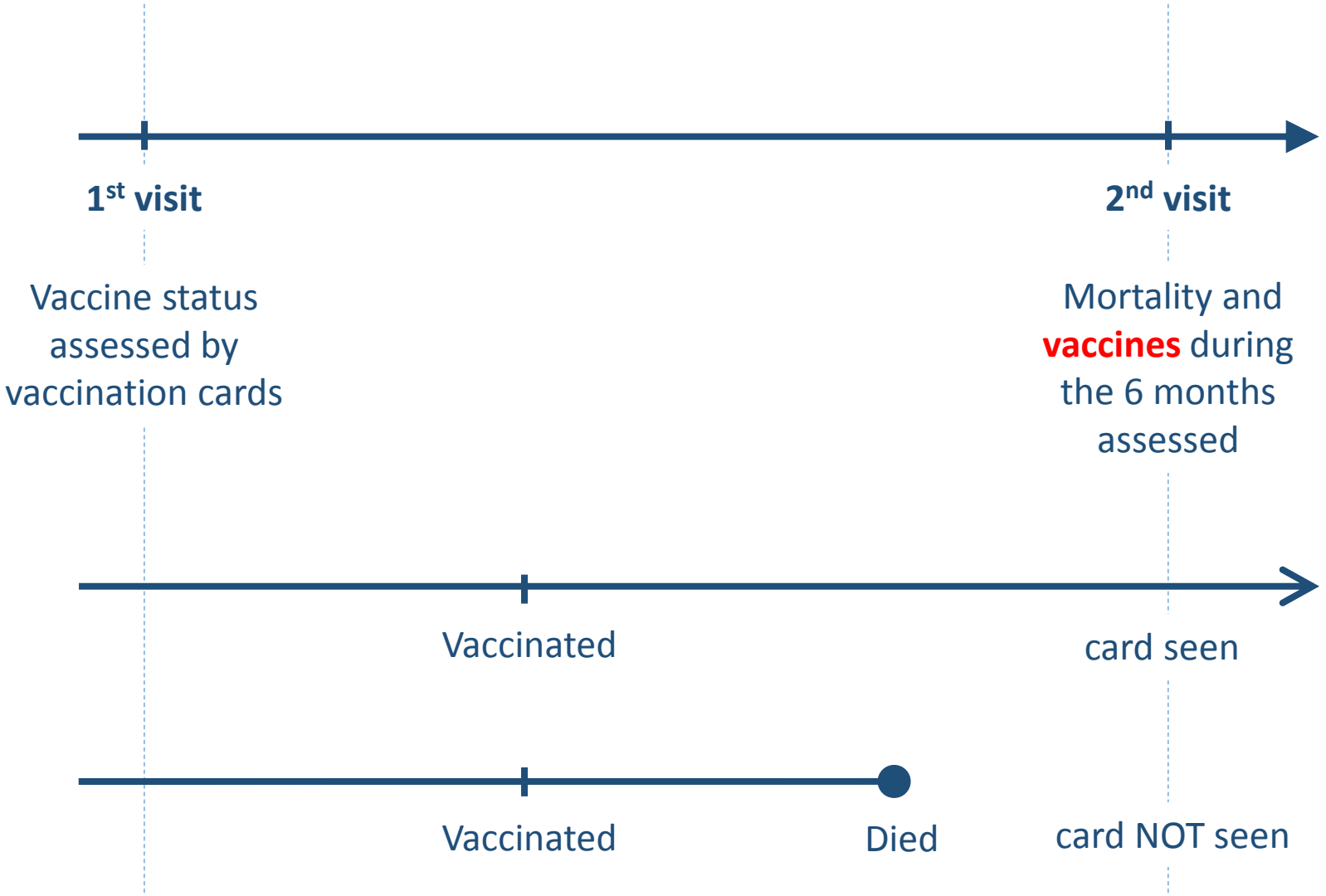
Peter Aaby, Badara Samb, Francois Simondon, Awa Marie Coll Seck, Kim Knudsen, Hilton Whittle

tality ratio=1·60; 0·76 to 3·37). In the cluster cohort study of 10 000 women of fertile age and their children in Guinea-Bissau 488 children were 2-3 months old when first seen. During six months of follow up mortality was 4% (9/245) for children who had already received diphtheria-tetanus-pertussis and oral polio vaccines at least once and 3% (8/243) for children who had not received these vaccines.

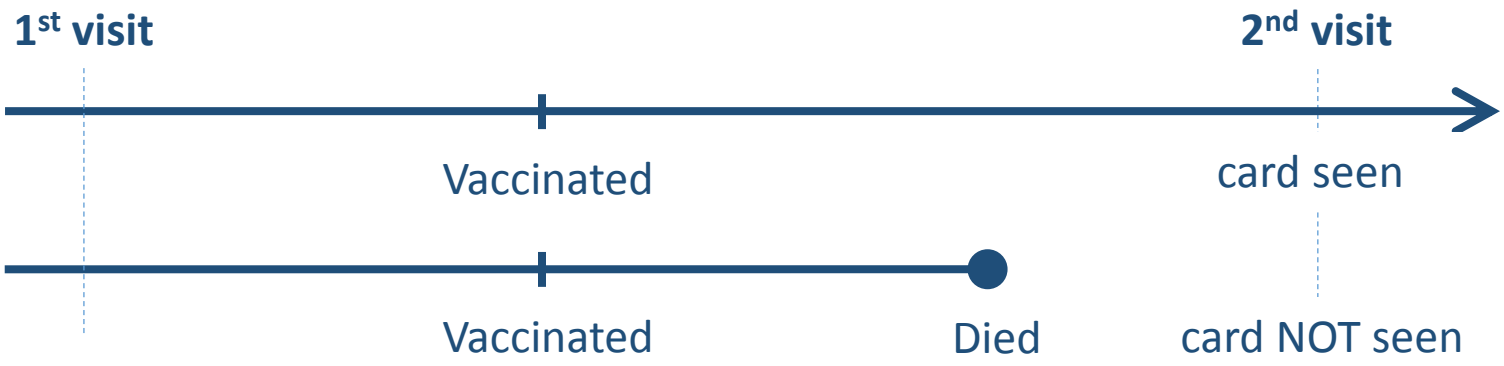
Brief DTP non-specific effect history



Survival bias

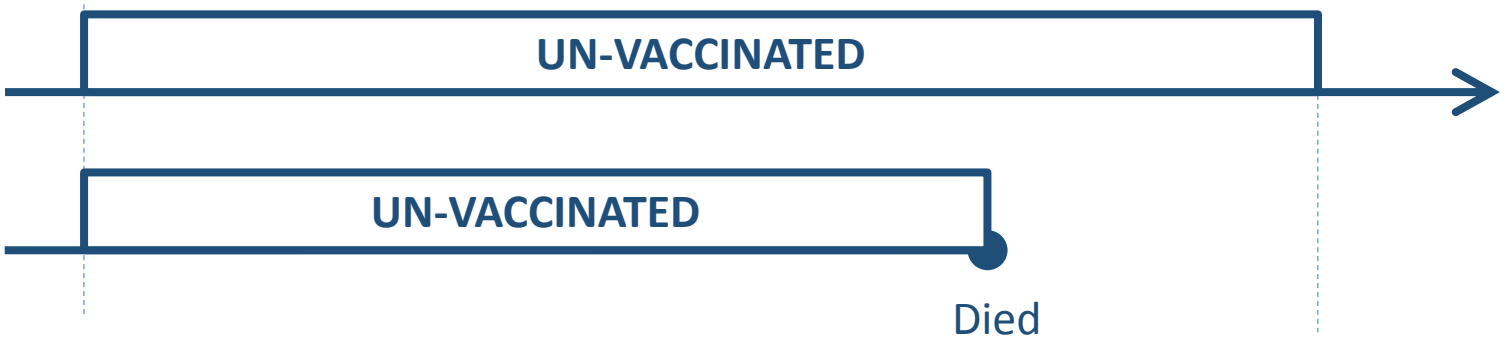


Reality - but hidden from us

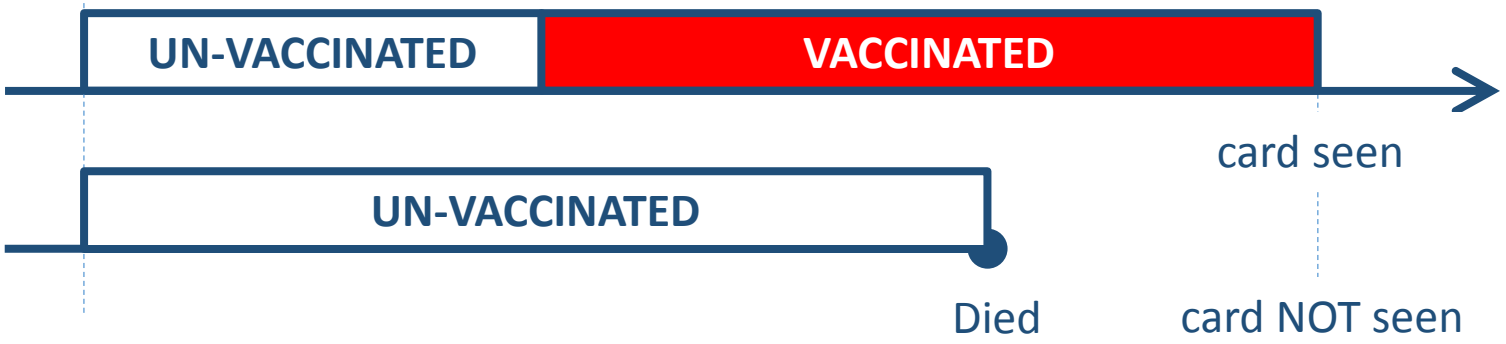


Observed

Landmark approach



Retrospective updating approach (RUA)



Landmark ignores vaccines during follow-up

RUA:

a) **Moves "risk free" time to the vaccinated**
b) **Leaves the death in the un-vaccinated**

Landmark vs. retrospective updating BMJ 2000 data

	Landmark BMJ 2000 Rate (deaths/pyrs)	Retrospective Updating Rate (deaths/pyrs)
Total	92 (222/2409)	92 (222/2409)
Totally unvaccinated	109 (95/875)	183 (92/503)
Any vaccine	83 (127/1534)	68 (130/1906)
Mortality Rate Ratio	**1.35 (0.97-1.89)**	**2.96 (2.15-4.08)**

Rate per 1000 person years of observation (pyrs)

RUA:

a) **Moves "risk free" time to the vaccinated**
b) **Leaves the death in the un-vaccinated**

Landmark *vs* retrospective updating BMJ 2000 data

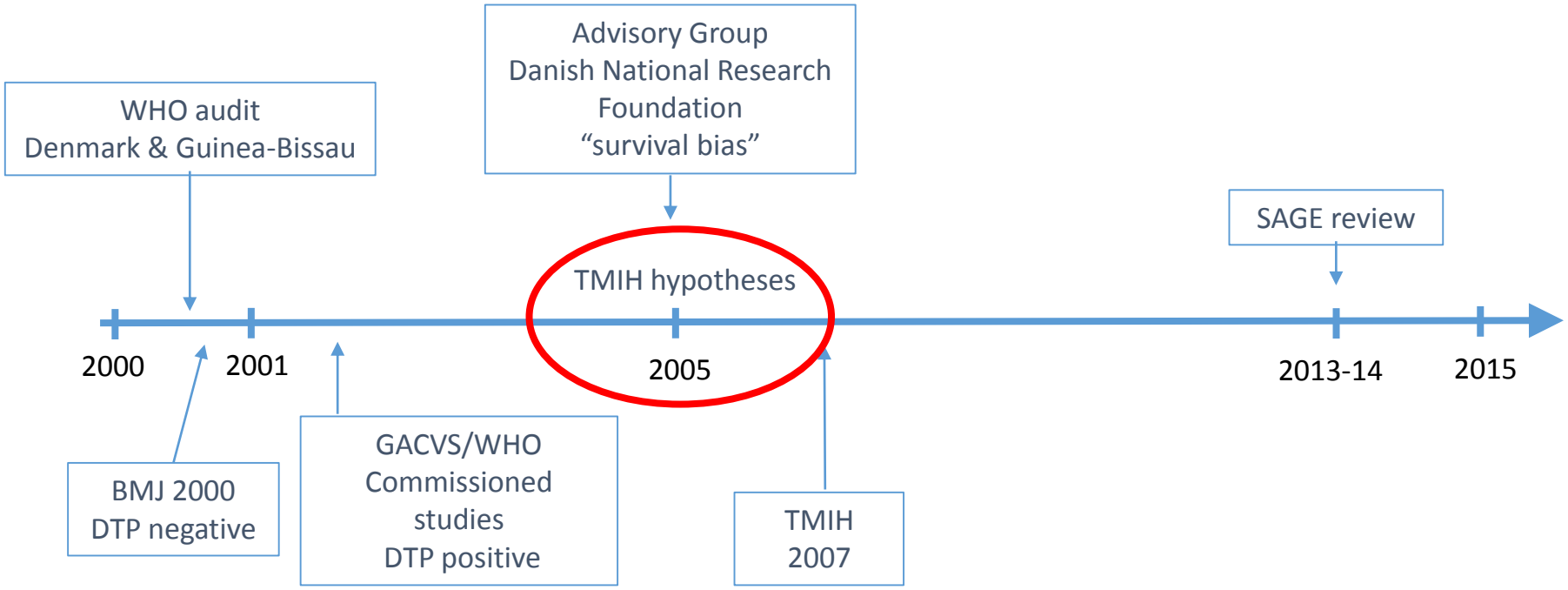
	Landmark BMJ 2000	Retrospective updating
DTP1 vs no DTP	1.84 (1.10-3.10)	0.68 (0.44-1.04)
DTP2 vs no DTP	1.39 (0.73-2.61)	0.26 (0.15-0.47)
DTP3 vs no DTP		0.16 (0.08-0.32)

Two and three doses of DTP were combined in BMJ2000

Direction of biases

- **RUA bias towards "zero"**
- **Landmark bias towards "null"**

Brief DTP non-specific effect history



Hypotheses formulated in 2005 (TMIH-hypotheses)

Hypothesis 1

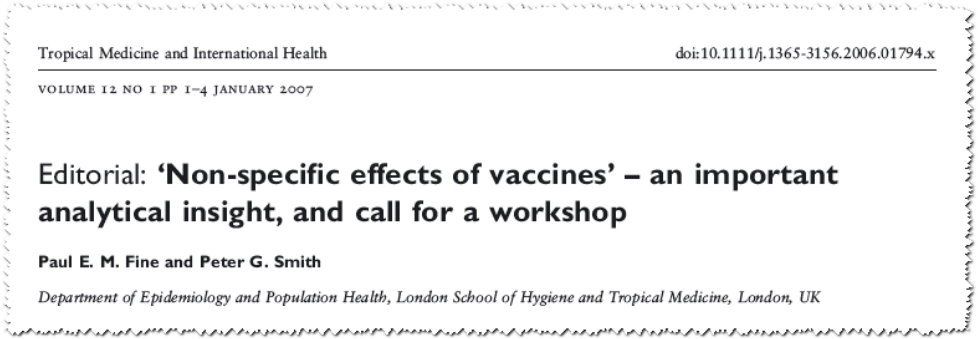
DTP-vaccinated girls have higher mortality than DTP-unvaccinated girls

Hypothesis 2

DTP-vaccinated girls have higher mortality than DTP-vaccinated boys (F/M-ratio > 1)

Hypothesis 3

Children having MCV given with DTP have higher mortality than MCV alone



Tropical Medicine and International Health doi:10.1111/j.1365-3156.2006.01794.x
VOLUME 12 NO 1 PP 1–4 JANUARY 2007

Editorial: **'Non-specific effects of vaccines' – an important analytical insight, and call for a workshop**

Paul E. M. Fine and Peter G. Smith

Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

The hypotheses 1+2 were formulated to hold as long as

a) DTP not given with other vaccines (than OPV)
b) DTP (+OPV) is the latest vaccine given

The hypothesis 3 was formulated to hold as long as

a) MCV is the latest vaccine given

SAGE review 2014

Systematic review of the non-specific effects of BCG, DTP and measles containing vaccines

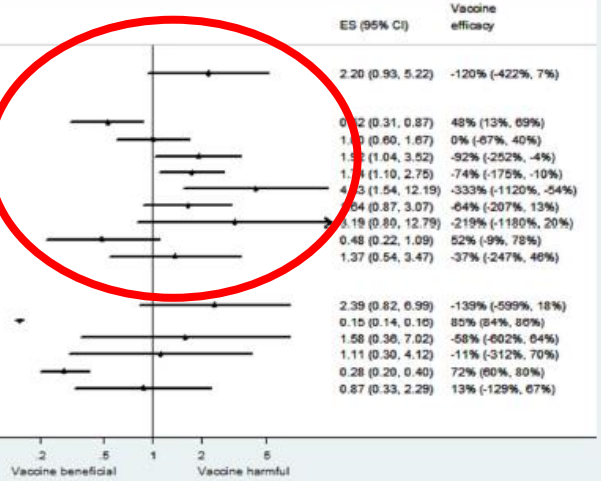
Higgins JPT, Soares-Weiser K, Reingold A

13 March 2014

Figure 7. DTP and all-cause mortality.

DTP and all-cause mortality

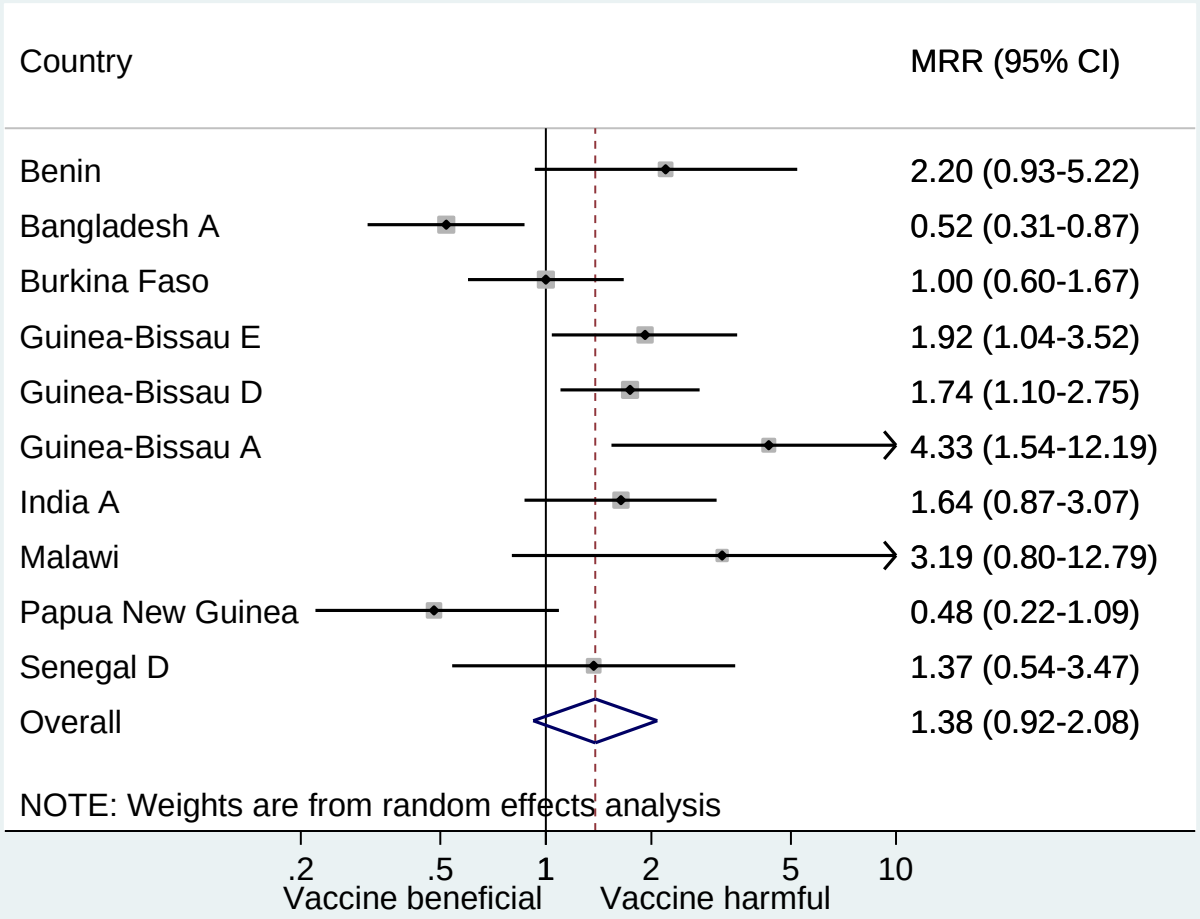
Birth cohort	Article Gp	Pub'n year	Deaths/ Children	Prior BCG*	Simult. OPV	Subseq. MV*	DTP doses	Age at first dose	Observation period**	Adjustment	ES (95% CI)	Vaccine efficacy
1. Case-control studies												
Benin 1983-1987	Benin	1991	(15+18)/132	NR	Yes	Many	1 dose	NR	age 4-36 months	Age, gender, others	2.20 (0.93, 5.22)	-120% (-422%, 7%)
2. Cohort studies												
Bangladesh 1986-2001	Bangladesh A	Unpub.	(26+51)/6410	All	Yes	Few [cens]	1 dose	Median 2.8 months	1.5-9 mo	Age, gender, others	0.52 (0.31, 0.87)	48% (13%, 69%)
Burkina Faso 1985-1993	Burkina Faso	2004	(33+28)/9085	All (SS)	NR	Many (SS)	1-3 doses	Mean 6.3 months	6 months follow-up	Age, others	1.00 (0.60, 1.67)	0% (-67%, 40%)
Guinea-Bissau 1984-1985	Guinea-Bissau E	2004	(47+20)/1667	Some	Yes	Few	1-3 doses	NR (3-8 months)	age 8 months	Age, gender, BCG, others	1.92 (1.04, 3.52)	-92% (-252%, -4%)
Guinea-Bissau 1990-1996	Guinea-Bissau D	2002	(61+128)/4418	Many	Yes	Some	1 dose	Median 3 months	6 months follow-up	Age, BCG, others	1.74 (1.10, 2.75)	-74% (-175%, -10%)
Guinea-Bissau 2002-2008	Guinea-Bissau A	2012	(20+14)/935	All	NR	Few [cens]	1 dose	NR (1.5-6 months)	age 6 months	Age, gender, others	4.33 (1.54, 12.19)	-333% (-1120%, -54%)
India 1998-2002	India A	2005	NR/1723	All	Yes	Few	1-3 doses	Median 2 months	age 6 months	Age	1.64 (0.87, 3.07)	-64% (-207%, 13%)
Malawi 1995-1997	Malawi	2006	NR/805	Many	Yes	Few	1 dose	Median 2.2 months	age 8 months	Age, others	3.19 (0.80, 12.79)	-219% (-1180%, 20%)
Papua New Guinea 1989-1994	Papua New Guinea	2005	NR/2788	All	Yes	Few	1 dose	Before 3 months for most	age 1-5 months	Age, others	0.48 (0.22, 1.09)	52% (-9%, 78%)
Senegal 1996-1999	Senegal D	Unpub.	(9+9)/319	All	Yes	Many [cens]	1 dose	NR (before 9 months)	age 24 months	Age, others	1.37 (0.54, 3.47)	-37% (-247%, 46%)
Excluded (Very high risk of bias)												
Ghana 1984-1991	Ghana A	2012	(25+4)/665	Many (OS)	Yes	Many (OS)	1-2 doses	NR	age 10-39 months	Age, others	2.39 (0.82, 6.99)	-139% (-599%, 18%)
Ghana 1998-2004	Ghana C	2010	NR/17967	NR	Yes	Many	1 dose	NR (by 12 months in 47%)	age 60 months	Age, others	0.15 (0.14, 0.16)	85% (84%, 86%)
Guinea-Bissau 1989-1999	Guinea-Bissau P	2002	(19+2)/533	Most	Yes	Few	1-3 doses	NR (from 1.2 months)	age 1.25-20 months	Age, gender, others	1.58 (0.36, 7.02)	-58% (-602%, 64%)
India 1987-1989	India E	2012	(9+3)/1723	All	Yes	Some	1-3 doses	Median 3.8 months	age 12 months	None	1.11 (0.30, 4.12)	-11% (-312%, 70%)
India 2006-2011	India G	2013	(136+44)/10274	Many	NR	Few	1-3 doses	Mean 2 months	age 8 months	None	0.28 (0.20, 0.40)	72% (60%, 80%)
Philippines 1988-1991	Philippines	2007	(79+6)/10231	All	Yes	Many [cens]	1-3 doses	NR (before 7 months)	age 30 months	Age, gender, others	0.87 (0.33, 2.29)	13% (-129%, 67%)



16 estimates

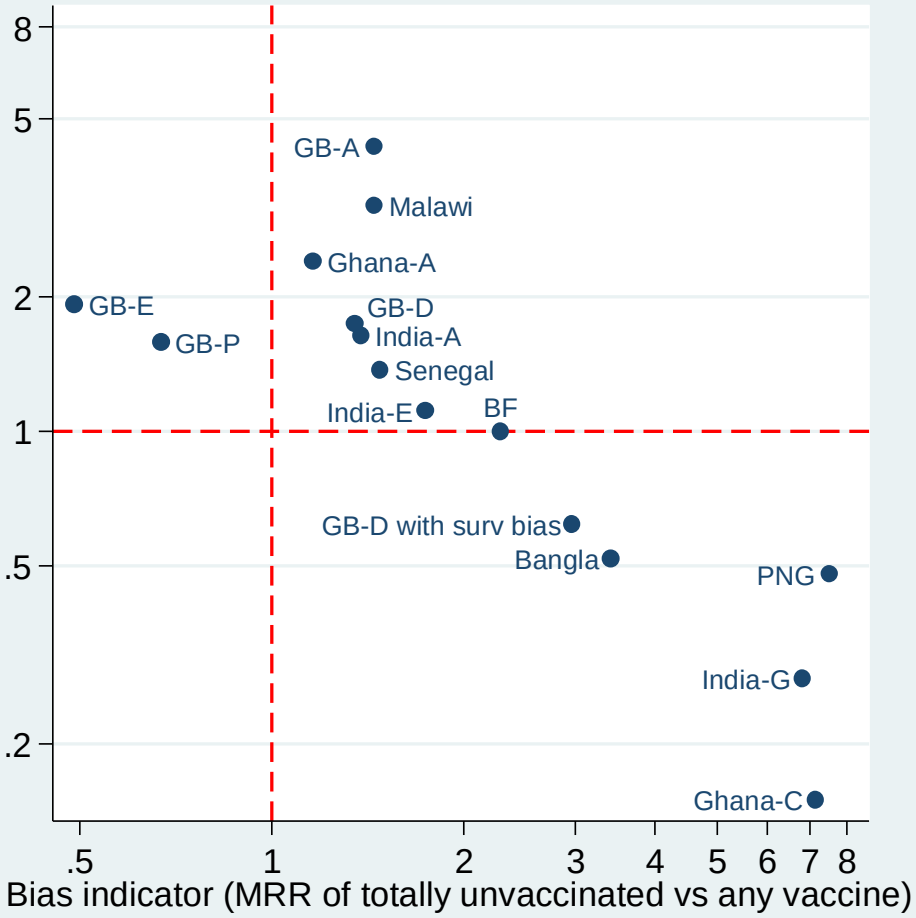
6 “very high risk of bias” – not used for testing hypothesis 1

SAGE Review – DTP overall



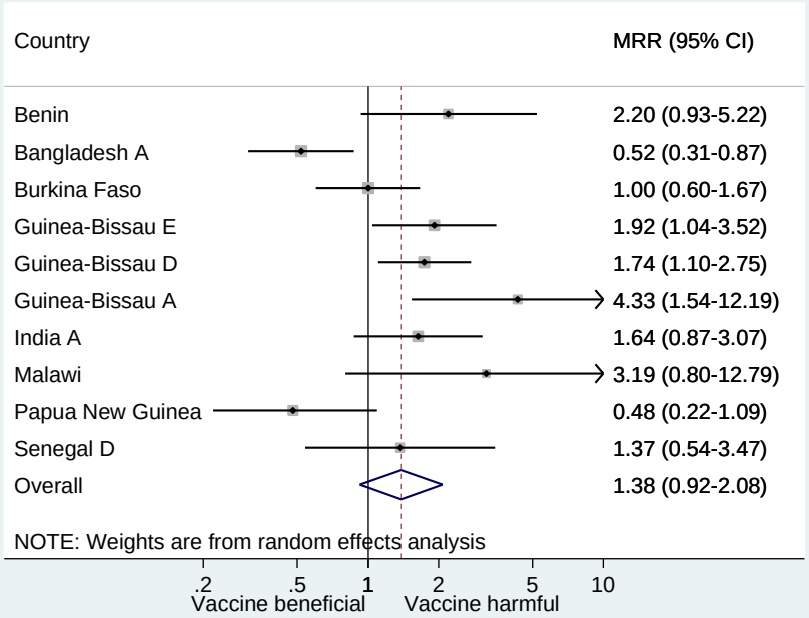
Survival Bias indicator

$$\frac{\text{Totally unvaccinated}}{\text{Any vaccine}} > 2$$

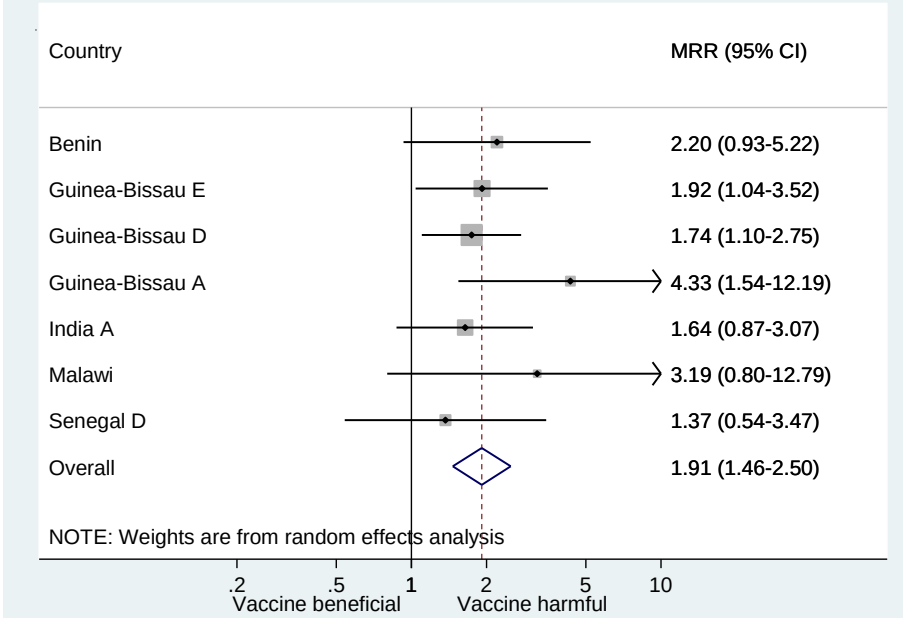


DTP and all-cause mortality

From SAGE review

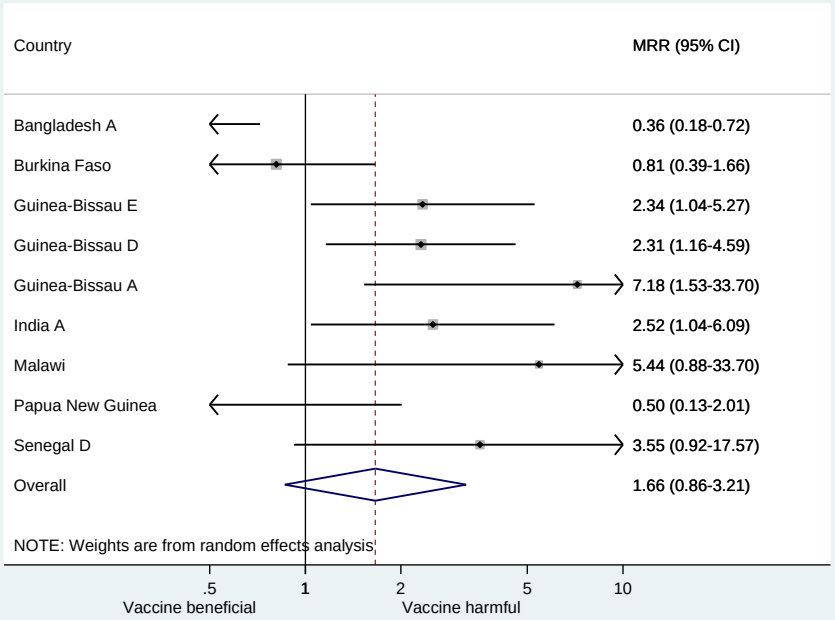


Bias indicator <2

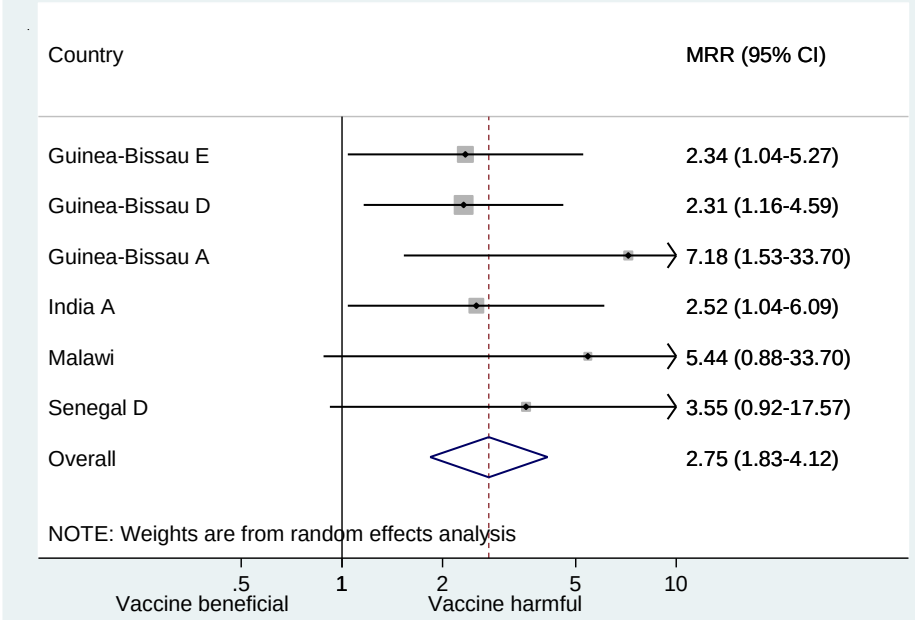


Hypothesis 1:
DTP-unvaccinated girls *vs* DTP-vaccinated girls

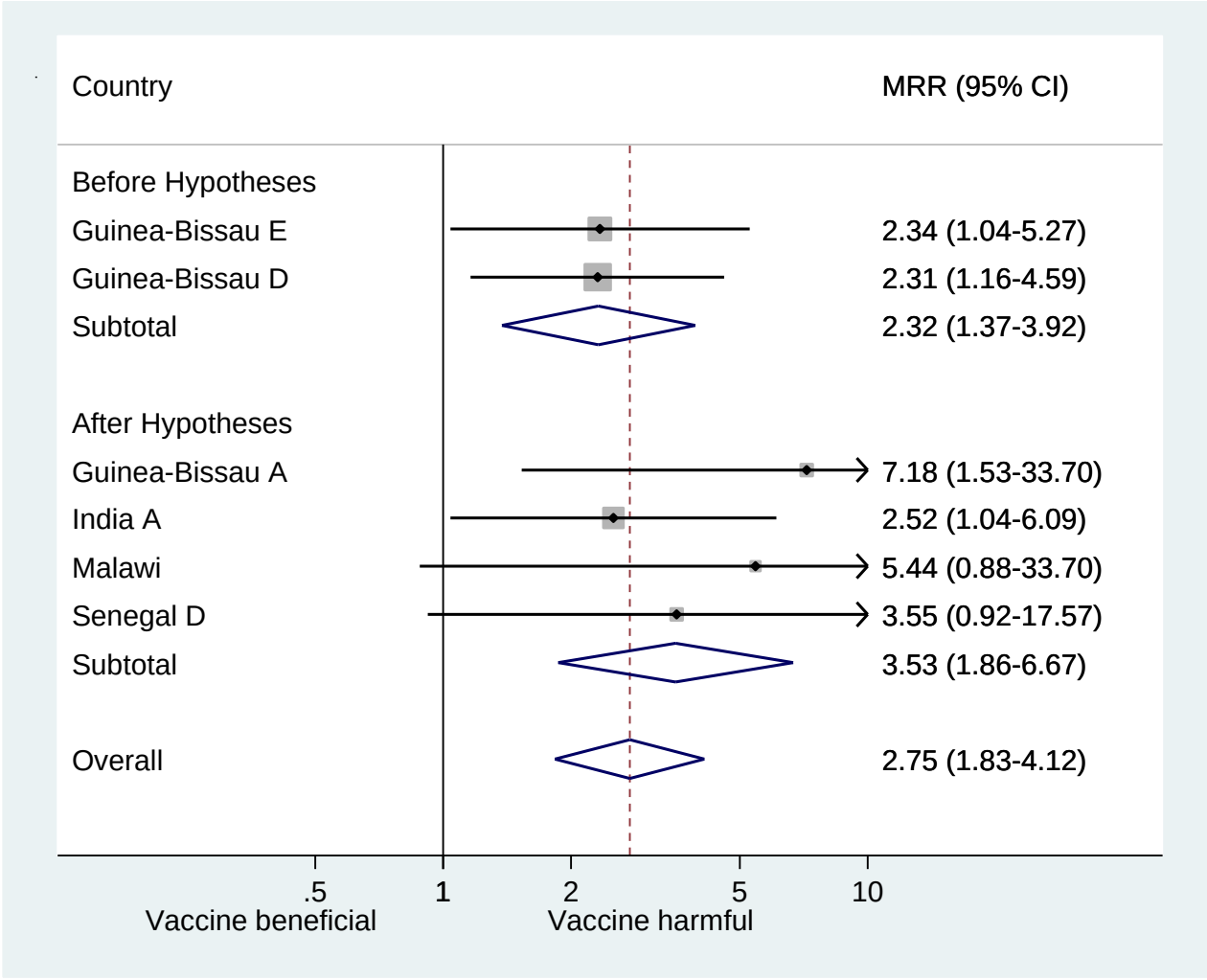
From SAGE review



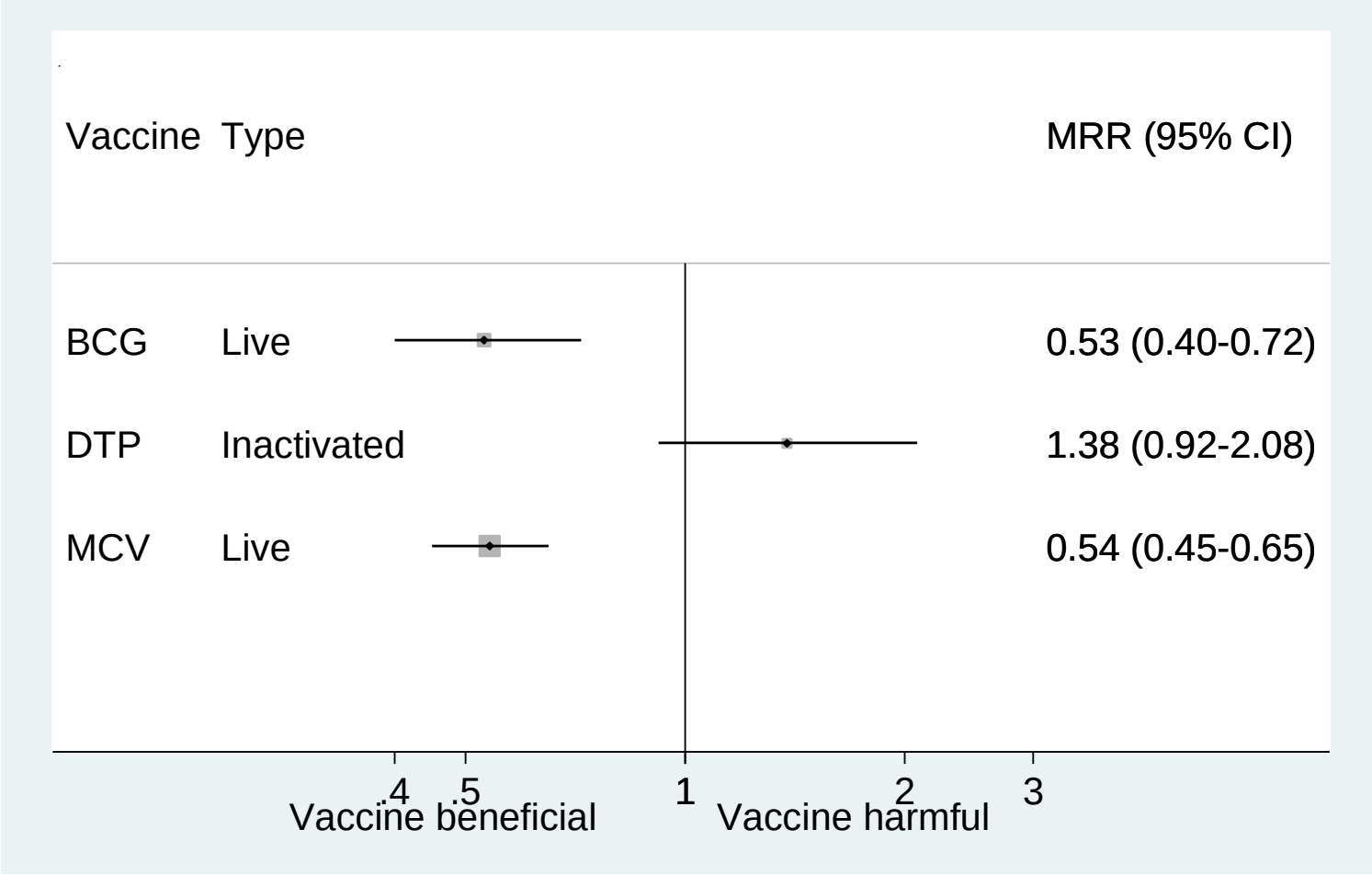
Bias indicator <2



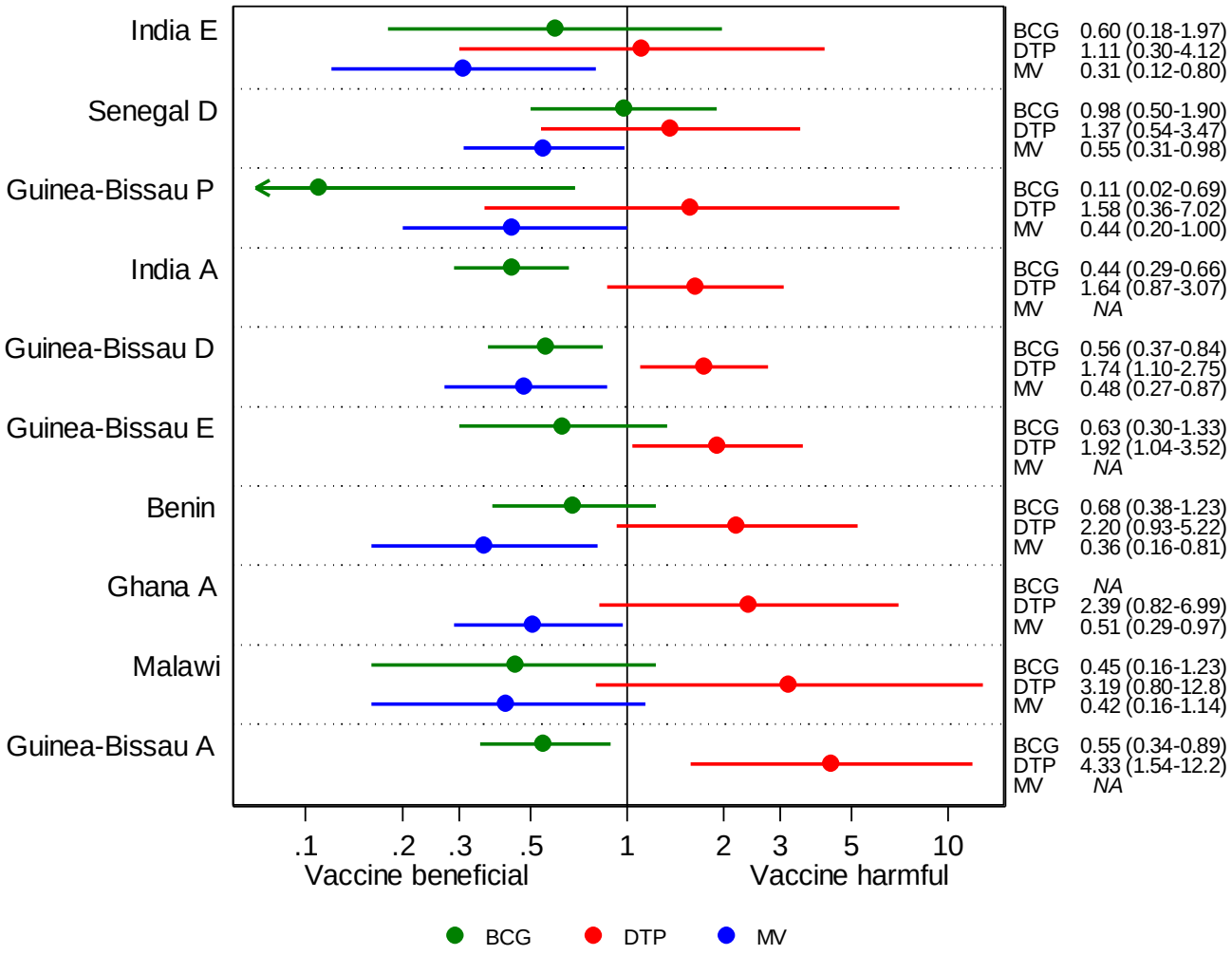
Hypothesis 1 – before and after 2005 hypotheses



SAGE: Contrasting meta estimates

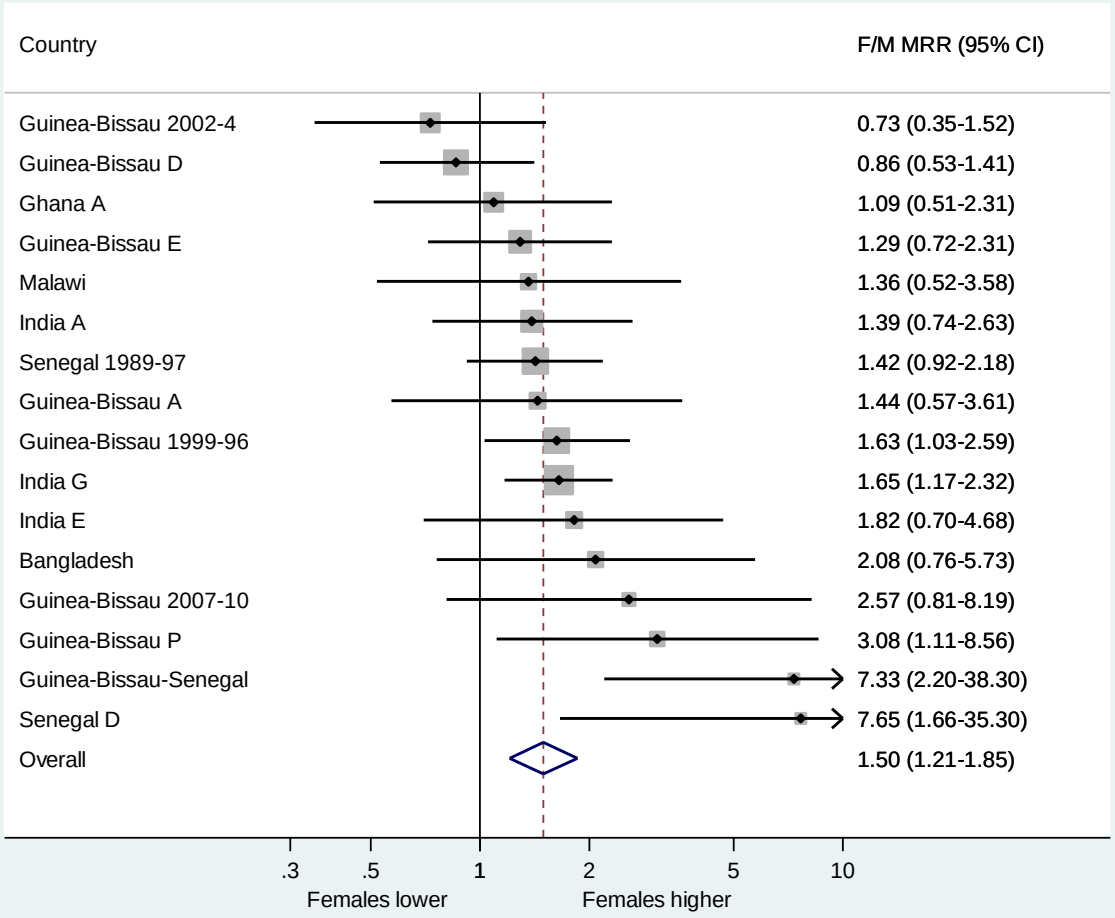


Contrasting vaccine effects within same study



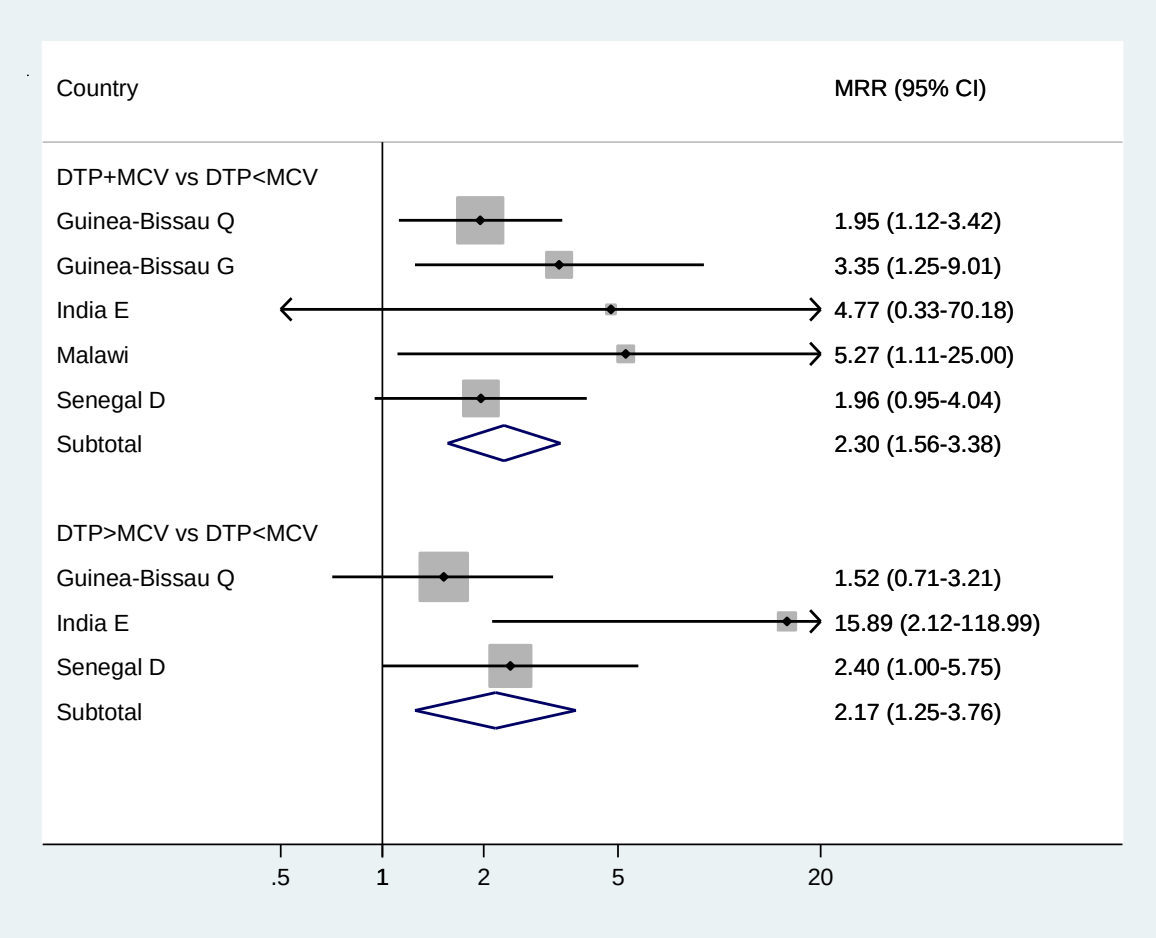
Hypothesis 2: DTP-girls *vs* DTP-boys (F/M-ratio)

All are DTP-vaccinated



Before 1.66 (0.98-2.79)
After 1.49 (1.20-1.84)

Hypothesis 3: DTP+MCV *vs* DTP<MCV (SAGE)



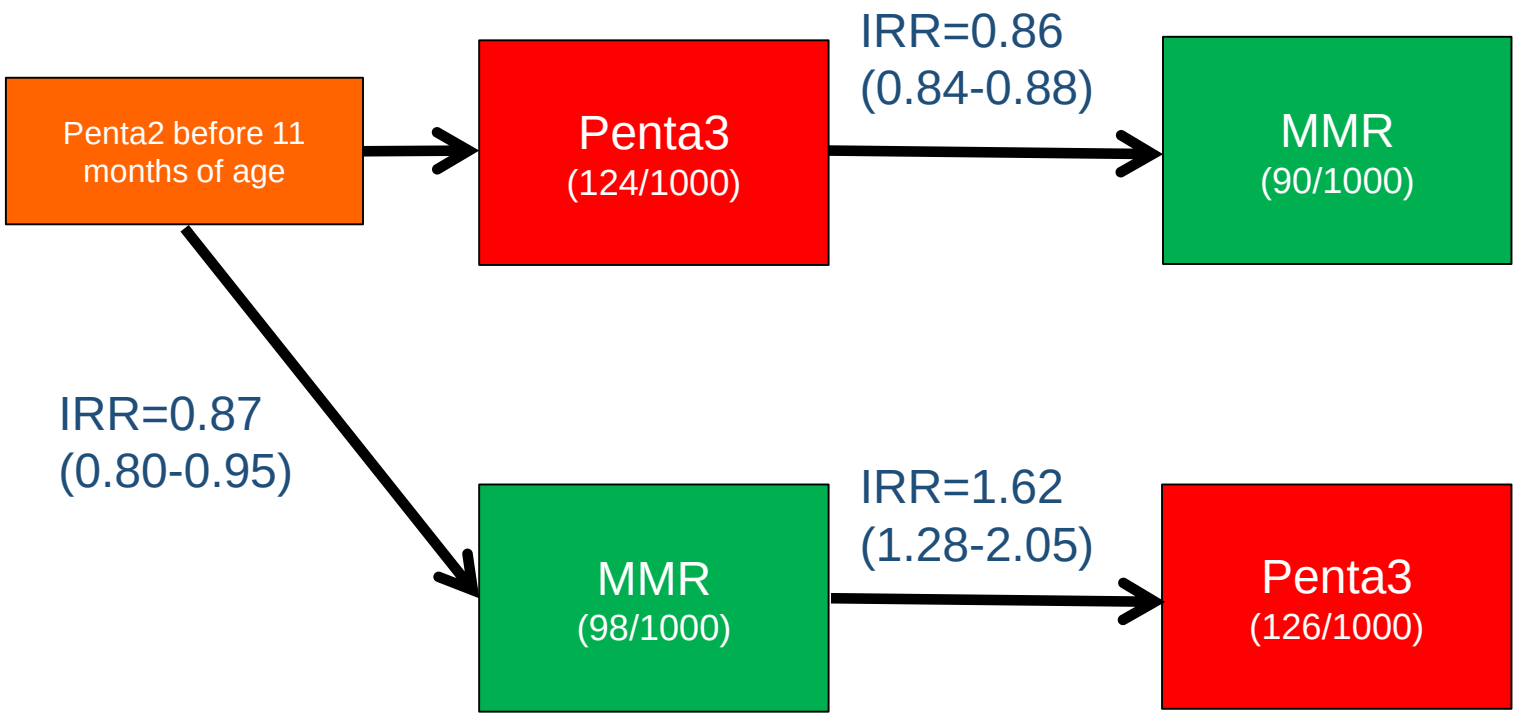
Sequence of DTP and MCV seems important

JAMA February 26, 2014

Live Vaccine Against Measles, Mumps, and Rubella and the Risk of Hospital Admissions for Nontargeted Infections

Signe Sørup, PhD; Christine S. Benn, DMSc; Anja Poulsen, PhD; Tyra G. Krause, PhD; Peter Aaby, DMSc; Henrik Ravn, PhD

Sequence of live and inactivated seems important



Penta: DTaP-IPV-Hib2

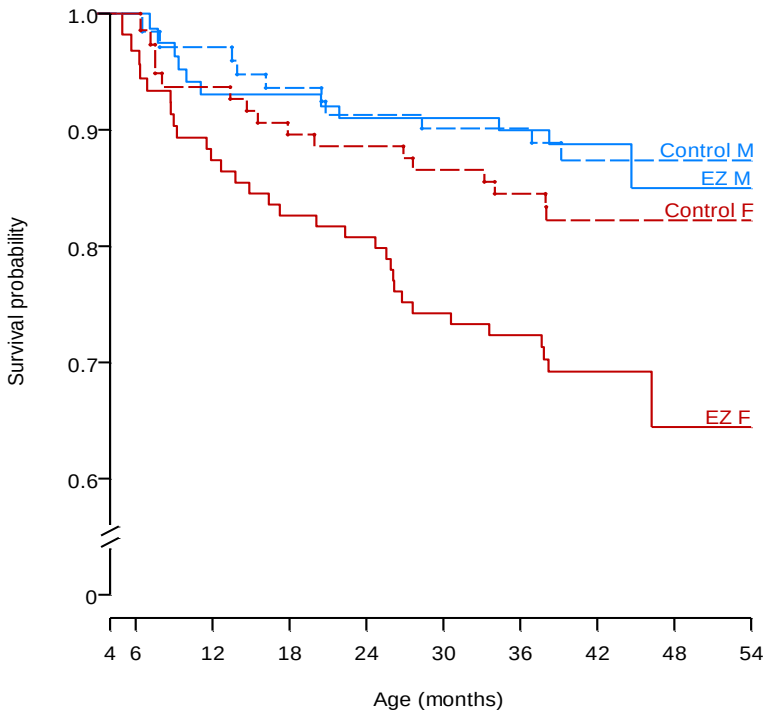
Summary

- RCTs for BCG, OPV, and MV – but not for DTP
- Contrasting results for live and inactivated
- Sequence of live and inactivated seems important
- Sex is important
- Bias? Need directionality (like for survival bias)
- Which studies are necessary to provide sufficient evidence that DTP is beneficial or harmful?

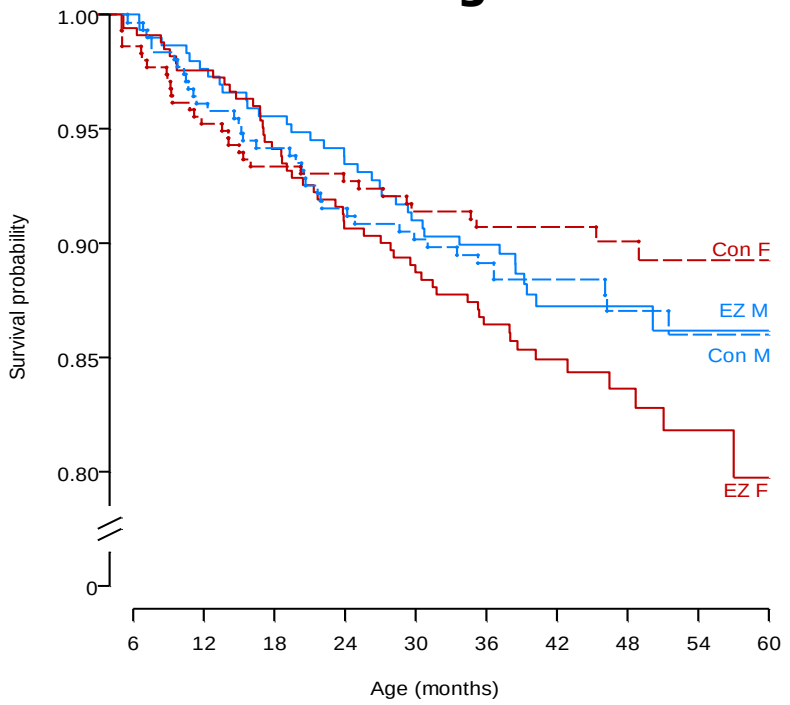
Bandim Health Project and Research Center for Vitamins and Vaccines (CVIVA)

High-titre Measles Vaccine (HTMV) at 4-5 mo, 1986-92

Bissau



Senegal



J Pediatr 1993 and Bull WHO 1994

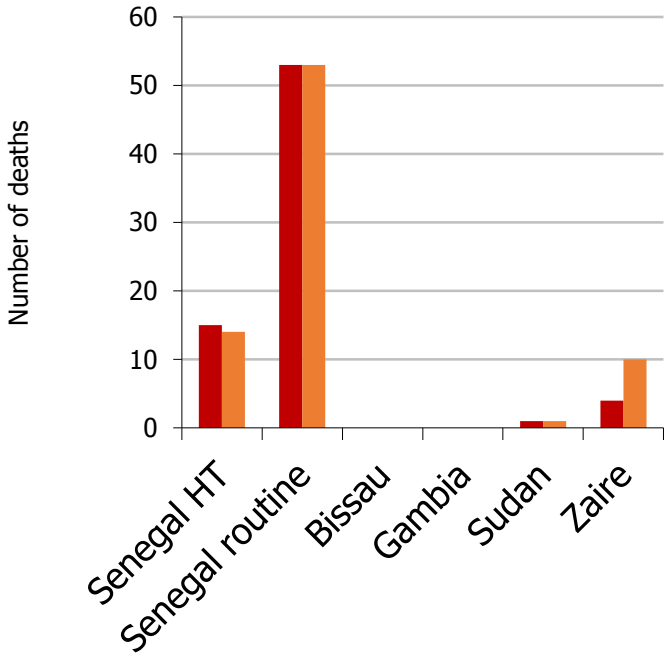
Intervention: EZ MV + IPV at 9 mo
Control: IPV + standard MV at 9-10 mo

Same effect in Haiti and Sudan
WHO withdrew HTMV 1992

HTMV protected measles infection but 2-fold higher female mortality
All African studies 33% excess mortality from 4 mo to 5 years
HTMV proved NSEs are very important
[Solution to this enigma: ?]

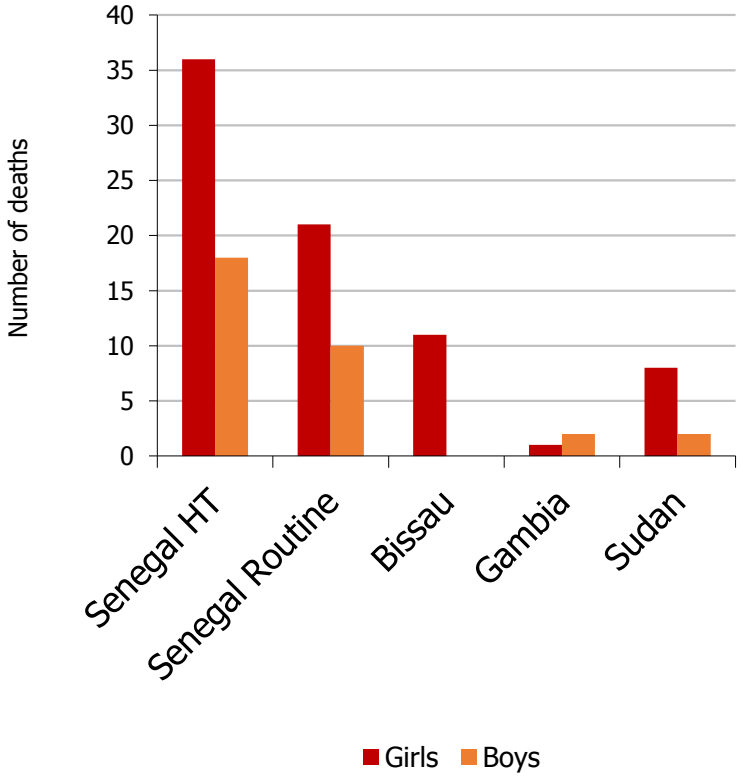
Resolution of contradiction-I: DTP/IPV after HTMV?

No DTP after HTMV



F/M ratio: 0.96 (0.7-1.3)

DTP/IPV after HTMV



F/M ratio: 1.93 (1.3-2.8)

Lancet 2003

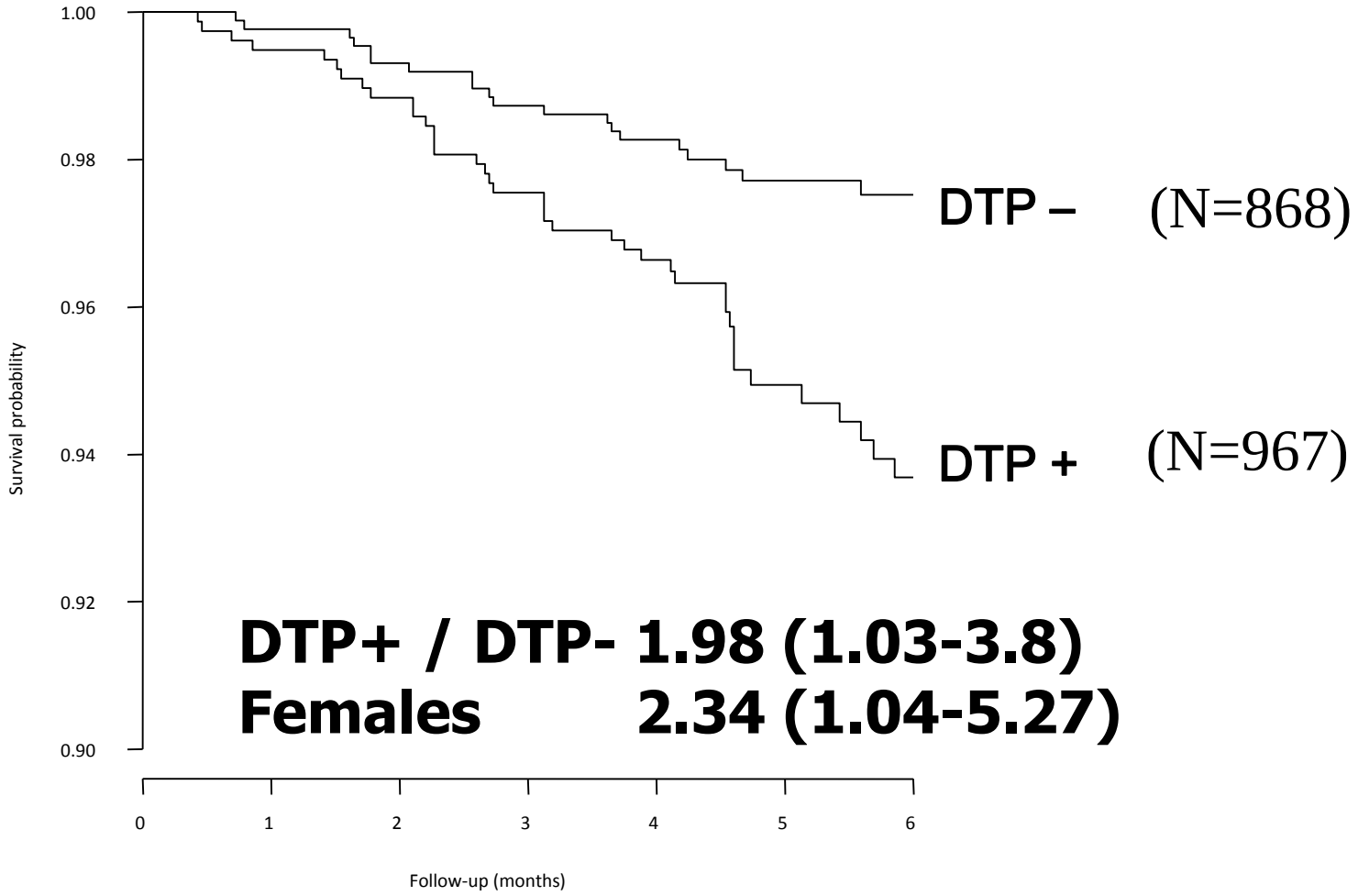
HTMV withdrawn for the wrong reason
The real problem was sequence of vaccinations
MV after DTP3 as most recent vaccine – has low mortality
DTP after MV as most recent vaccine – has high mortality

Introduction of DTP

Rural areas of Guinea-Bissau 1984-87

Children aged 2-8 mo

Unvaccinated: travelling; sick; days without vaccines

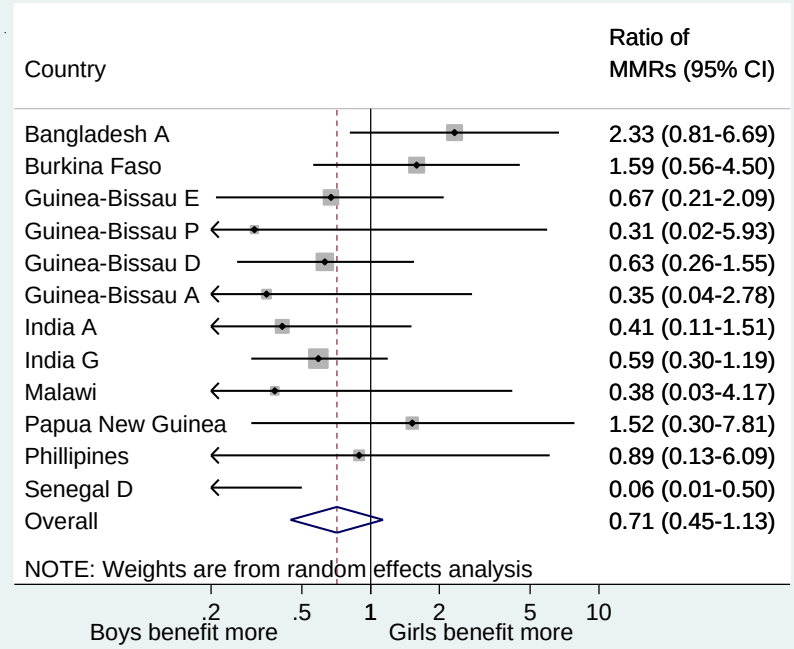


The only study of the introduction of DTP in the global literature

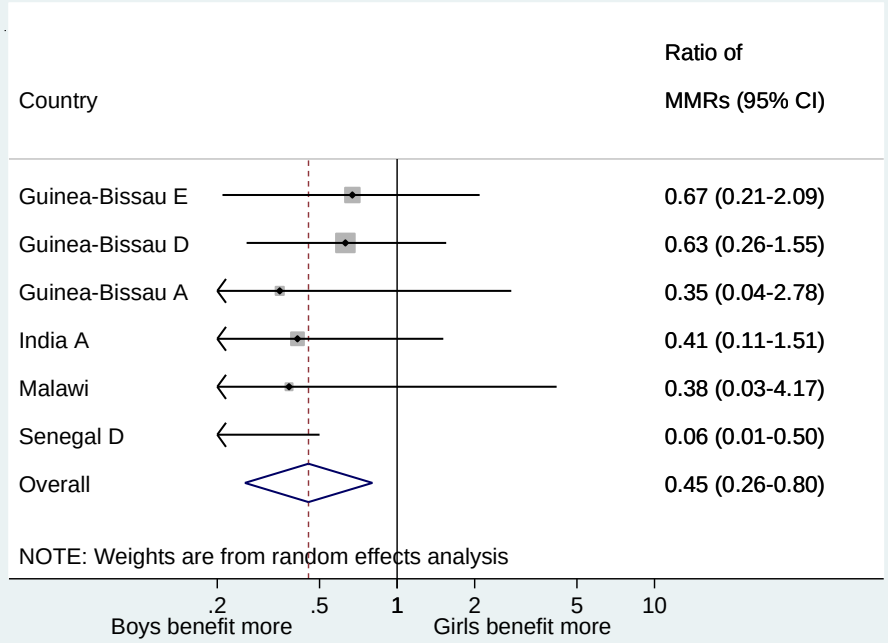
Aaby et al, Int J Epidemiol 2004

DTP and all-cause mortality: differences between effects in boys and girls

From SAGE review



Bias indicator <2



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Live Vaccine Against Measles, Mumps, and Rubella and the Risk of Hospital Admissions for Nontargeted Infections

Signe Sørup, PhD; Christine S. Benn, DMSc; Anja Poulsen, PhD; Tyra G. Krause, PhD; Peter Aaby, DMSc; Henrik Ravn, PhD

RESULTS The study included 495 987 children contributing with 56 889 hospital admissions for any type of infection during 509 427 person-years (rate, 11.2 per 100 person-years). Receiving the live MMR vaccine after the inactivated DTaP-IPV-Hib-vaccine was associated with a lower rate of hospital admissions for any infection.

Most Recent Vaccination	Children, No.	Infectious Disease Admissions per 100 Person-Years (Admissions/Person-Years)	Adjusted Incidence Rate Ratio (95% CI)
Recommended-schedule cohort	456 043		
DTaP-IPV-Hib3 (no MMR)		12.4 (20 743/167 693)	1 [Reference]
MMR after DTaP-IPV-Hib3		8.9 (21 311/239 642)	0.86 (0.84-0.88)
MMR vs DTaP-IPV-Hib2	490 838		
DTaP-IPV-Hib2 (no MMR)		15.1 (13 682/90 691)	1 [Reference]
MMR after DTaP-IPV-Hib2 (no DTaP-IPV-Hib3)		9.9 (1025/10 399)	0.87 (0.80-0.95)
Reversed-schedule cohort	19 219		
MMR after DTaP-IPV-Hib2 (no DTaP-IPV-Hib3)		9.9 (1025/10 400)	1 [Reference]
DTaP-IPV-Hib3 after MMR		12.8 (128/1001)	1.62 (1.28-2.05)

RUA bias

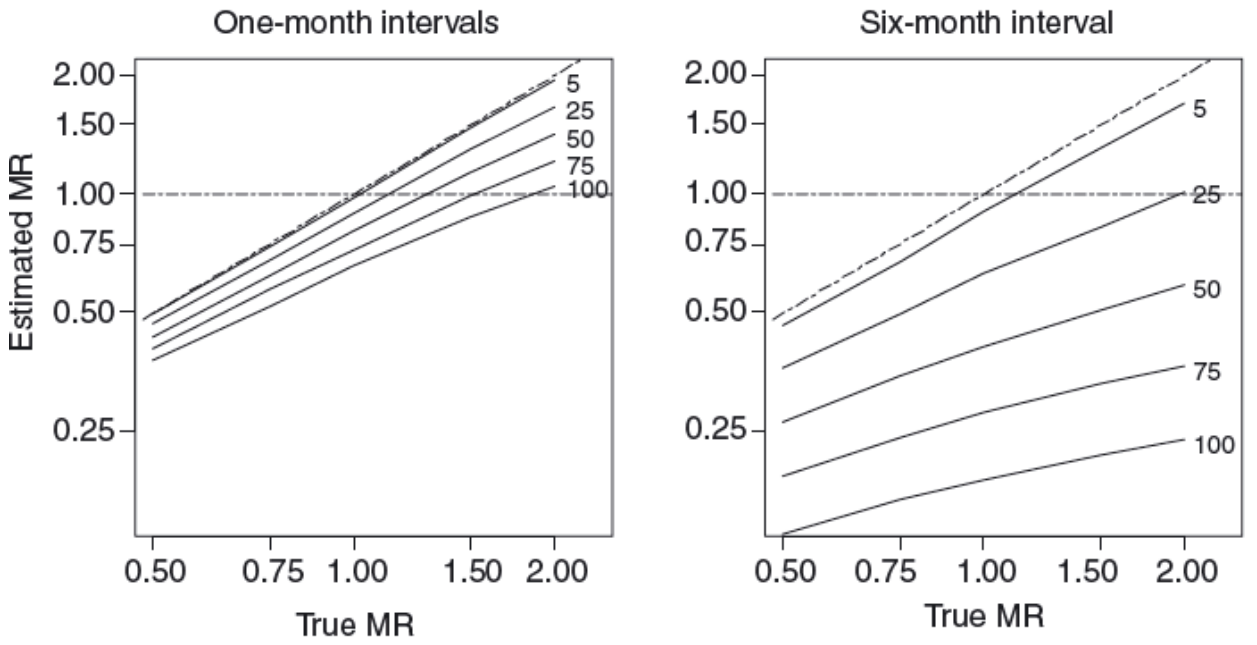

Figure 3 Retrospective updating approach. Results from computer simulation study showing effect of interval between visits, mortality rate ratios (MR), and percentage of dead children whose vaccination status could not be updated. Vaccination coverage is assumed to be 95% at 9 months of age and mortality rate among unvaccinated children is 55 per 1000. Each full line with number corresponds to percentage of dead children whose vaccination status could not be updated. Dotted lines represent the identity line and MR = 1. Note the log scale on both axes.

Landmark bias

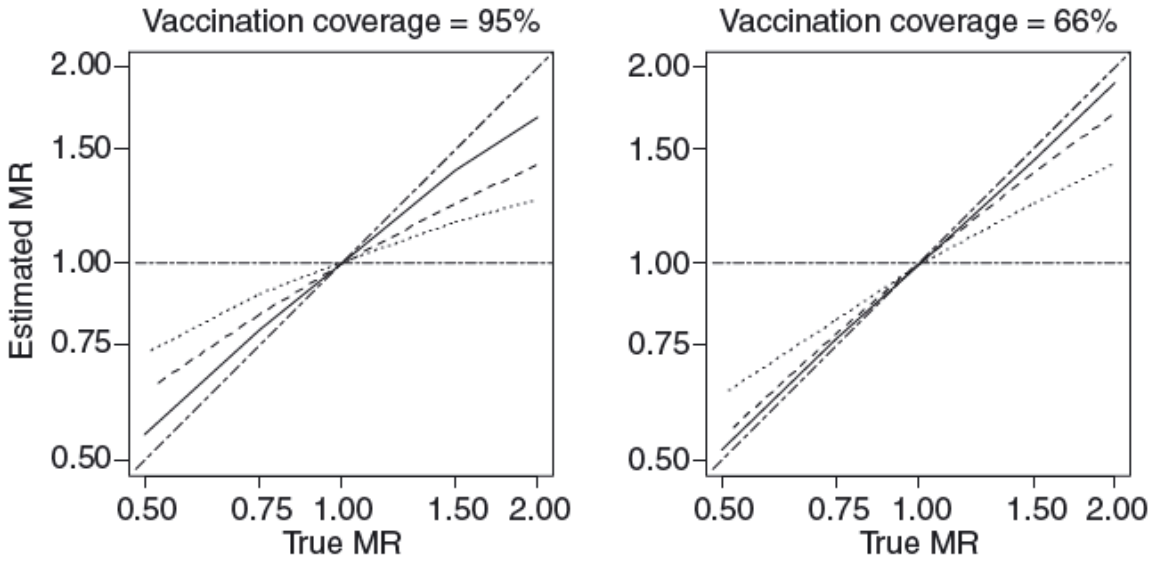

Figure 4 Landmark approach. Results from computer simulation study showing effect of interval between visits, vaccination coverage, and mortality rate ratios (MR). Mortality rate among unvaccinated children is 55 per 1000. Line types correspond to interval between visits: (—) 1 month, (– – –) 3 months and (· · ·) 6 months. Other dotted lines represent the identity line and MR = 1. Note the log scale on both axes.