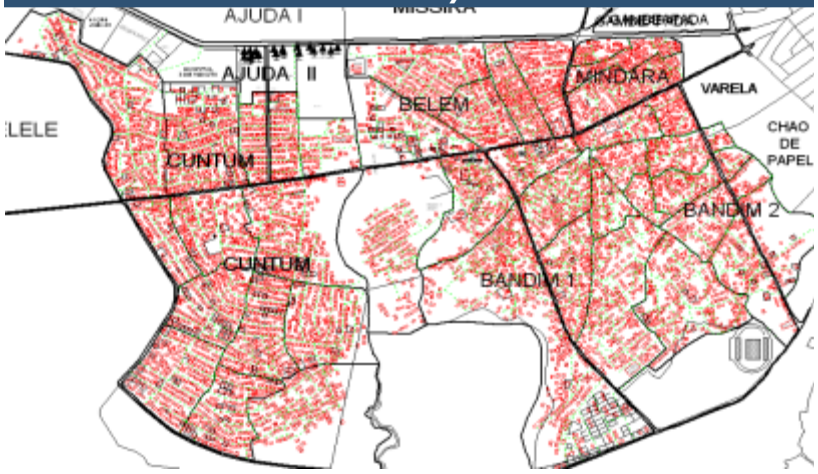
Bandim Health Project

Guinea-Bissau

Bissau City

Urban study area



Rural study area

Urban study area **> 100,000 persons**
Rural study area **> 100,000 persons in 180 villages**

Peter Aaby: The non-specific effects (NSEs) of vaccines

Demographic surveillance of real-life effects of health interventions since 1978

”State of the art”: Specific effect of vaccination

	Single-disease-eradication paradigm
Focus for vaccine development	Single-disease burden => Specific immune responses => Clinical protection => Reduction in mortality (assumed)
Overall effect	Specific protection - always good
Sex	Same effect for boys and girls
Sequence	Sequence does not matter
Ultimate goal	Eradicate - save money by removing vaccine

Measles vaccination (MV) policy at 9 months

Based on *Projected reduction in measles in Kenya – 1974-81*

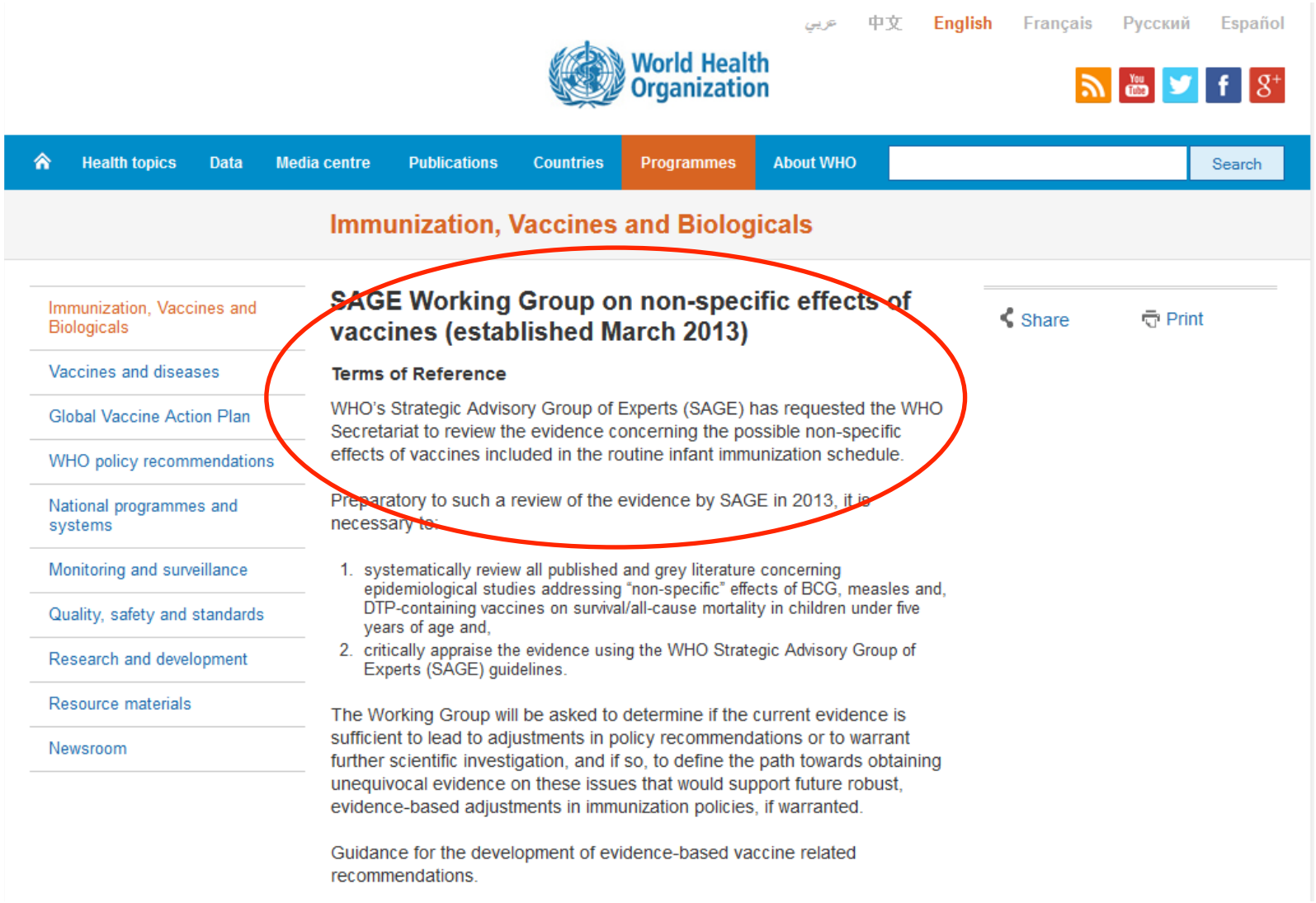
Age	Accumulate incidence	Conversion	Prevented cases (%)	Unvaccinated cases	Vaccine failures	Deaths by measles/1000 Case fatality 4%
5	1	35%	35	0	65	26
6	3	52%	51	1	48	20
7	6	72%	69	3	28	12
8	10	86%	79	6	15	8
9	***14***	***95%***	***84***	***10***	***7***	***6***
10	19	98%	82	14	4	7

BMJ Open 2012

Impact of MV at different ages was not tested in real life
So effect on mortality assumed to be proportional to antibody response

What if the assumption is not correct?

WHO 2013: WHO/SAGE review



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Immunization, Vaccines and Biologicals

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

Share Print

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.

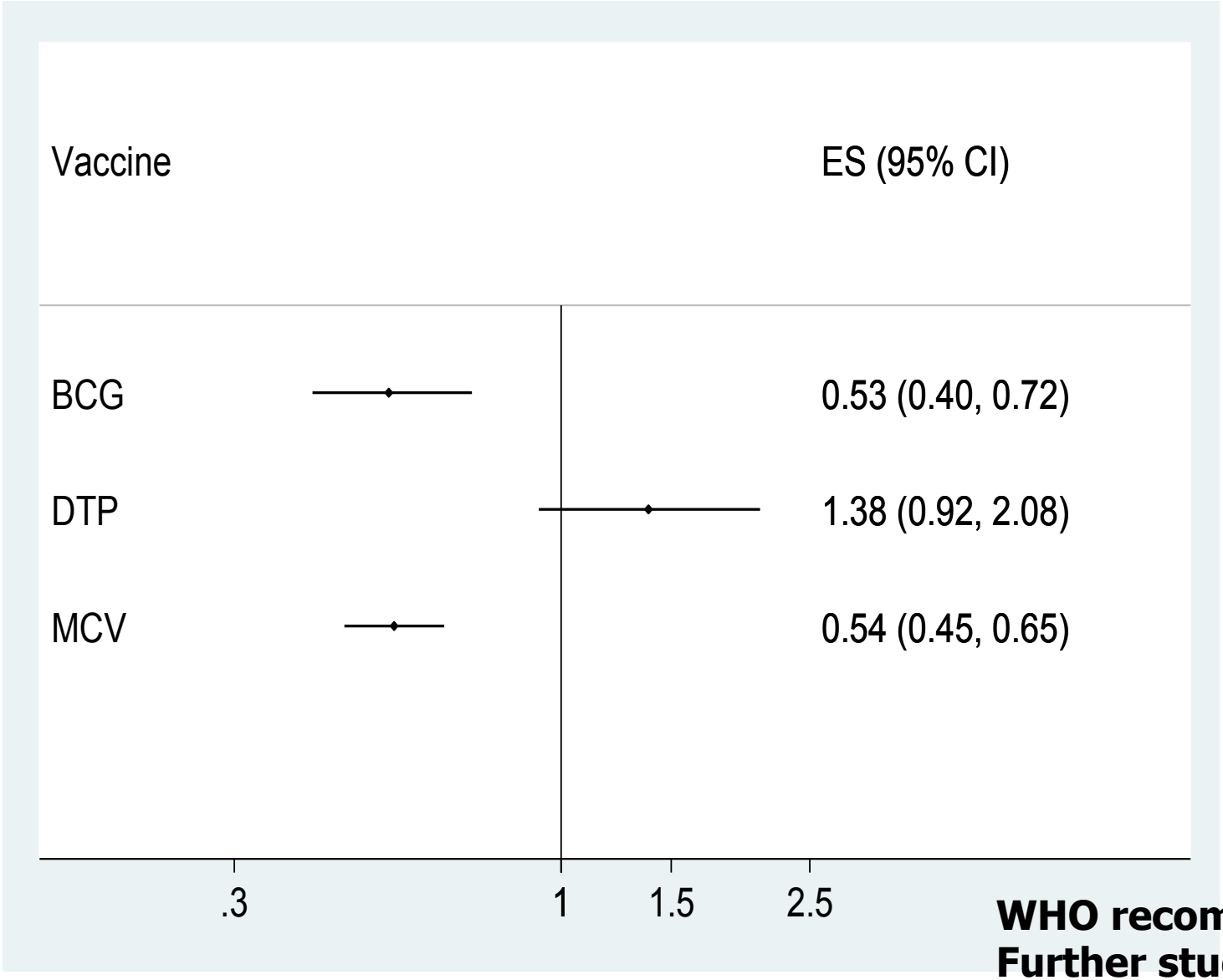
Preparatory to such a review of the evidence by SAGE in 2013, it is necessary to:

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.

WHO-SAGE review of NSEs of BCG, DTP and Measles Vaccine
Mortality hazard ratio estimates for different vaccines



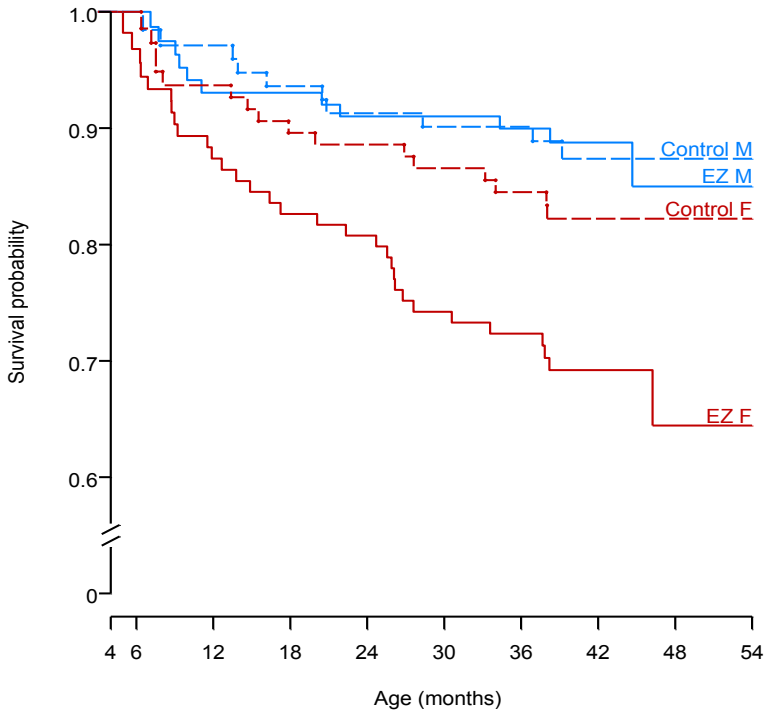
WHO recommended
Further studies of NSEs

Principles of Non-specific effects of vaccines

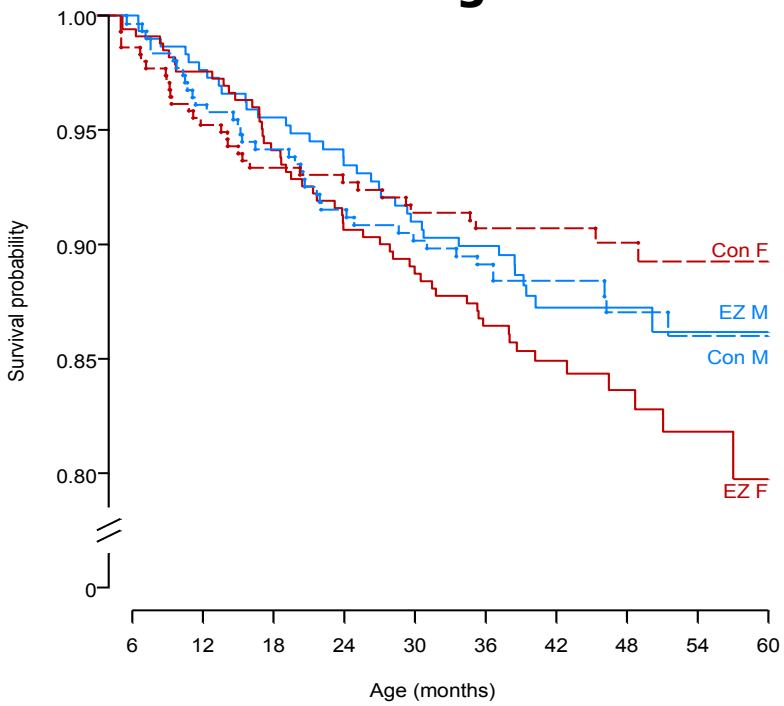
- **How were the NSEs detected**
- **Summarize the evidence for the main vaccines: Measles vaccine (MV), BCG, oral polio vaccine (OPV) and diphtheria-tetanus-pertussis (DTP)**
- **Summarize the emerging principles of NSEs**
- **Give examples of the implications of not taking the NSEs into consideration**

Contradiction – I: High titre measles vaccine was protective against measles infection – but associated with 2-fold higher female mortality

Bissau



Senegal



J Pediatr 1993 and Bull WHO 1994

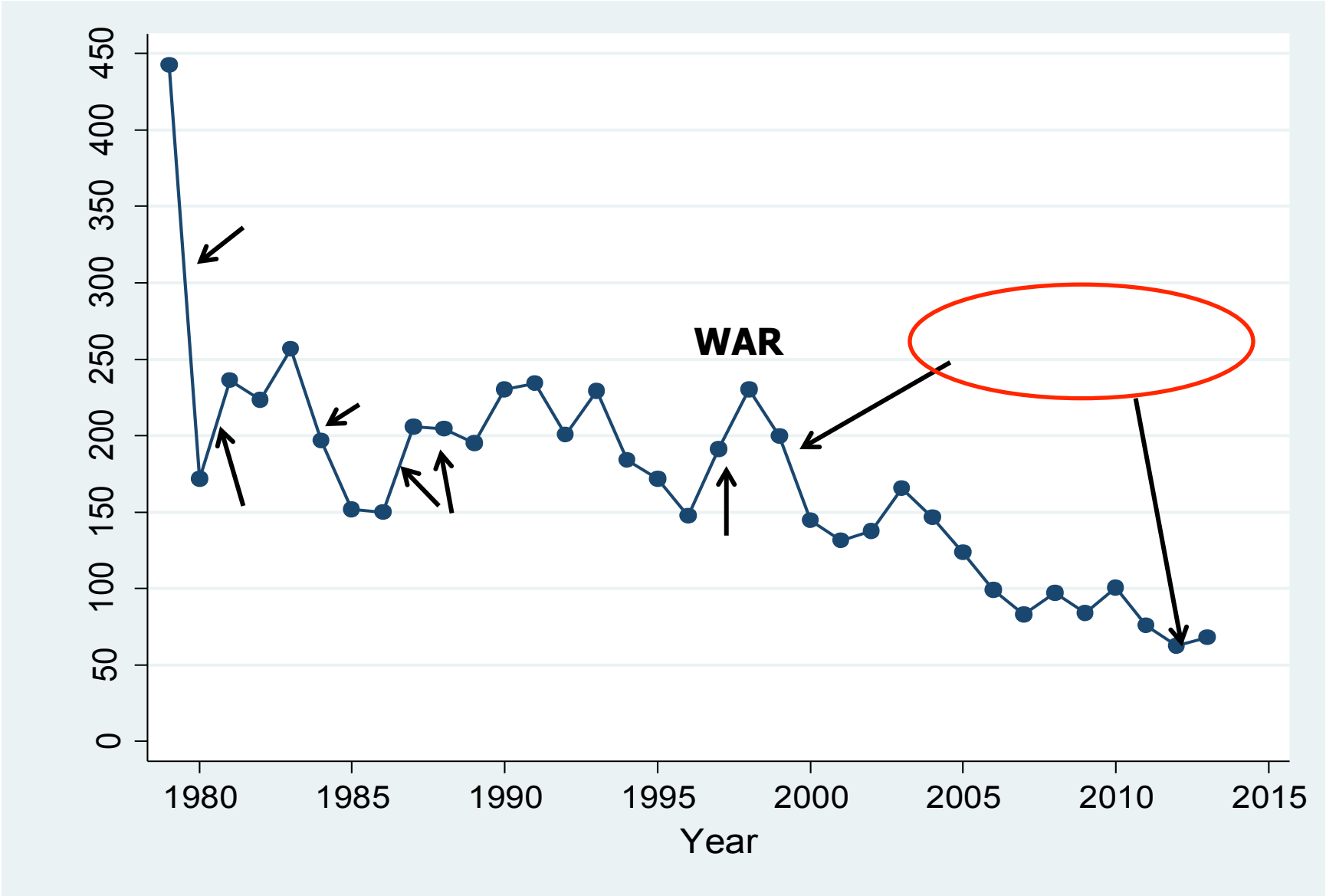
Intervention: EZ MV + IPV at 9 mo
Control: IPV + standard MV at 9-10 mo

Same effect in Haiti and Sudan
WHO withdrew HTMV 1992

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

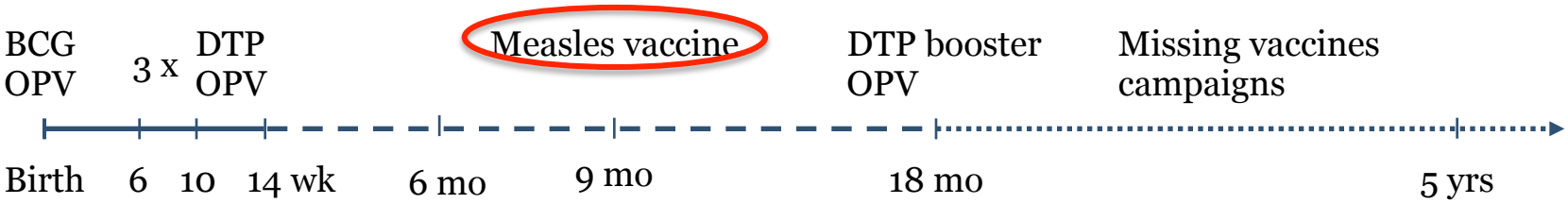
African studies 33% excess mortality from 4 mo to 5 years

Contradiction – II – Under-5 mortality in Bissau. Mortality should go down gradually with introduction of vaccines



No routine vaccination program in Bissau in 1978

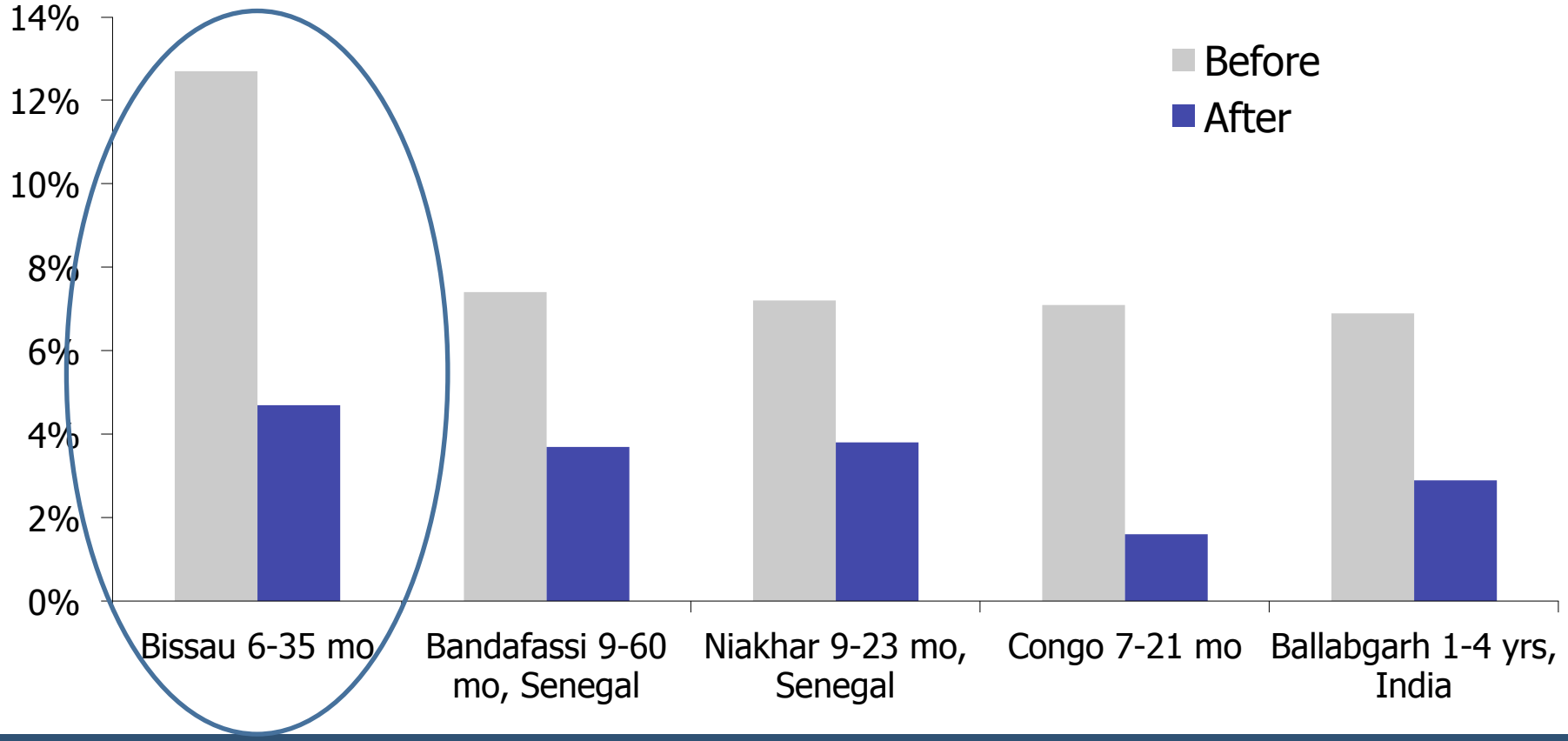
WHO vaccination policy in low-income countries



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

Before-after introduction of measles vaccine

Annual mortality rate in community studies

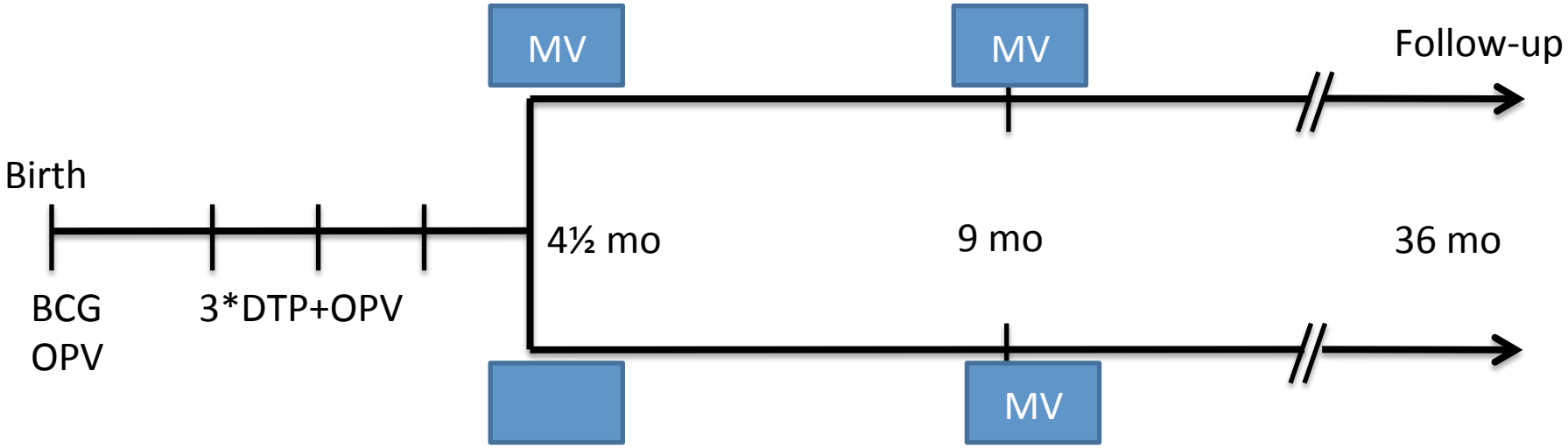


First campaign Dec 1979: Vaccinated vs travelling 70% (27-88%) lower mortality

>50% reduction - Measles was 10-15% of deaths (WHO)

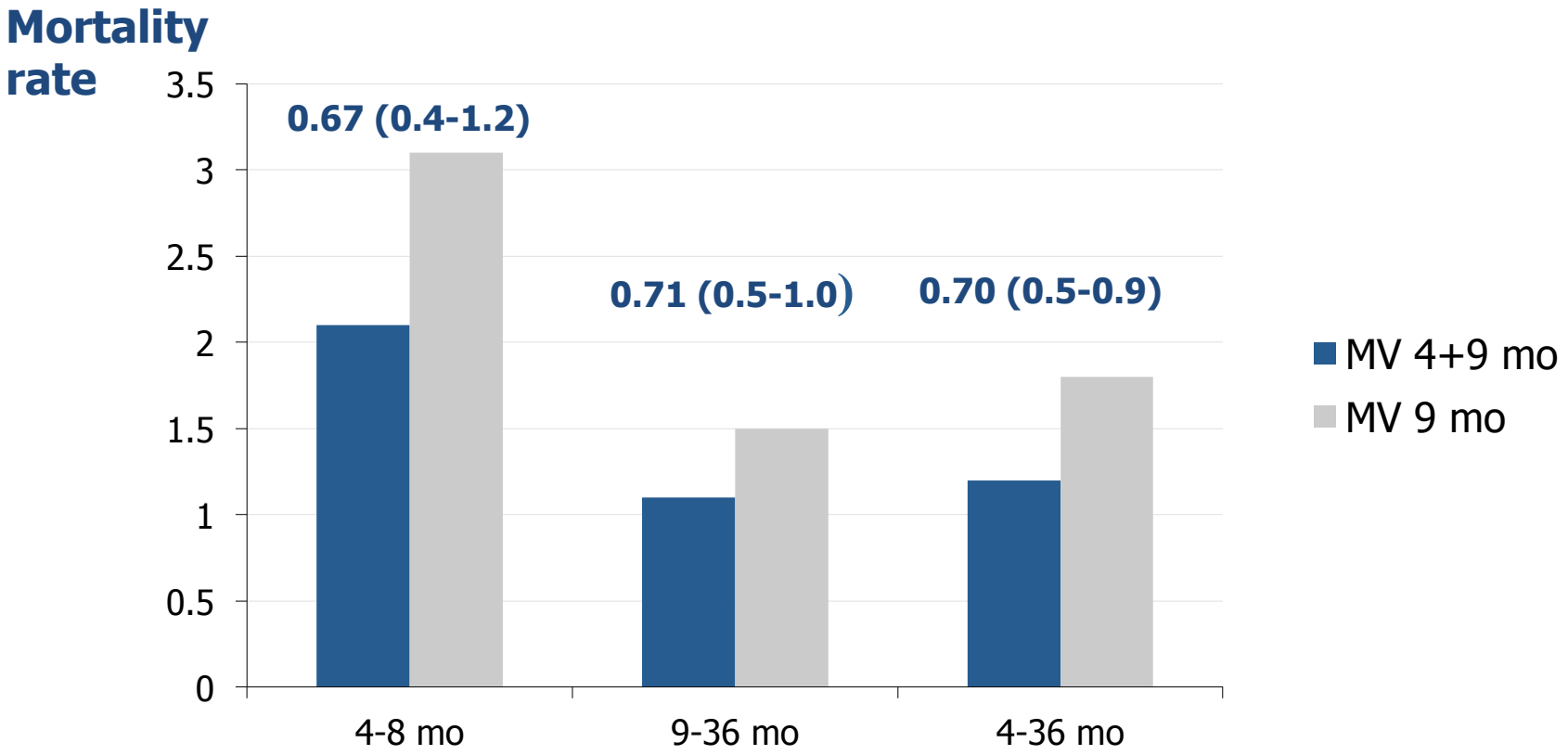
Aaby J Infect 1984; Aaby Am J Epidemiol 1995; Am J Epidemiol 1993; Kasongo Lancet 1981; Kapoor Ind J Pediatr 1991

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



Tested a 25% difference in mortality

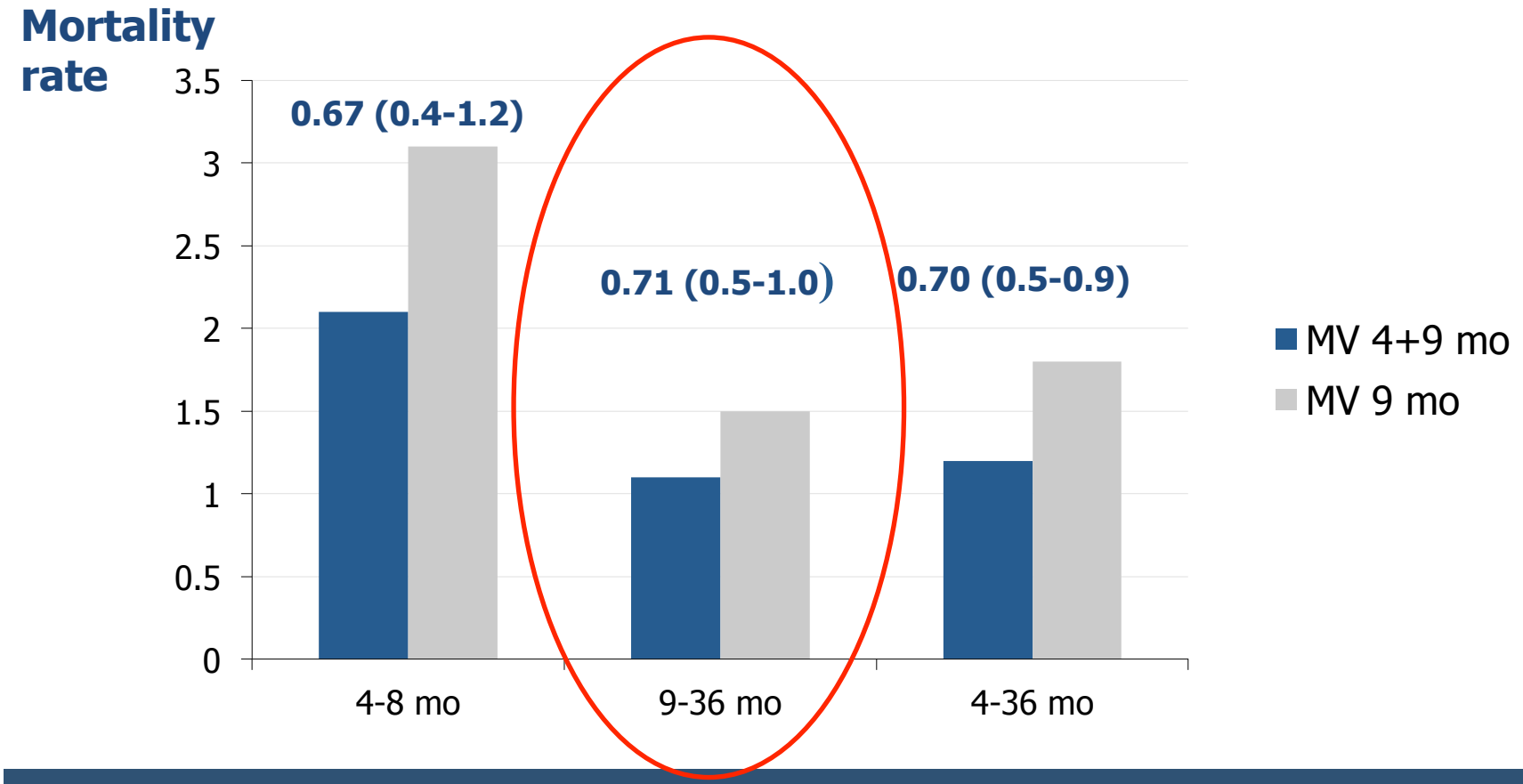
Randomised trial: MV at 4½+9 mo vs MV at 9 mo



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

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

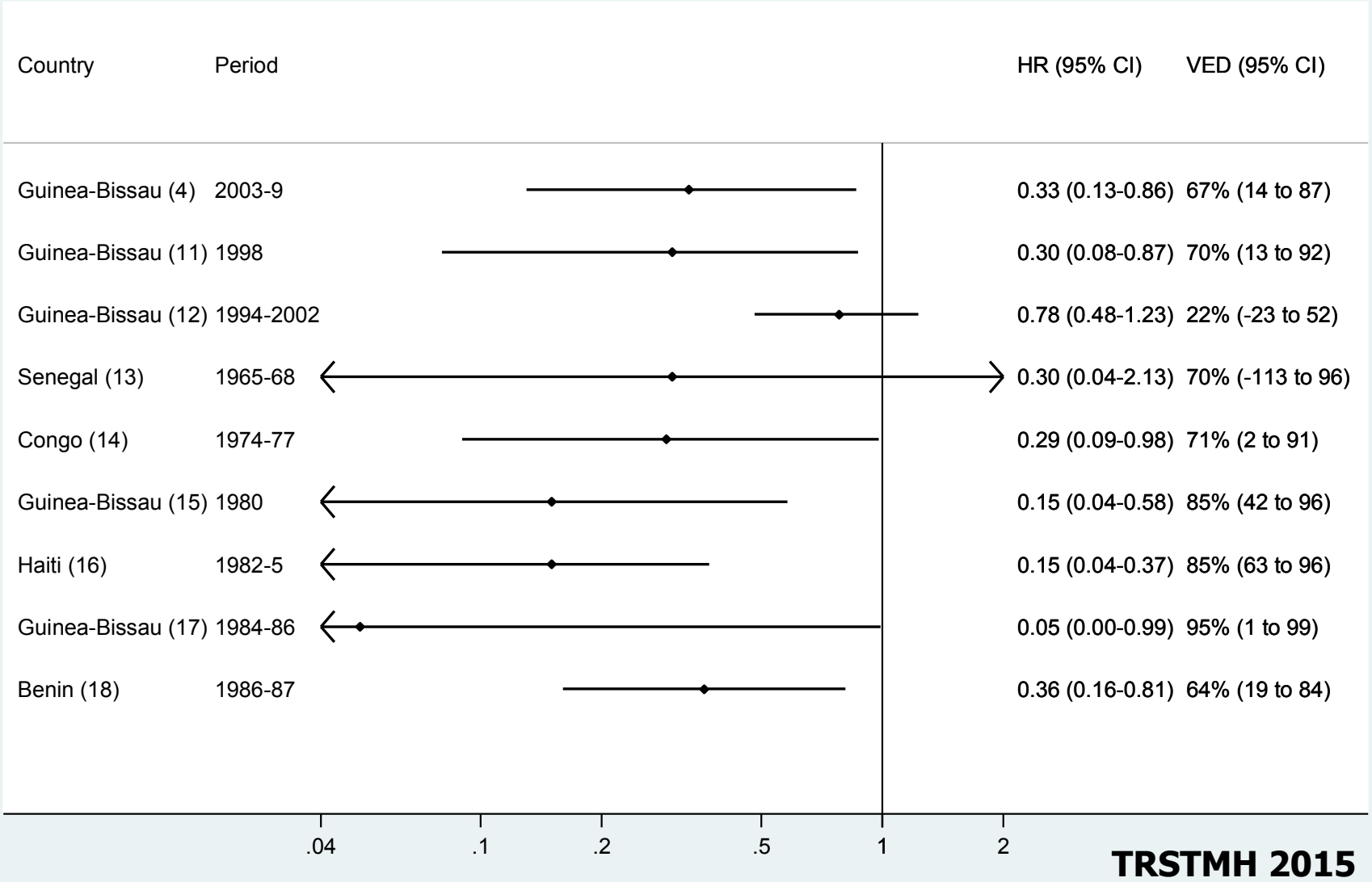


MVs at 4 and 9 mo: 30% (6-49%) (F: 41 %; M: 18%)
Measles infection censored: 26% (0-46%)
Boosting is beneficial

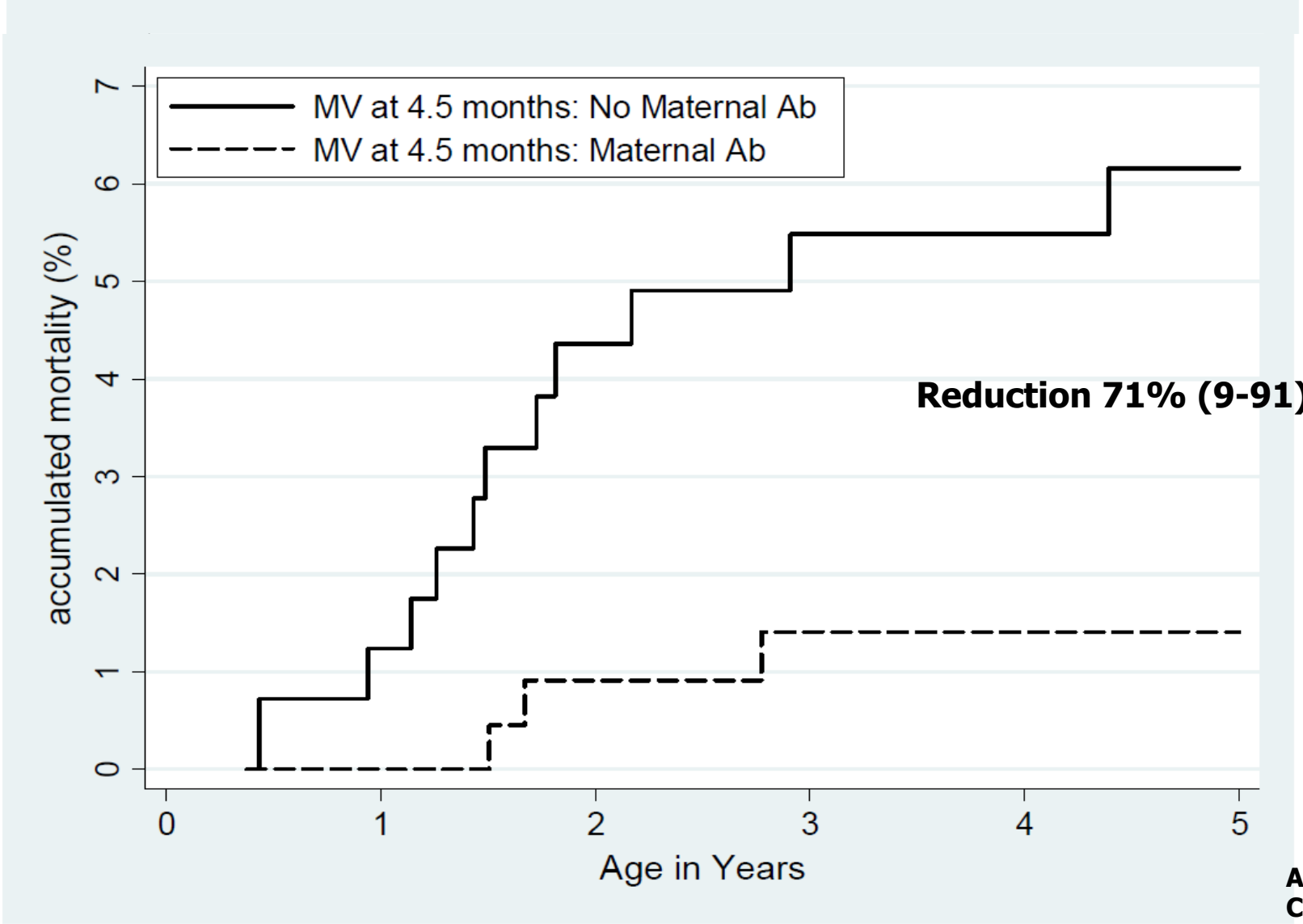
Aaby et al, BMJ 2010

MV gives higher antibody responses after 12 months

But MV gives better effect on mortality before 12 months



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



Aaby et al
CID 2014

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

Measles vaccination (MV) policy at 9 months

Based on *Projected reduction in measles in Kenya – 1974-81*

Age	Incidence	Conversion	Prevented cases (%)	Unvaccinated cases	Vaccine failures	Deaths by measles/1000 Case fatality 4%
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10	19	98%	82	14	4	7

BMJ Open 2012

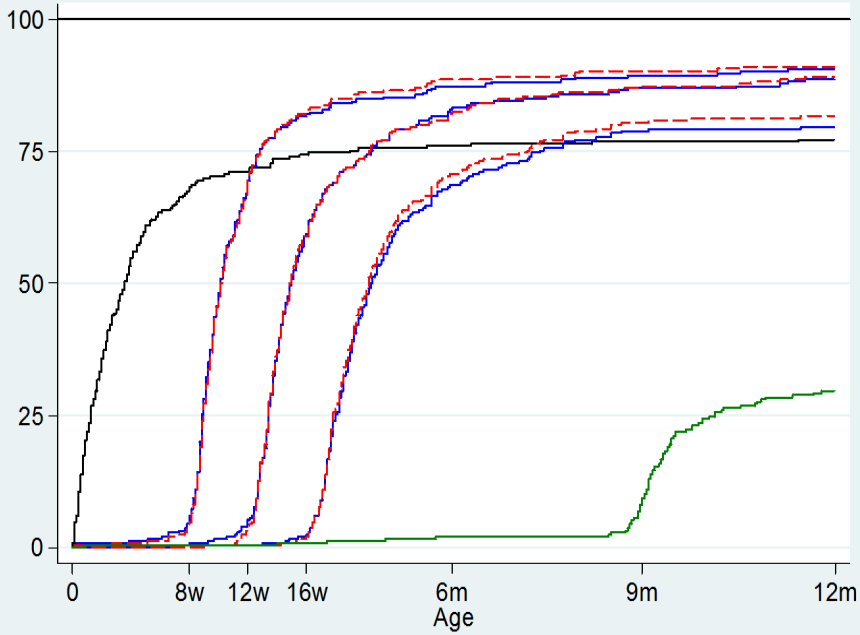
Impact of MV at different ages was not tested

The optimal age for MV would probably have been 5-6 months

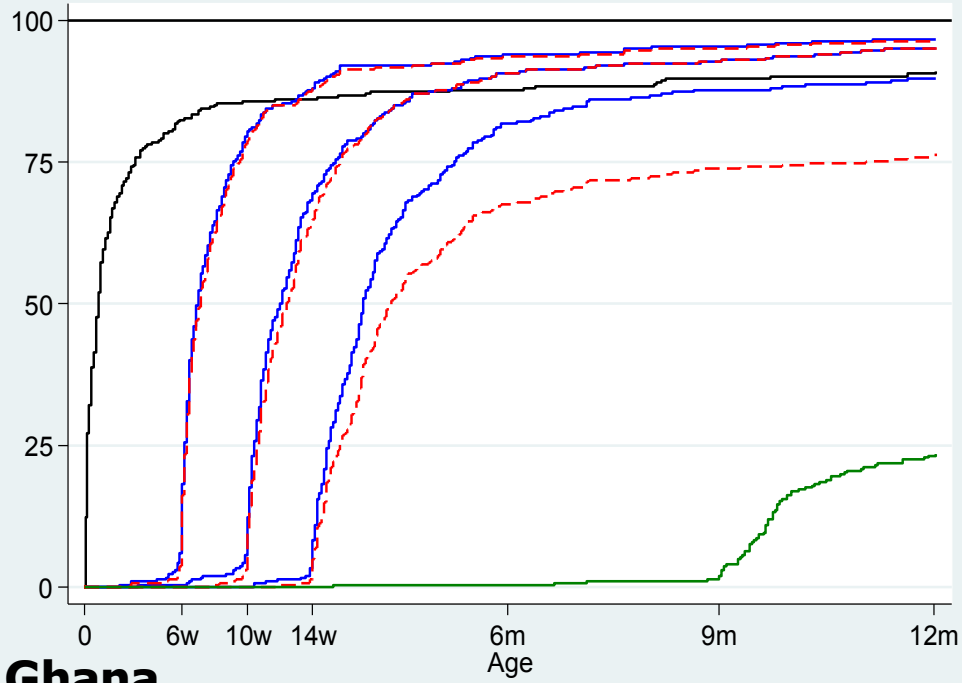
Vaccination status at 12 mo. Main risk factor for not being fully immunized child (FIC) by 12 mo: Lack of MV!

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

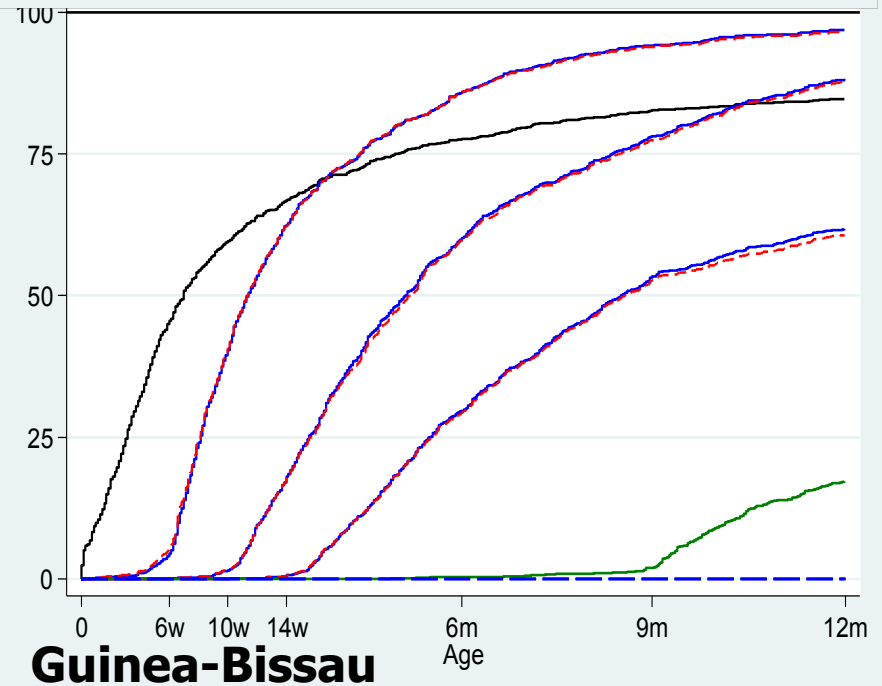
Burkina Faso not FIC 2014



Not FIC at 12 months: 2012

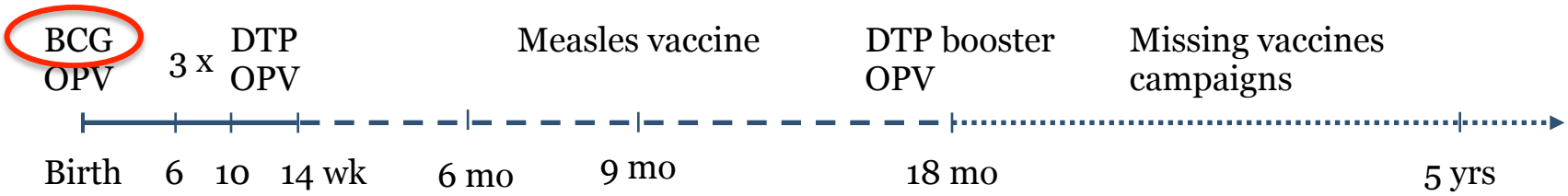


Ghana



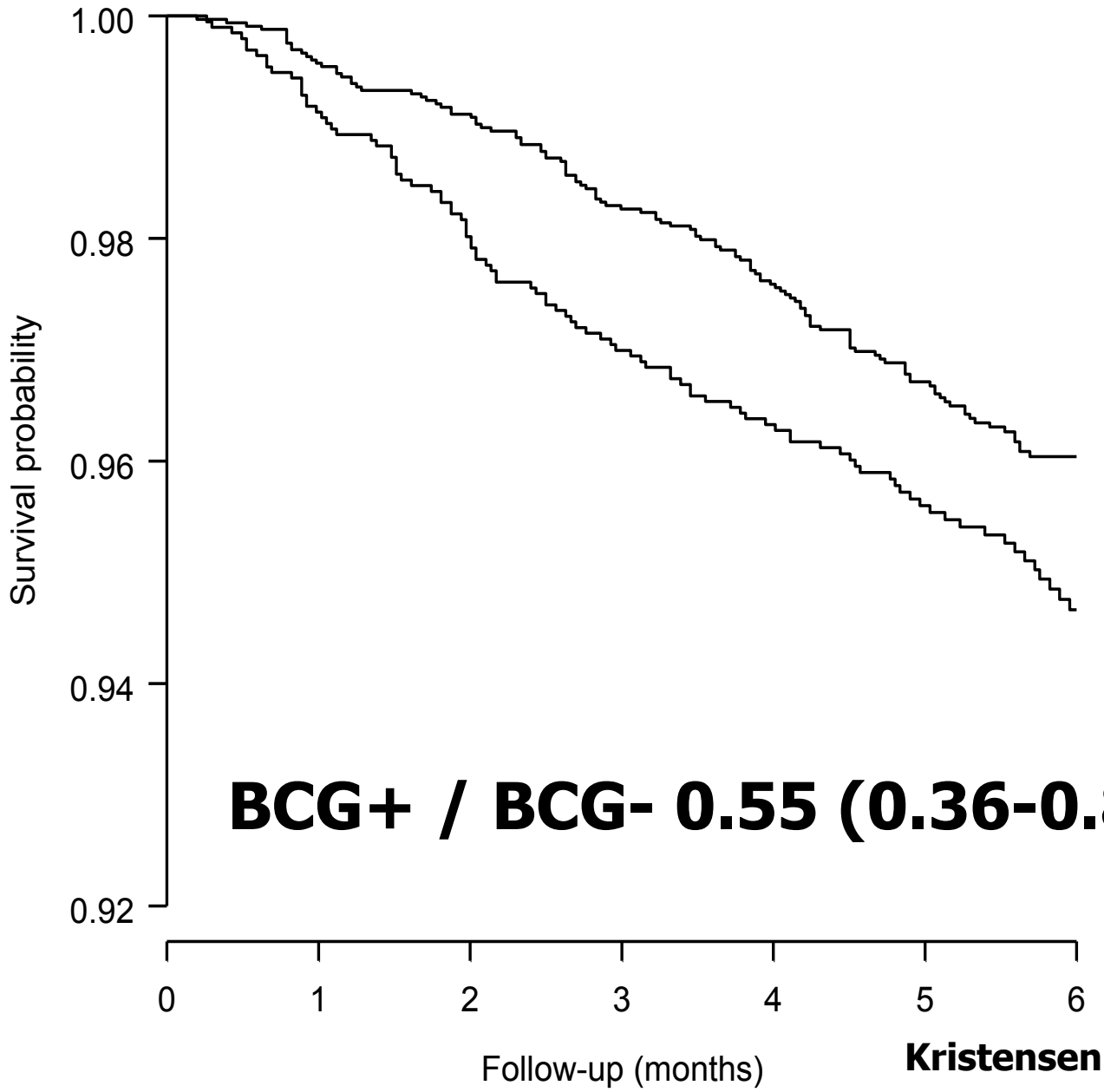
Guinea-Bissau

WHO vaccination policy in low-income countries



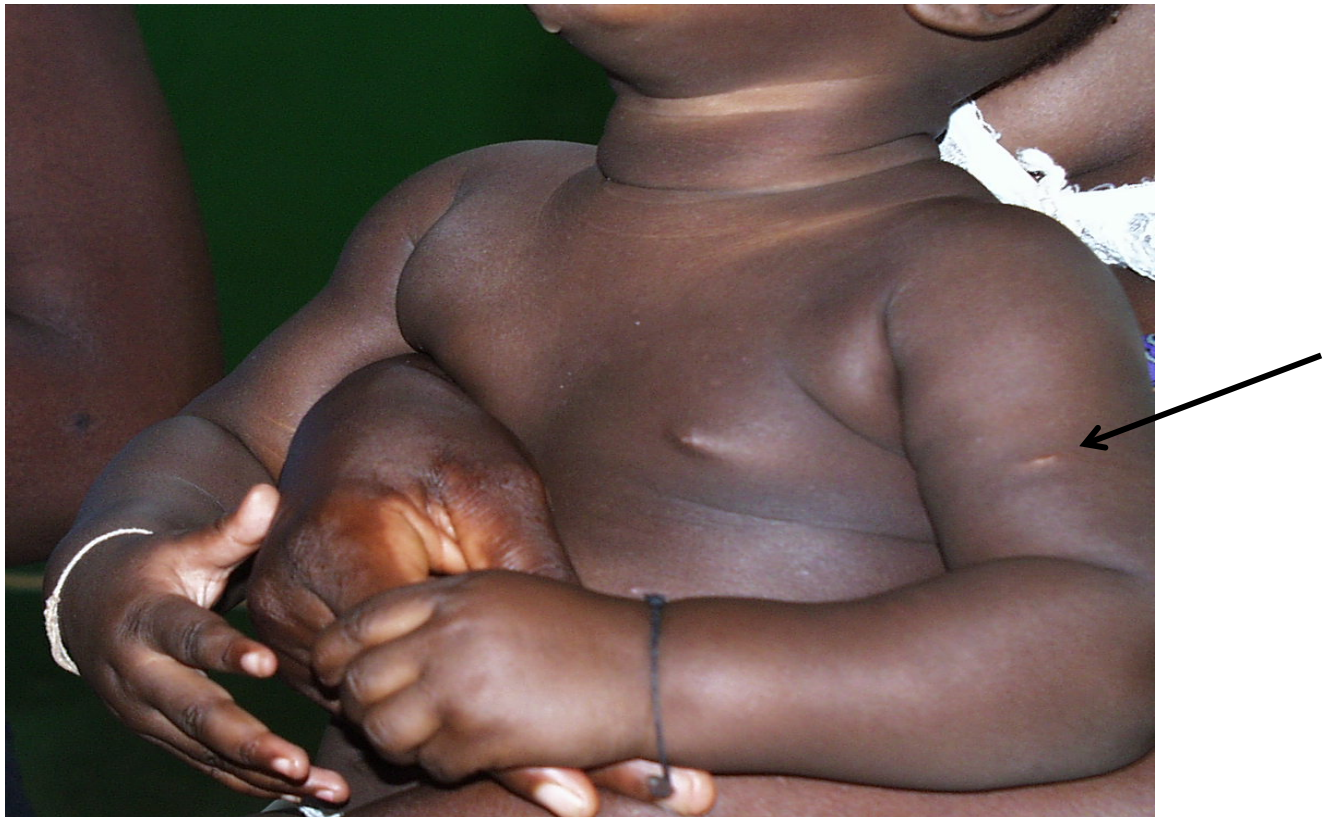
BCG=Bacille Calmette Guérin; DTP=diphtheria-tetanus-pertussis vaccine; OPV=oral polio vaccine; VAS=vitamin A supplementation

Mortality by vaccination status for children aged 0-6 mo at initial visit – 6 mo follow-up, rural areas of Guinea-Bissau



Kristensen et al, BMJ 2000

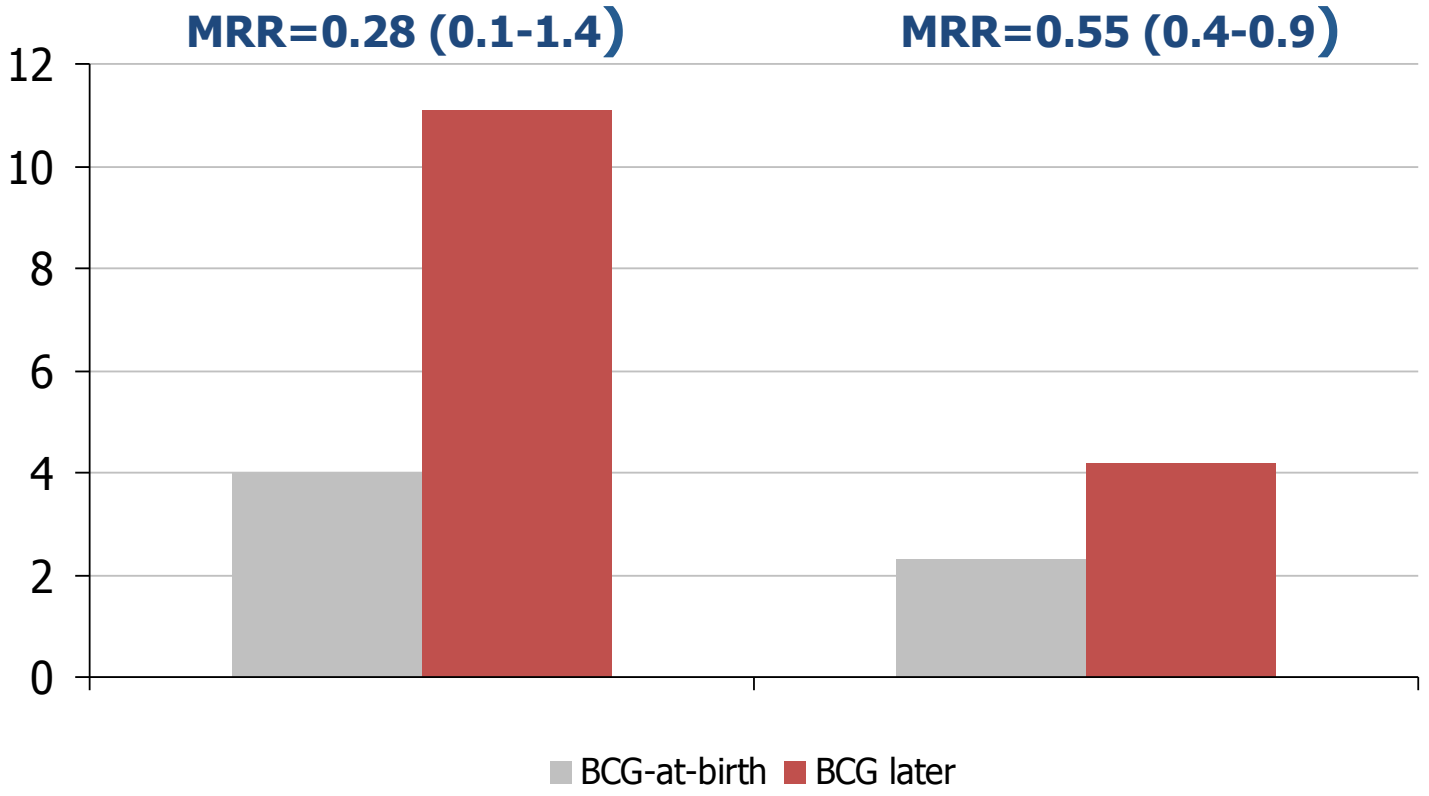
If BCG-effect not selection bias, reduction in mortality should be stronger for children with a BCG-scar



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%
Child scar+maternal scar	0.54 (0.33-0.87)	86%
Child scar – no maternal scar	0.76 (0.49-1.17)	

2 trials of BCG-at-birth in LBW children

Neonatal mortality: 0.52 (0.33-0.82)
Within 3 days: 0.42 (0.19-0.92)



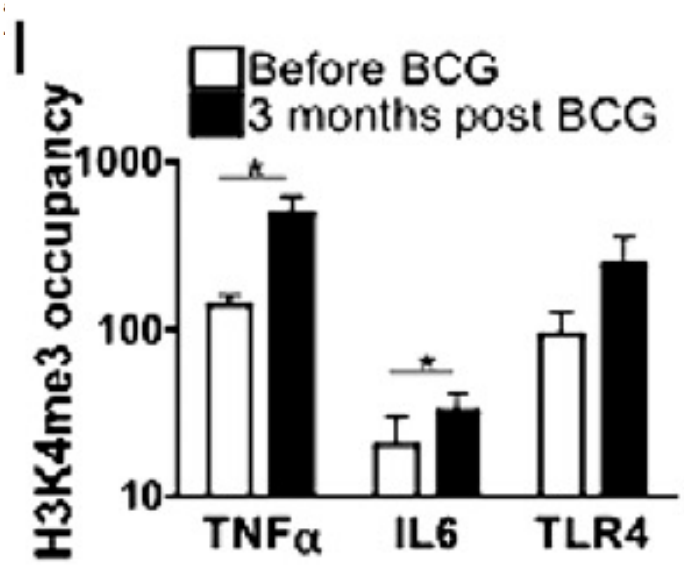
Biering et al, PIDJ 2012 **Aaby et al, JID 2011**

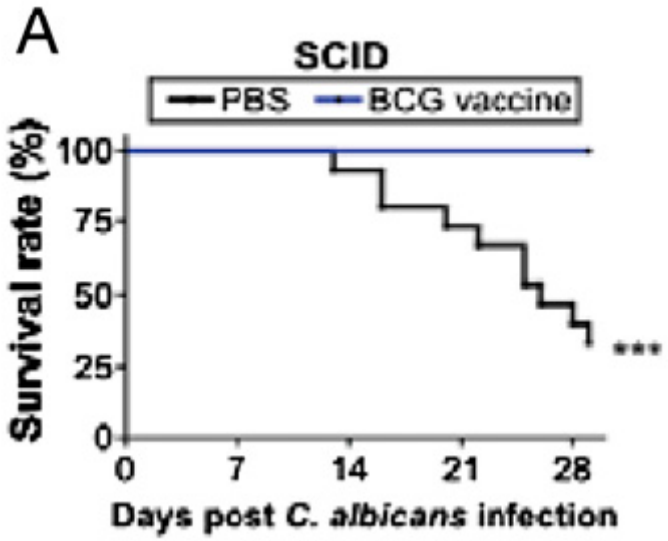
The NSEs of BCG may be due to epigenetic reprogramming of innate immunity (PNAS 2012)

PNAS

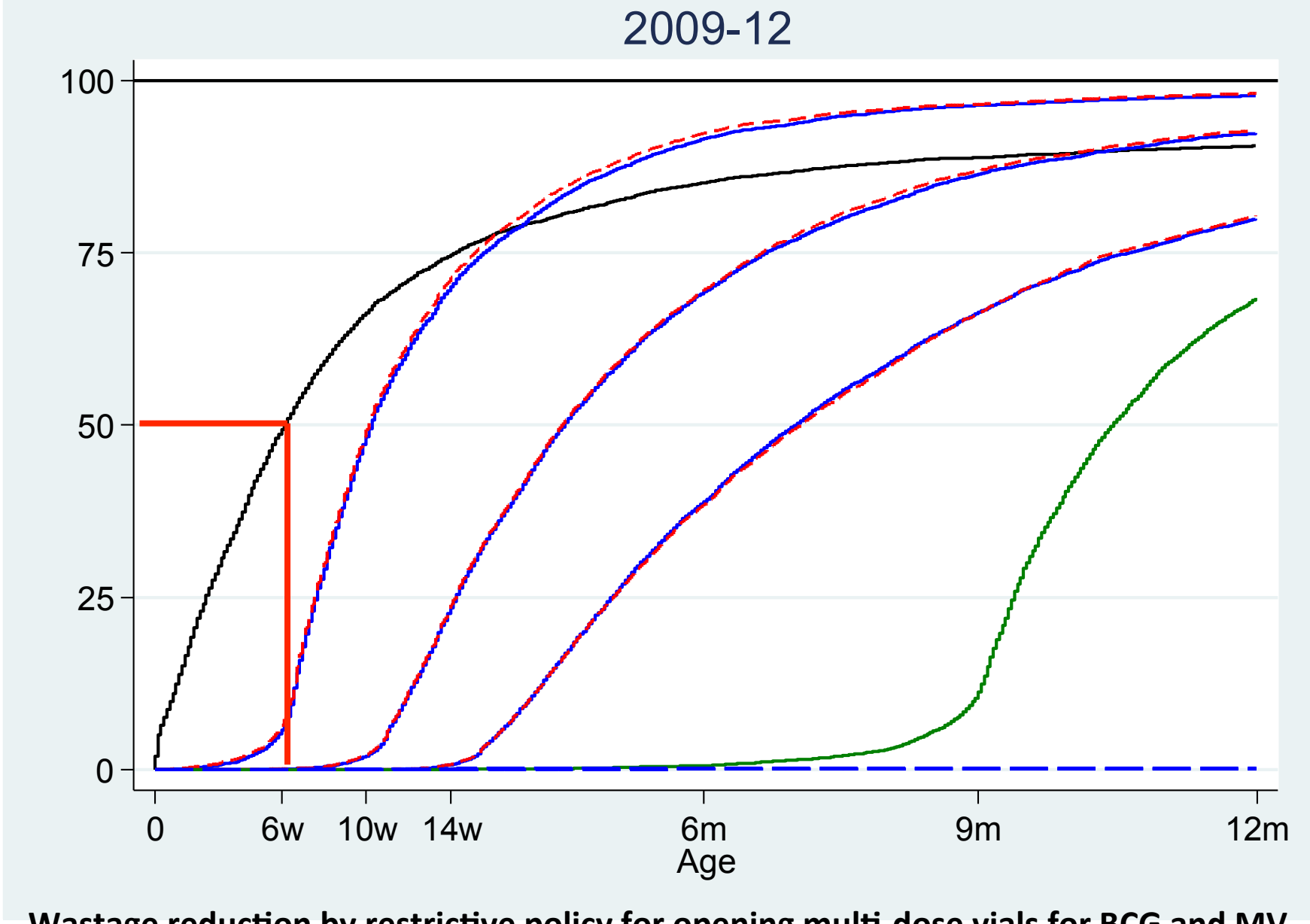
Bacille Calmette-Guérin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes

Johanneke Kleinnijenhuis[a,b,1], Jessica Quintin[a,b,1], Frank Preijers[c], Leo A. B. Joosten[a,b], Daniela C. Ifrim[a,b], Sadia Saeed[d], Cor Jacobs[a,b], Joke van Loenhout[e], Dirk de Jong[f], Hendrik G. Stunnenberg[d], Ramnik J. Xavier[g,h], Jos W. M. van der Meer[a,b], Reinout van Crevel[a,b], and Mihai G. Netea[a,b,2]



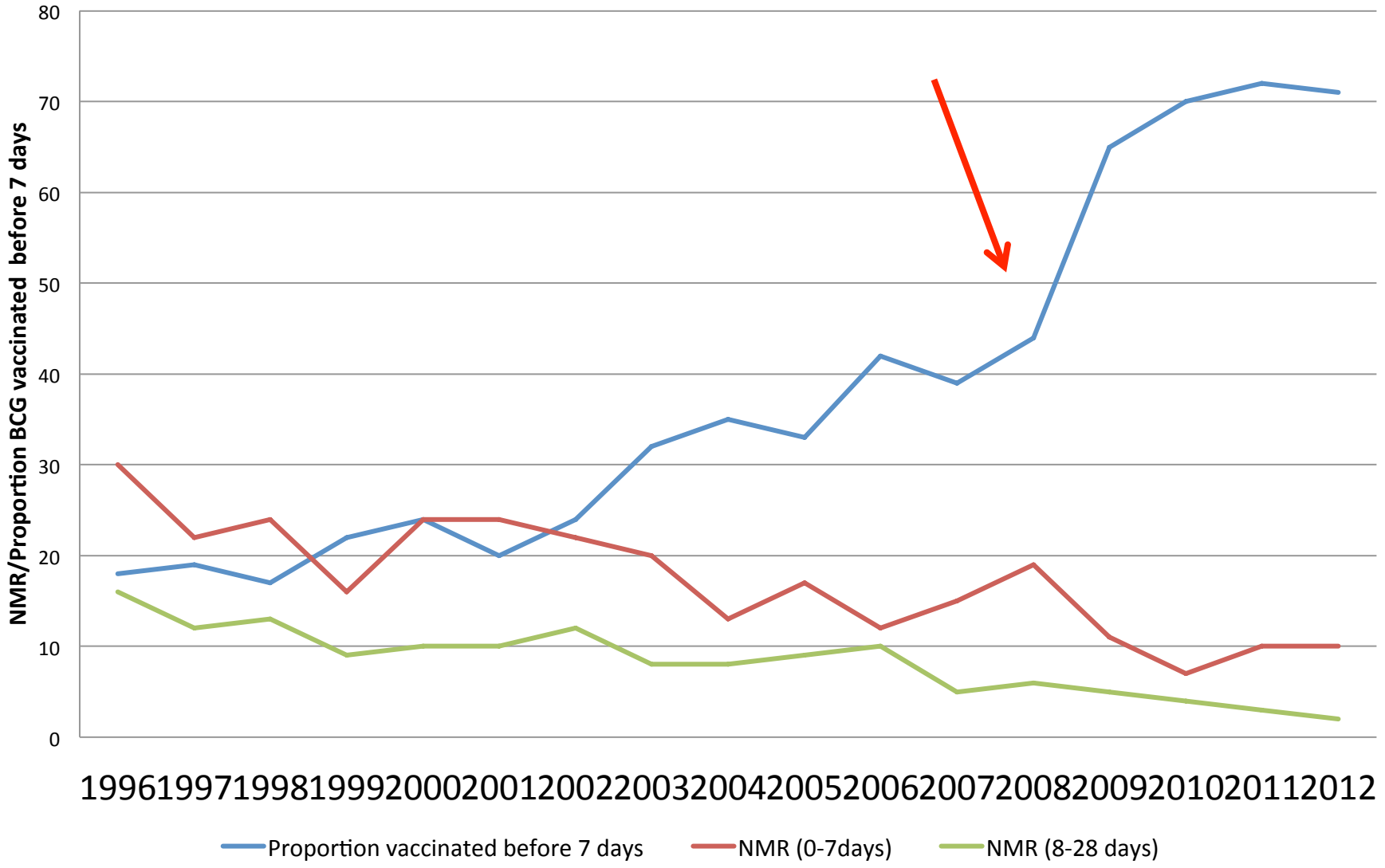


Median ages of vaccination in rural Guinea-Bissau

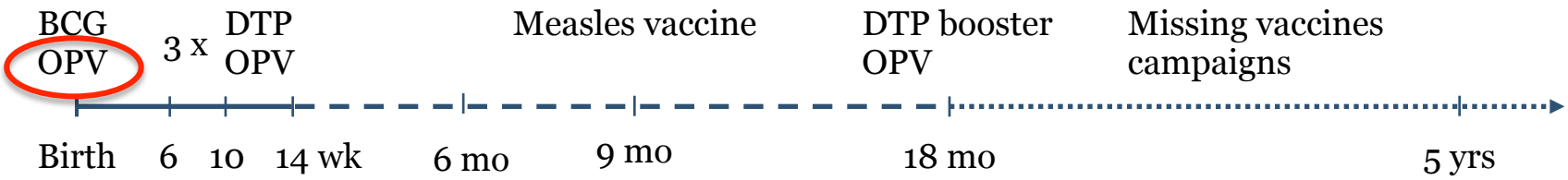


Wastage reduction by restrictive policy for opening multi-dose vials for BCG and MV

Median BCG vaccination age and neonatal mortality rates rates in Navrongo HDSS: 1996-2012



WHO vaccination policy in low-income countries



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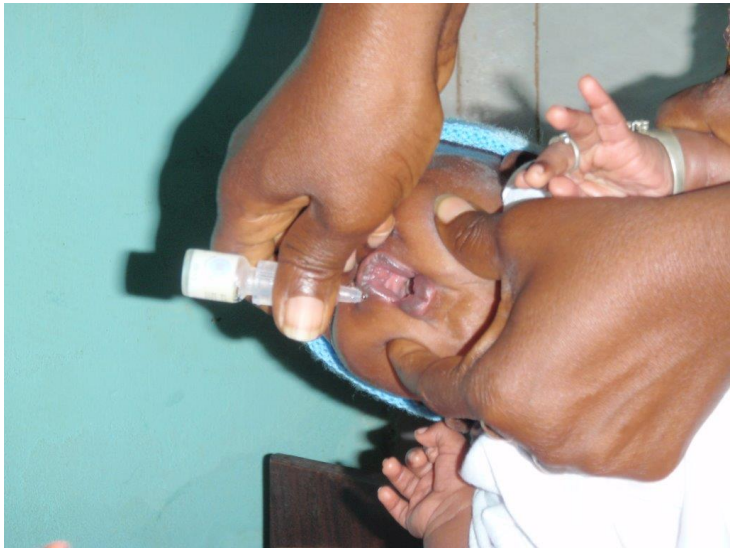


RCT of infant mortality for BCG+OPV0 vs BCG-only

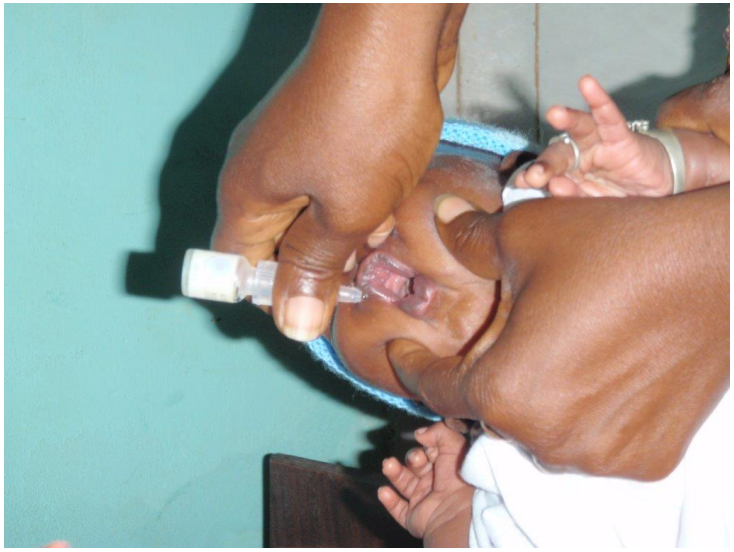
(N=7000; No polio in Bissau)
Effect of OPV campaigns censored

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)

Lund et al CID 2015

Principles of Non-specific effects of vaccines

- **Live vaccines (MV, BCG, OPV) have beneficial NSEs**
- **Maternal priming may enhance the beneficial effect**



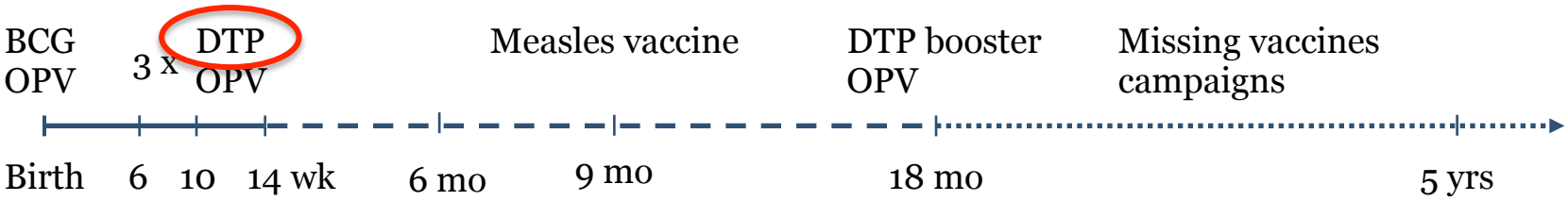
Live vaccines have beneficial non-specific effects in randomised trials

So live vaccines may train the immune system beneficially

Randomised Trials	Outcome	Overall reduction in mortality	Nonspecific reduction	Specific disease reduction
MV at 4+9 vs 9 mo	Mortality 4-36 mo	30% (10-50%)	26% (0-45%)	4%
3 Trials of BCG at birth	Neonatal mortality	38% (17-54%)	38% (17-54%)	0%
Oral polio vaccine at birth	Infant mortality	32% (0-57%)	32% (0-57%)	0%

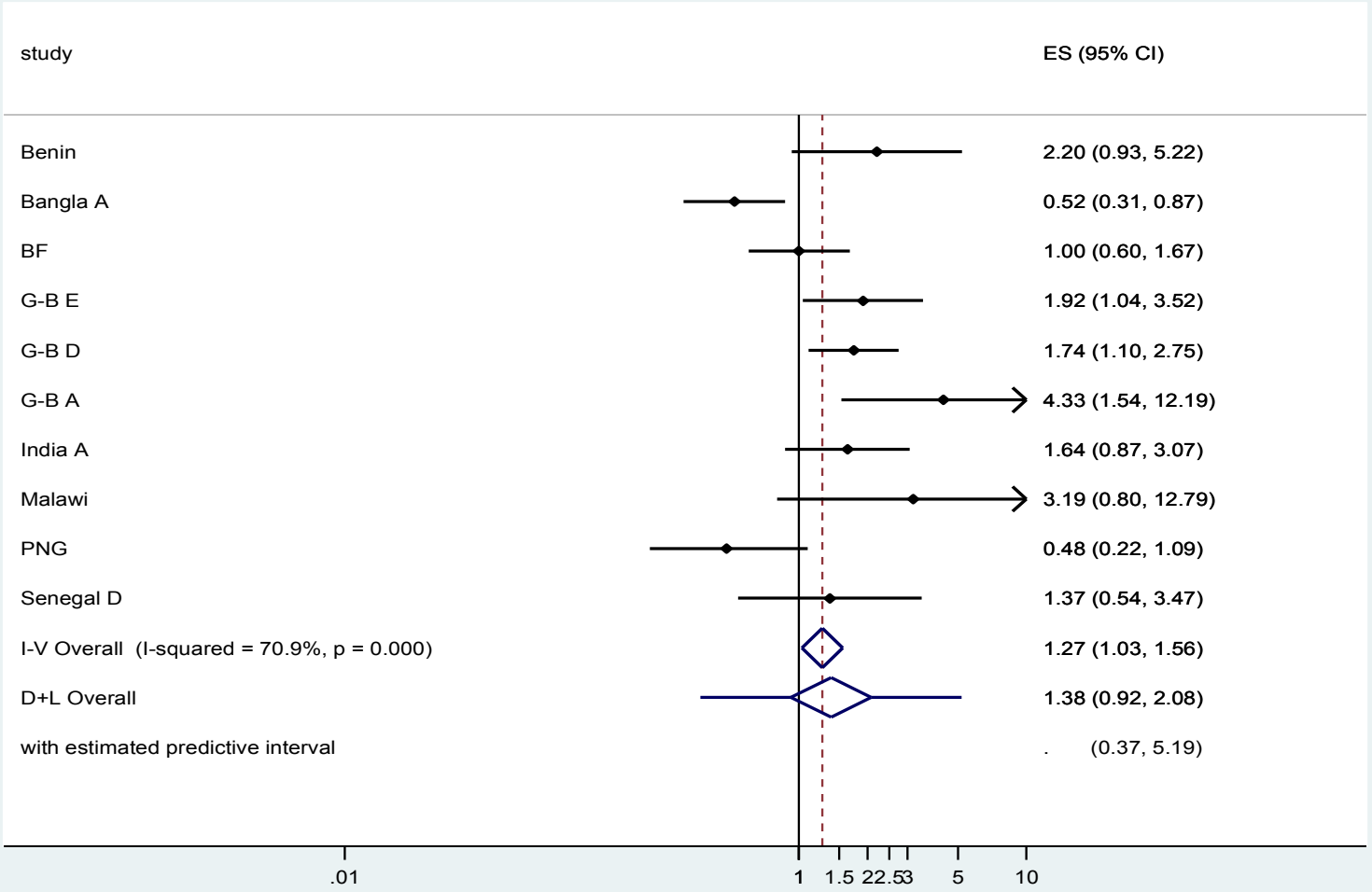
Non-specific effects provide protection against lower respiratory infection and sepsis

WHO vaccination policy in low-income countries



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

Strategic Advisory Group of experts on immunization(SAGE) 2014: DTP associated with 38% higher mortality (both sexes)



SAGE review: ***"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 effects of OPV and DTP; herd immunity to pertussis***

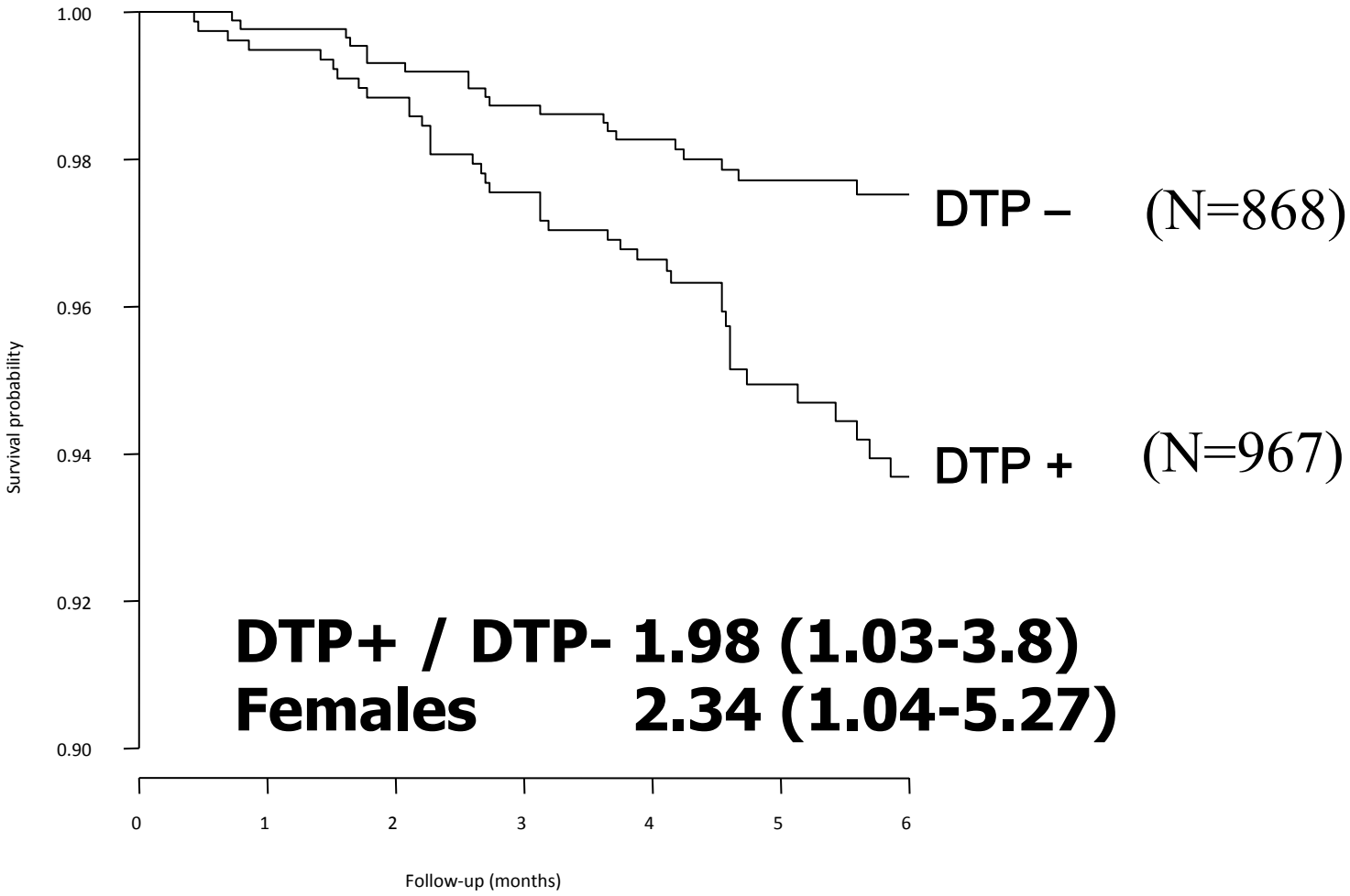
Higgins 2014

Introduction of DTP

Rural areas of Guinea-Bissau 1984-87

Children aged 2-8 mo

Unvaccinated: travelling; sick; days without vaccines

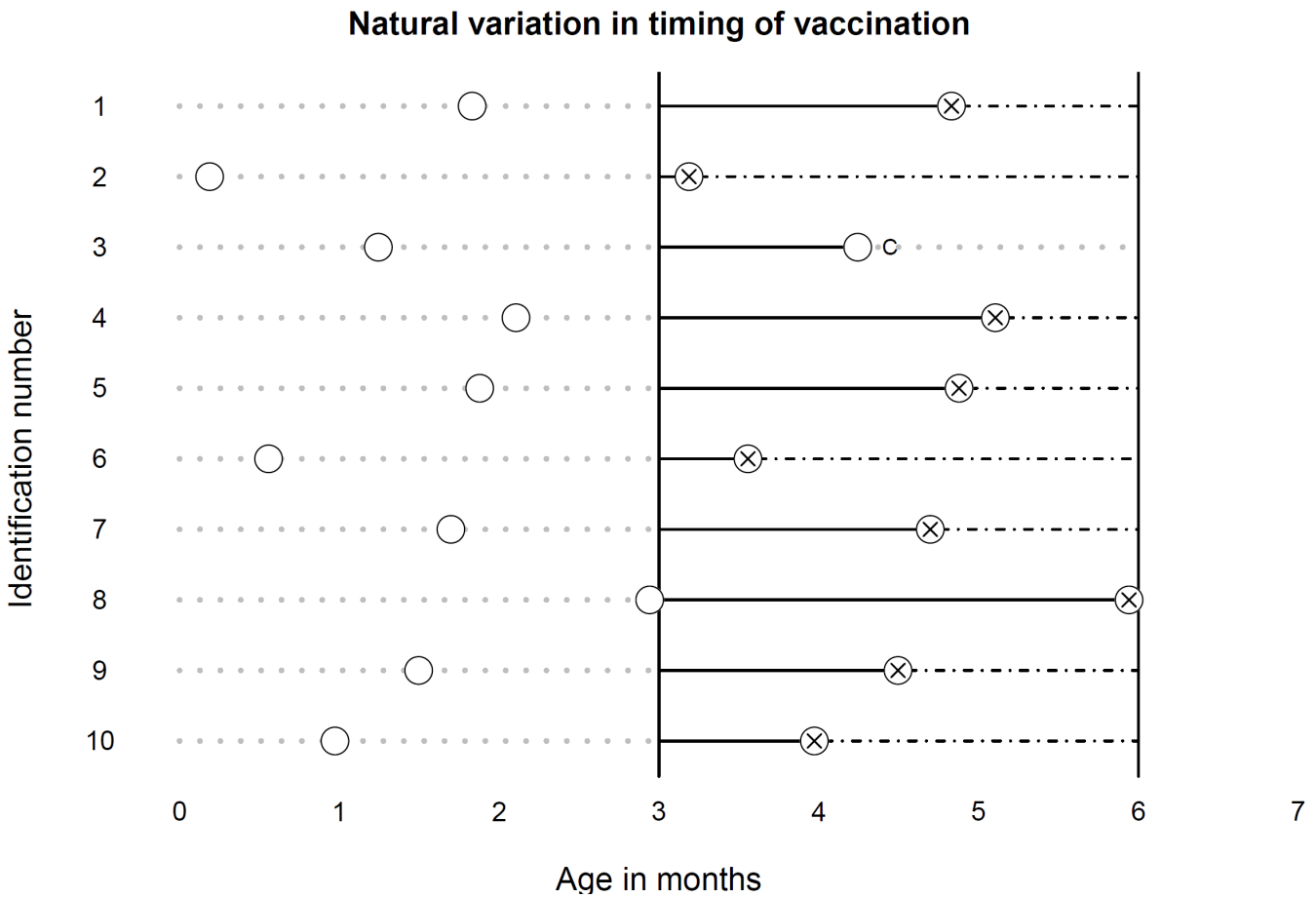


DTP+ / DTP- 1.98 (1.03-3.8)
Females 2.34 (1.04-5.27)

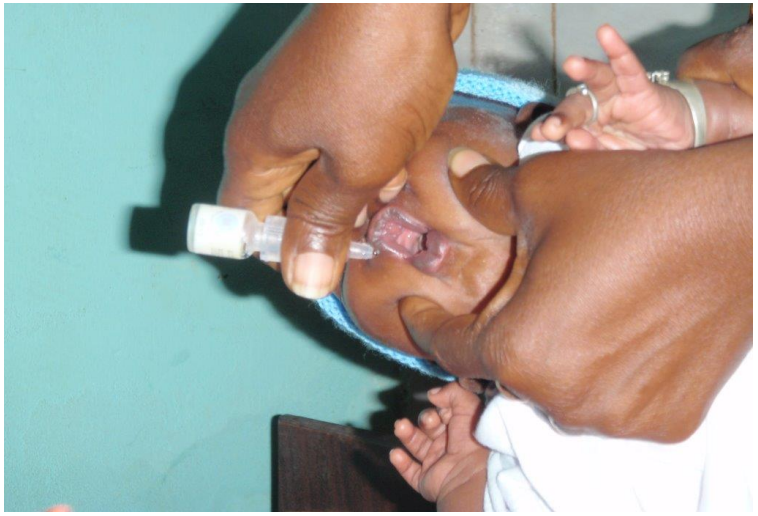
The only study of the introduction of DTP in the global literature

Aaby et al, Int J Epidemiol 2004

Introduction of DTP in Bissau in 1981-3



Age group 3-5 (months)	Mortality rate ratio DTP vs no Vaccine	GIRLS	BOYS
DTP(+/-OPV)	5.00 (1.5-16.3)	10.0 (0.8-123)	3.93 (1.0-15.3)



OPV may modify the negative effect of DTP

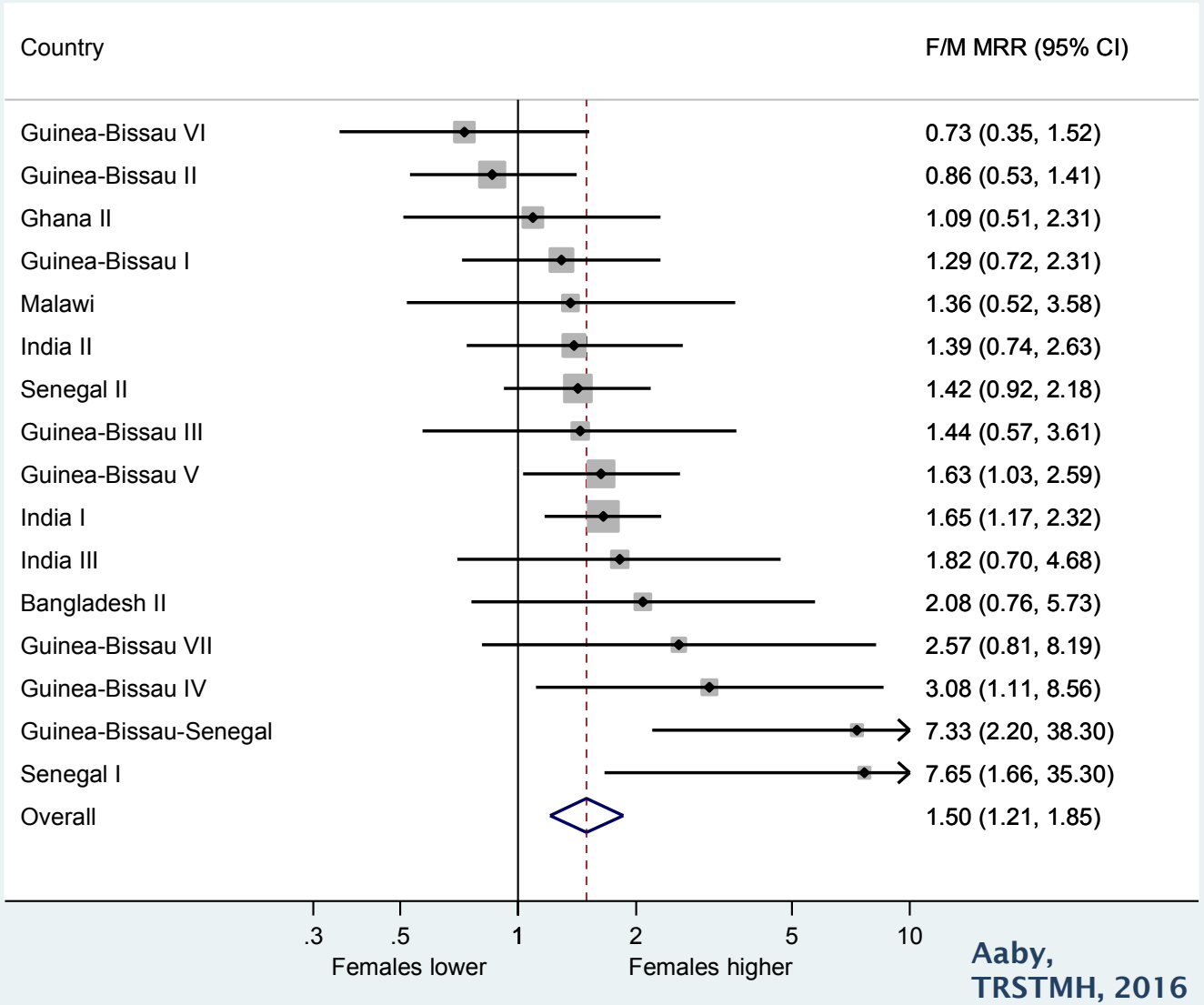
Mortality for DTP versus unvaccinated children

Introduction of DTP and OPV	HR DTP-only vs unvaccinated	HR DTP+OPV vs unvaccinated
Urban Bissau 1981-1983 (in revision)	10.0 (2.6-39)	3.52 (1.0-12.9)
Rural Bissau 1984-1987 (IJE 2004)	5.00 (0.6-40)	1.90 (0.9-4.0)
Combined increase in mortality	8.1-fold (2.6-25) Increase in mortality	2.2-fold (1.2-4.2) Increase in mortality

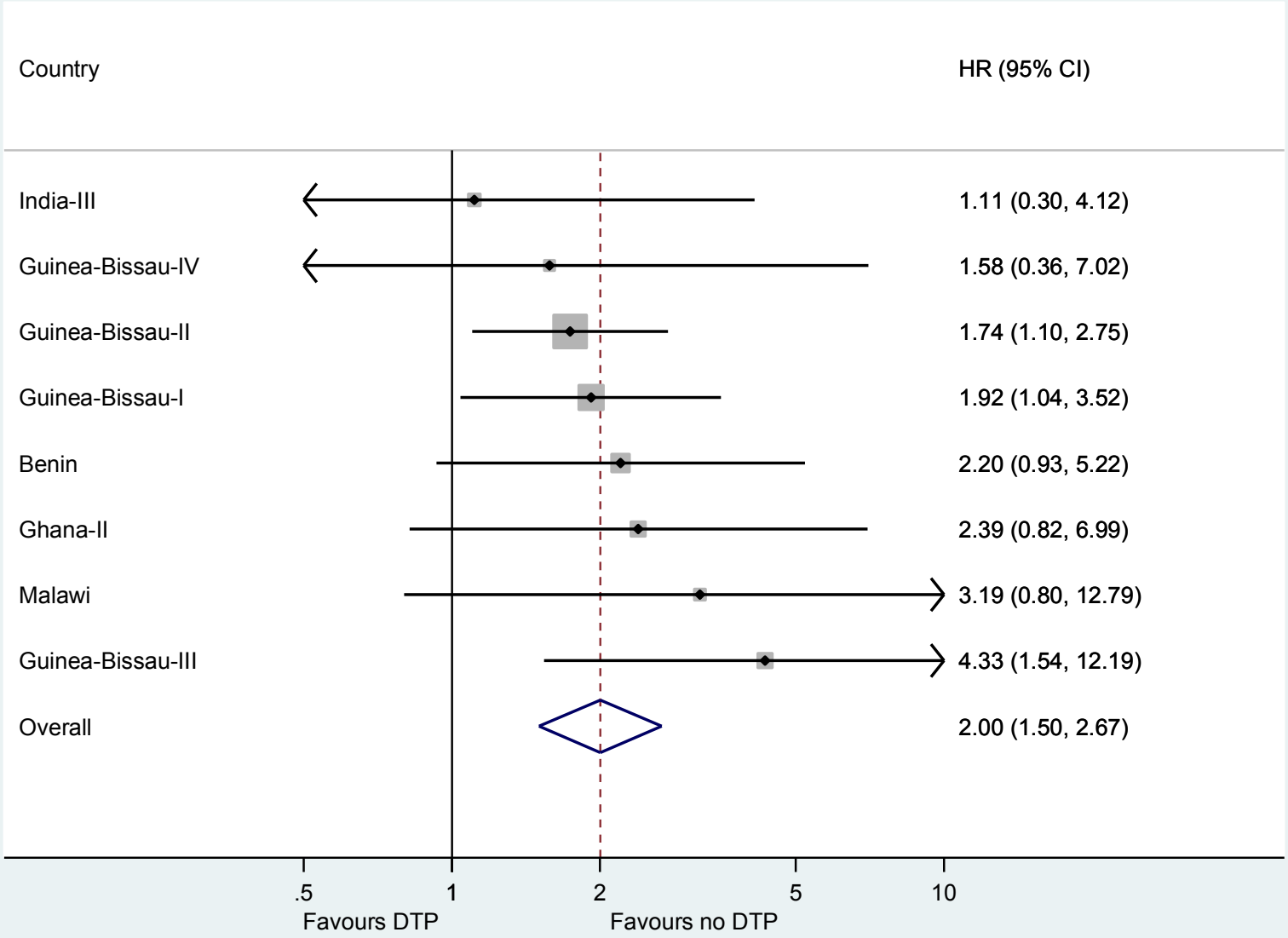
Hypothesis II: Female/Male Mortality Rate Ratio among DTP-vaccinated children

Before (5 studies):
1.66 (0.98-2.79)

After (11 studies):
1.49 (1.20-1.84)



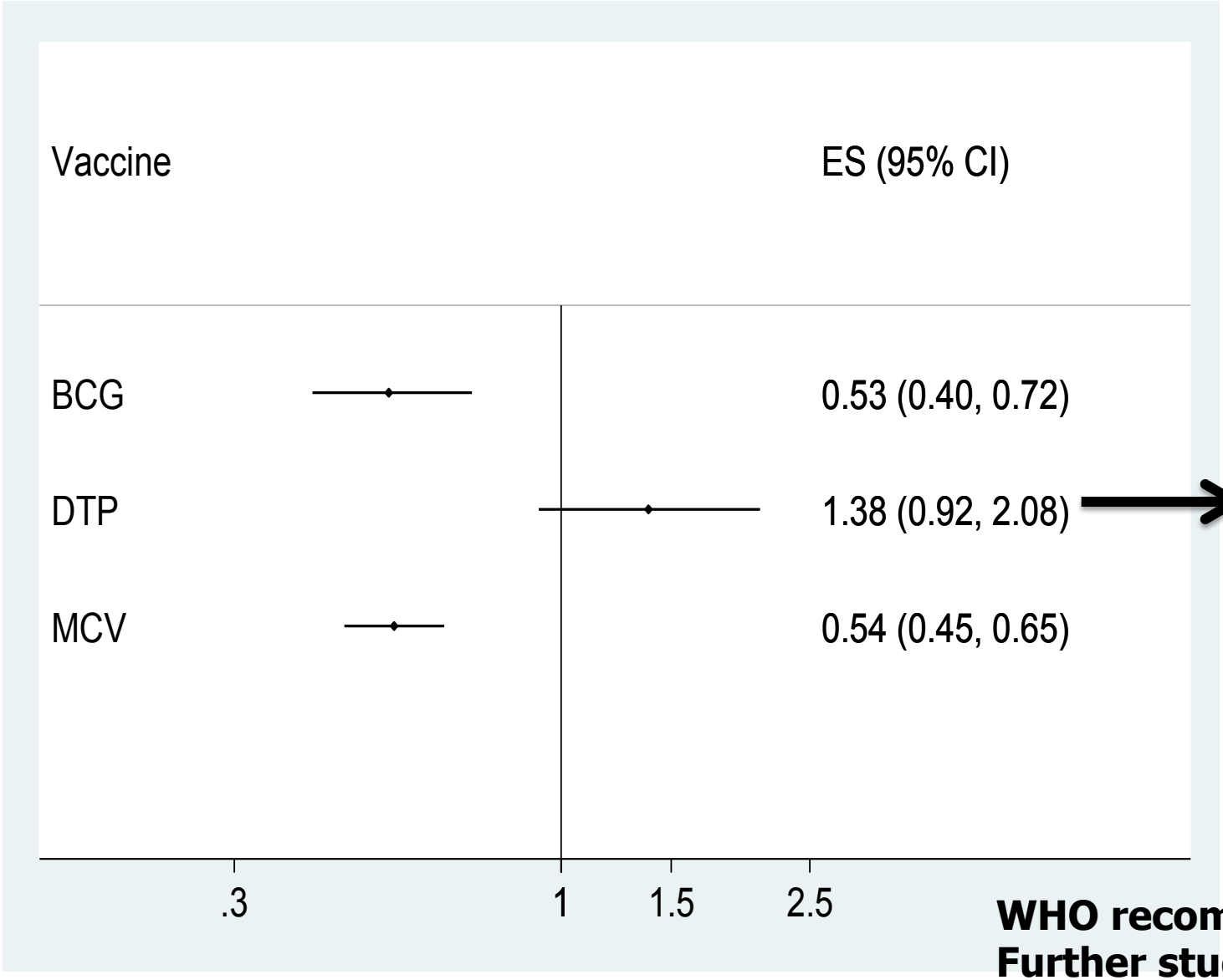
Impact of DTP in studies with no survival bias



Findings in SAGE studies with prospective follow-up were not inconsistent – Methodologies used in the included studies were inconsistent

Aaby PIDJ 2016

WHO-SAGE review of NSEs of BCG, DTP and Measles Vaccine HR estimates for different vaccines



RTS,S malaria vaccine and child mortality

RTS,S/AS01 malaria vaccine and child mortality

Period	Deaths RTS,S vaccine	Deaths Controls	MRR
0-14 mo (NEJM 2012)	122/10306	56/5153	1.09 (0.80-1.49)
14 mo-end of study (Lancet 2015)	96/10184	32/5097	1.50 (1.01-2.24) Aaby Lancet 2015

No results by sex

RTS,S malaria vaccine and child mortality by sex

Sex and age group	Deaths/N RTS,S vaccine	Deaths/N Controls	MRR
Males/overall	95/5215	55/2550	0.84 (0.61-1.17)
Females/overall	123/5091	33/2603	1.91 (1.30-2.79)

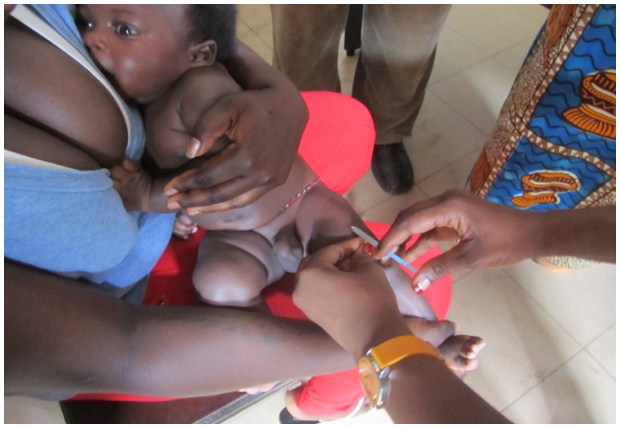
RTS,S Female/male MRR 1.33 (1.02-1.74)

WHO planning to pilot test the RTS,S in 800,000 children in Africa
GACVS: Female mortality a danger signal

Klein mBio 2016

Non-live vaccines may have negative effects for all-cause mortality for girls

Vaccine	Studies	Female vs Male HR for vaccinated children
DTP (Aaby TRSTMH, revision)	**16 studies**	**1.50 (1.21-1.85)**
Penta (Fisker Vaccine 2016)	**1 study**	**1.73 (1.11-1.74)**
IPV (Aaby PIDJ 2007)	**3 trials**	**1.52 (1.02-2.28)**
HBV (Garly PIDJ 2004)	**1 natural experiment**	**2.20 (1.07-4.54)**
Malaria vaccine (Klein mBio 2016)	**2 trials**	**1.33 (1.02-1.74)**



DTP with MV or after standard MV

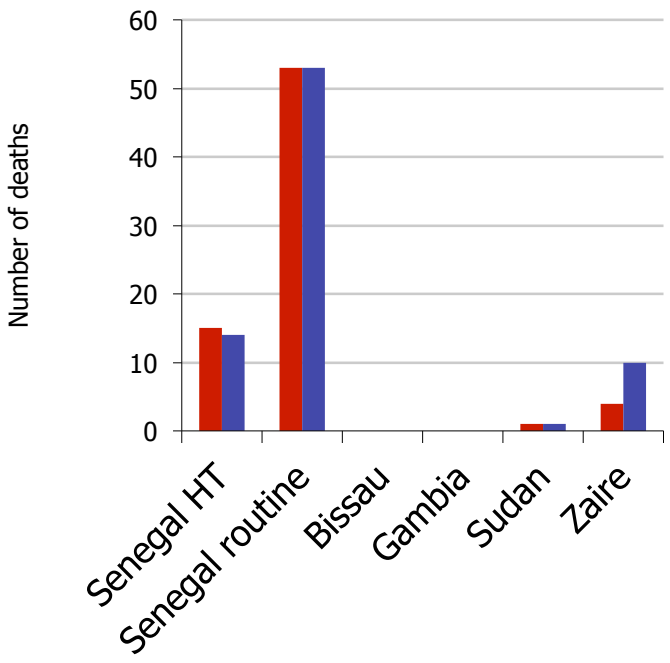
Data from Navrongo, Northern Ghana, 1996-2012

Most recent vaccination	DTP>= MV	MV-after-DTP3	Adjusted MRR (95%CI)
	Mortality rate per 1000 pyrs		
1996-2001 (DTP)	36	20	1.91 (1.32-2.75)
2002-2012 (Penta)	29	12	1.77 (0.90-3.51)
Overall	35	15	1.84 (1.33-2.53)

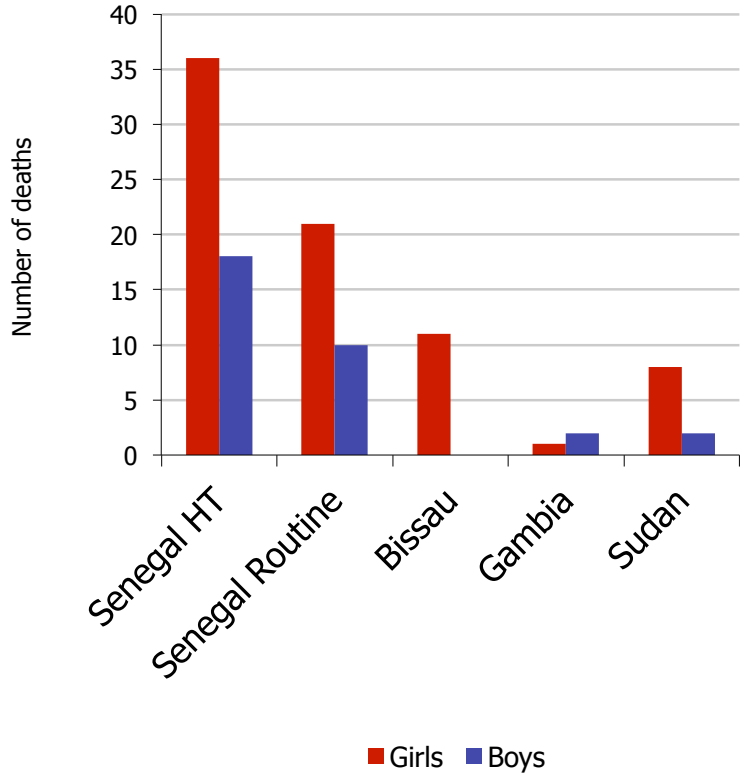
Welaga (submitted)

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)

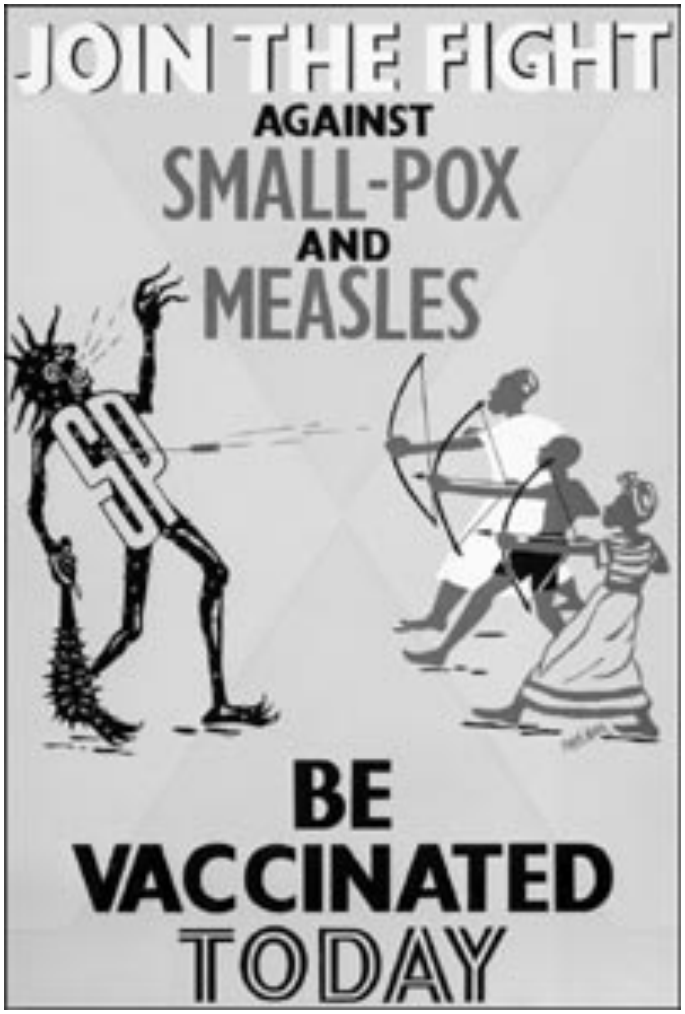
Lancet 2003

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

Principles of Non-specific effects of vaccines

- **Live vaccines (MV, BCG, OPV) have beneficial NSEs**
- **Non-live vaccines (DTP, Penta, HBV, IPV, RTS,S) may have negative NSEs**
- **NSEs are often sex-differential**
- **Interventions interact: co-administration and sequence may be very important for child survival**
- **Maternal priming may enhance the beneficial effect**

Single-disease-eradication paradigm



Single disease perspective

If eradicated we can stop vaccination:

1. **Save costs**
2. **Prevent side-effects**

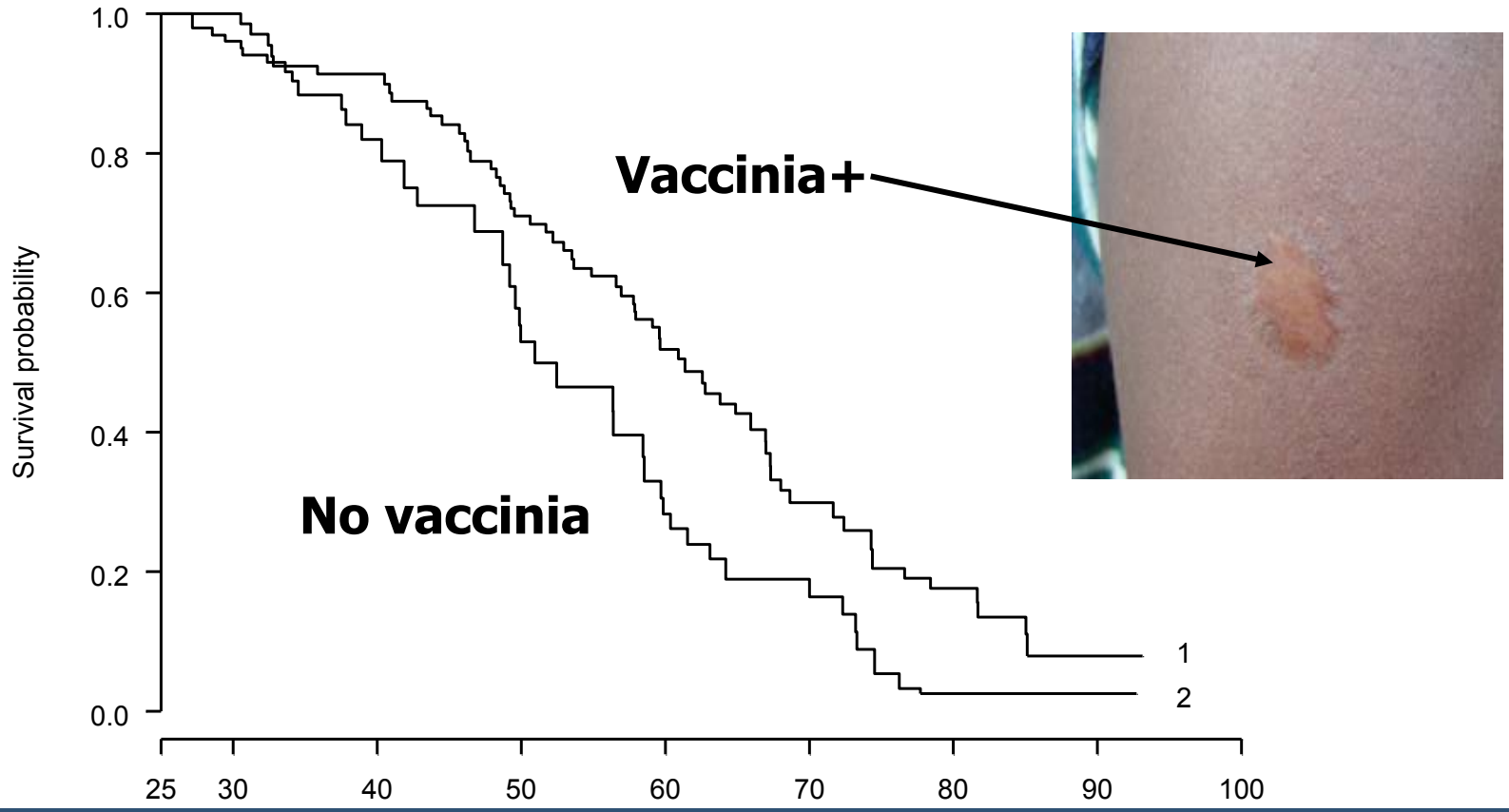
Smallpox eradicated – vaccinia stopped
BCG stopped in high-income countries

Eradication planned within the next 10-20 years for Polio and Measles (and Rubella)

No study examined the effect of stopping Vaccinia in 1980

But what if vaccinia had a beneficial effect?

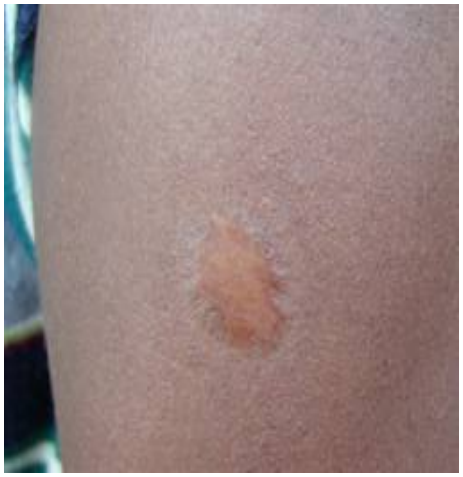
We started reading vaccinia and BCG scars in urban Bissau in 1998 and followed for mortality



1893 individuals 25+ years in 1998 followed to 2002 (Vaccine 2006)
Vaccinia scar/no scar: Reduction in mortality 40% (13-59%)
1 scar: 35% ; 2 scars: 46% ; 3+ scars: 56% - **trend: 27% (5-44%)/per scar**

British MRC (The Gambia) started scar reading in a HIV case-control study in rural Bissau in 2003 – followed for mortality to 2006

	% (Deaths/Number)		Mortality rate ratio*
	Vaccinia scar	No scar	
Females	7%(12/174)	26%(8/31)	0.19(0.06-0.57)
Males	22%(17/77)	25%(1/4)	0.40(0.04-3.74)
All			**0.22(0.08-0.61)**
*Adjusted age, village, HIV-status			



367 individuals 30+ years in 2003 followed to 2006 (PLoS ONE 2006)

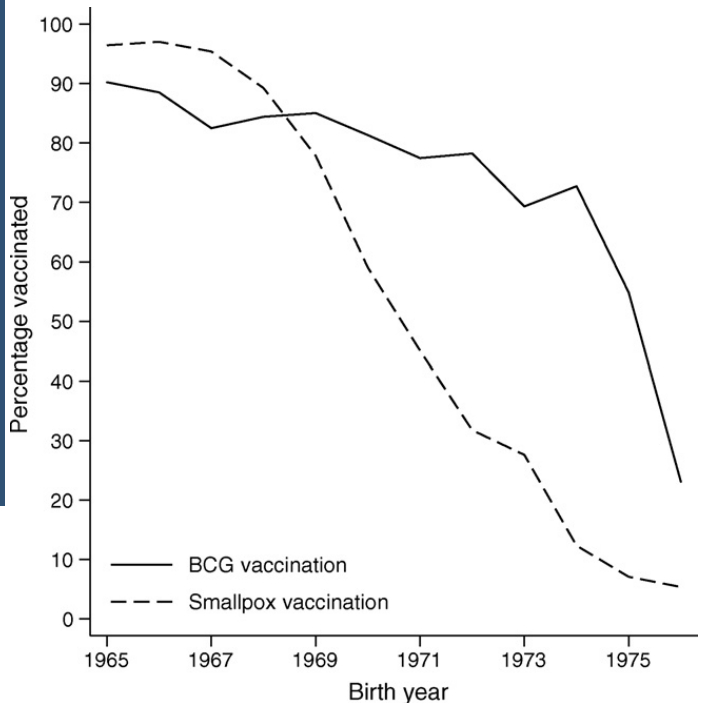
Vaccinia scar/no scar: Reduction 78% (39-92%)

1 scar: 76%(32-91%) ; 2+ scars: 86% (44-97%);

Vaccinia and BCG removed in Denmark 1965-76

Copenhagen school health cards had information on vaccinations => link to Danish health registers

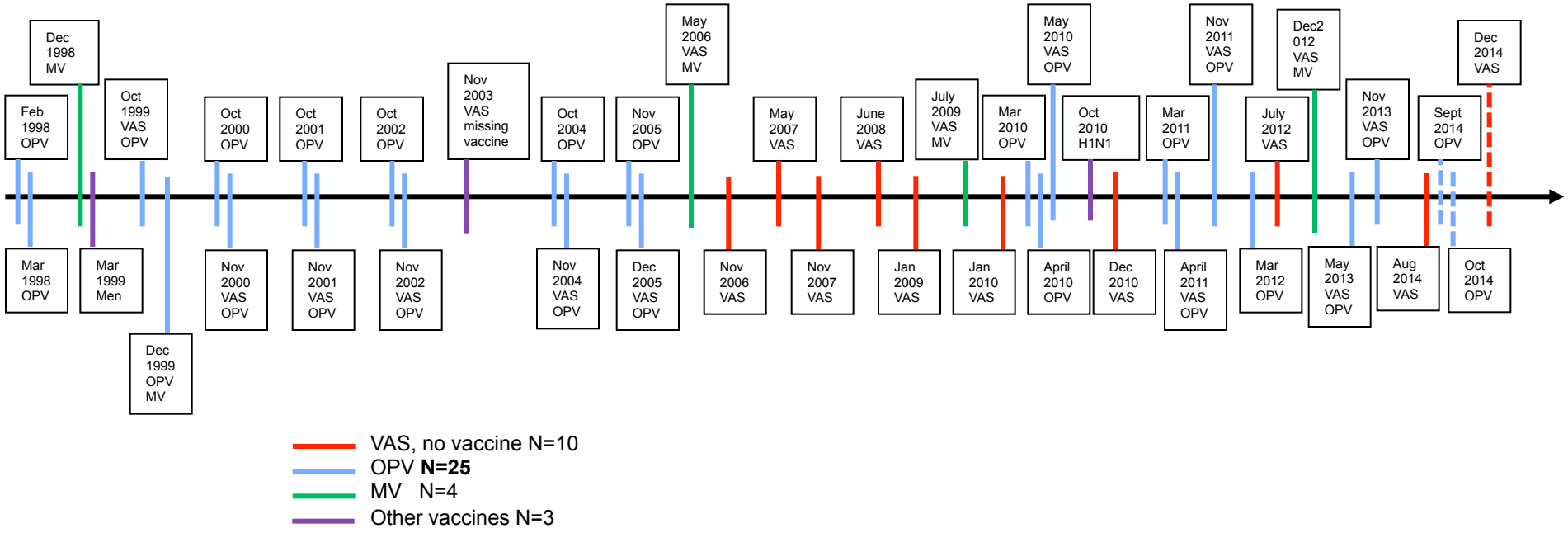
Asthma reduced by 45% (0-70%)
(J Allergy Clin Imm 2003)
Infectious admissions reduced by 16%(2-28%)
(Int J Epidemiol 2011)



Mortality 1971-2010	Natural causes of death (N=401)		Accident, suicides, murders (N=316)	
	Deaths/pyrs	Adjusted HR	Deaths/pyrs	Adjusted HR
No vaccine	53/24414	1.0	35/13355	1.0
Vaccinia + BCG	239/85618	**0.54 (0.36-0.81)**	189/85618	0.92 (0.57-1.46)
Vaccinia or BCG	348/140036	**0.57 (0.40-0.81**)	281/140036	0.90 (0.60-1.37)

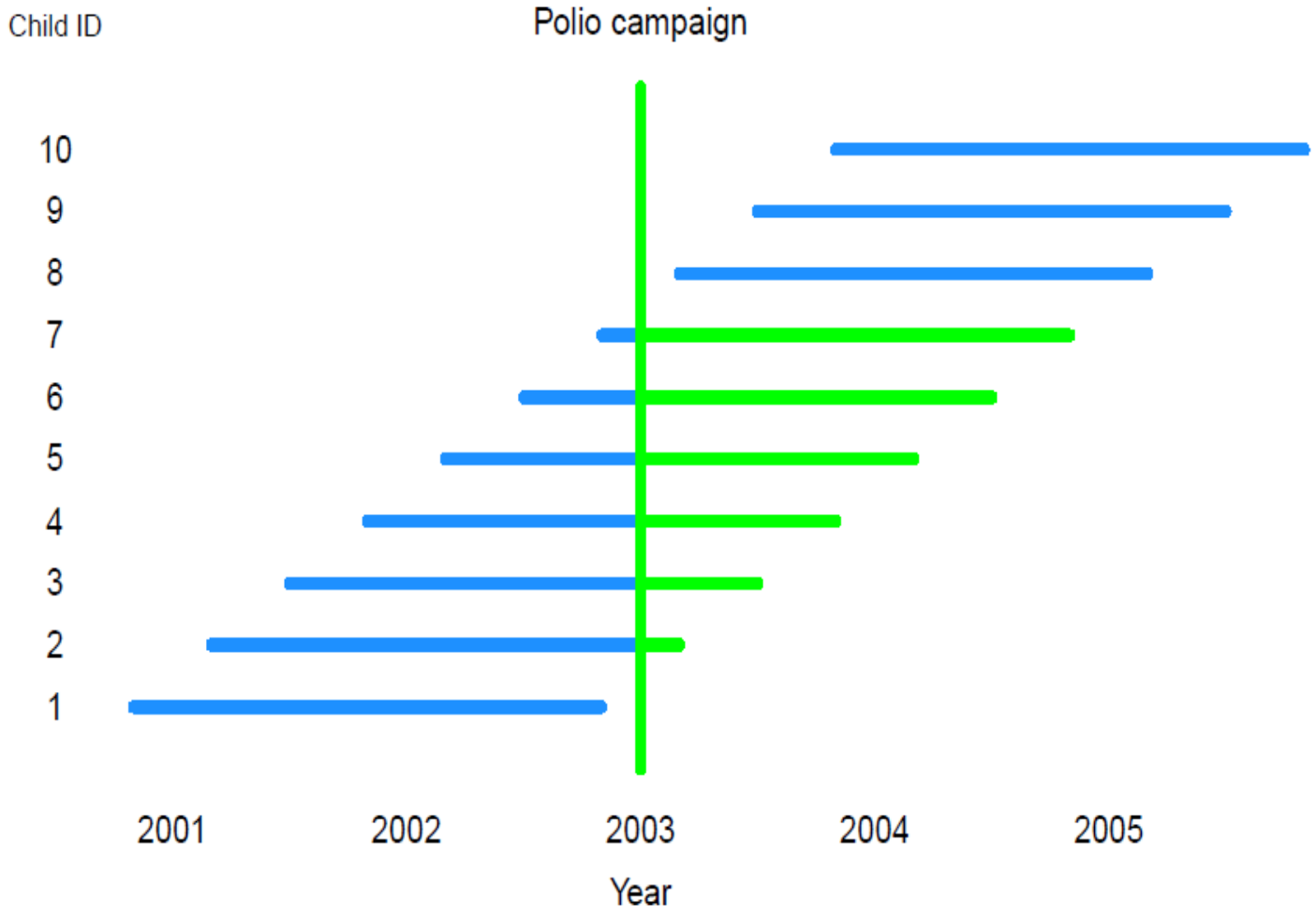
Reickmann Int J Epid 2016

17 years of campaigns in Guinea-Bissau

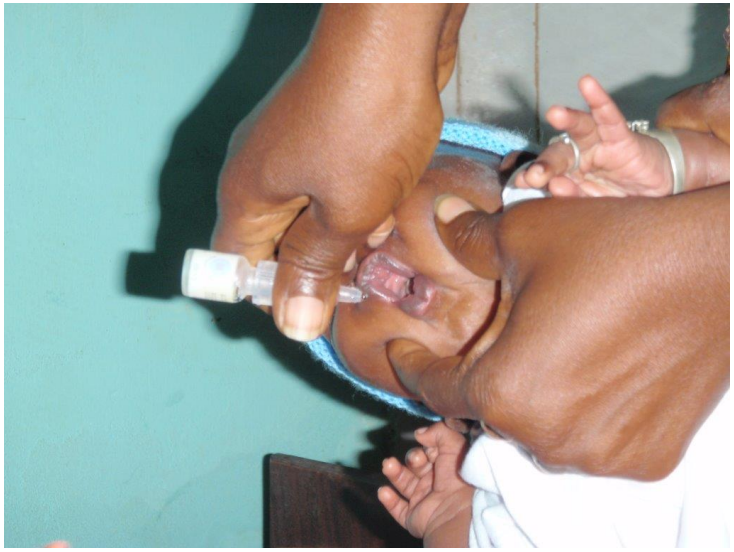


Polio and measles are not major killer diseases now so no effect on child survival expected. Effect of campaigns not measured

Assessing mortality from vaccination campaigns



We assessed effect of campaigns within RCTs so that children were their own controls – blue time before campaign; green time after campaigns



Tested campaigns within RCTs

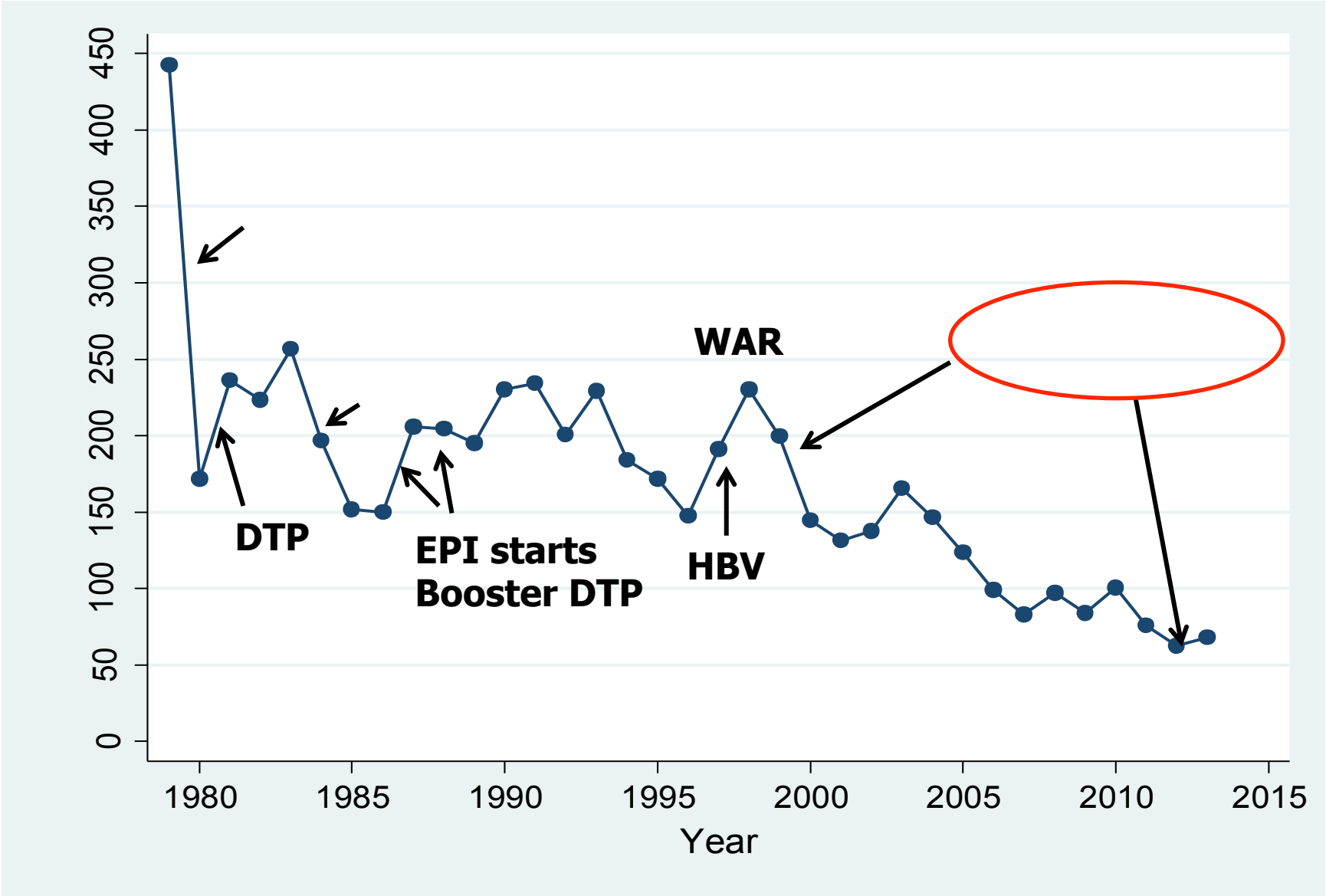
25 campaigns to eradicate polio
1 H1N1 campaign

OPV reduced mortality by 19%
H1N1 increased it by 57%

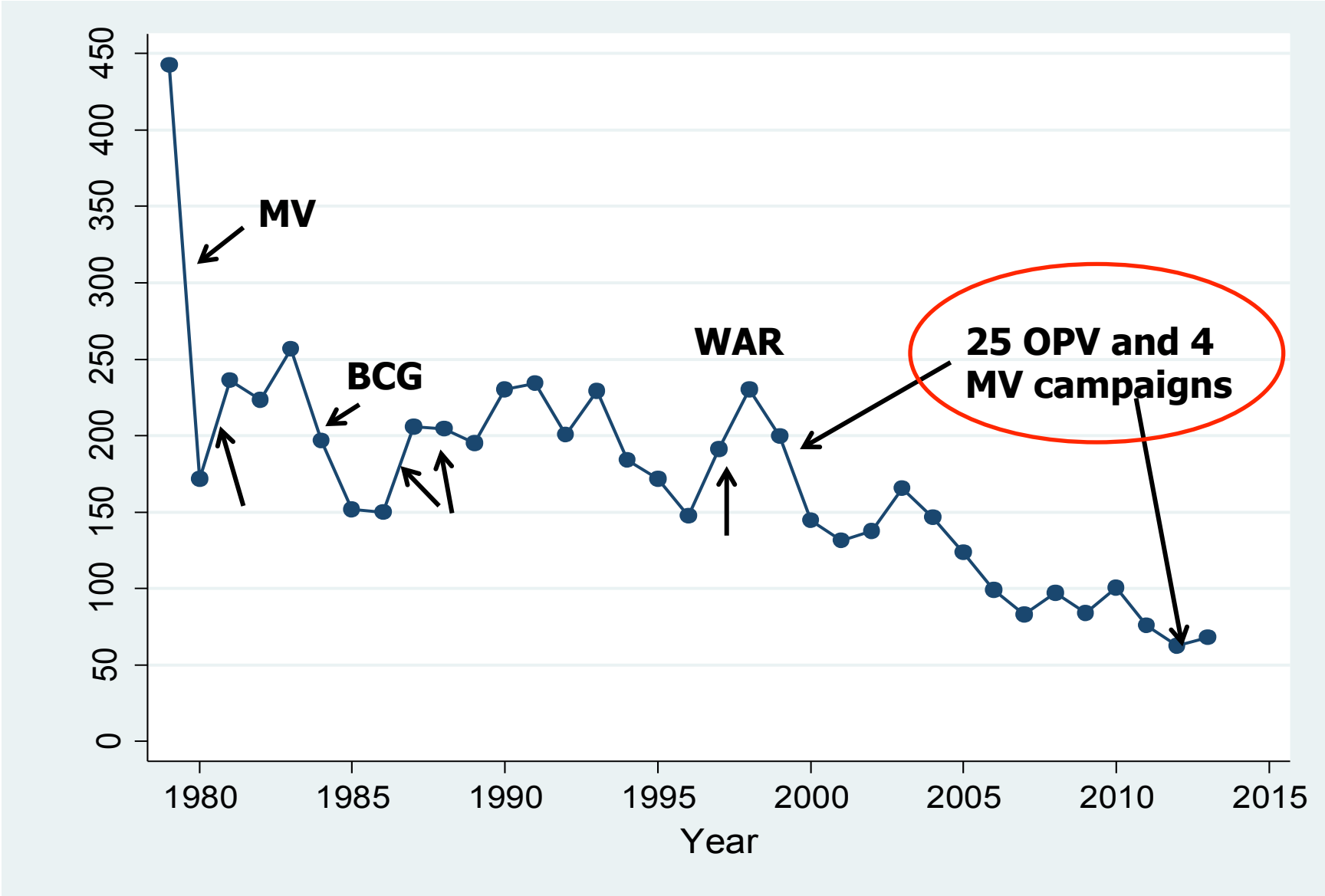
Randomised Trials	MRR after-OPV vs before-OPV	MRR after-H1N1 vs before-H1N1
3 RCTs of Vitamin A	0.75 (0.55-1.01)	1.57 (0.92-2.70)
Early MV	0.95 (0.71-1.28)	
2 RCTs BCG-at-birth	0.81 (0.63-1.05)	2.58 (1.09-6.07)
OPV at birth	0.90 (0.61-1.32)	0.77 (0.27-2.16)
All	**0.81 (0.70-0.93)**	**1.57 (1.04-2.39)**
		Females 1.85 (1.11-3.09)

So what will happen when OPV is removed?

Resolution to contradiction - II –
The introduction of non-live vaccines



Resolution to contradiction - II –
The road to MDG4 is paved with live vaccines



MDG4 1990: 236/1000 to 2013: 68/1000 => 68%

Changing the paradigm:
The current focus is on specific prevention

Single-disease perspective

- Not tested overall effect
- Not tested sex and interactions effects
- Delayed vaccination for high antibody responses
- Emphasized inactivated vaccines (DTP3,IPV)
- DTP after MV
- Eradicated good vaccines (Vaccinia, BCG, OPV)

Principles of Non-specific effects of vaccines

- **Live vaccines (MV, BCG, OPV) have beneficial NSEs**
- **Non-live vaccines (DTP, HBV, IPV) have negative NSEs, especially for girls**
- **NSEs are often sex-differential**
- **Interventions interact: co-administration and sequence may be very important for child survival**
- **Maternal priming may enhance the beneficial effect**
- **Boosting with live vaccines have beneficial effect**
- **Eradication can lead to higher mortality**