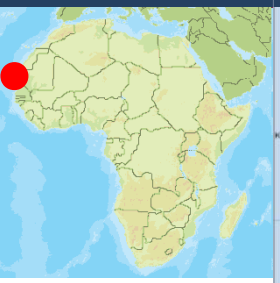
Bandim Health Project

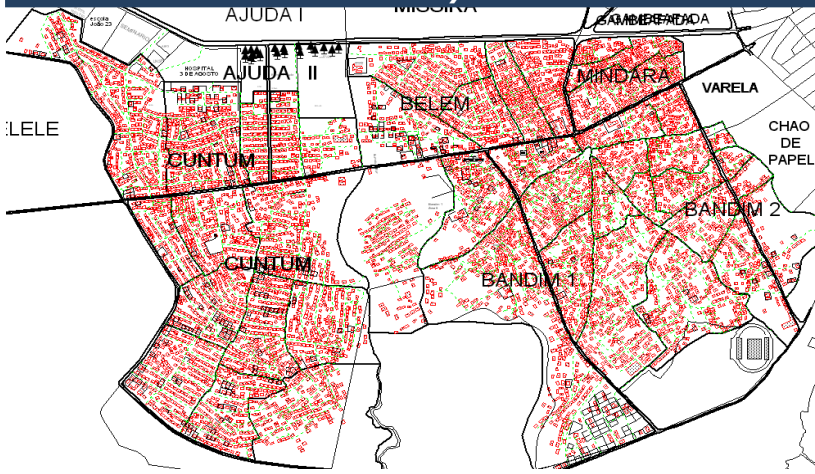
A platform for testing real-life effects of health interventions since 1978

Guinea-Bissau

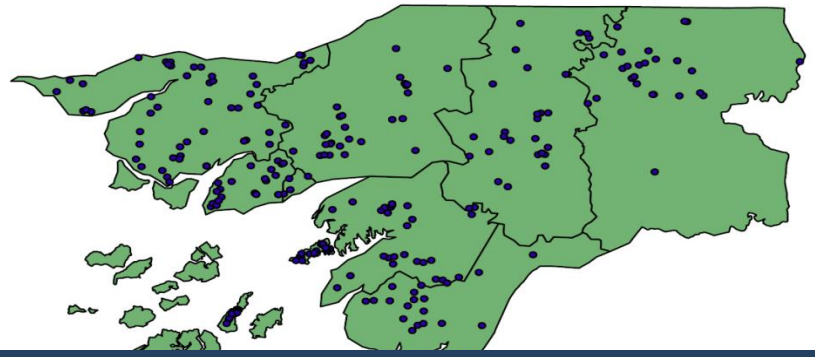


Bissau City

Urban study area



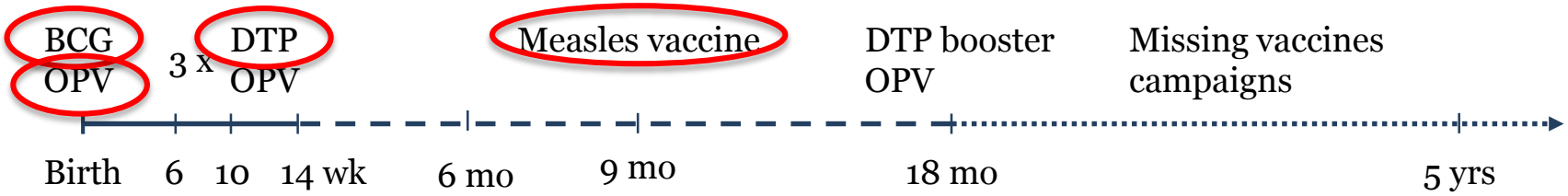
Rural study area



Urban study area **> 100,000 persons**
Rural study area **> 100,000 persons in 182 villages**
1978-79: Under-5 mortality ~500/1000

Live vaccines and off-target effects: BCG, measles vaccine and oral polio vaccine (OPV)

WHO vaccination policy in low-income countries



BCG=Bacille Calmette Guérin; DTP=diphtheria-tetanus-pertussis vaccine; OPV=oral polio vaccine; VAS=vitamin A supplementation

Measles vaccination (MV) at 9 months

Projected reduction in measles in Kenya–1974-81

Age	Accumulate incidence	Conversion	Prevented cases (%)	Unvaccinated cases	Vaccine failures	Deaths by measles/1000 Case fatality 4%
5	1	35%	35	0	65	26
6	3	52%	51	1	48	20
7	6	72%	69	3	28	12
8	10	86%	79	6	15	8
9	***14***	***95%***	***84***	***10***	***7***	***6***
10	19	98%	82	14	4	7

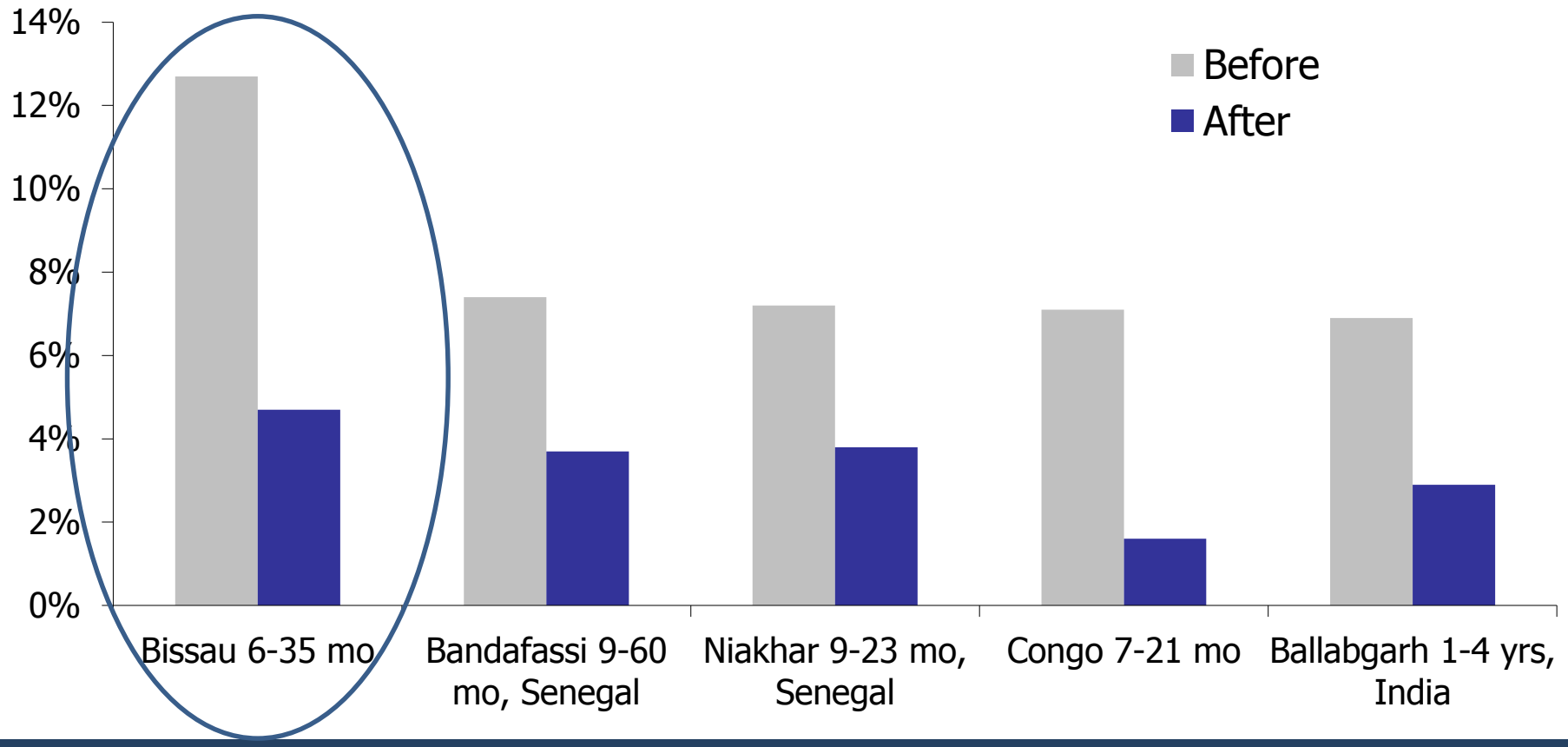
Two studies of incidence and seroconversion by age in months

Single-disease perspective: disease-burden=>specific-immune responses=>projected-impact

Over-all effect was not tested in any trial

The introduction of measles vaccine (MV)

Annual mortality rate before and after in community studies

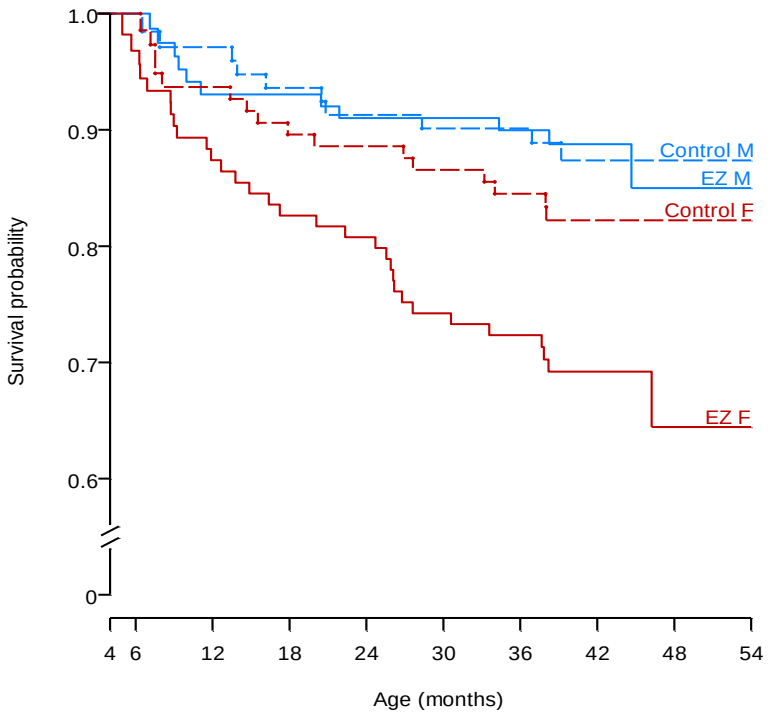


MV Campaign Dec 1979: mortality dropped from 13% to 4%
>50% reduction - Measles infection was 10-15% of deaths (WHO)
Studied delayed excess mortality as a possible explanation
That hypothesis was wrong

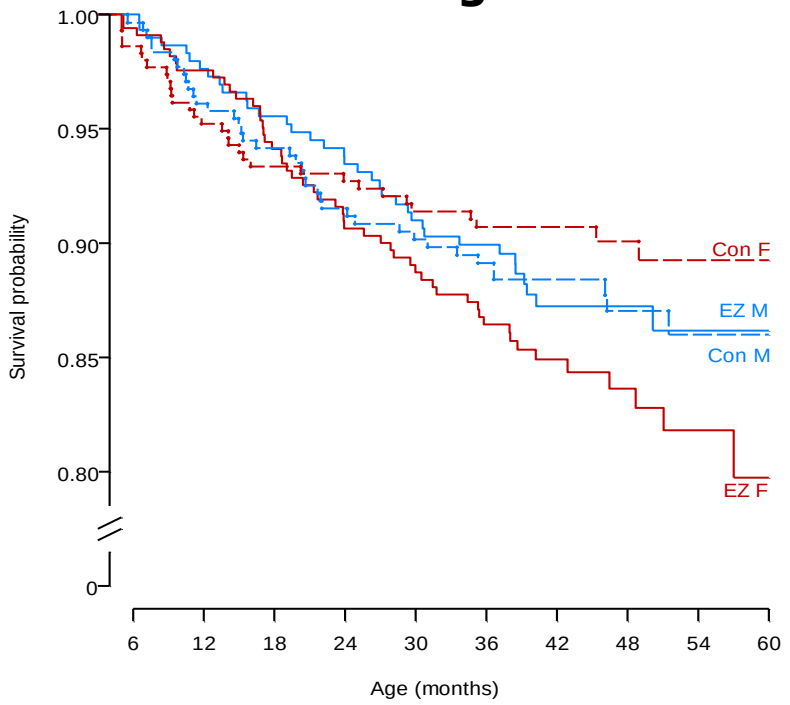
Aaby J Infect 1984; Am J Epidemiol 1995; Am J Epidemiol 1993; Kasongo Lancet 1981; Kapoor Ind J Pediatr 1991

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: ?]

The hypothesis of beneficial non-specific effects (NSEs) of measles vaccine

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

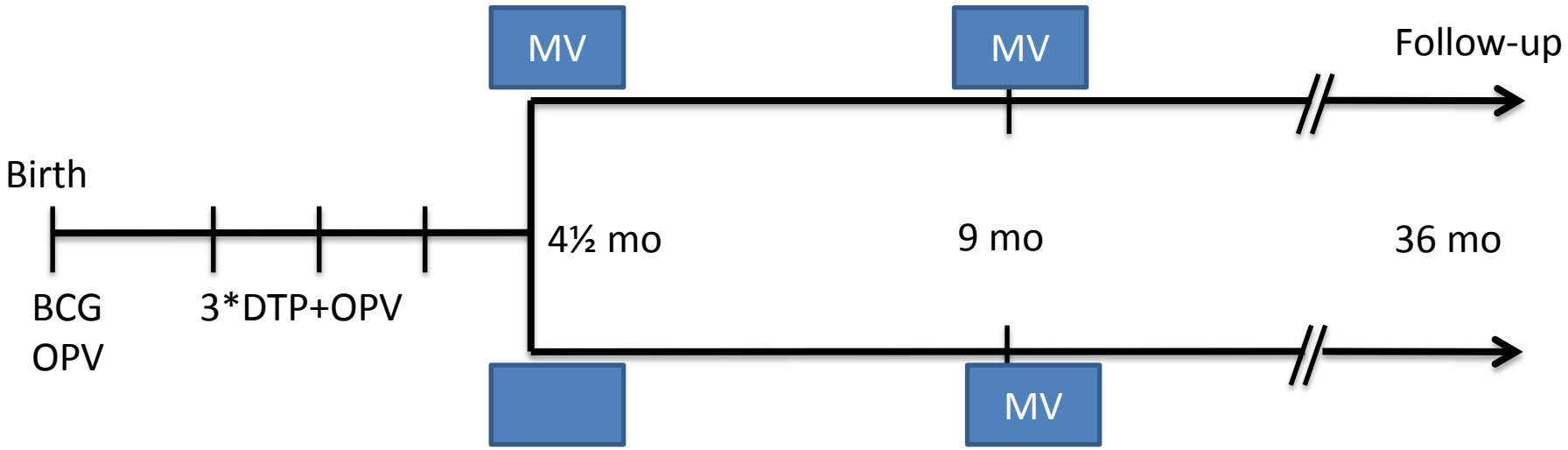
BMJ VOLUME 311 19 AUGUST 1995

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

Hypothesis to explain HTMV: standard MV had beneficial NSEs that HTMV did not have:

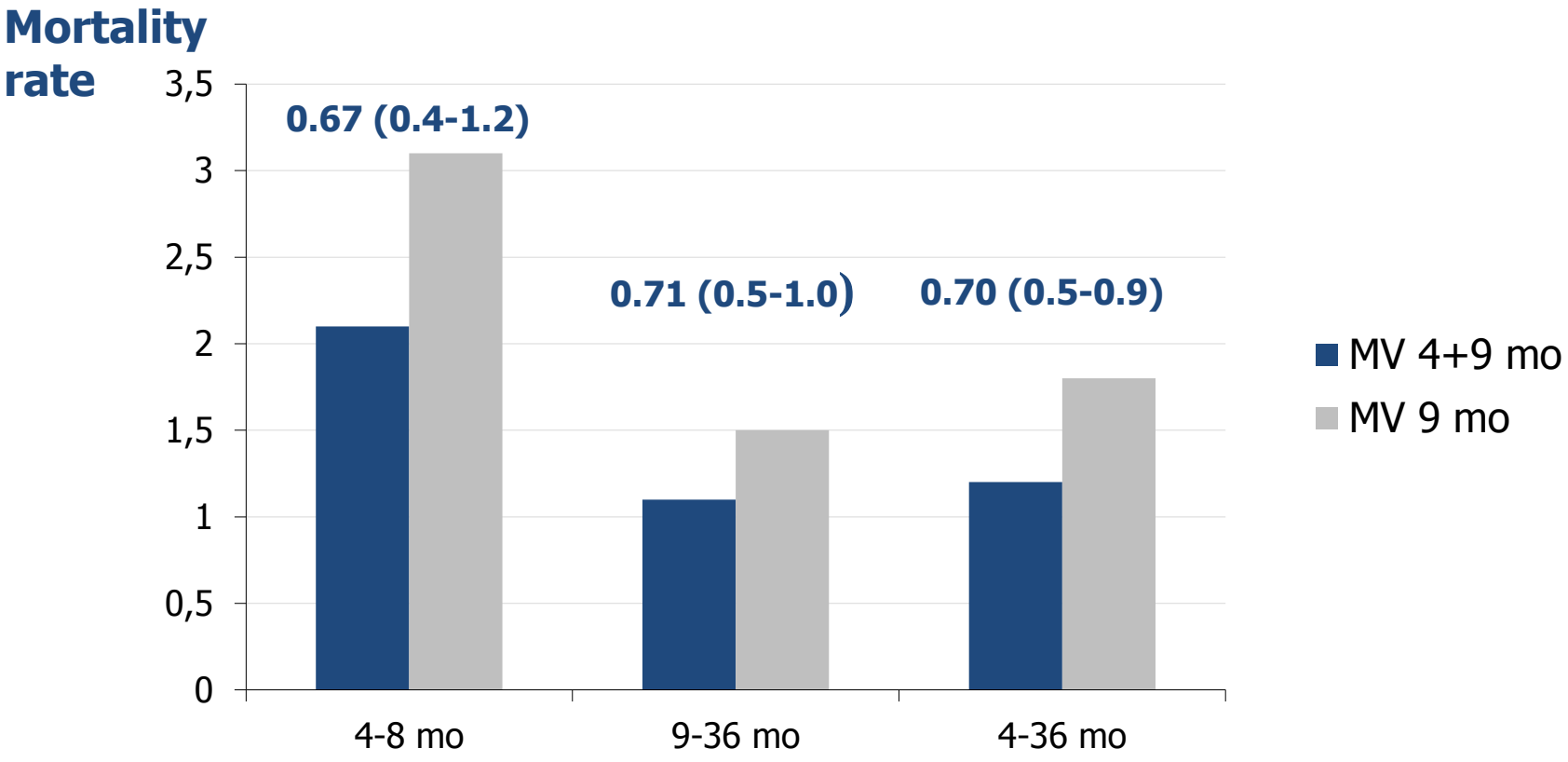
- MV vs unvaccinated 30-86% lower mortality
- Better effect when given in infancy
- Censoring measles inf. little change in estimate
- Stronger benefical effect for girls
- No beneficial effects of DTP+OPV

Testing non-specific effect of standard MV
(recruitment 2003-7; follow-up 2009)



Tested a 25% difference in mortality

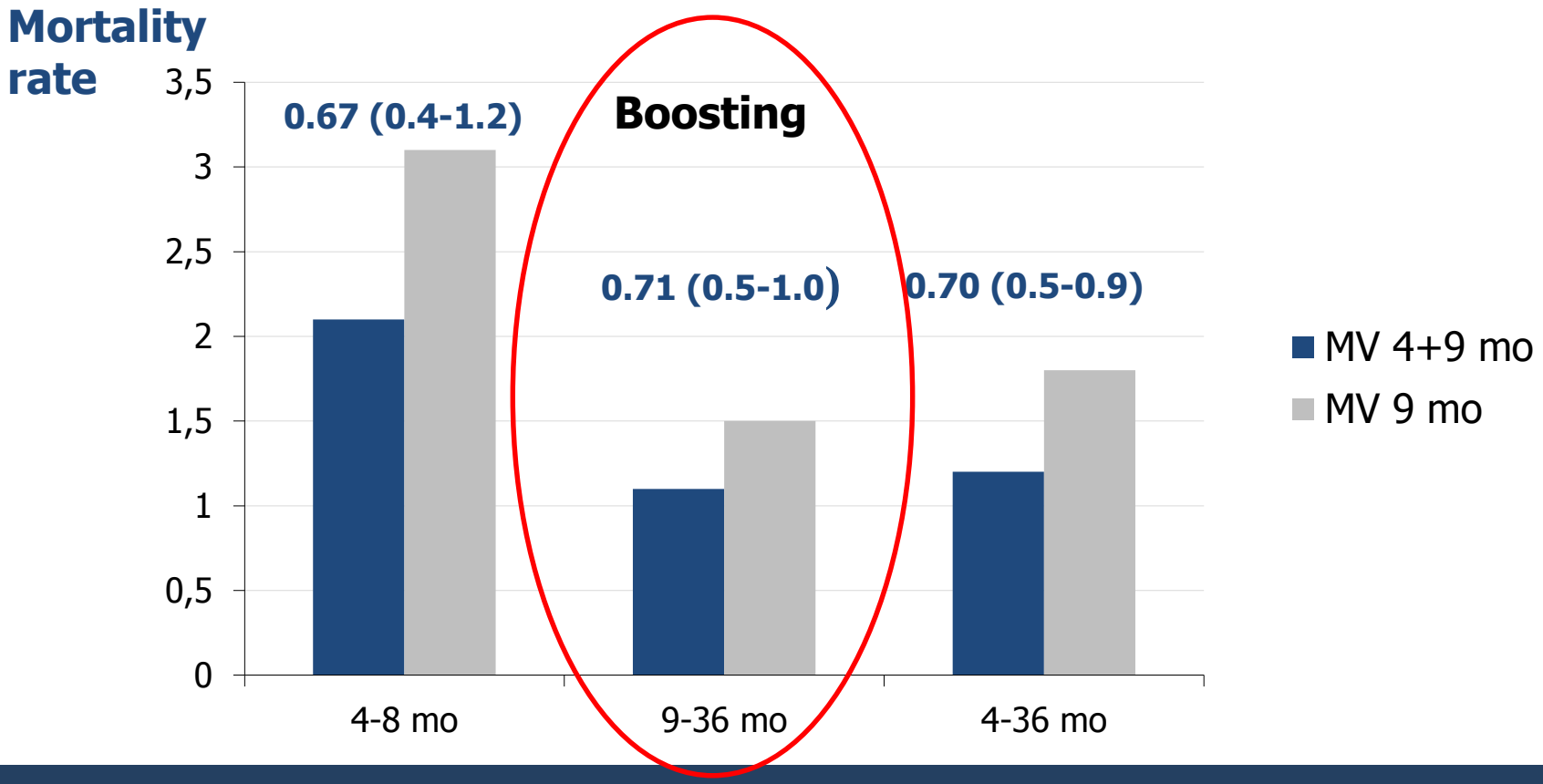
Randomised trial: MV at 4½+9 mo vs MV at 9 mo



MV at 4 and 9 mo: 30% (6-49%) (F: 41 %; M: 18%)
Measles infection censored: 26% (0-46%)
Effect on admissions for lower respiratory infections

Aaby et al, BMJ 2010, JID 2014

Randomised trial: MV at 4½+9 mo vs MV at 9 mo



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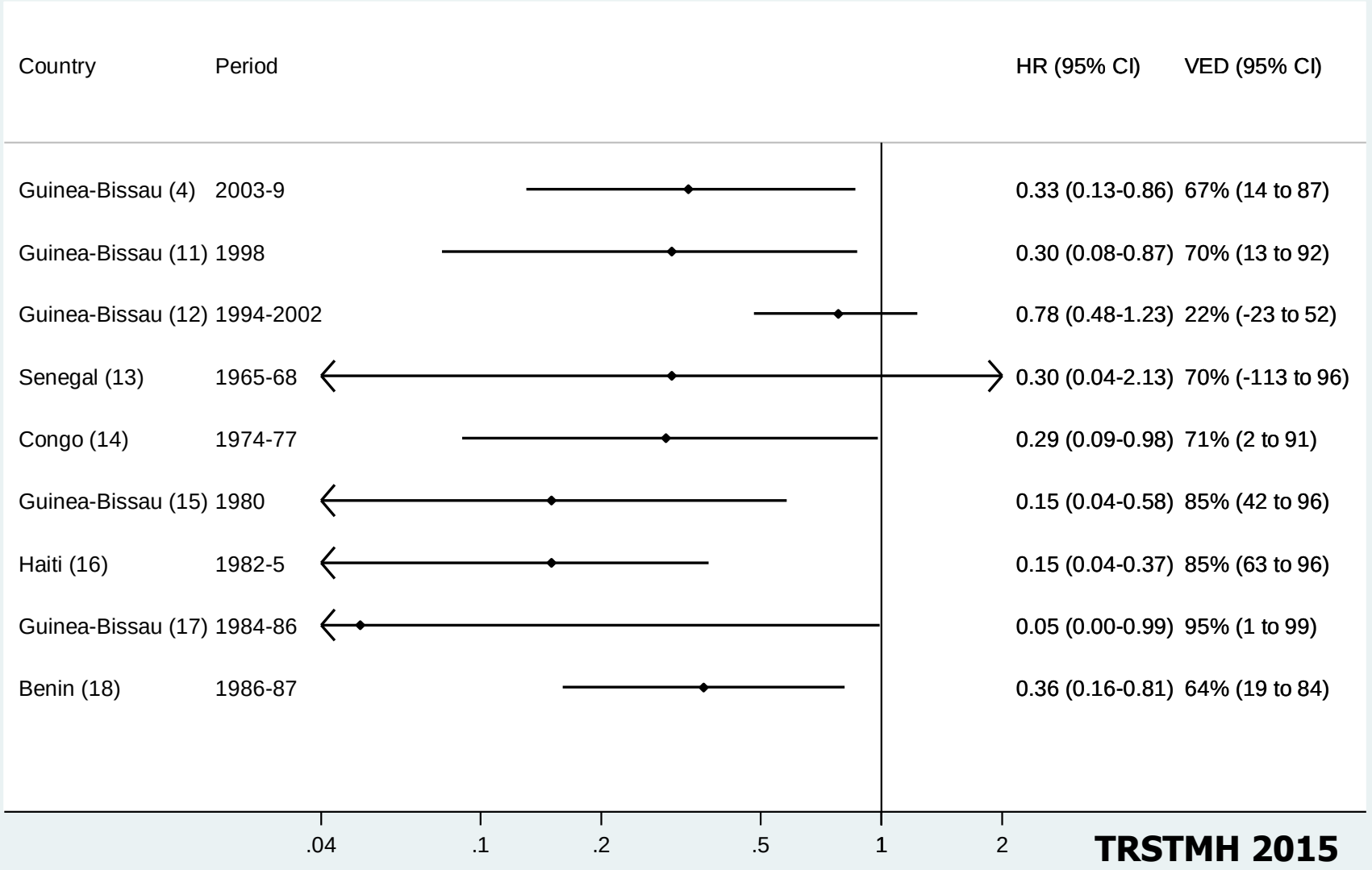
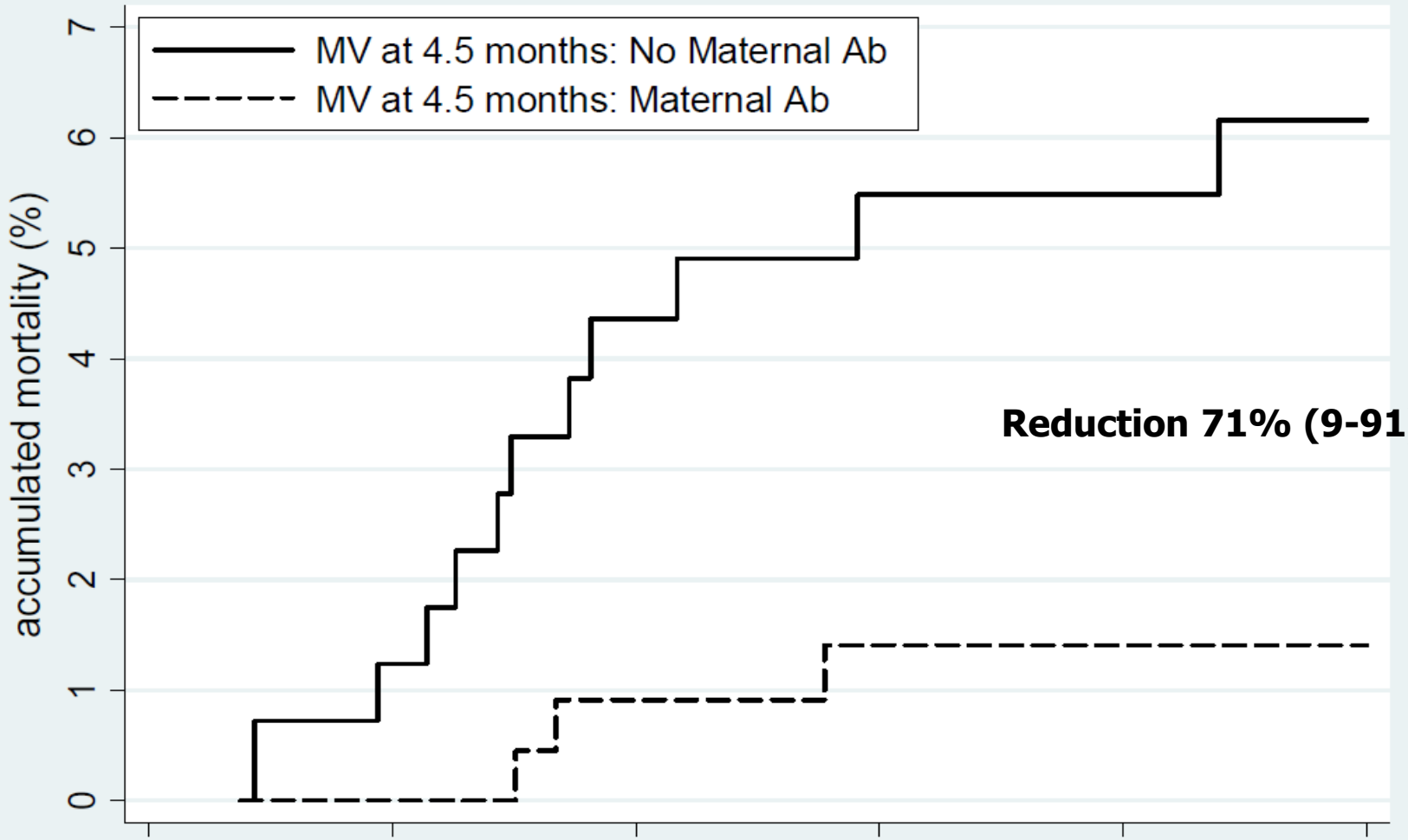
WHO MV policy: Not vaccinate in presence of maternal antibodies => Increase age from 9 to 12 mo when measles is controlled

Better effect on survival of MV < 12 mo



TRSTMH 2015

But what does maternal antibodies do to MV?



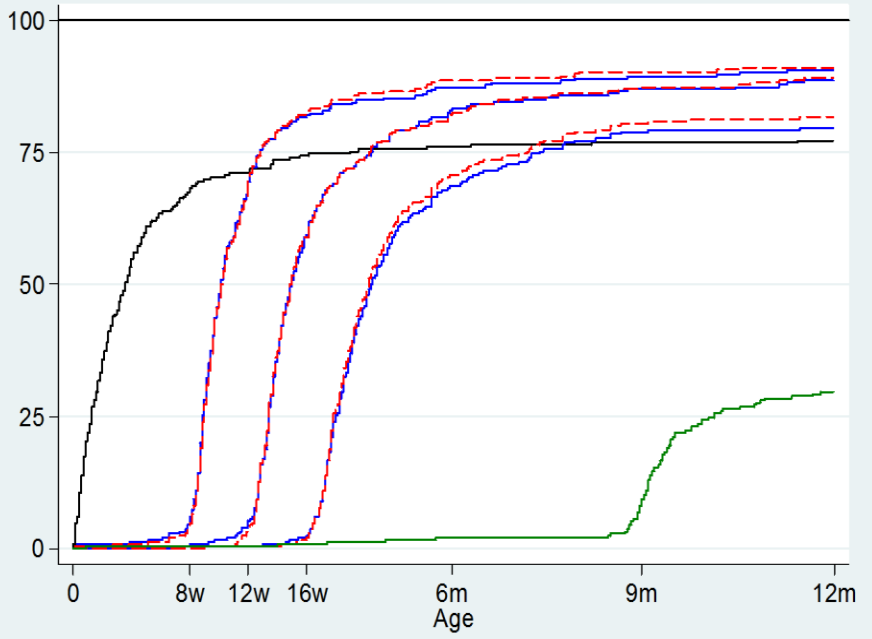
Aaby et al
CID 2014

Figure 1: Kaplan-Meier accumulated mortality curves between 4½ months and 5 years of age

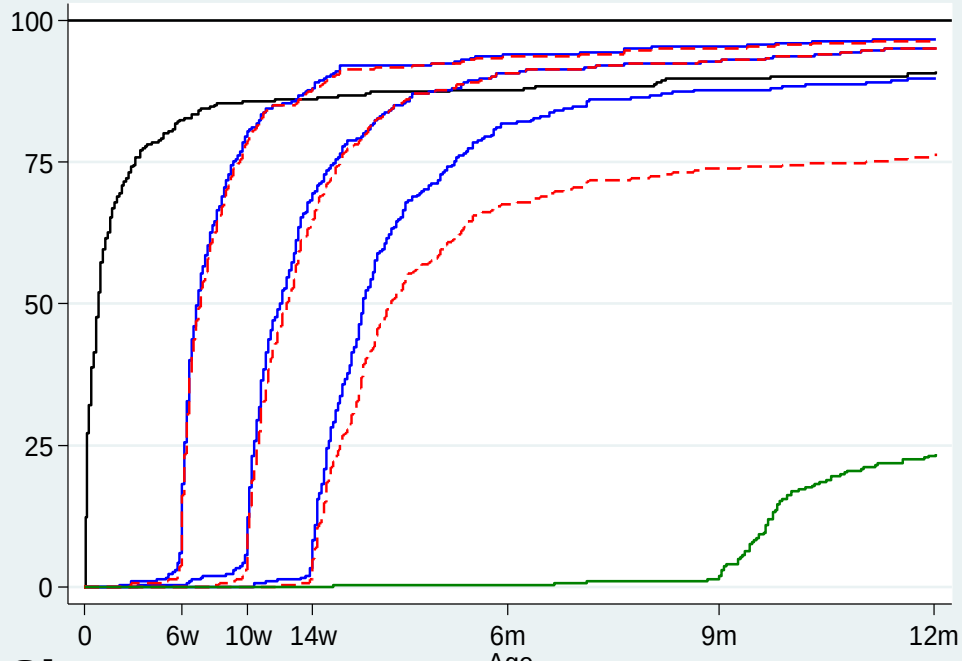
Main risk factor for not being a fully immunized child (FIC) by 12 mo: Lack of MV!

Not-FIC has 32% (18-47%) higher mortality from 1-3 yrs

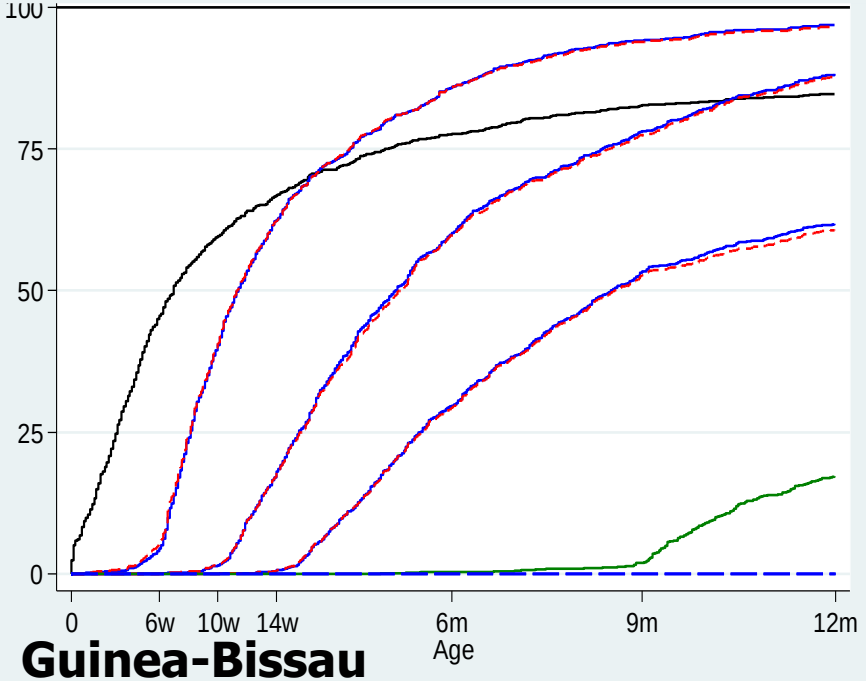
Burkina Faso not FIC 2014



Not FIC at 12 months: 2012

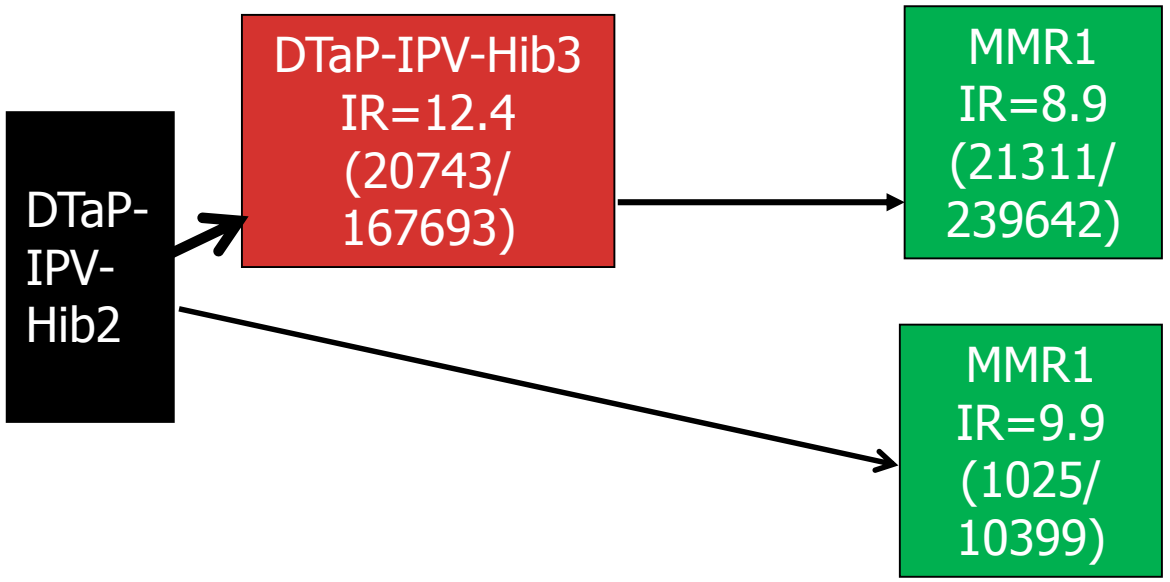


Ghana



Guinea-Bissau

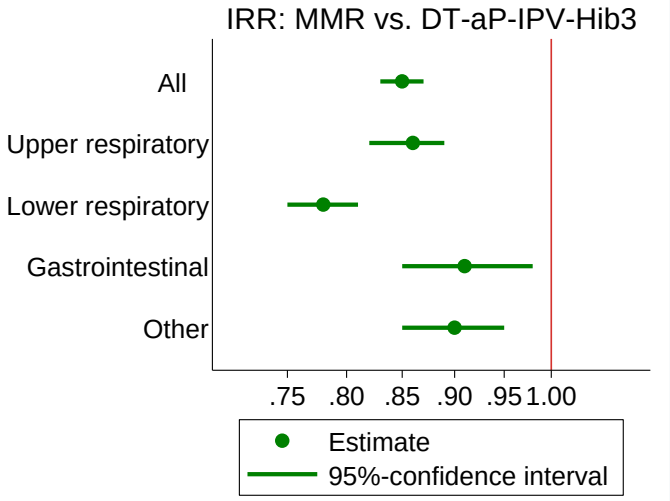
High-income: Infectious hospital admissions MMR vs.DTaP-IPV-Hib3 in Denmark



IRR=0.86 (0.84-0.88)

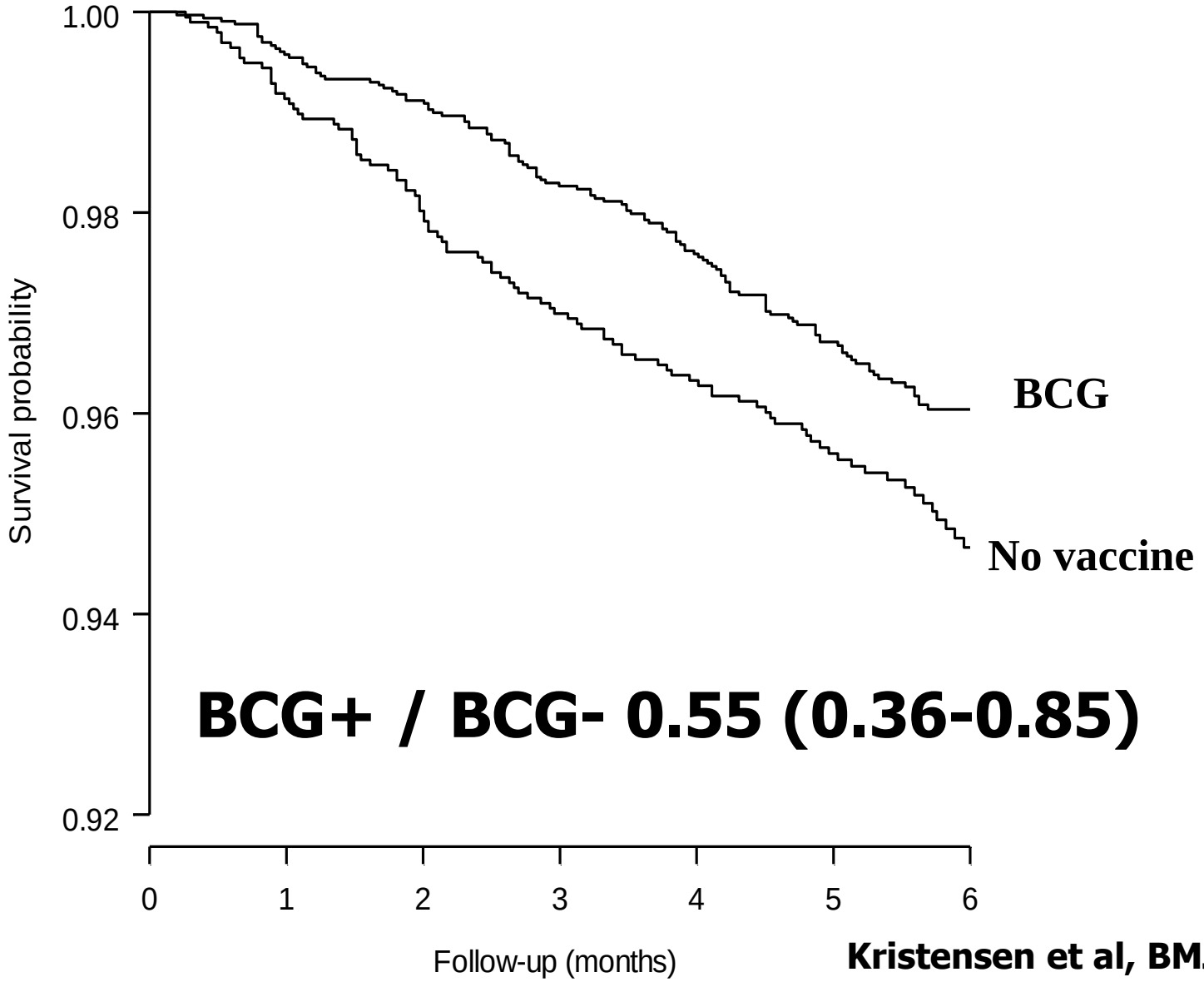
IRR=0.87 (0.80-0.95)

Hospital admission in 2nd year of life
475,000 children in 1997-2006 –
44,000 hospital admission

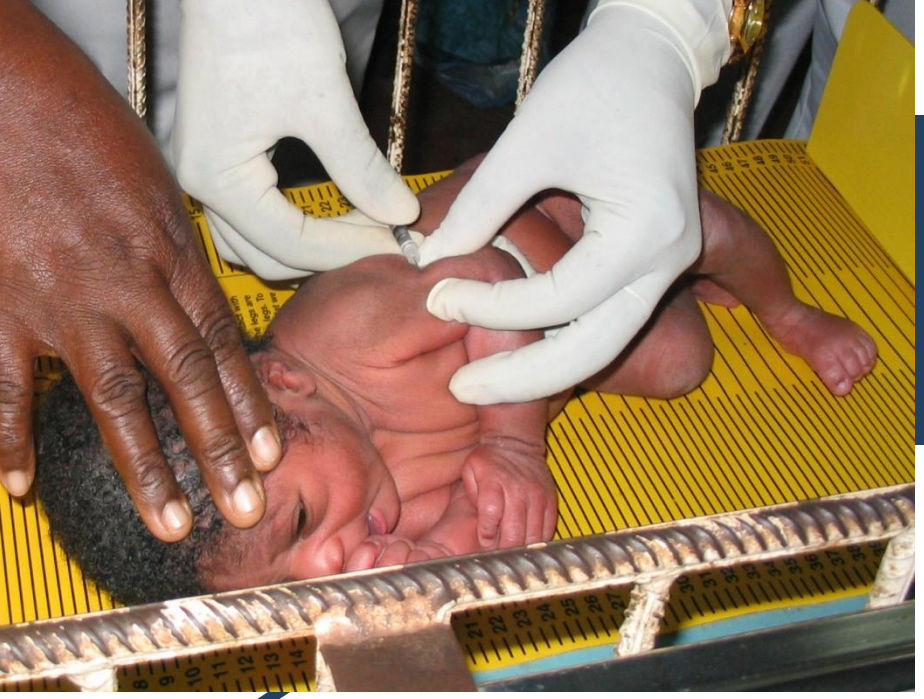


Sørup JAMA 2014

If MV has beneficial NSEs – What about other vaccines?
Tested mortality by vaccination status in rural Guinea-Bissau; Children aged 0-6 mo at first visit – 6 mo follow-up



Kristensen et al, BMJ 2000



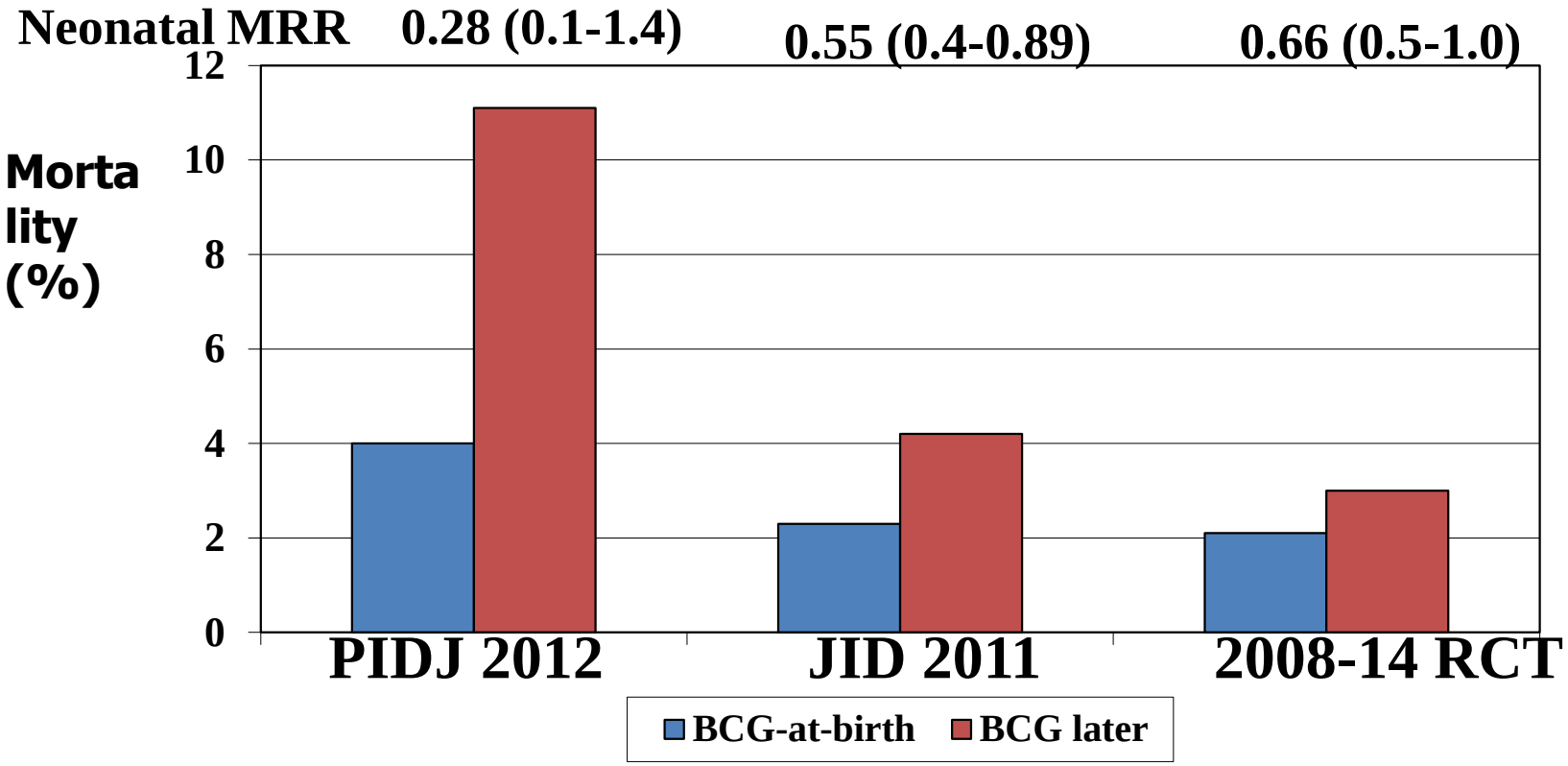
Testing NSEs of BCG among LBW children who do not get BCG

- We randomised to BCG-at-birth or later (current practice)
- Infant mortality was main outcome (25% reduction)

3 trials of BCG-at-birth in LBW children

3-days MRR=0.55 (0.32-0.93)

Neonatal MRR=0.59 (0.44-0.81)

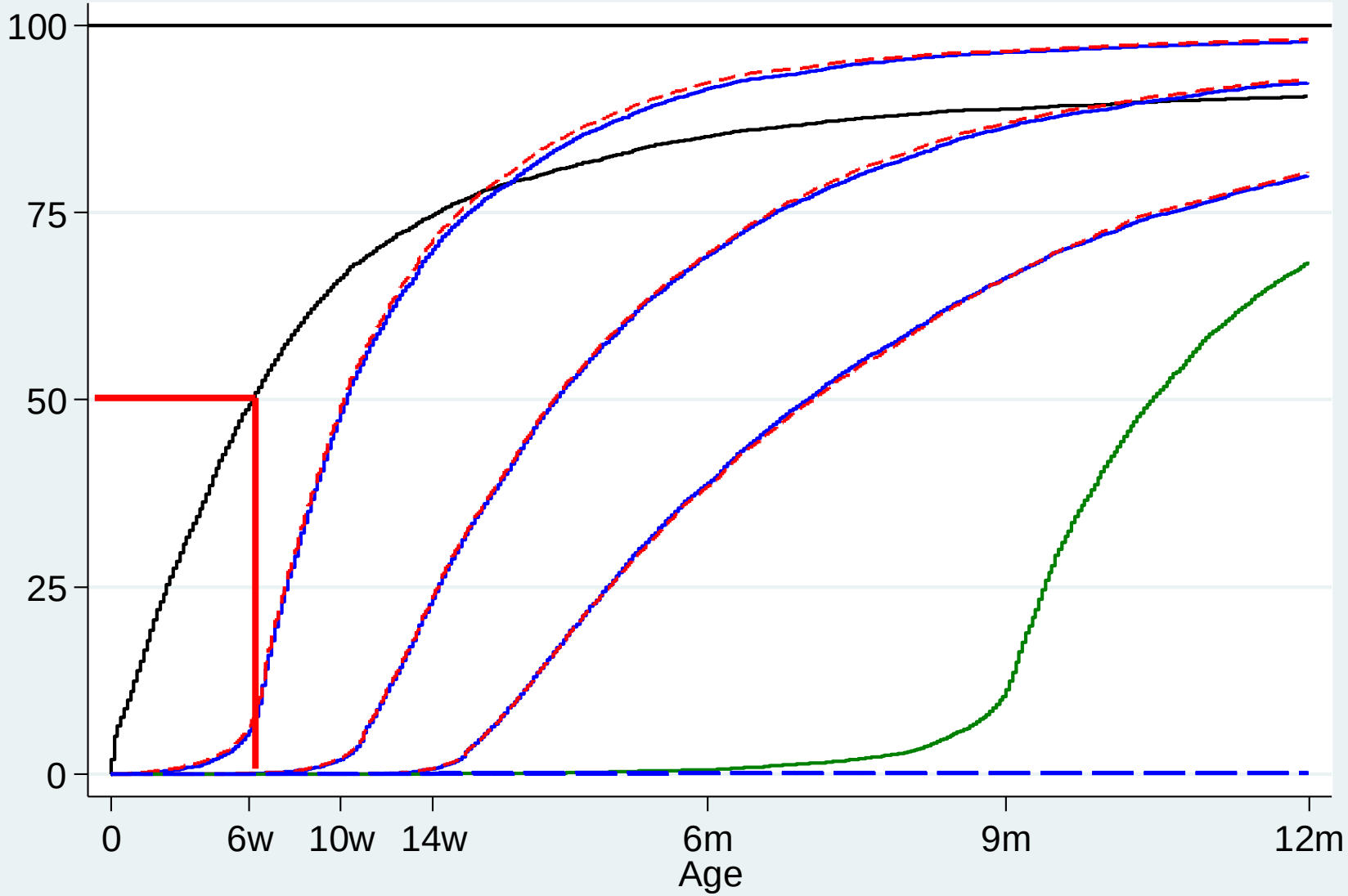


Reduction in neonatal sepsis and respiratory infections

Not prevention of TB => Beneficial NSE of BCG

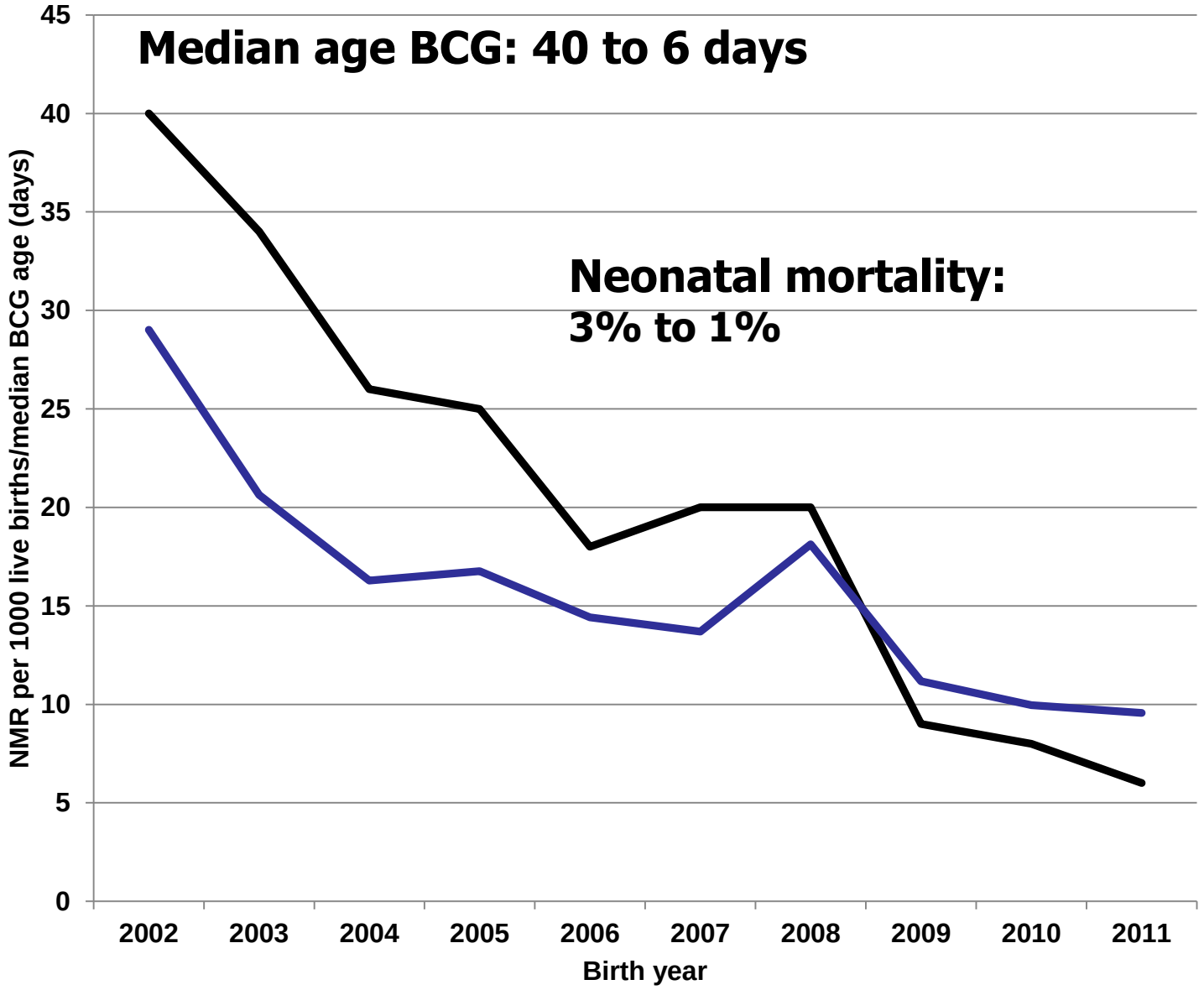
Median ages of vaccination in rural Guinea-Bissau

2009-12



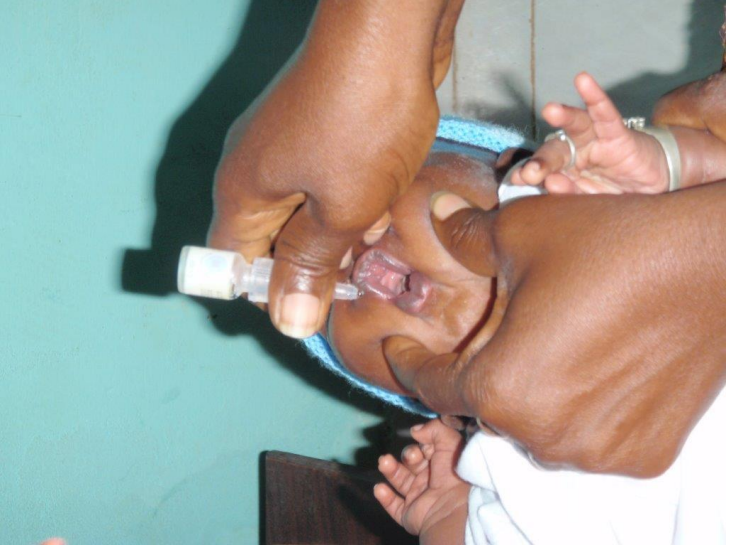
Wastage reduction by restrictive policy for opening multi-dose vials for BCG and MV

Home deliveries: Median age of BCG and neonatal mortality rate (day 1-28)



Hospital Deliveries No change

Navrongo, Ghana Welaga MPhil



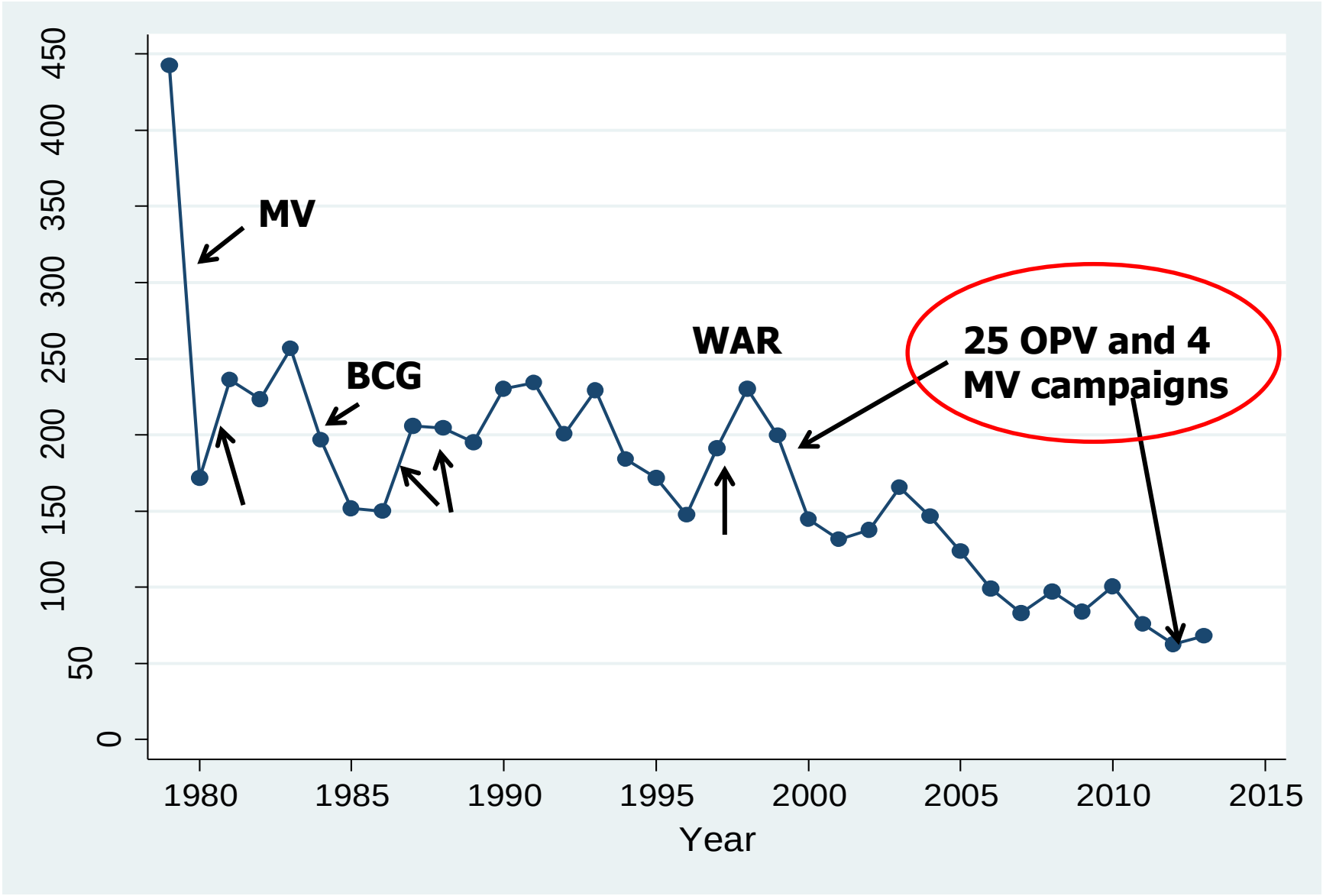
Last of the *live* vaccines

RCT of infant mortality for BCG+OPV0 vs BCG-only

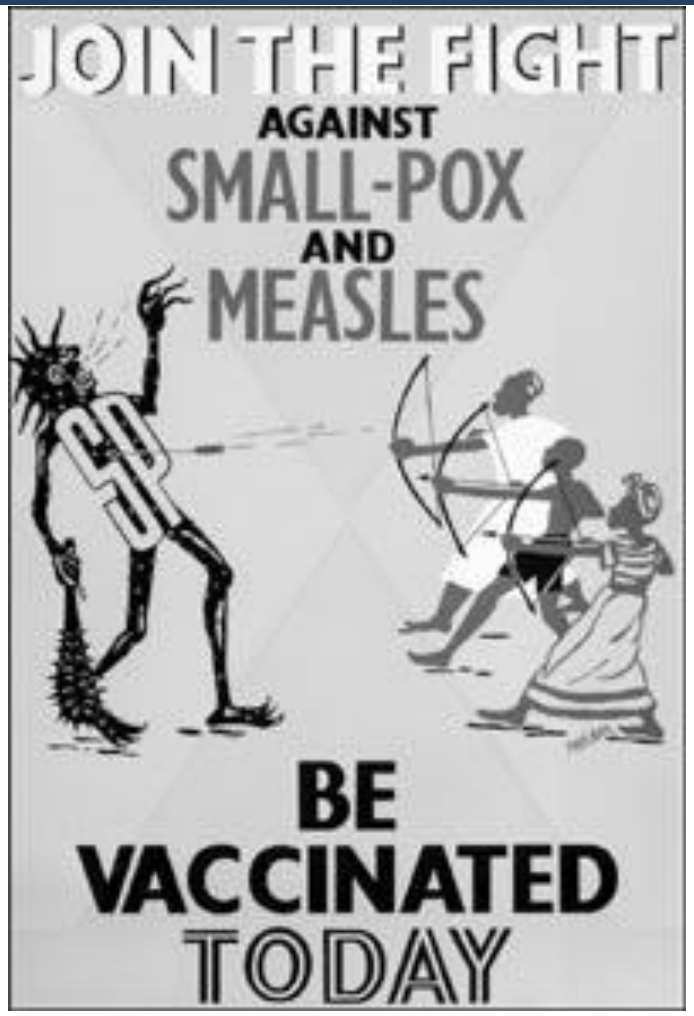
(N=7000; No polio in Bissau)
Effect of OPV campaigns censored

Group	Mortality rate ratio for OPV0+BCG vs BCG-alone
All children	0.68 (0.45-1.00)
Boys	0.57 (0.33-0.98)
Girls	0.86 (0.48-1.56)
Enrolled day 0-2	0.58 (0.38-0.90)

Under-5 mortality in Guinea-Bissau: Mortality should go down gradually with introduction of new vaccines – The role of *live* vaccines



We live in a Single-disease-paradigm



We

- **Emphasize inactivated vaccines (DTP3, IPV)**
- **Remove *live* vaccines (Vaccinia, BCG, OPV)**

But we have not tested

- **Overall effect**
- **Sex-differential effects**
- **Interactions with other vaccines**
- **Interaction with vitamin A**

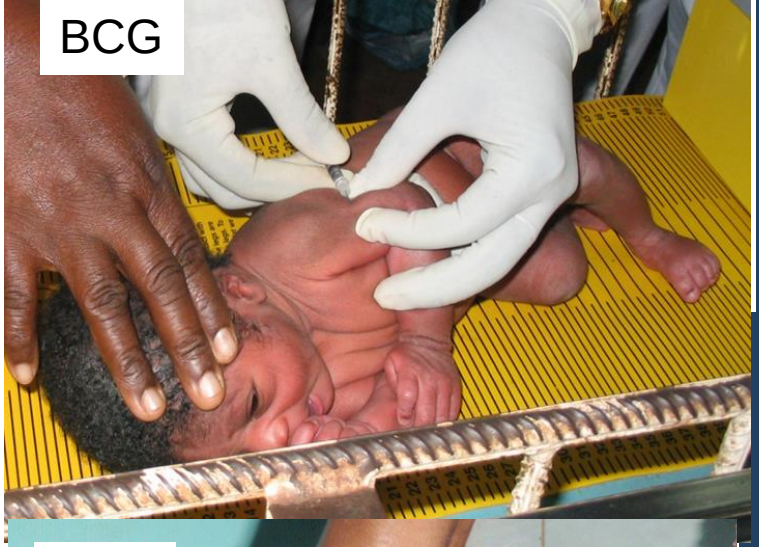
The single-disease perspective may be dangerous

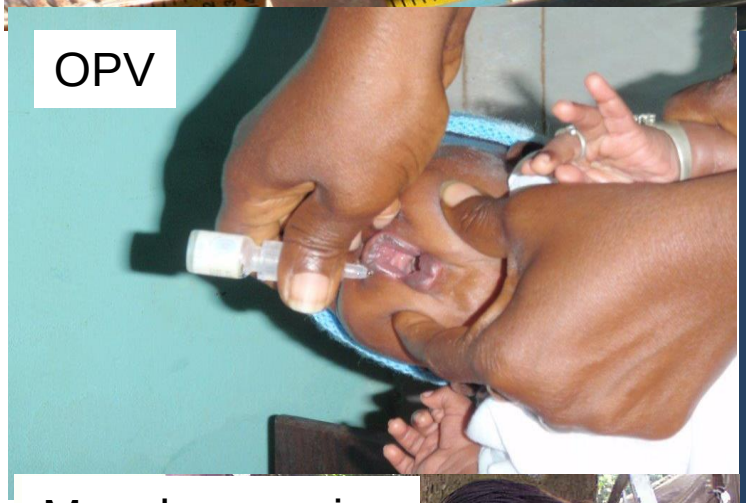
RTS,S/AS01 malaria vaccine protects 18-36% against clinical malaria (Lancet 2015)

across Africa, Asia, and South America. Based on the information now available it would be surprising if RTS,S were not to proceed to widespread deployment. The costs and challenges of such an exciting project will be great. However, in the hope that 2015 will be remembered as a turning point in malaria prevention, a vaccine rollout programme deserves our full support. ■ *The Lancet*

”No protection was noted against all-cause mortality”

Period	Deaths RTS,S vaccine	Deaths Controls	MRR
0-14 mo	122/10306	56/5153	1.09 (0.80-1.49)
14 mo-end of study	96/10184	32/5097	1.50 (1.01-2.24)
Overall	218/10306	88/5153	1.24 (0.97-1.58)

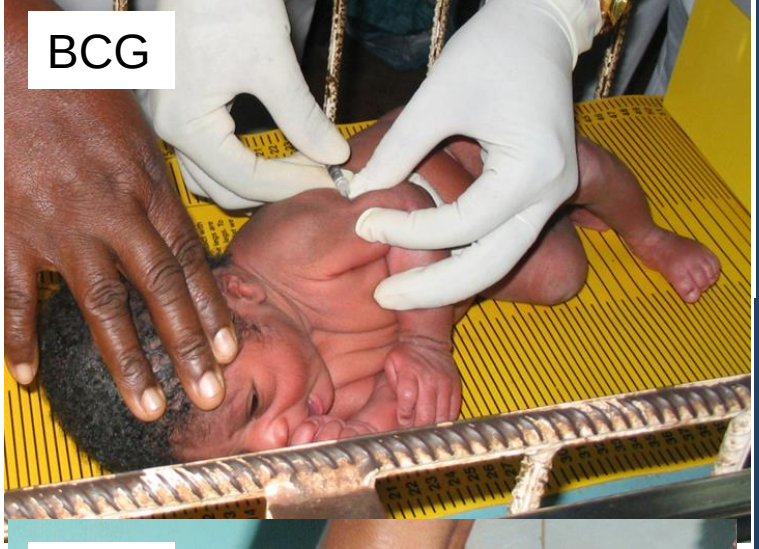


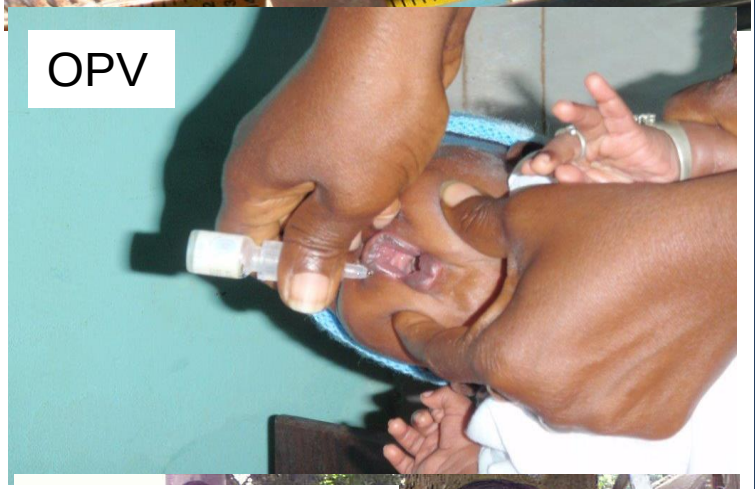


Live vaccines have beneficial NSEs

- Consistent beneficial NSEs in observational studies
- At least 25% reduction in off-target mortality in RCTs:
- MV: 26% (0-46%)
- BCG: 41% (19-56%)
- OPV: 32% (0-55%)

- => We need an Immune-training paradigm





Live vaccines have beneficial NSEs => Immune-training paradigm

- Major research questions
  - Sex
  - Live vs inactivated
  - Boosting
  - Maternal antibodies – early priming
  - Interaction between vaccines
- Immediate actions:
  - BCG-at-birth
  - MV earlier
  - 100% coverage for MV
  - Continue OPV and MV campgn
  - Not replace OPV with IPV
  - No DTP after MV
  - Do not monitor with DTP3

Long-term excess mortality after measles (Science 2015)

Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality

Michael J. Mina,[1,2*] C. Jessica E. Metcalf,[1,3] Rik L. de Swart,[4] A. D. M. E. Osterhaus,[4] Bryan T. Grenfell[1,3]

1. **Measles associated with long-term excess mortality**

conclude that long-term immunologic sequelae of measles drive interannual fluctuations in nonmeasles deaths. This is consistent with recent experimental work that attributes the immunosuppressive effects of measles to depletion of B and T lymphocytes. Our data provide an explanation for the long-term benefits of measles vaccination in preventing

2. **Explains the NSEs of measles vaccine**

immunosuppressive effects of measles to depletion of B and T lymphocytes. Our data provide an explanation for the long-term benefits of measles vaccination in preventing all-cause infectious disease. By preventing measles-associated immune memory loss, vaccination protects polymicrobial herd immunity.

Long-term excess mortality after measles

Study	Follow-up period after measles infect	Mortality rate ratio for measles infected vs. uninfected	MRR for index cases
Bissau 1979-81	6-18 mo	0.52 (0.13-2.10)	
Bissau 1988-92	1mo-5yrs	0.50 (0.22-1.16)	
Bissau 1990-94	1mo-3yrs	1.03 (0.66-1.61)	0.48(0.22-1.03)
Senegal 1983-86	1mo-4yrs	1.04 (0.80-1.35)	0.27(0.09-0.85)
Senegal 1992-96	1mo-4yrs	0.20 (0.06-0.74)	
Bangladesh 1982-85	3-12 mo	0.40 (0.16-0.98)	
Germany 1861-62	1-12 mo	0.23 (0.06-0.89)	
Overall		0.60 (0.38-0.94)	0.40 (0.21-0.75)

No individual level data to support Science paper
If anything: better survival after measles infection

Long-term excess mortality after measles infection explains the NSEs of measles vaccine (Mina,Science 2015)

The beneficial effect of MV is not explained by prevention of measles-associated immune memory loss:

1. The is not a general excess mortality after measles infection

2. Furthermore, censoring for measles infection does not change the estimated effect of MV in observational studies

3. Beneficial effect shown in RCT to be independent of presence of measles infection

4. There is a beneficial effect of MV even when there is no measles infection, e.g. Denmark, now in low-income countries

5. Boosting has a beneficial effect which has nothing to do with further prevention of measles infection

6. MV to immune children reduces mortality significantly

7. The beneficial effect is reversed/neutralised when an inactivated vaccine is given with or after MV even though the MV was protective

Measles vaccination at 9 months of age – established in 1970s

Projected reduction in measles in Kenya – 1974-1981

Age	Incidence	Conversion	Prevented cases (%)	Unvac cases	Vac failure	Deaths by measles/1000
5	1	35%	35	0	65	26
6	3	52%	51	1	48	20
7	6	72%	69	3	28	12
8	10	86%	79	6	15	8
9	***14***	***95%***	***84***	***10***	***7***	***7***
10	19	98%	82	14	4	7

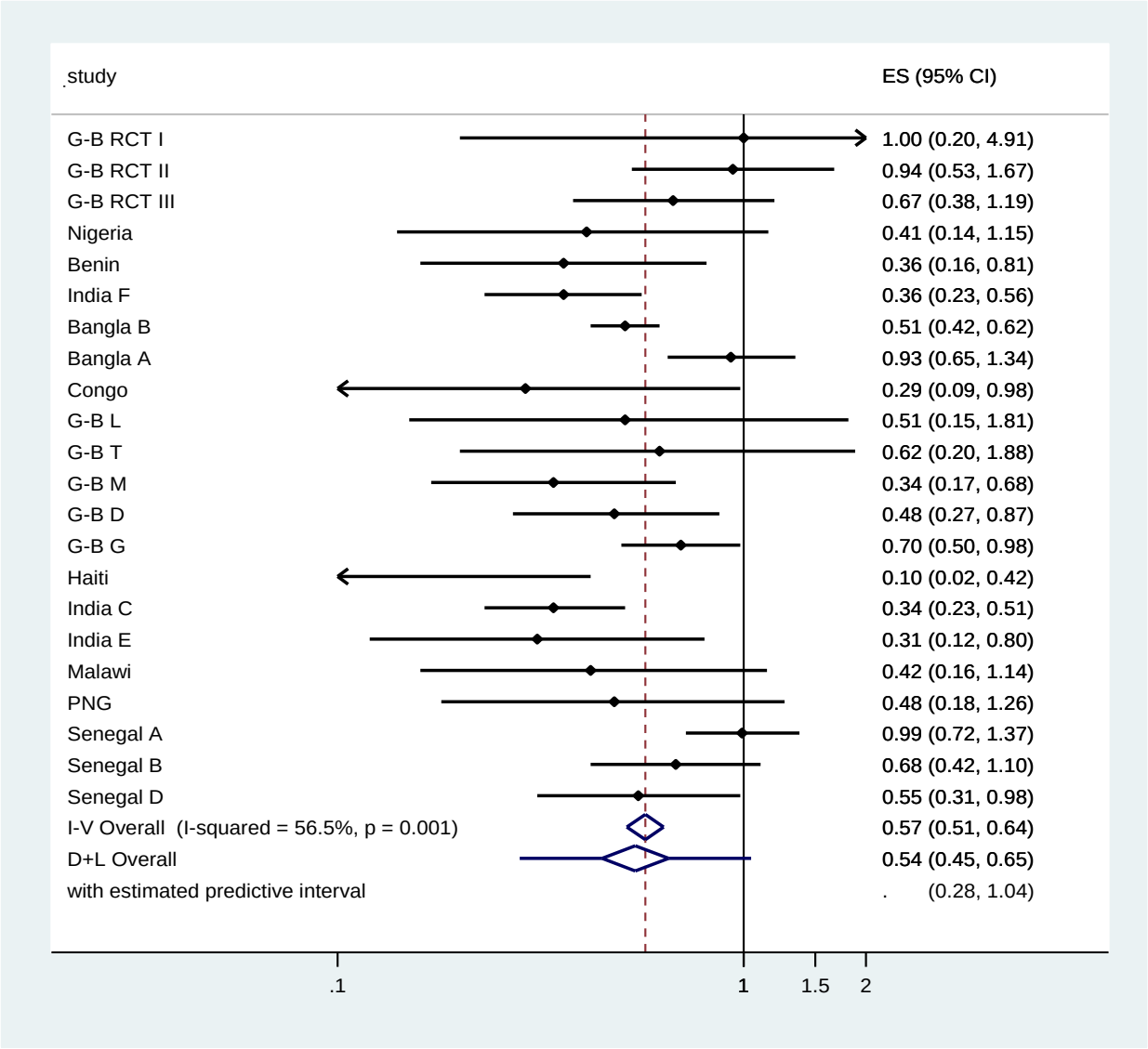
BMJ Open 2012

Impact on survival by vaccination at different ages was never tested

6 assumptions: 1. Seroconversion=protection; 2. non-seroconversion =susceptibility; 3. Vac cases and unvac cases equally severe; 4. age does not matter; 5. Vaccine failure will lead to lack of confidence; 6. had to be one-dose.

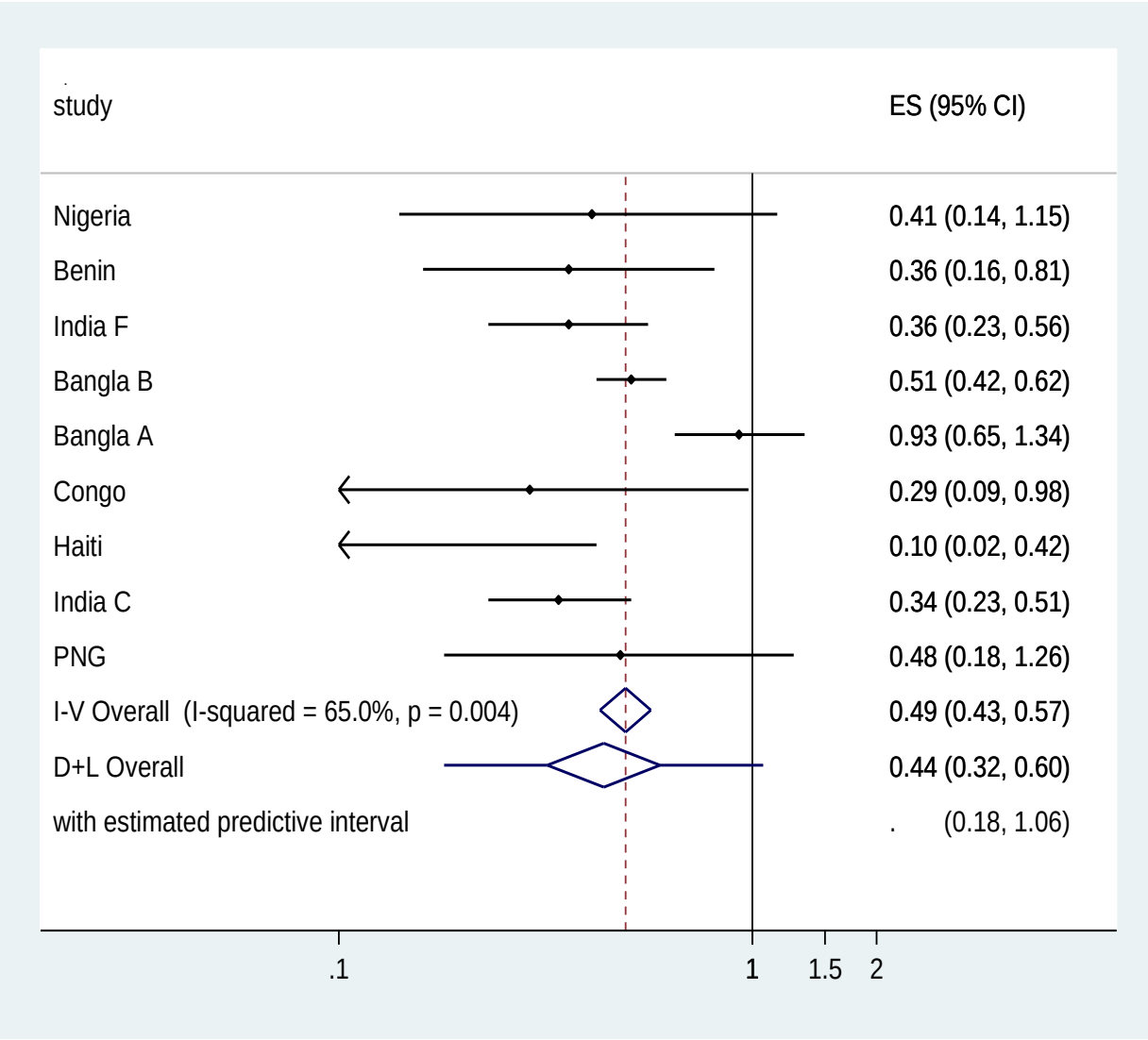
All assumptions were wrong => if corrected optimal age would 6 months

WHO's Strategic Advisory Group of Experts on Immunization (SAGE): Review of Measles vaccine



Measles vaccine reduced mortality by 46% (35-55%)

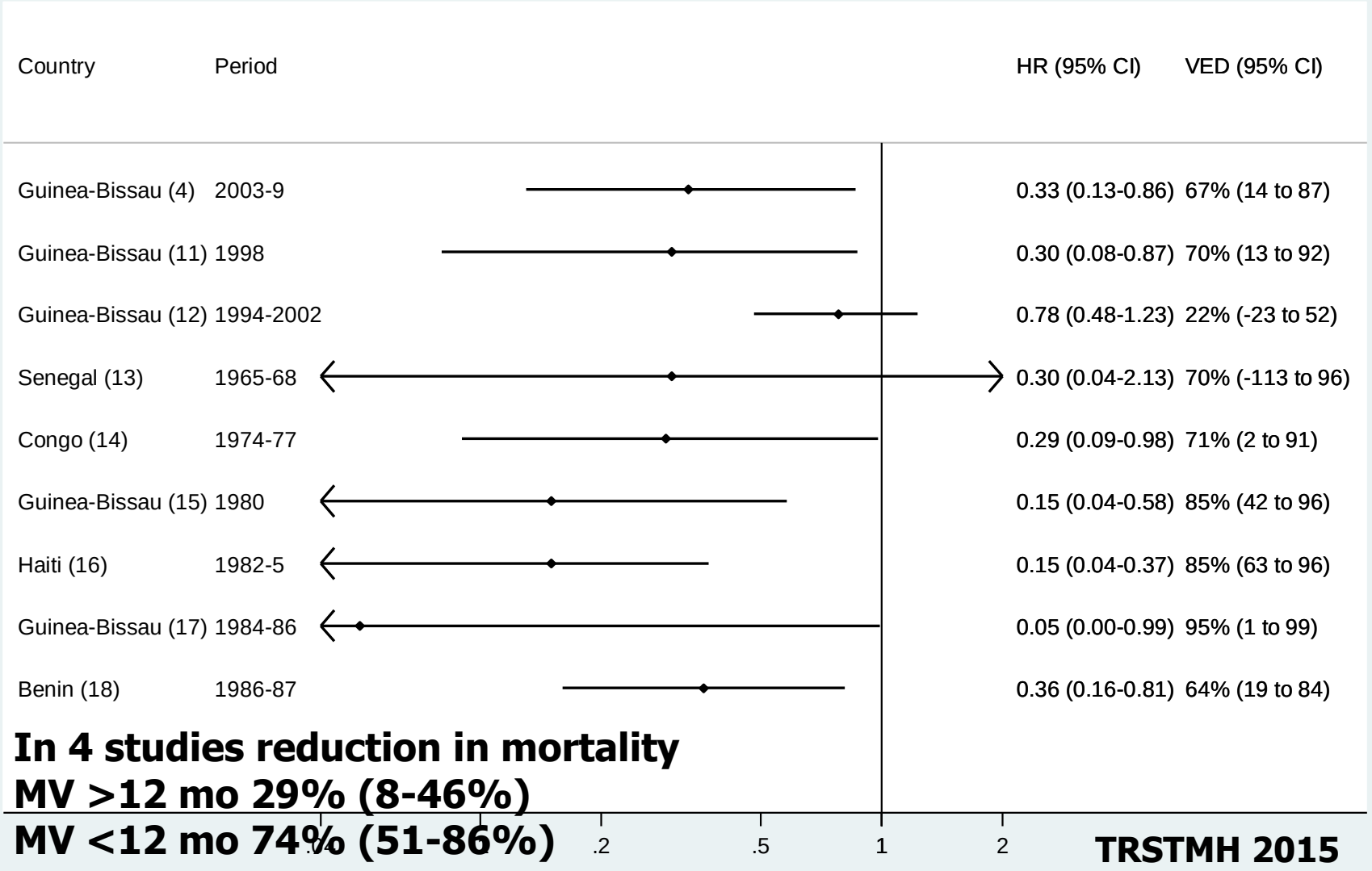
WHO's Strategic Advisory Group of Experts on Immunization (SAGE): Review of Measles vaccine



Measles vaccine reduced mortality by 56% (40-68%) in studies not done by the Guinea-Bissau group

WHO MV policy: Not vaccinate in presence of maternal antibodies => Increase age from 9 to 12 mo when measles is controlled

Better effect on survival of MV < 12 mo

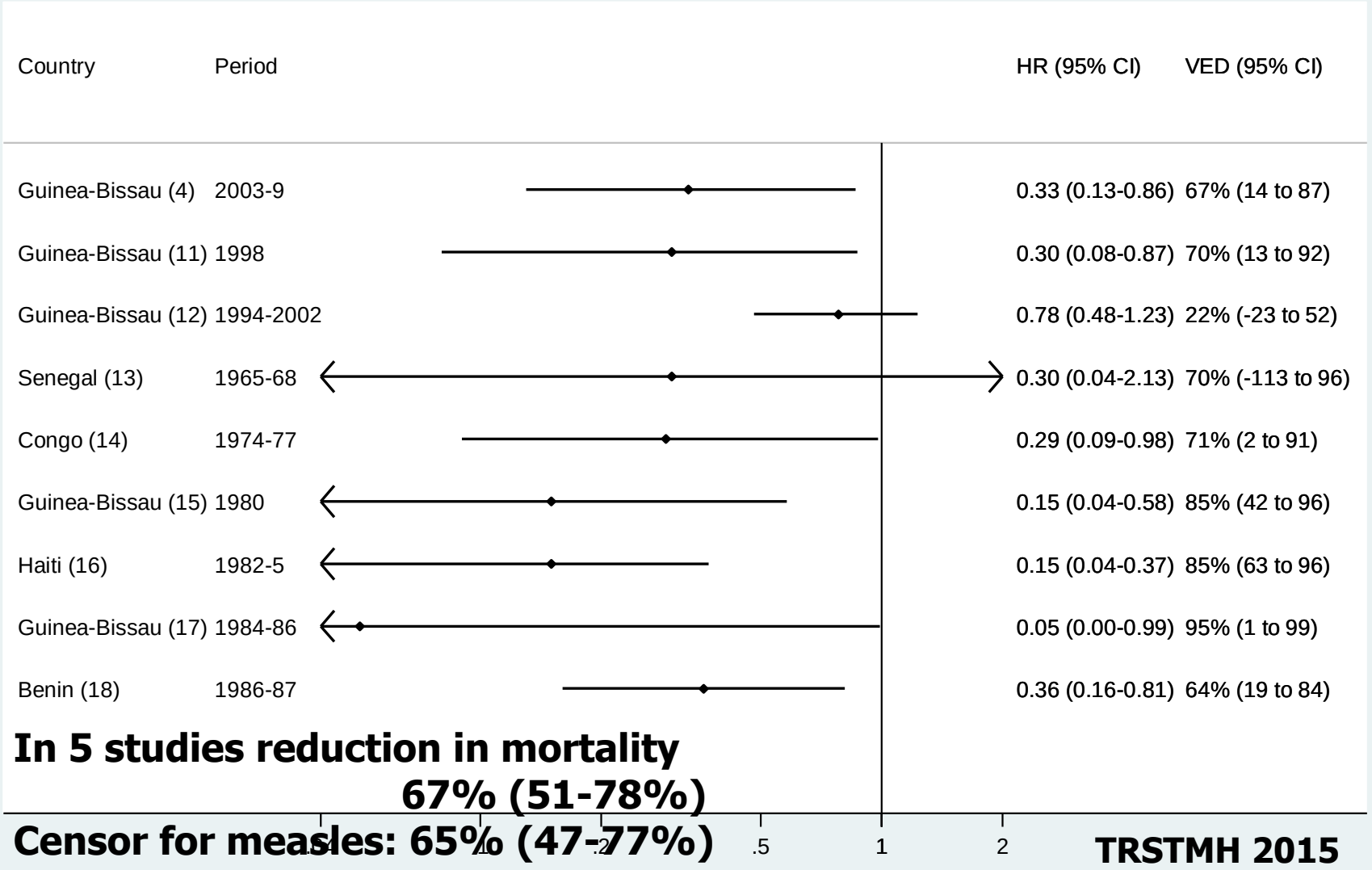


In 4 studies reduction in mortality
MV >12 mo 29% (8-46%)
MV <12 mo 74% (51-86%)

TRSTMH 2015

WHO MV policy: Not vaccinate in presence of maternal antibodies => Increase age from 9 to 12 mo when measles is controlled

Better effect on survival of MV < 12 mo



In 5 studies reduction in mortality 67% (51-78%)

Censor for measles: 65% (47-77%)

TRSTMH 2015

Effect of maternal antibodies (matab) in two-dose measles vaccine trials

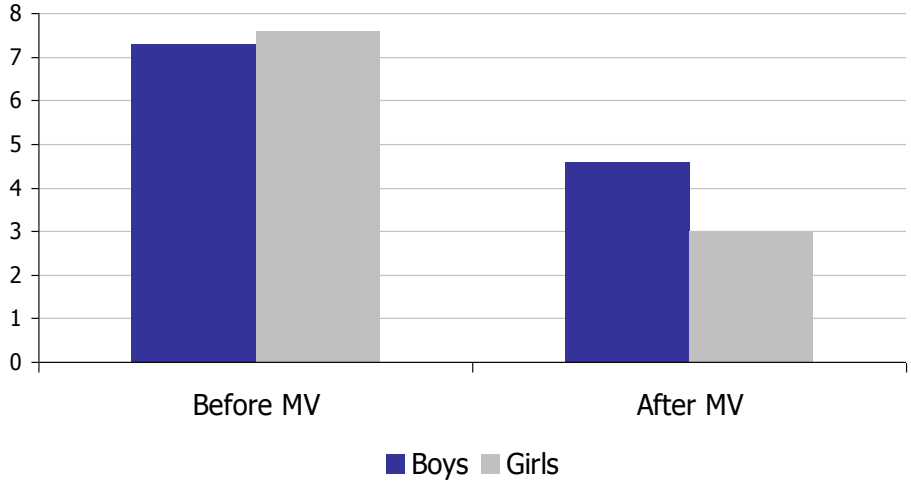
Study	Deaths/person-years [N]		MRR
	MV with matab	MV with no matab	
1993-1995#	**0/121 [27]**	**16/495 [123]**	**0 (0-0.52)**
2003-2007	**4/956 [249]**	**11/760 [201]**	**0.29 (0.09-0.91)**
Combined			**0.22 (0.07-0.64)**

#No benefit from IPV in presence of maternal antibodies in controls

Boosting – effect is mainly after the 2nd dose of MV

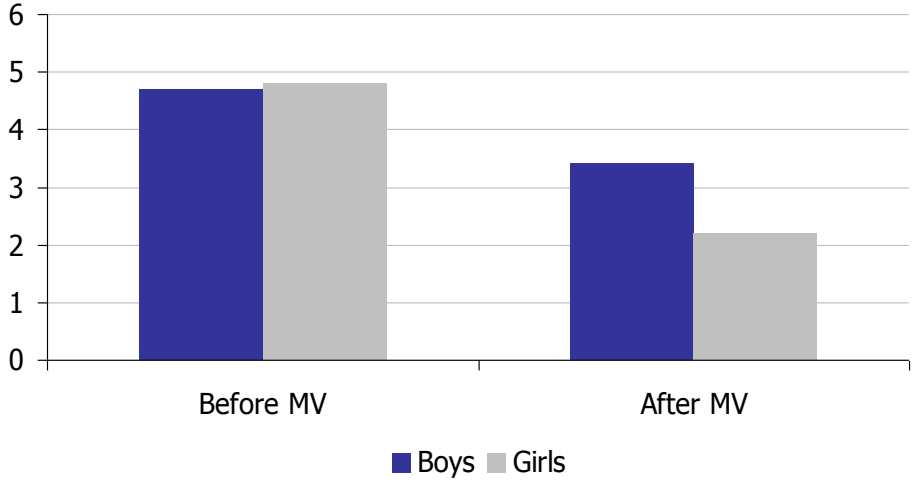
Male and female mortality before and after standard MV in Senegal

Bandafassi 1981-1988



F/M **1.04 (0.9-1.3)** **0.65 (0.4-1.0)**

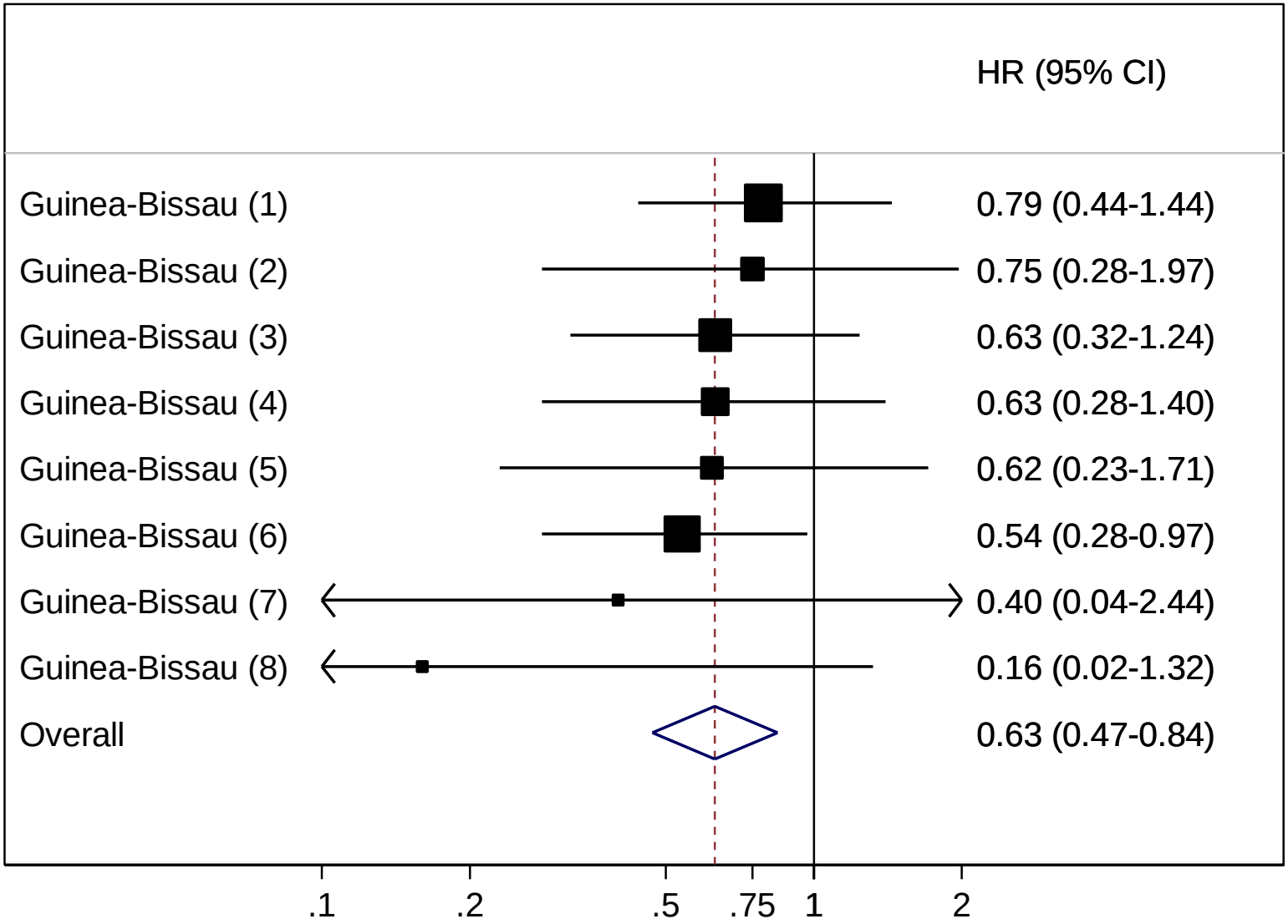
Niakhar 1985-1988



1.02 (0.9-1.3) **0.63 (0.4-1.1)**

If MV beneficial we should vaccinate earlier!

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



F/M MRR 0.63 (0.47-0.84)

Excluded MV+DTP and studies with possible DTP during follow-up

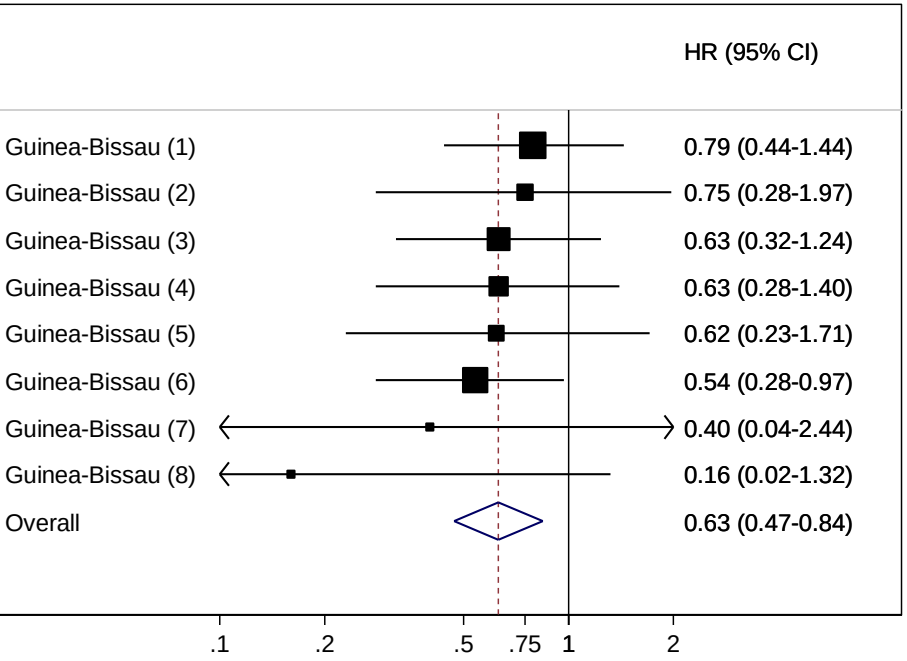
Mortality in MV trials by DTP status at enrolment

Study	Girls			Boys		
	No DTP3	DTP3 < MV	MR	No DTP3	DTP3 < MV	MR
Bissau 1995-02	7.5%	3.8%	1.97 (1.0-3.7)	6.4%	6.0%	1.06 (0.6-1.9)
Sudan	6.0%	2.8%	2.16 (0.3-17.3)	1.4%	1.9%	0.71 (0.1-7.9)
Congo	10.0%	2.8%	3.06 (0.6-16.1)	10.6%	5.1%	2.06 (0.5-9.2)
Bissau 1992-93	6.1%	1.7%	3.55 (1.2-10.3)	3.2%	3.2%	0.97 (0.3-2.8)
Total			2.36 (1.4-3.9)			1.11 (0.7-1.8)

DTP after MV associated with 2 fold higher mortality for girls
Overall effect of DTP after MV 1.60 (1.14-2.24)

Female-male mortality rate ratio for most recent vaccine

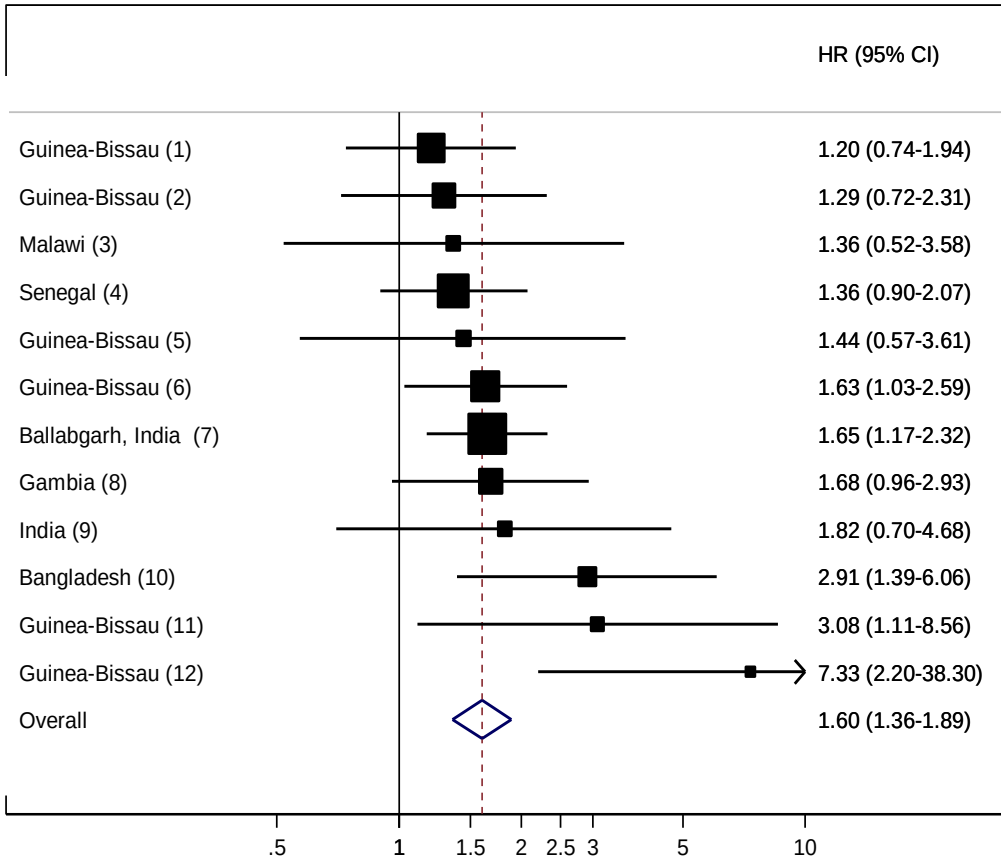
Measles vaccine



F/M MRR 0.63 (0.47-0.84)

Excluded MV+DTP and studies with possible DTP during follow-up

DTP

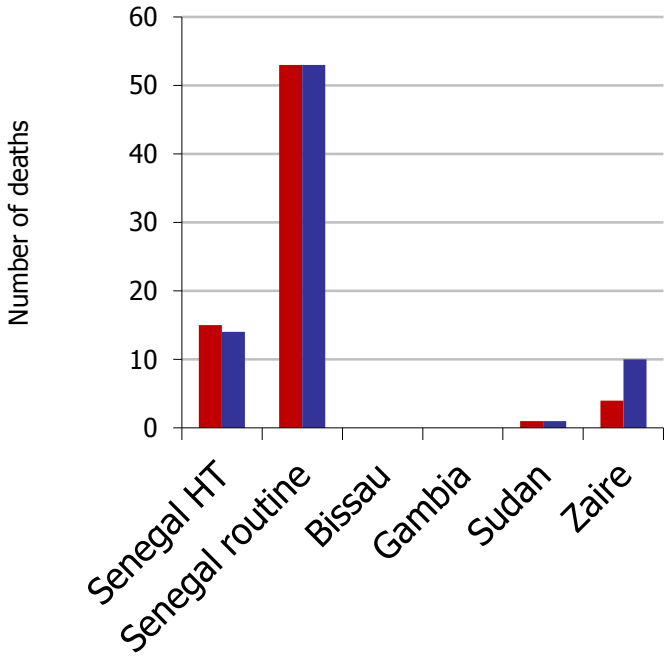


F/M MRR 1.60 (1.36-1.89)

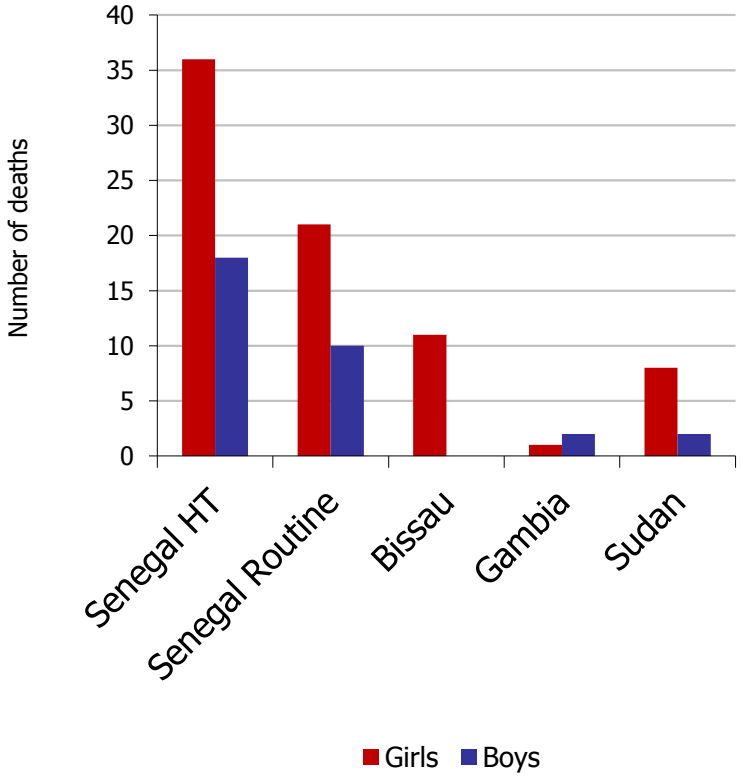
Excluded BCG=DTP1 and studies with MV during follow-up

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

No DTP after HTMV



DTP/IPV after HTMV



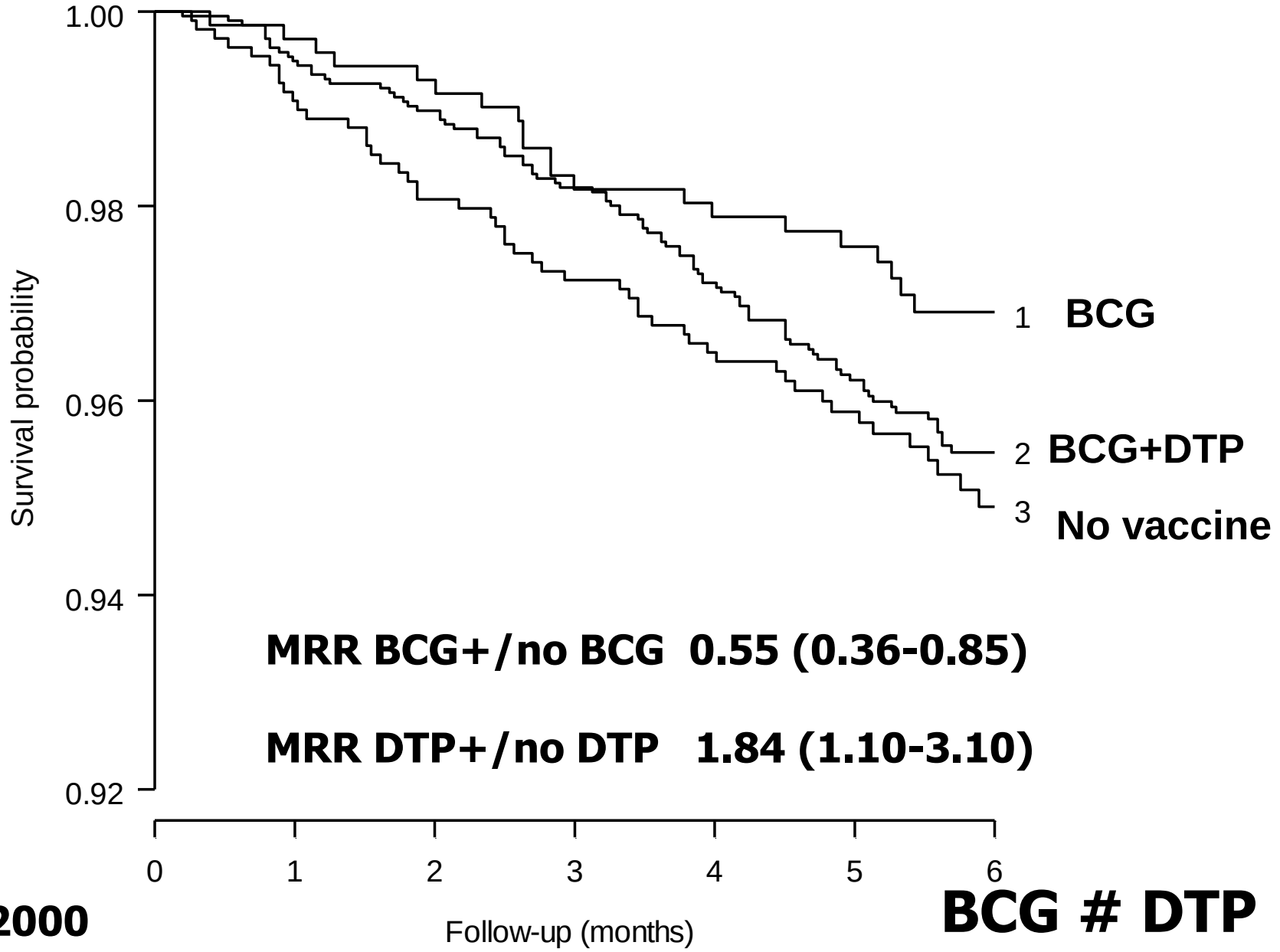
F/M ratio: 0.96 (0.7-1.3)

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

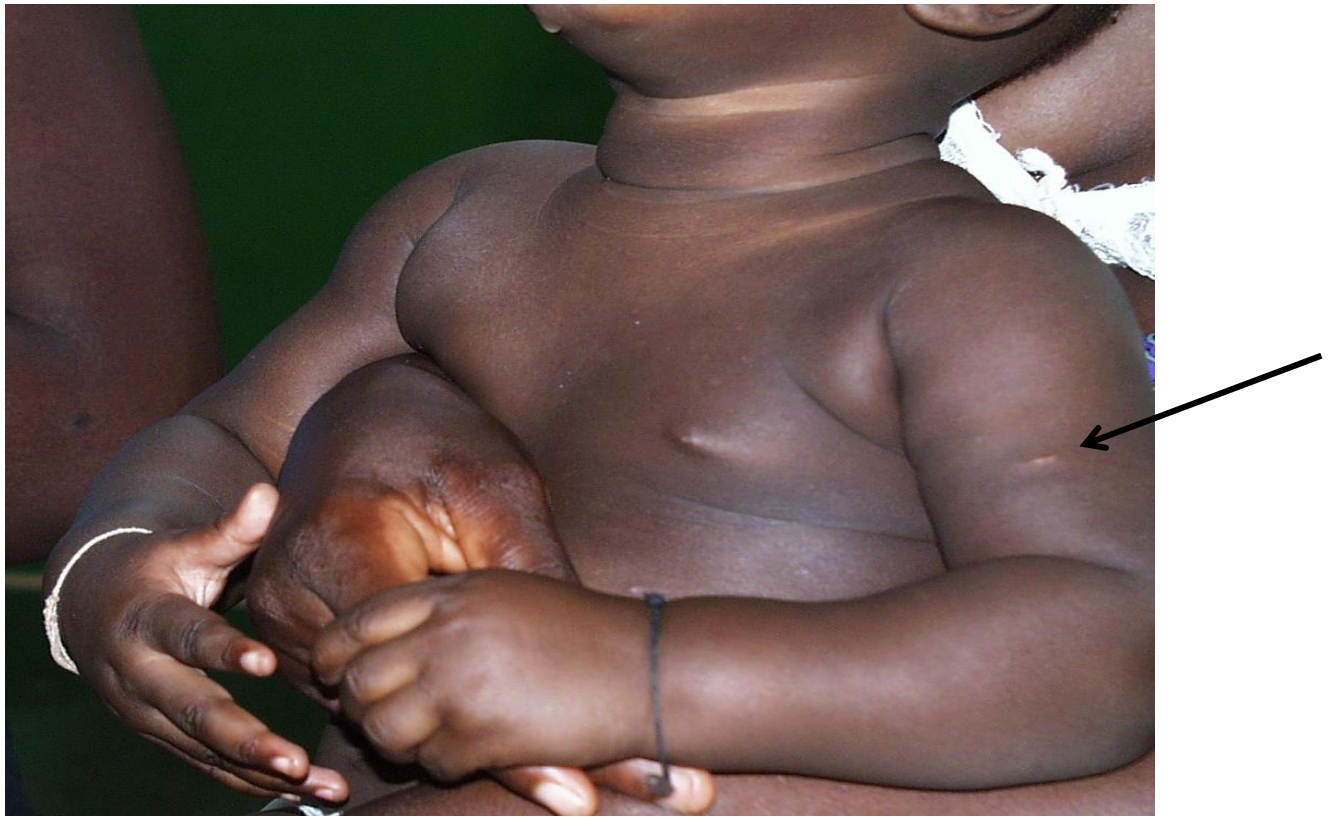
Mortality by vaccination status for children aged 0-6 mo at initial visit – 6 mo follow-up, rural areas (1990-96)



BMJ 2000

BCG # DTP

If BCG-effect not selection bias, reduction in mortality should be stronger for children with a BCG-scar



Among BCG-vaccinated children:	MRR Scar/noScar:	% with scar
Vaccine 2003:	0.41 (0.25-0.67)	92%
Int J Epidemiol 2005:	0.43 (0.28-0.65)	83%
Epidemiology 2006:	0.55 (0.31-0.96)	91%
CID 2015 (Rural):	0.50 (0.27-0.93)	52%

BCG strains differ in proportion giving a scar

BCG-Revaccinations

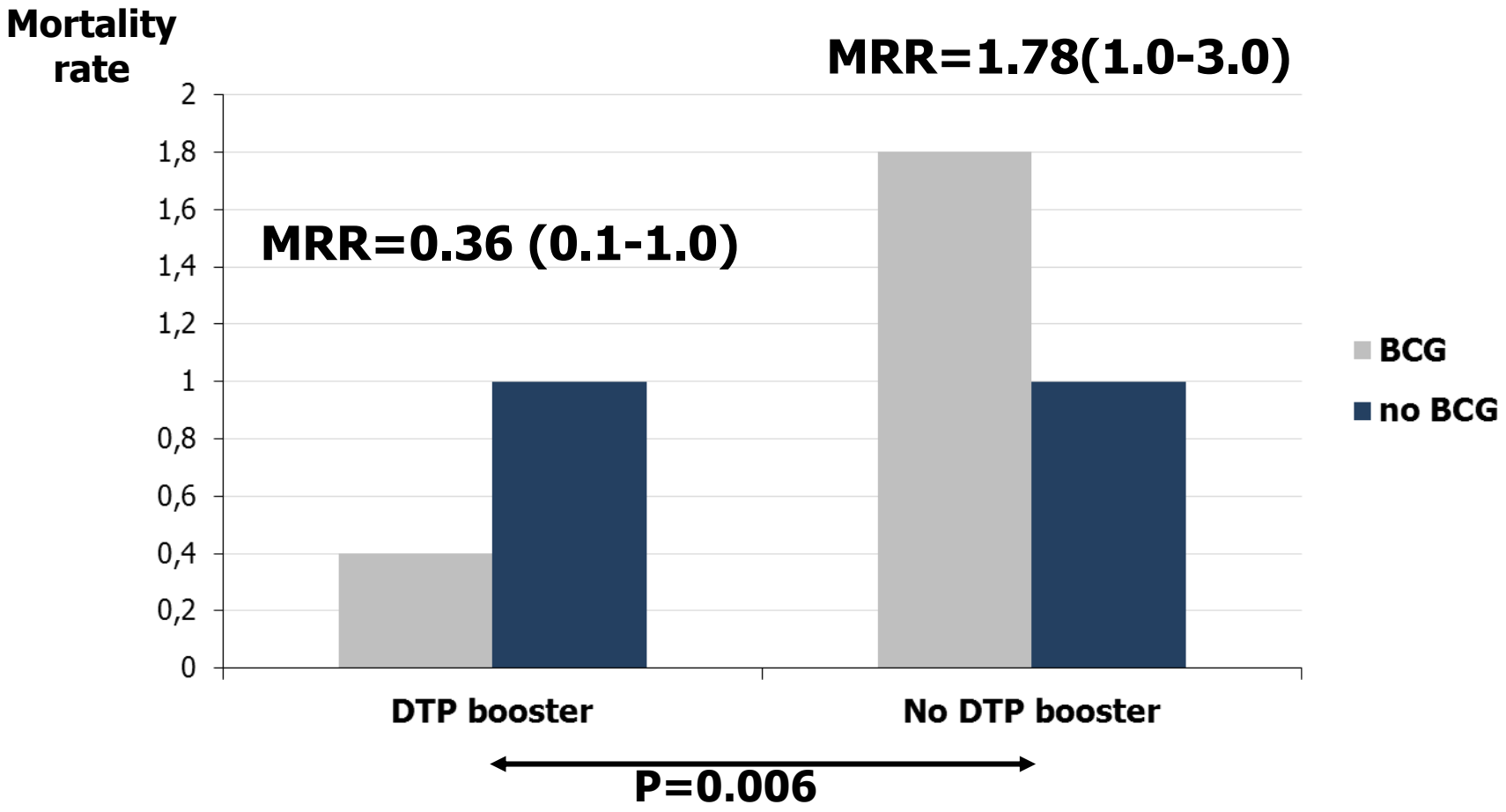
Study	Follow-up period	Reduction mortality
RCT: Alger, Algeria, 1935-50 1st oral BCG revaccination vs no BCG	12-36 months	**17% (11-22%)**
RCT: Alger, Algeria, 1935-50 2nd oral BCG revaccination vs no BCG	36-60 months	**47% (38-55%)**
RCT: Bissau BCG-revaccination after booster DTP vs no BCG	19-60 months	**64% (1-90%)**

Sargent Arch Inst Pasteur Algerie 1954; Roth BMJ 2010

BCG revaccination boosts the beneficial NSE of BCG

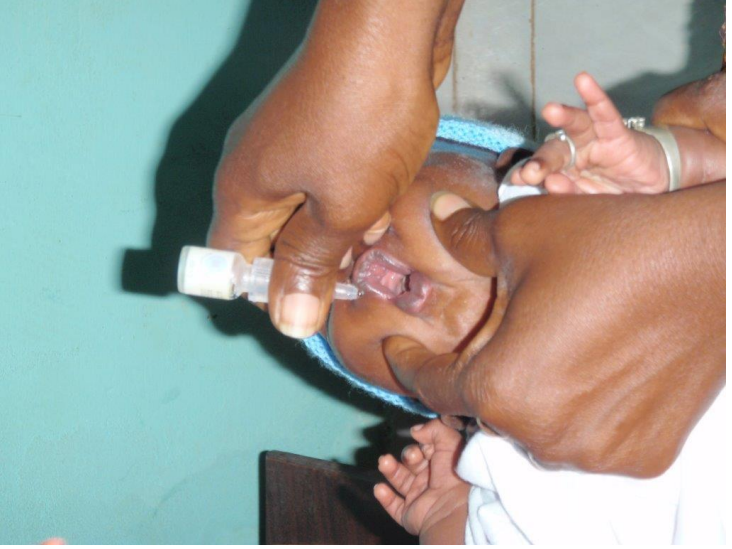
RCT1: BCG-revaccination vs nothing at 19 mo by vac. status

Mortality from 19 mo to 5 years of age



I. BCG after booster DTP → expected beneficial effect

II. Not taken into account: No DTP booster → received DTP later

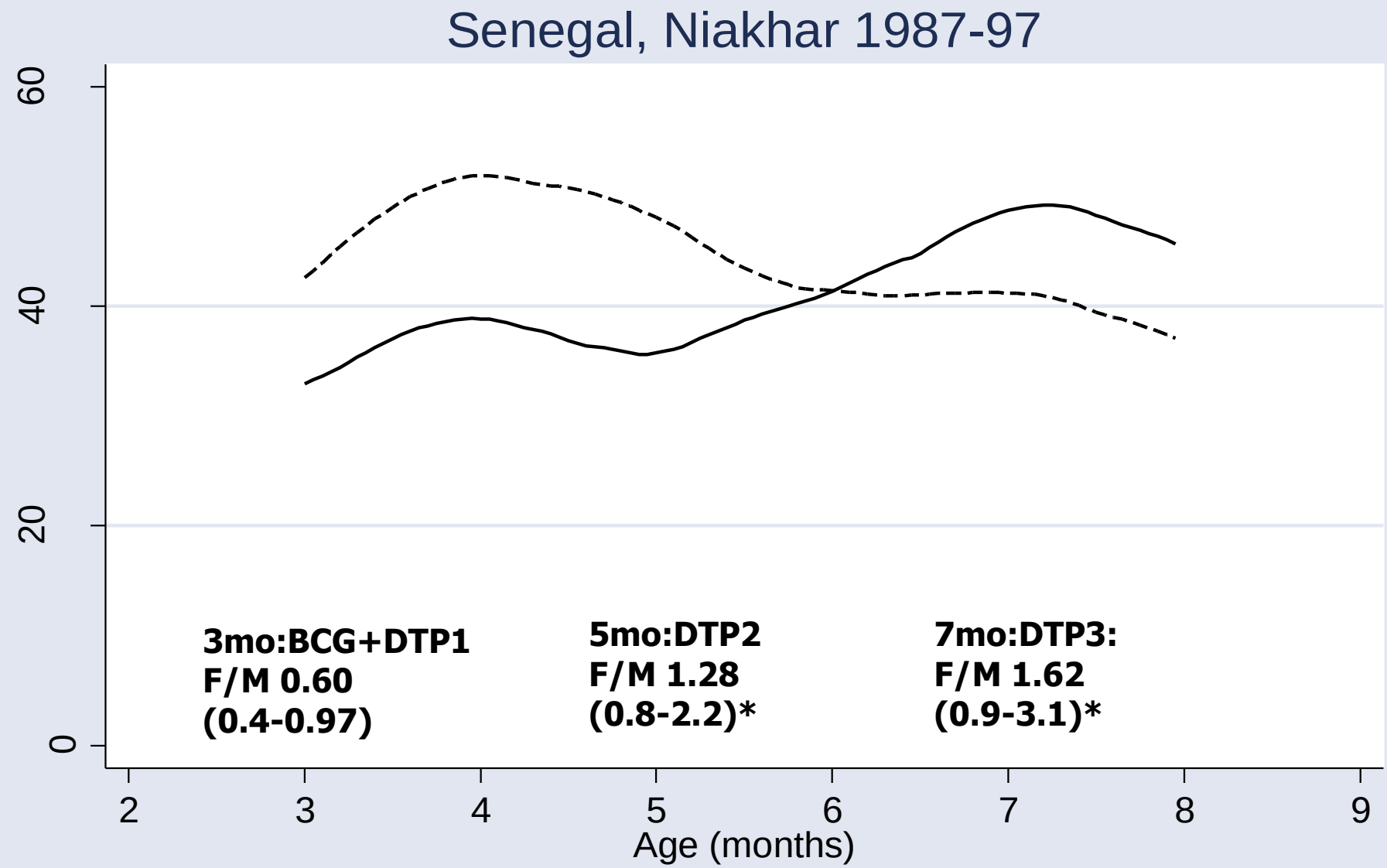


Numerous OPV campaigns since 1998 (in Bissau) to eradicate polio
Usually given to all children aged 0-59 months

OPV campaigns interfere with results of RCTs

Randomised Trials	MRR without censoring for OPV campaigns	MRR with censoring for OPV campaigns
Early MV RCT 2 MVs (4+9 mo) vs 1MV (9 mo);From 4-36 mo	0.70 (0.52-0.94)	0.54 (0.34-0.86)
OPV0 RCT OPV0+BCG vs BCG-only From 0-12 months	0.83 (0.61-1.13)	0.68 (0.43-1.00)
BCG-at-birth RCT BCG at birth vs delayed BCG;From 0-28 days	0.70 (0.47-1.04)	0.66 (0.45-1.00)

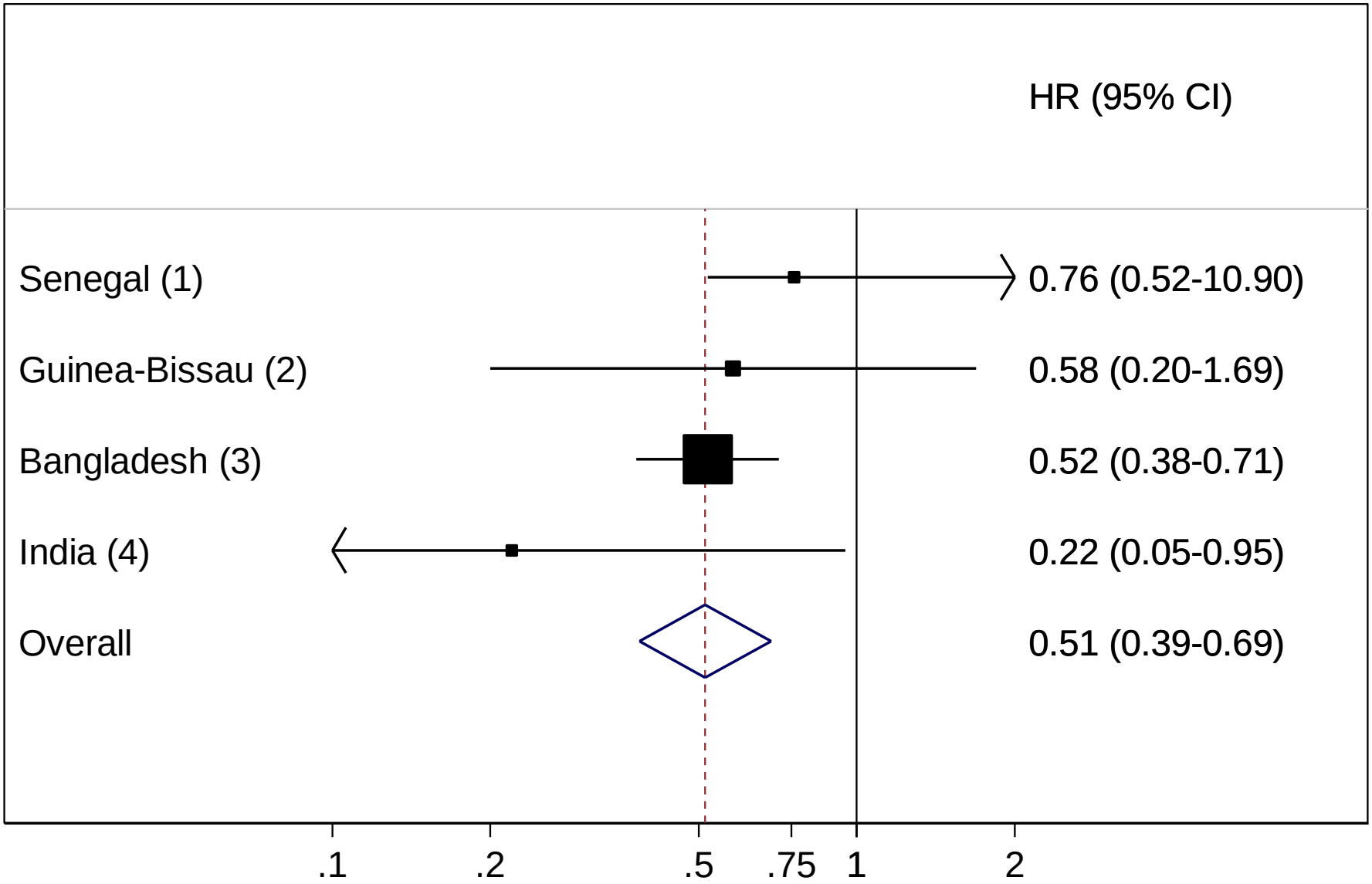
Sequence matters: BCG+DTP1 reduce negative effect for girls



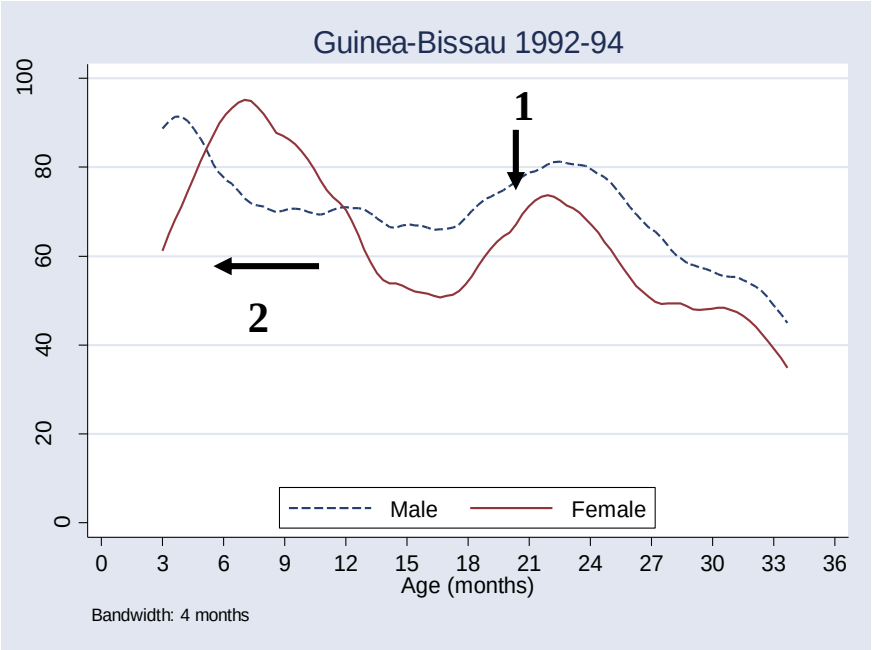
- Differ significantly From BCG+DTP1

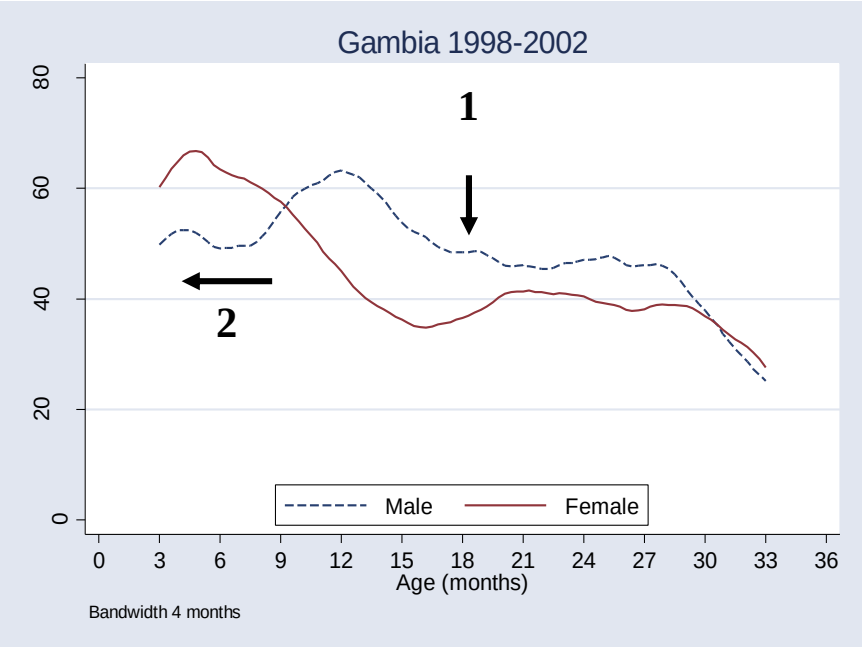
Aaby subm

Sequence matters: BCG+DTP1 first vs BCG first or DTP1 first



What can be done to reduce the negative effect of DTP?





Increased female mortality in the age groups of DTP
→ Change the immunological profile →

RCT1: BCG revaccination (19 months)
RCT2: Early MV (4½ months)

Under-5 mortality in Guinea-Bissau: Single-disease perspective =>Mortality should go down gradually with the introduction of new vaccines