

# Vaccinations and child survival: The Optimunize study

4 PhDs to submit thesis within next year

**DANIDA-EU**  
4½ mill €

## **INDEPTH Network**

Associated: Rufiji, Vadu, Kisumu  
Niakhar, Keneba

Chakaria  
Nairobi  
Kintampo

Navrongo  
Nouna  
Bandim

**I. Monitoring childhood interventions for child survival. DANIDA research training proposal**

1. Routine surveillance
2. Determinants of delay
3. Variation in implementation
4. Out-of-sequence
5. Sex-differences

**II. Optimising the impact and cost-effectiveness of child health intervention programmes for vaccines and micronutrients in low-income countries. EU-funding**

1. Measure real life effects
2. Combining observ. and RCT
4. INDEPTH dissemination

**III. Stimulate research in child interventions**

1. Help with analysis of data
2. Workshops
3. More trials
4. Eradications research

# Optimunise built on a paradigm conflict

	Single-disease-eradication paradigm	Non-specific immune training effects
<b>Mission</b>	Reduce mortality	Reduce mortality
<b>Focus</b>	Protective immune responses; clinical protection	Change in overall mortality – overall morbidity
<b>Effect</b>	Always beneficial, proportional to single-disease protection	<i>Live vaccines</i> -> good effects – > more than specific protection <i>Inactivated vaccines</i> ->bad effect
<b>Sex</b>	Same effect for boys and girls	Sex-differential effects are likely
<b>Sequence</b>	Give vaccines when possible	Live-vaccine-last should be policy
<b>Ultimate goal</b>	Eradicate – remove vaccine	Removing may have negative effect



# WHO 2013: WHO/SAGE review

WHO 2013: WHO/SAGE review

World Health Organization

English Français Русский Español

Health topics Data Media centre Publications Countries Programmes About WHO

## Immunization, Vaccines and Biologicals

**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

Immunization, Vaccines and Biologicals

Vaccines and diseases

Global Vaccine Action Plan

WHO policy recommendations

National programmes and systems

Monitoring and surveillance

Quality, safety and standards

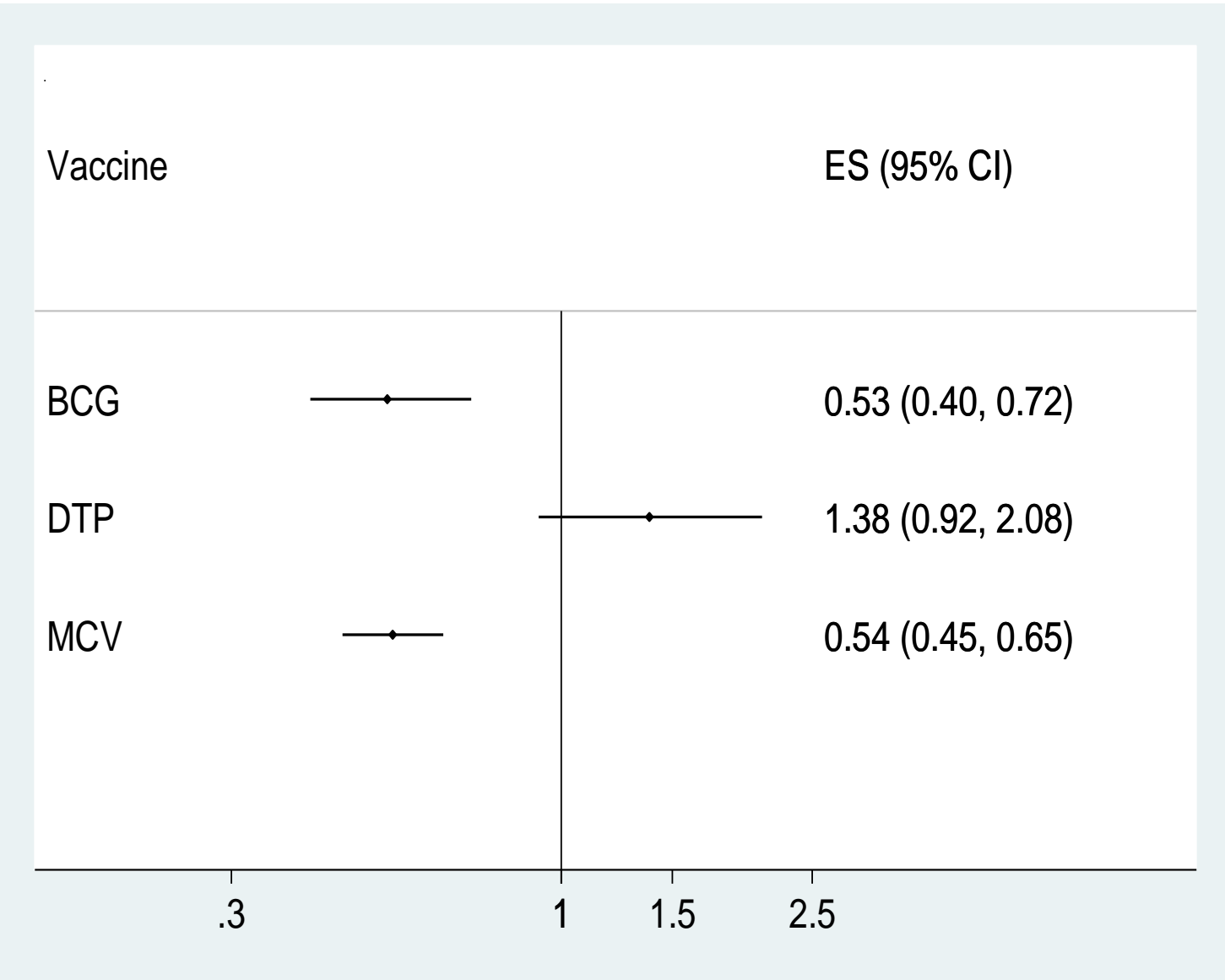
Research and development

Resource materials

Newsroom

**SAGE=Strategic  
Advisory Group of  
Experts on  
Immunization**

# WHO-SAGE estimates for different vaccines





**Live vaccines have beneficial non-specific effects in randomised trials (RCTs)**

**Vaccines may train the immune system**

<b>Randomised Trials</b>	<b>Outcome</b>	<b>Mortality rate ratio (MMR)</b>	<b>Censoring targeted deaths</b>	<b>References</b>
<b>3 RCTs of BCG at birth to LBW children</b>	<b>Neonatal mortality</b>	<b>0.59 (0.4-0.8)</b>	<b>0.59 (0.4-0.8)</b>	<b>JID 2011, PIDJ 2012</b>
<b>OPV0: BCG+OPV0 vs BCG</b>	<b>Infant mortality</b>	<b>0.68 (0.4-1.0)</b>	<b>0.68 (0.4-1.0)</b>	<b>CID 2015</b>
<b>RCT: MV at 4+9 vs 9 mo</b>	<b>Mortality 4-36 mo</b>	<b>0.70 (0.5-0.9)</b>	<b>0.74 (0.5-1.0)</b>	<b>BMJ 2010</b>



# Campaigns

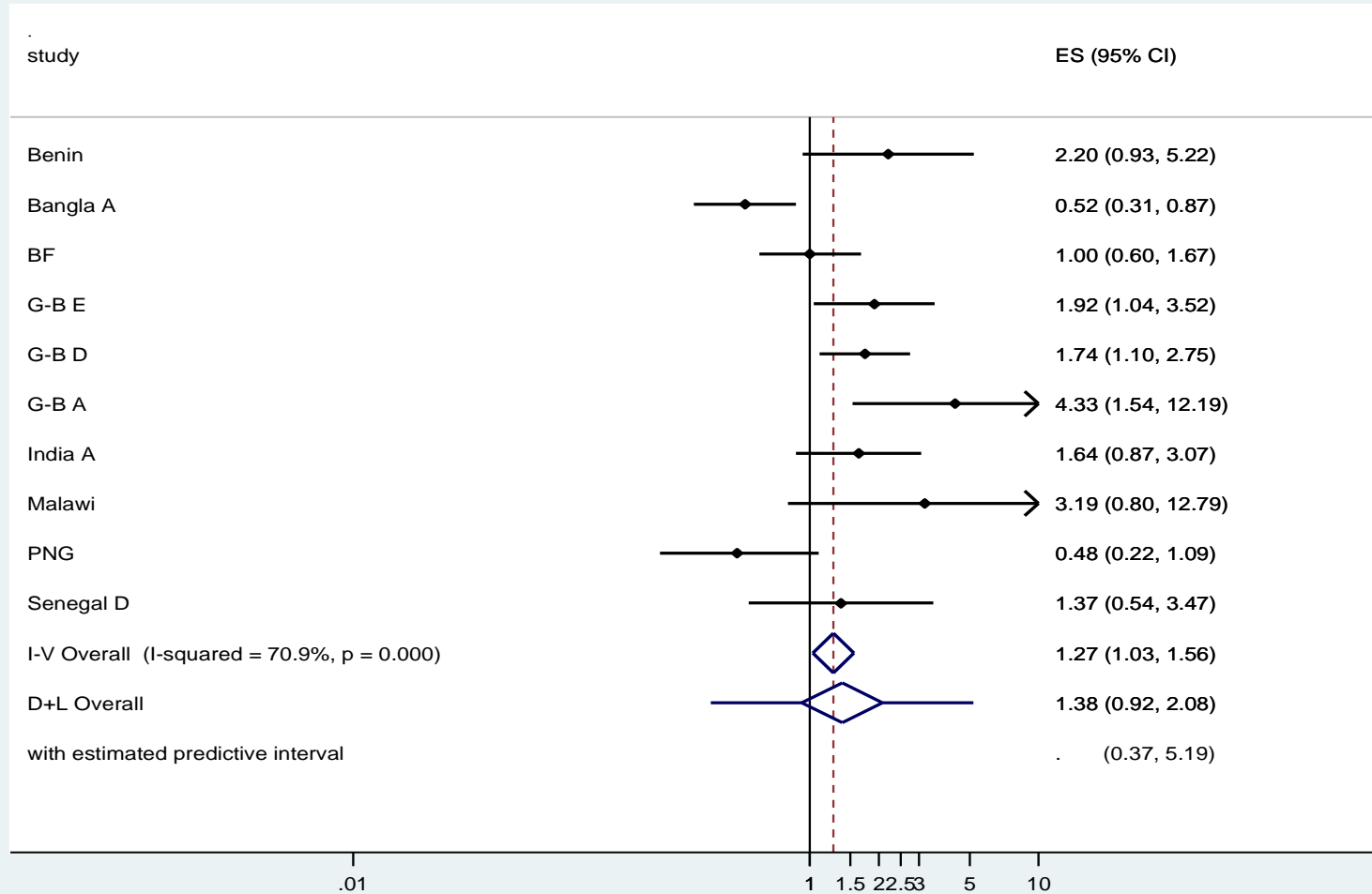
**15 OPV**

**10 VAS**

**1 H1N1**

Randomised Trials	MRR after-OPV vs before-OPV	MRR after-VAS vs before-VAS	MRR after-H1N1 vs before-H1N1
Vitamin A: 3 RCTs	<b>0.75 (0.55-1.01)</b>	<b>1.47 (0.75-2.88)</b>	<b>6.48 (1.42-29.6)</b>
Early MV	<b>0.95 (0.71-1.28)</b>	<b>1.00 (0.70-1.43)</b>	
BCG at birth: 2 RCTs	<b>0.81 (0.63-1.05)</b>	<b>0.68 (0.38-1.20)</b>	<b>2.16 (0.94-4.99)</b>
OPV at birth	<b>0.90 (0.61-1.32)</b>	<b>0.53 (0.16-1.68)</b>	<b>1.44 (0.52-3.96)</b>
All	<b>0.81 (0.70-0.95)</b>	<b>1.04 (0.80-1.35)</b>	<b>1.86 (1.02-3.42)</b>

# 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 effect of OPV and DTP***



# 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
<b>3-5</b>	<b>34.5 (6/17.4)</b>	<b>0 (0/8.6)</b>	<b>P=0.10</b>
<b>6-11</b>	<b>13.4 (9/67.1)</b>	<b>2.1 (1/48.4)</b>	<b>0.61 (0.8-52)</b>
<b>3-11</b>	<b>17.8 (15/84.5)</b>	<b>1.8 (1/57.0)</b>	<b>10.4 (1.4-79)</b>



# RTS,S vaccine and child 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)

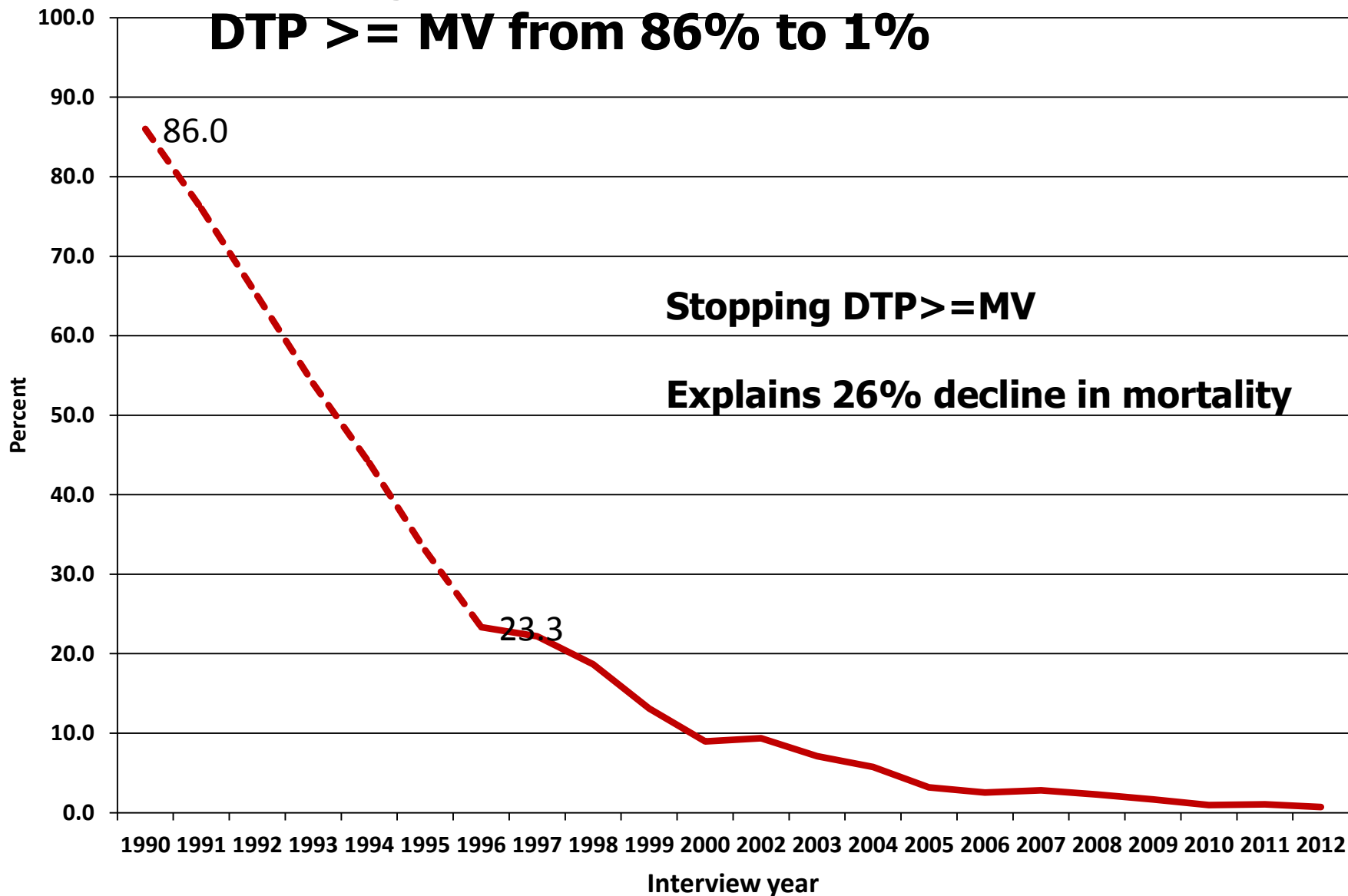


# Inactivated vaccines have negative effects for all-cause mortality for girls

## Vaccines may misdirect the immune system

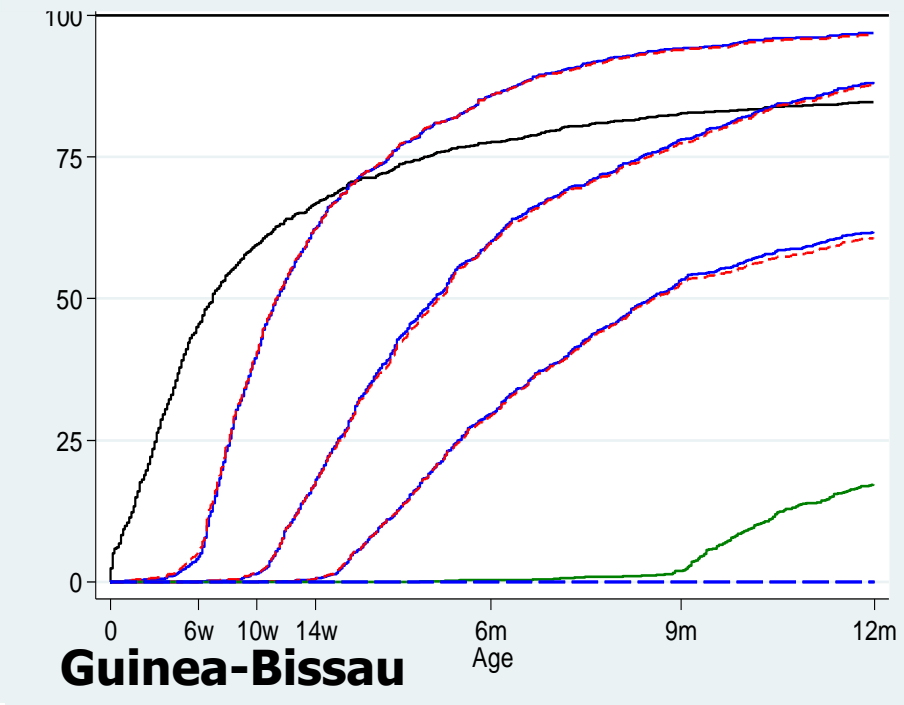
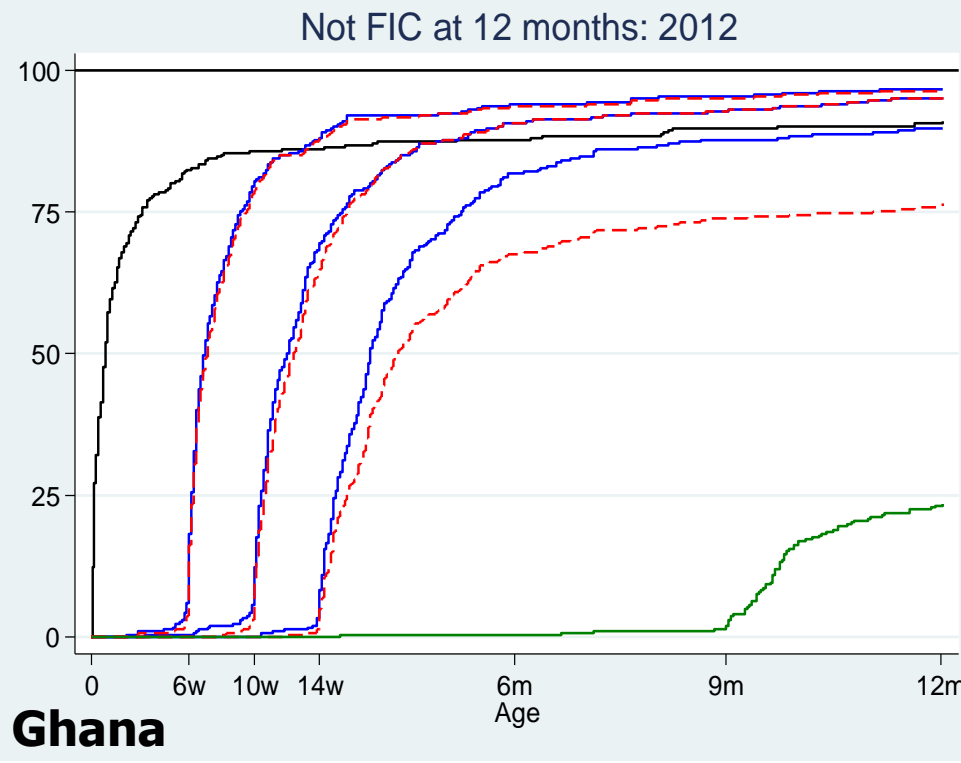
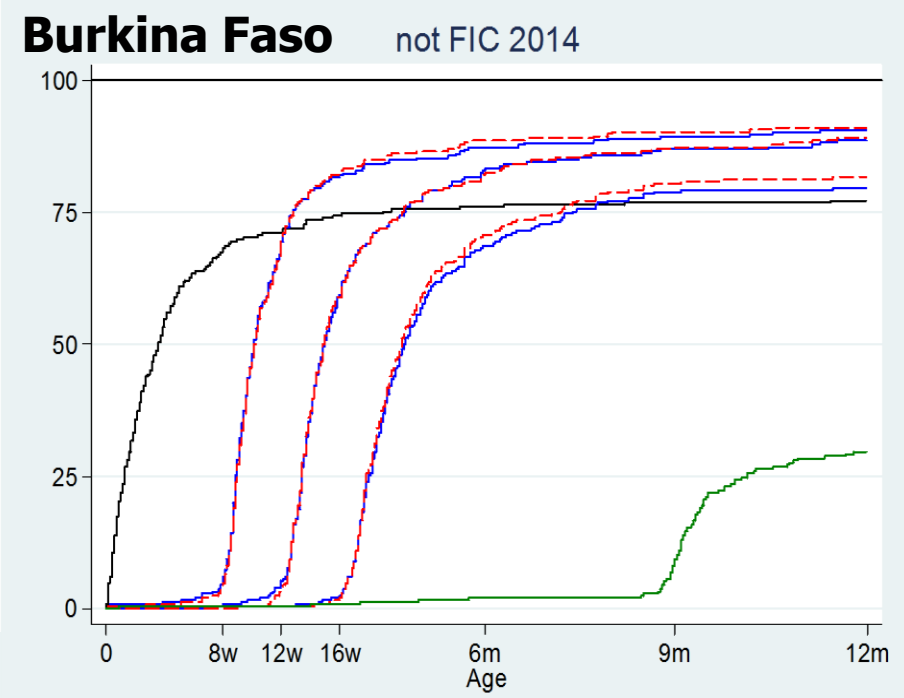
Vaccine	Studies [Number]	Mortality rate ratio for vaccine vs unvaccinated	Mortality rate ratio for female vs male among vaccinated
<b>DTP</b>	<b>Obs. and natural experiments</b>	<b>2.00 (1.5-2.7) [8]</b>	<b>1.60 (1.4-1.9)[12]</b>
<b>IPV</b>	<b>3 RCTs</b>	<b>NA</b>	<b>1.52 (1.0-2.3)</b>
<b>HBV</b>	<b>1 natural experiment</b>	<b>1.81 (1.2-2.8)</b>	<b>2.20 (1.1-4.5)</b>
<b>Influ H1N1</b>	<b>1 natural experiment</b>	<b>1.86 (1.0-3.4)</b>	<b>Girls: 2.32 (1.2-4.5)</b>
<b>RTS,S malaria vaccine</b>	<b>2 RCTs</b>	<b>1.24 (1.0-1.6) Long-T: 1.50(1.0-2.2)</b>	

# Navrongo, Ghana 1990-2012: DTP $\geq$ MV from 86% to 1%



**GAVI: Vaccination status assessed at 12 months of age**  
**Risk factors for not being fully immunized child (FIC) by 12 months: Lack of MV!**

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



# Single-disease-eradication paradigm



## Single disease perspective

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

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

tOPV will be eradicated April 2016

No study examined the effect of stopping Vaccinia in 1980  
**But what if vaccinia had a beneficial effect?**

# Vaccinia removed in Bissau and Denmark in 1970s

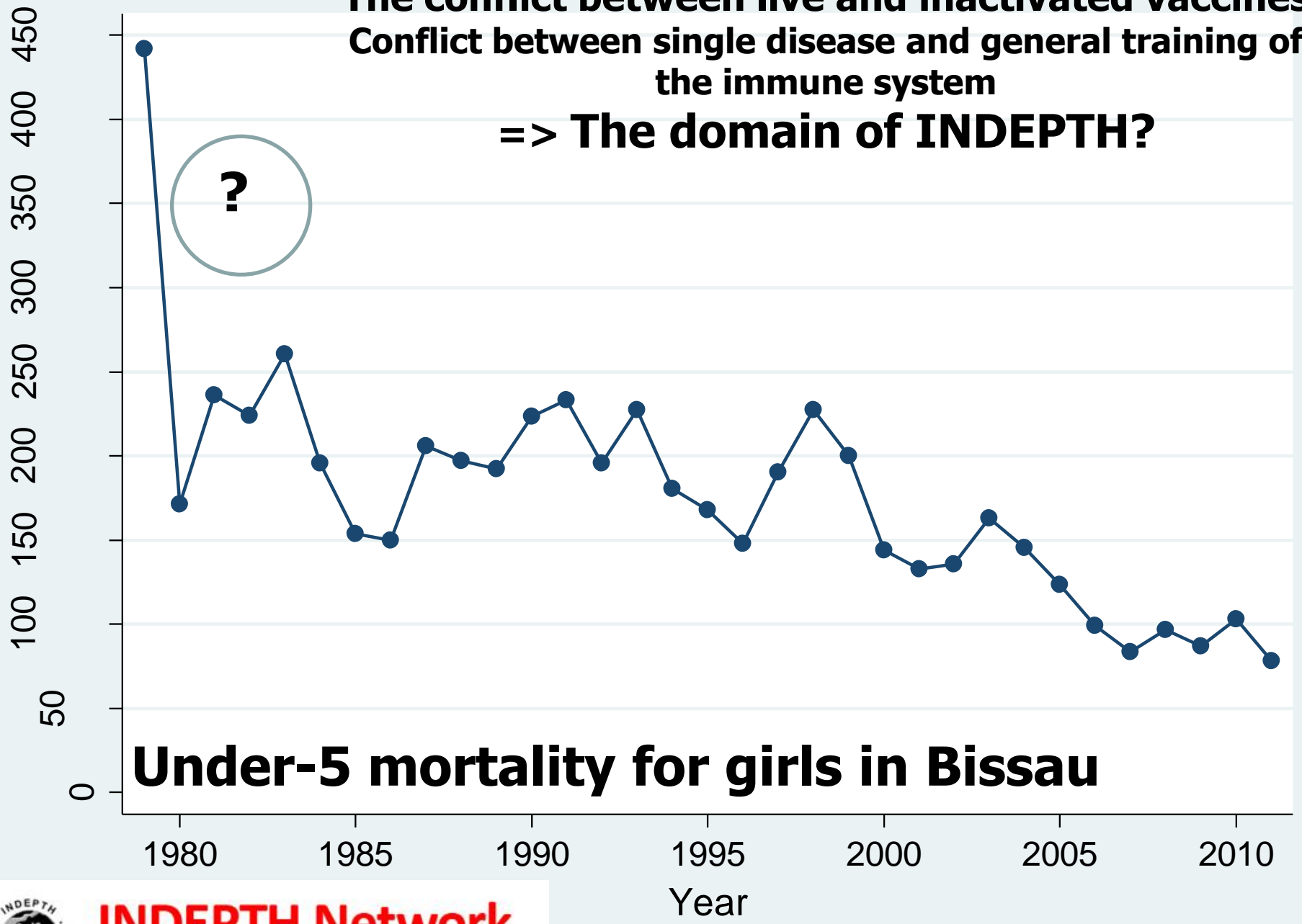
Bissau 1998-2002 Vaccinia scar/no scar  
 40% (13-59%) reduction in mortality (Vaccine 2006)  
 1 scar: 35%; 2 scars: 46%; 3+ scars: 56% =>  
 Trend: 27% (5-44%) per scar



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

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	<b>0.54 (0.36-0.81)</b>	189/85618	0.92 (0.57-1.46)
Vaccinia or BCG	348/140036	<b>0.57 (0.40-0.81)</b>	281/140036	0.90 (0.60-1.37)

**The conflict between live and inactivated vaccines**  
**Conflict between single disease and general training of**  
**the immune system**  
**=> The domain of INDEPTH?**



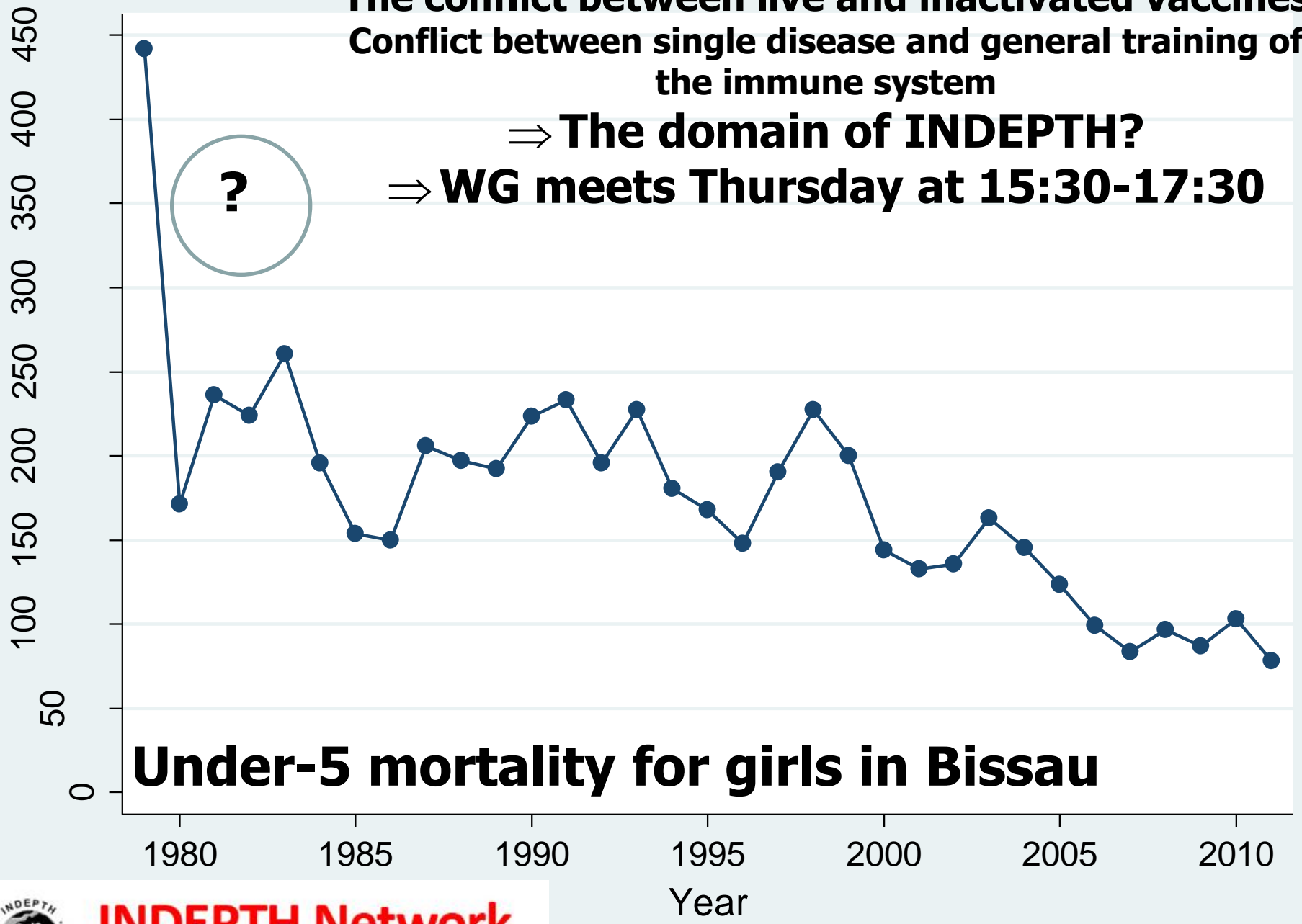
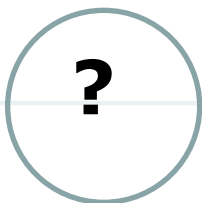
**Under-5 mortality for girls in Bissau**



# The conflict between live and inactivated vaccines Conflict between single disease and general training of the immune system

⇒ **The domain of INDEPTH?**

⇒ **WG meets Thursday at 15:30-17:30**

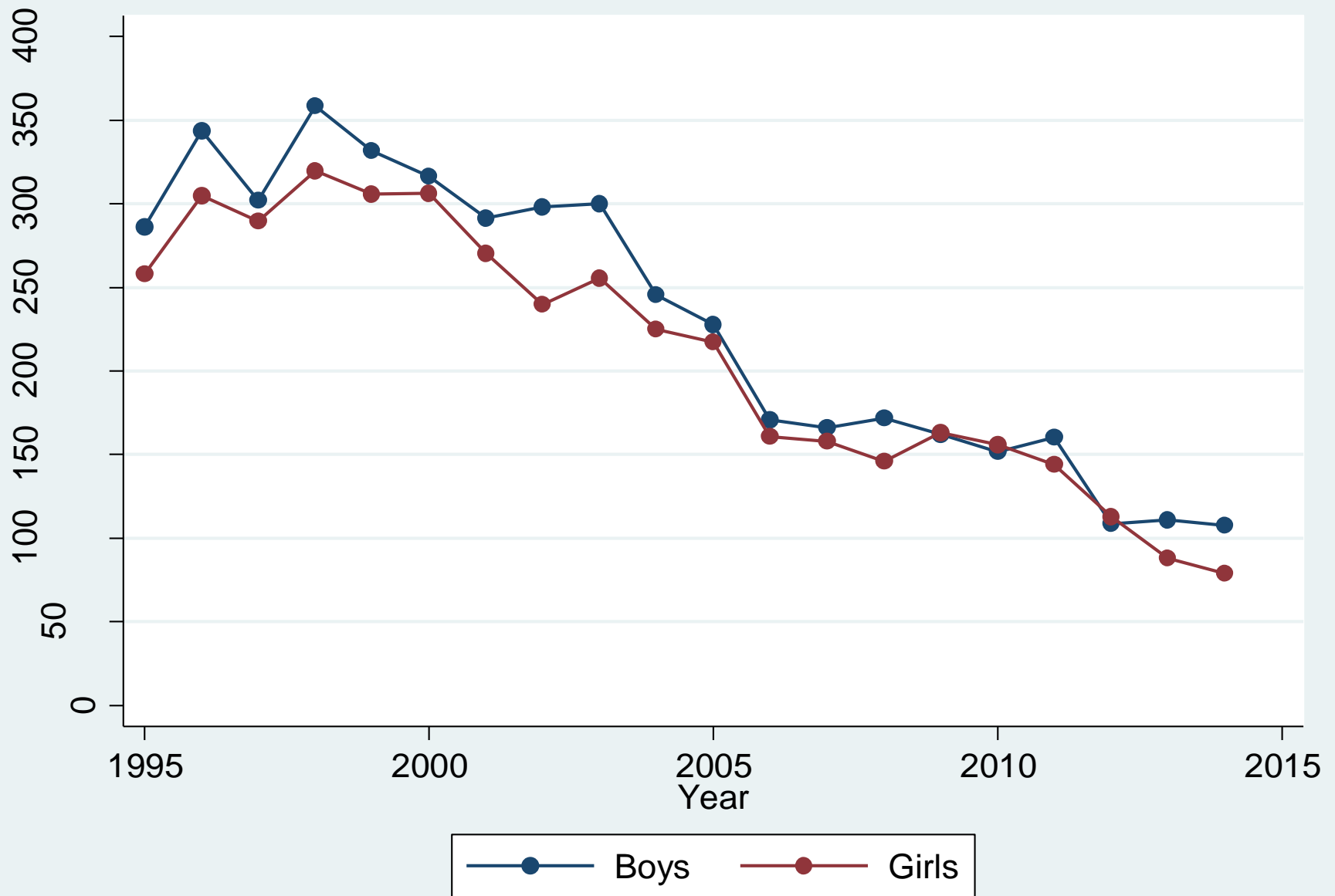


## Under-5 mortality for girls in Bissau



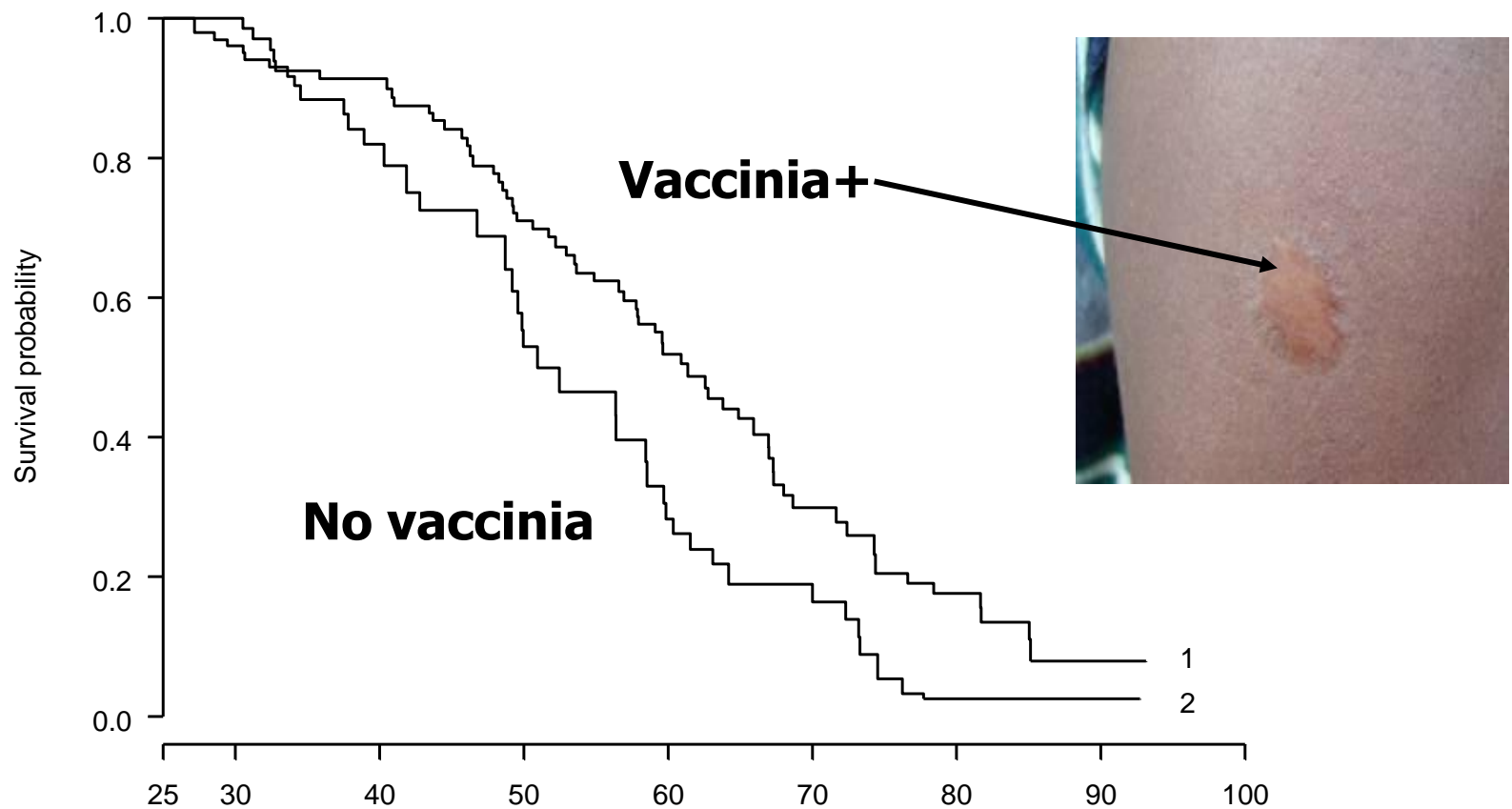






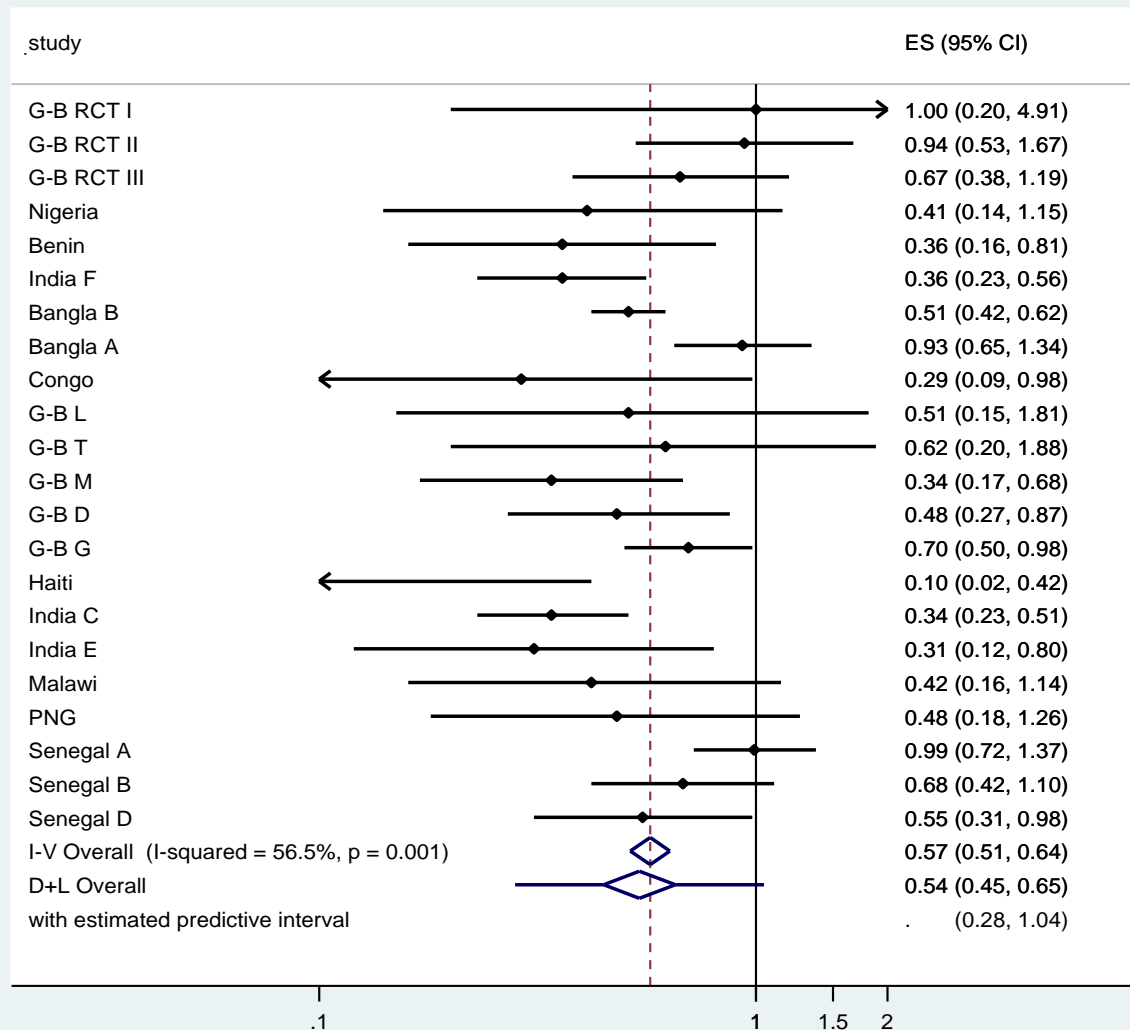
**Rural Bissau: MDG4 300/1000 to 97/1000 => 68%**  
**This can only be understood with reference to vaccination campaigns**

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



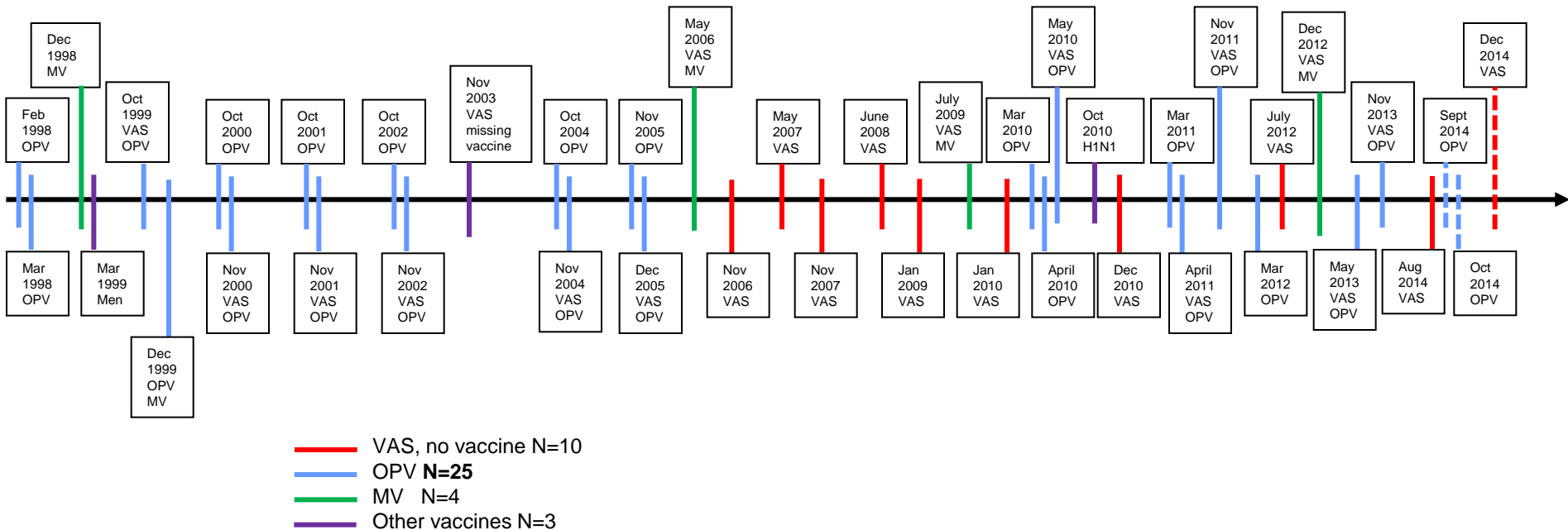
**1893 individuals 25+ years in 1998 followed to 2002 (Vaccine 2006)**  
**Vaccinia scar/no scar: Reduction in mortality 40% (13-59%)**  
**1 scar: 35% ; 2 scars: 46% ; 3+ scars: 56% - trend: 27% (5-44%)/per scar**

# WHO's Review of Measles vaccine



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

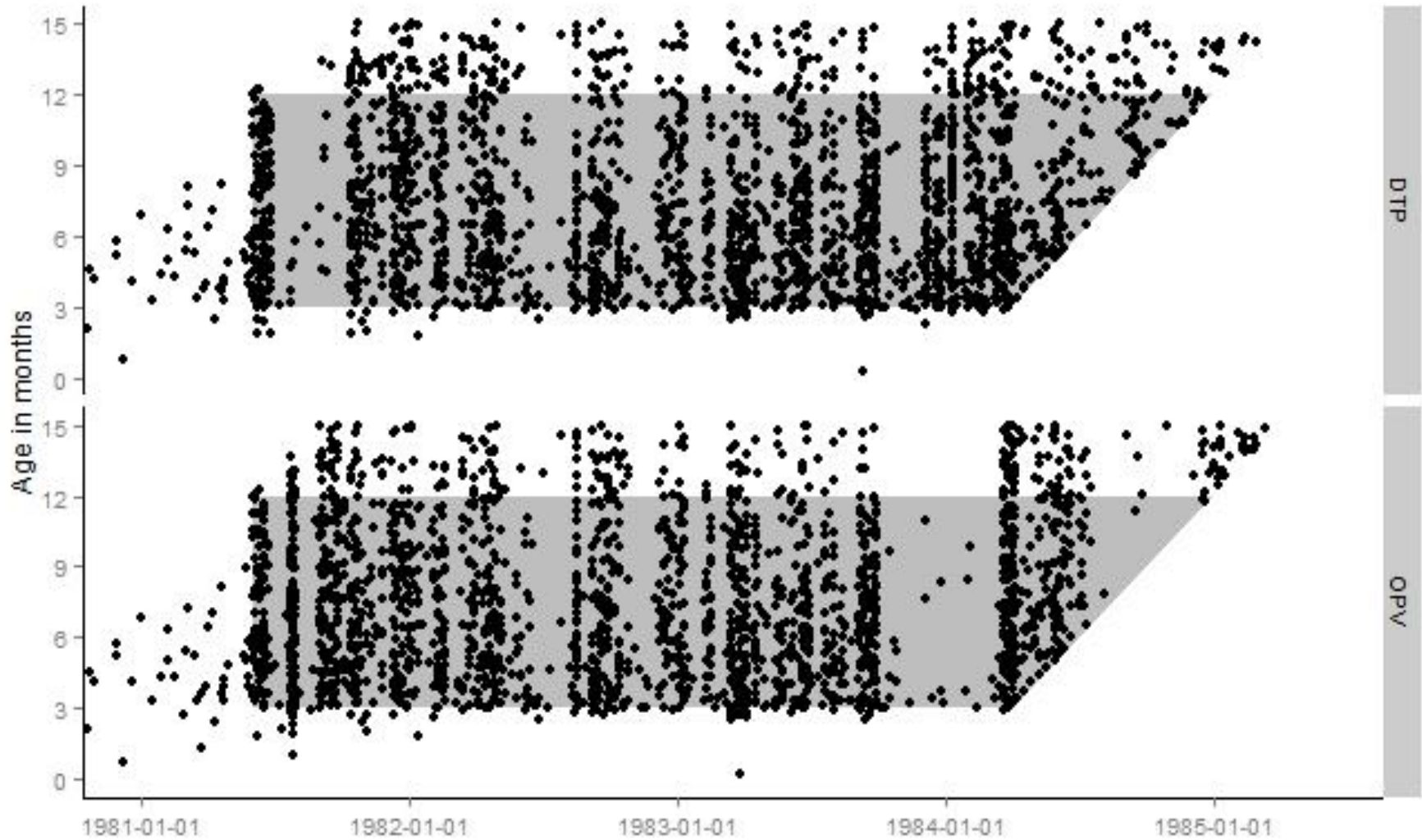
# Implications: Campaigns not evaluated 17 years of campaigns in Guinea-Bissau



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

**OPV reduced mortality rate by 19%; MV by 20%**

# Introduction of DTP and OPV in Bissau in 1981



# Optimunise is built on a conflict of paradigms

## Current paradigm: Single disease prevention

	<b>Single-disease-eradication paradigm</b>
<b>Mission</b>	<b>Prevent specific disease to reduce mortality</b>
<b>Focus</b>	<b>Specific immune responses =&gt; Clinical protection =&gt; Reduction in mortality</b>
<b>Overall effect</b>	<b>Specific protection - always good</b>
<b>Sex</b>	<b>Same effect for boys and girls</b>
<b>Interaction</b>	<b>Age, maternal antibodies</b>
<b>Sequence</b>	<b>Give when possible; sequence does not matter</b>
<b>Ultimate goal</b>	<b>Eradicate - save money by removing vaccine</b>





# GAVI collaboration – determinants of the fully immunized child (FIC) and the consequences of FIC for child survival

## B. Mortality ratio of FIC vs non-FIC

Routine registration by centre	Child mortality from 12-36 mos Adjusted MRR for FIC versus – non-FIC
Navrongo	<b>0.71 (0.53-0.95)</b>
Bandim	<b>0.81 (0.71-0.93)</b>
Nairobi	<b>0.47 (0.21-1.02)</b>
Chakaria	<b>0.84 (0.19-3.77)</b>
Nouna	<b>0.75 (0.33-1.71)</b>
<b>All</b>	<b>0.78 (0.70-0.88)</b>

**This is MV versus Not MV => Measles vaccination coverage should be strengthened**





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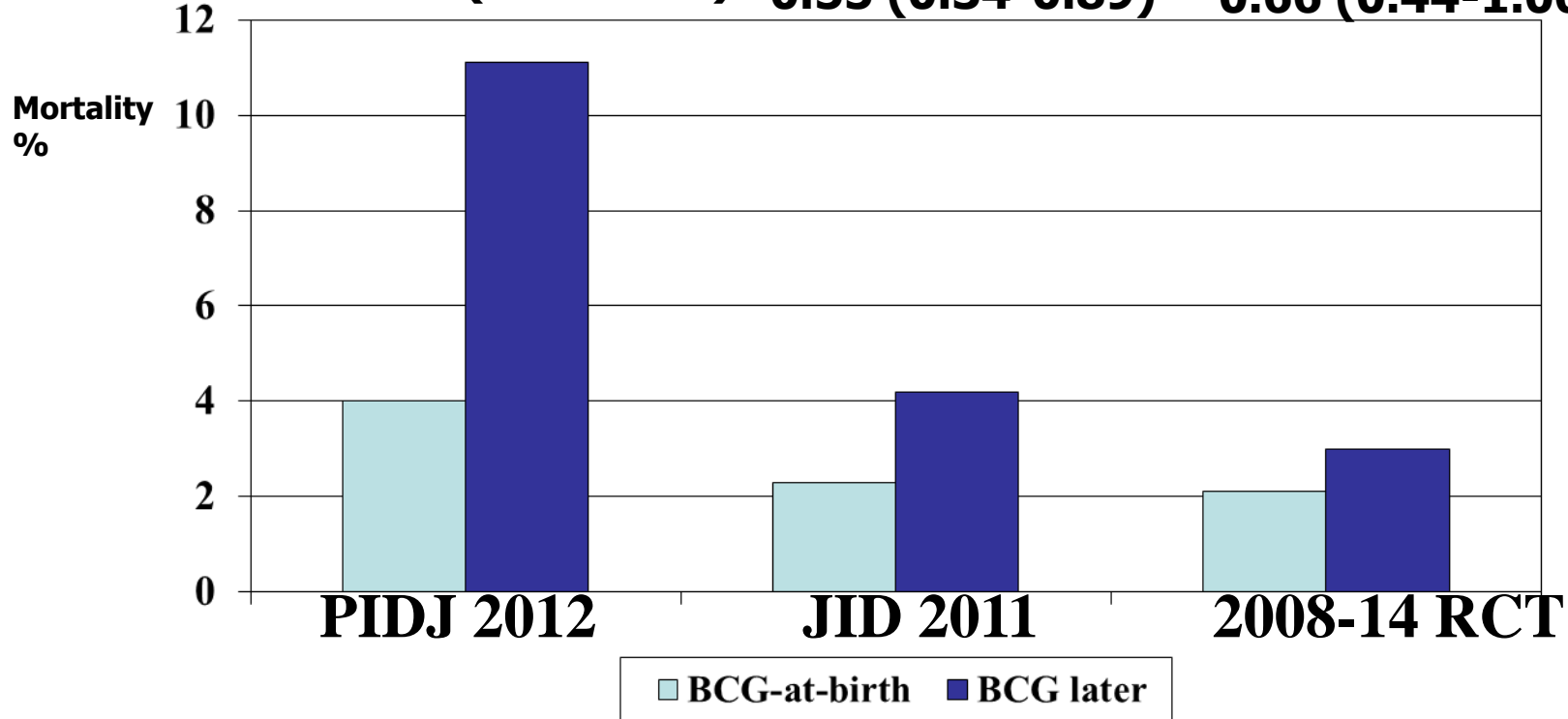
**This is MV versus Not MV => Measles vaccination coverage should be strengthened**

# 3 RCTs of BCG-at-birth in LBW children

3-days MRR=0.55 (0.32-0.93)

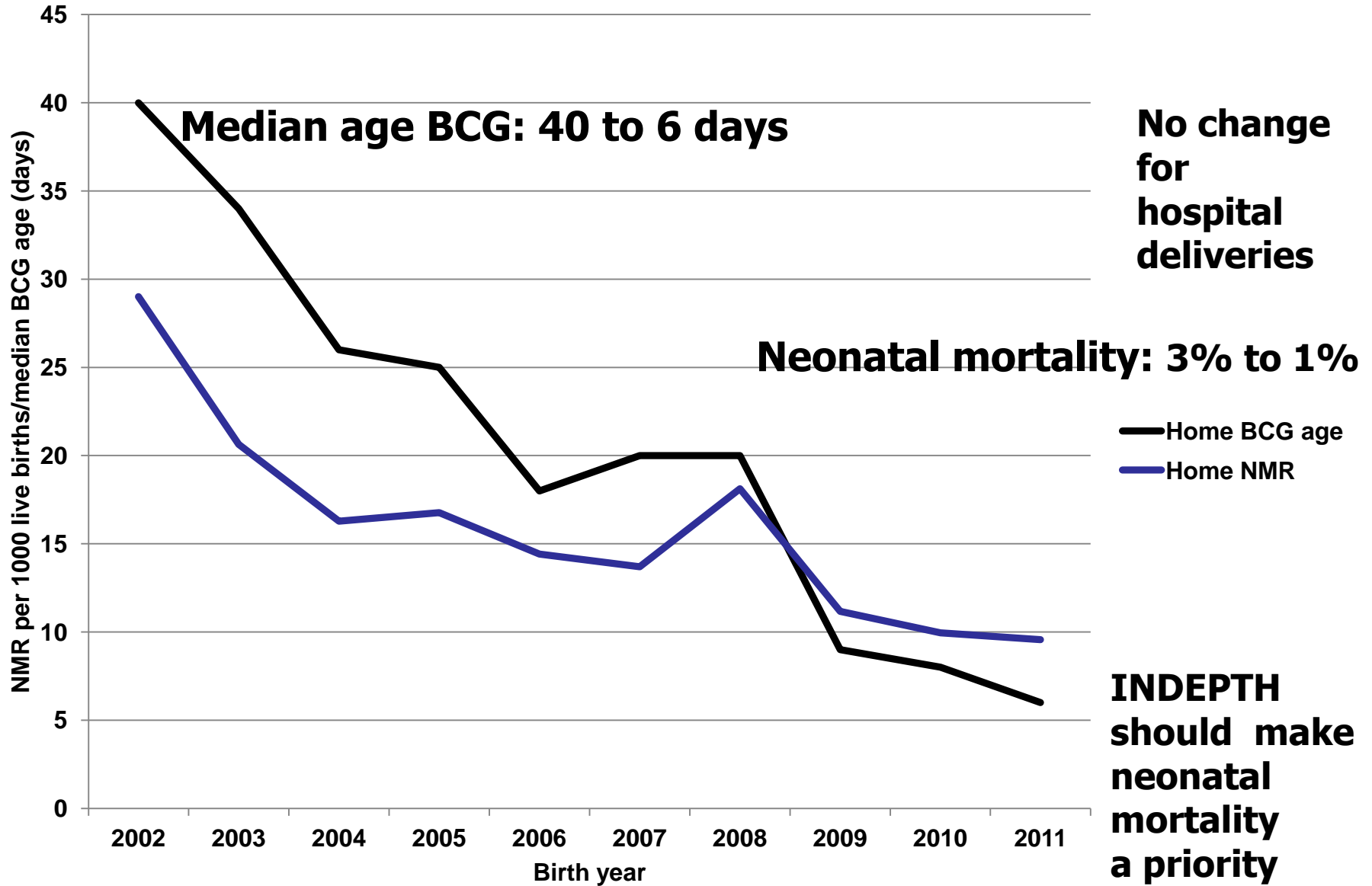
Neonatal MRR=0.59 (0.44-0.81)

Neonatal MRR 0.28 (0.06-1.37) 0.55 (0.34-0.89) 0.66 (0.44-1.00)

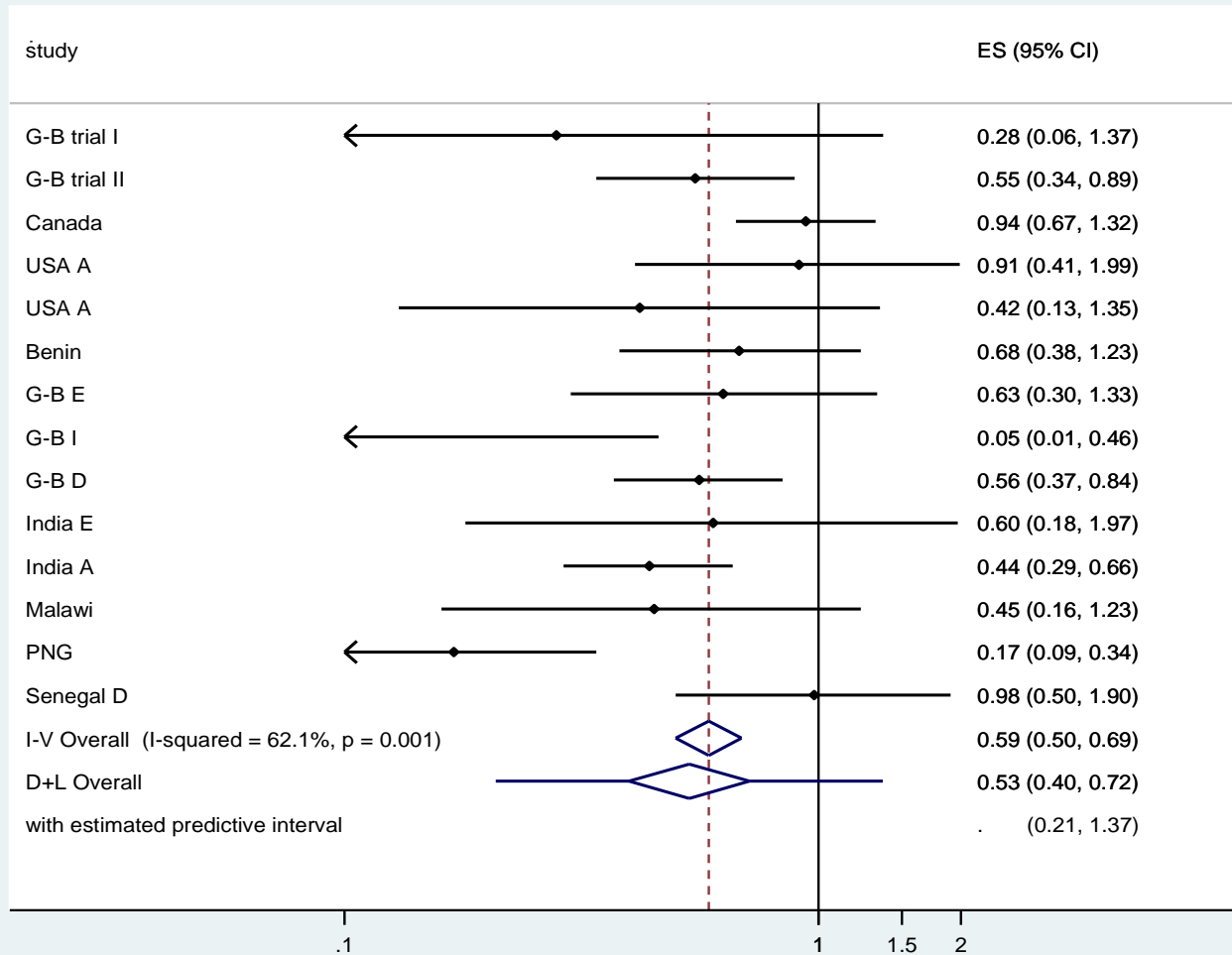


**Reduction in neonatal sepsis and respiratory infections**  
***Not prevention of TB => Beneficial NSE of BCG***

# Navrongo: Neonatal mortality rates (day 1-28) and median age at BCG vaccination for home deliveries



# SAGE review: BCG – studies without “very high risk of bias”



***“The results indicated a beneficial effect of BCG on overall mortality”***

***“Estimated effects are in the region of a halving of mortality risk”***

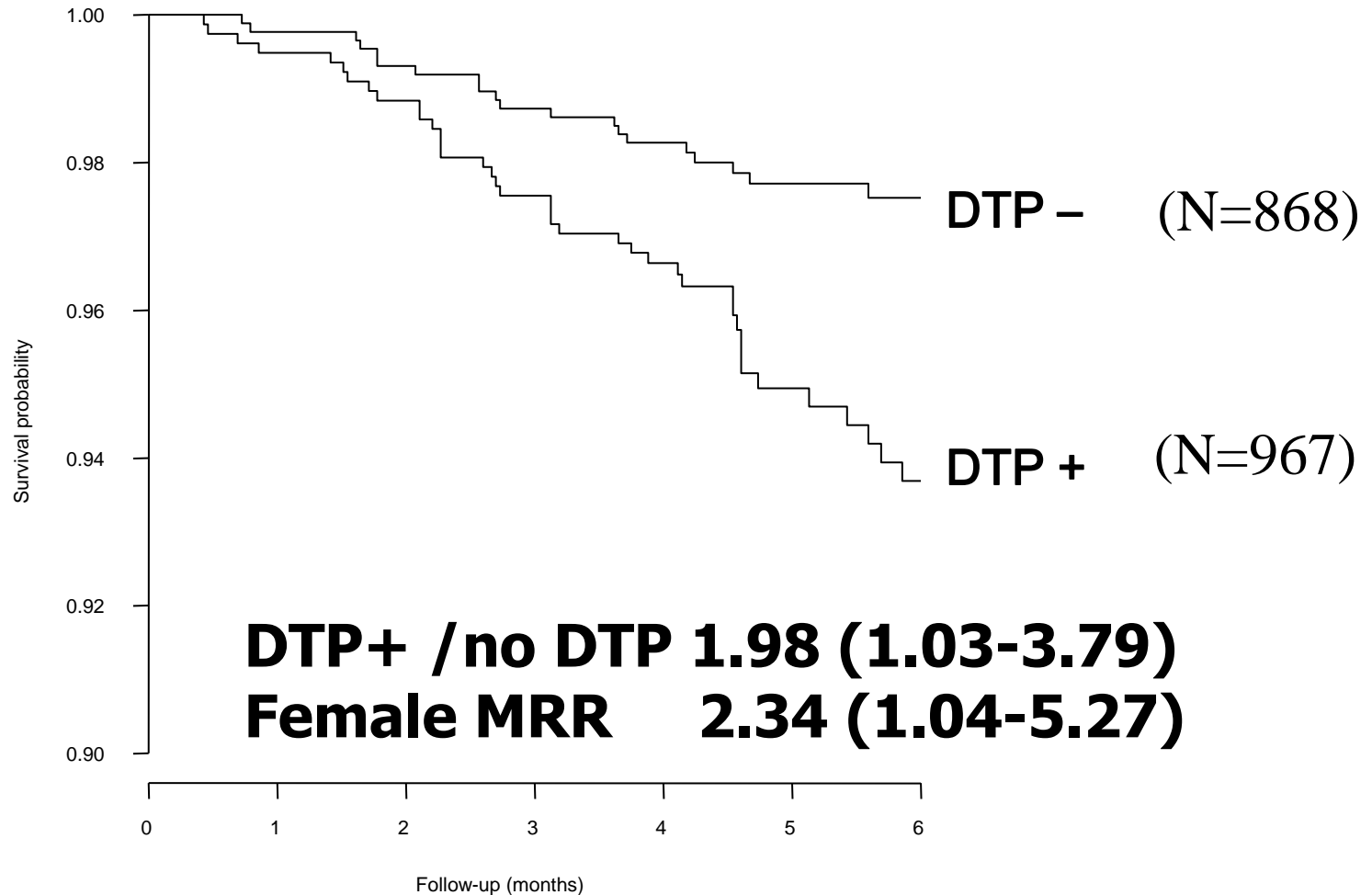
***” not likely to be attributable to any great extent to fewer deaths from tuberculosis”***

# Introduction of DTP

*Rural areas of Guinea-Bissau 1984-87*

**Children  
aged 2-8 mo**

**Unvaccinated:  
travelling; sick;  
days without  
vaccines**

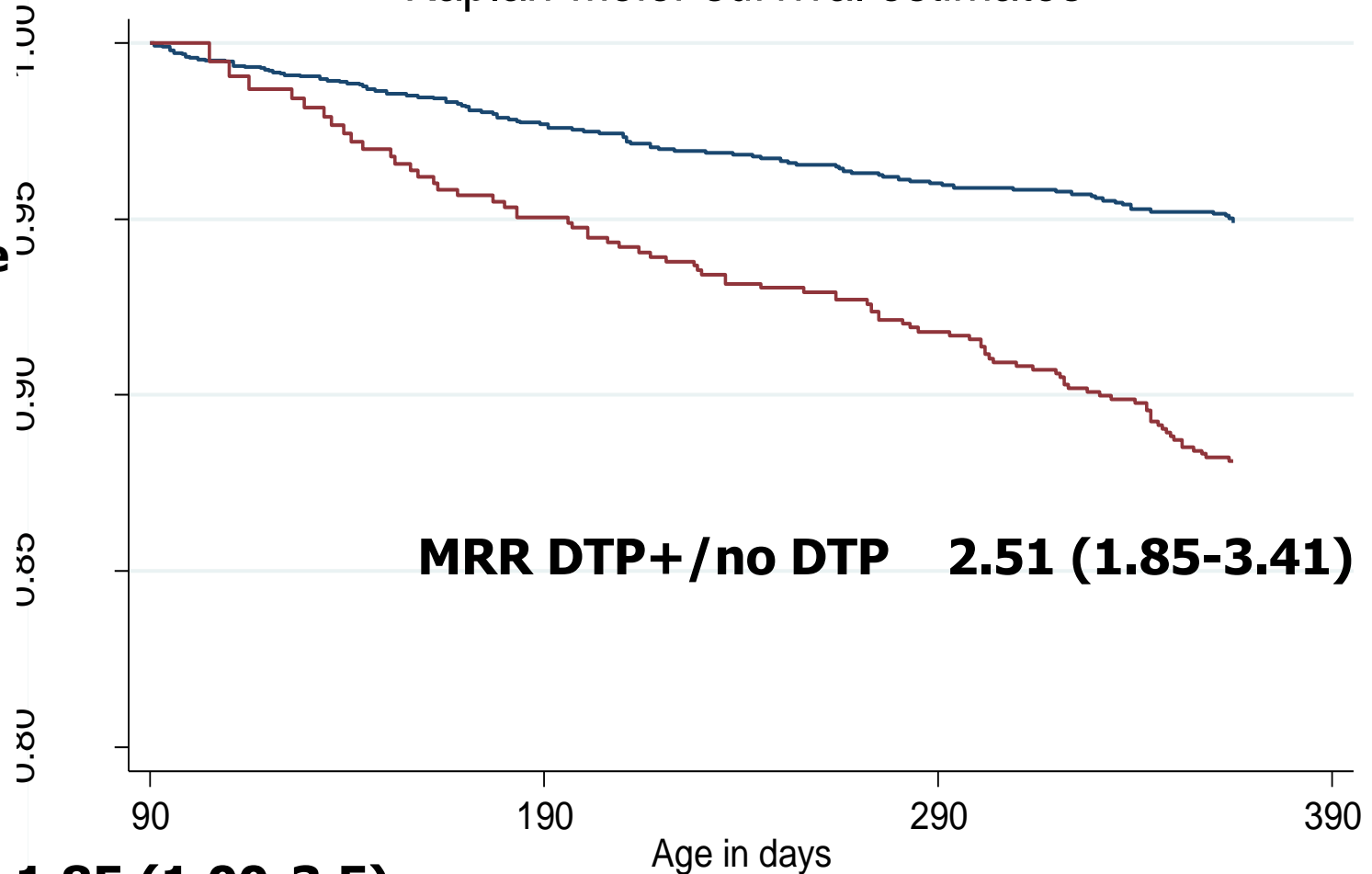


**1-dose MRR 1.81 (1.0-3.5); 2-3 doses 4.36 (1.3-14.9)**

# Introduction of DTP

*Urban areas of Guinea-Bissau 1981-88*

Kaplan-Meier survival estimates



**MRR DTP+ /no DTP 2.51 (1.85-3.41)**

**Try to find more Data but no other site may have data on introduction of DTP**

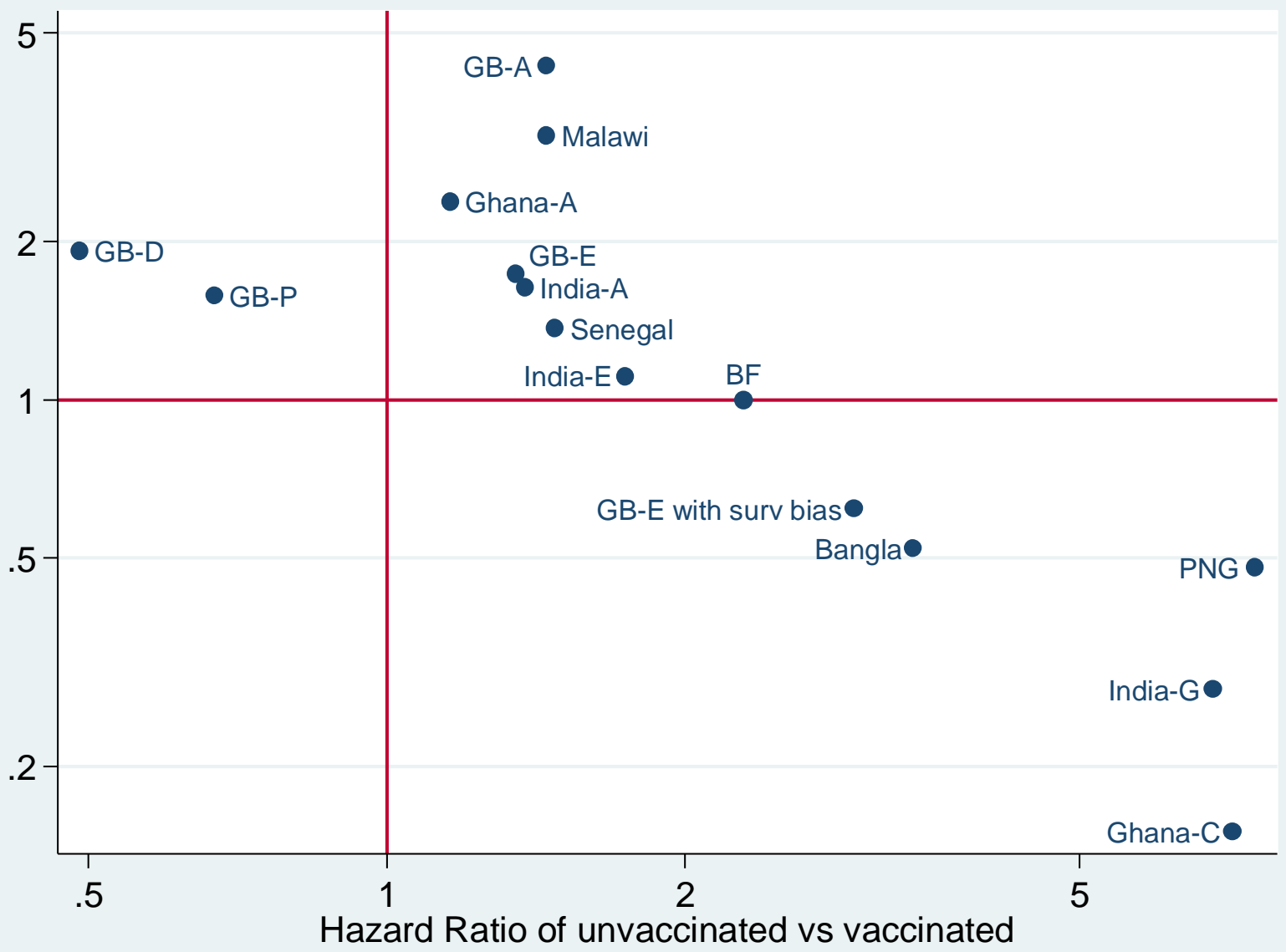
**1-dose MRR 1.85 (1.00-3.5);  
2-3-dose MRR 3.12 (1.44-6.8)**



# SAGE: "Most studies of DTP suggest detrimental effect – but inconsistent results". Studies have survival bias!

**MRR unvac/  
Vaccinated  
<2.0  
DTP had 94%  
Higher  
mortality**

**MRR unvac/  
vaccinated  
>2.0  
DTP has 61%  
lower  
mortality**





# RCTs of infant mortality for OPV0 vs no OPV0 – Censoring for OPV in campaigns

(No polio in Bissau)

RCT-I#	Mortality rate ratio (MRR) for OPV0+BCG vs BCG-only
All children	<b>0.68 (0.43-1.00)</b>
Boys	<b>0.55 (0.33-0.95)</b>
Girls	<b>0.87 (0.48-1.56)</b>
RCT-II##	MRR for OPV0 vs Vitamin A
All LBW boys	<b>0.68 (0.30-1.54)</b>





**25 OPV campaigns since 1998 to eradicate polio**  
**Given to children aged 0-59 month**

**OPV reduced mortality by 22% =>**  
**OPV campaigns interfere with results of RCTs**

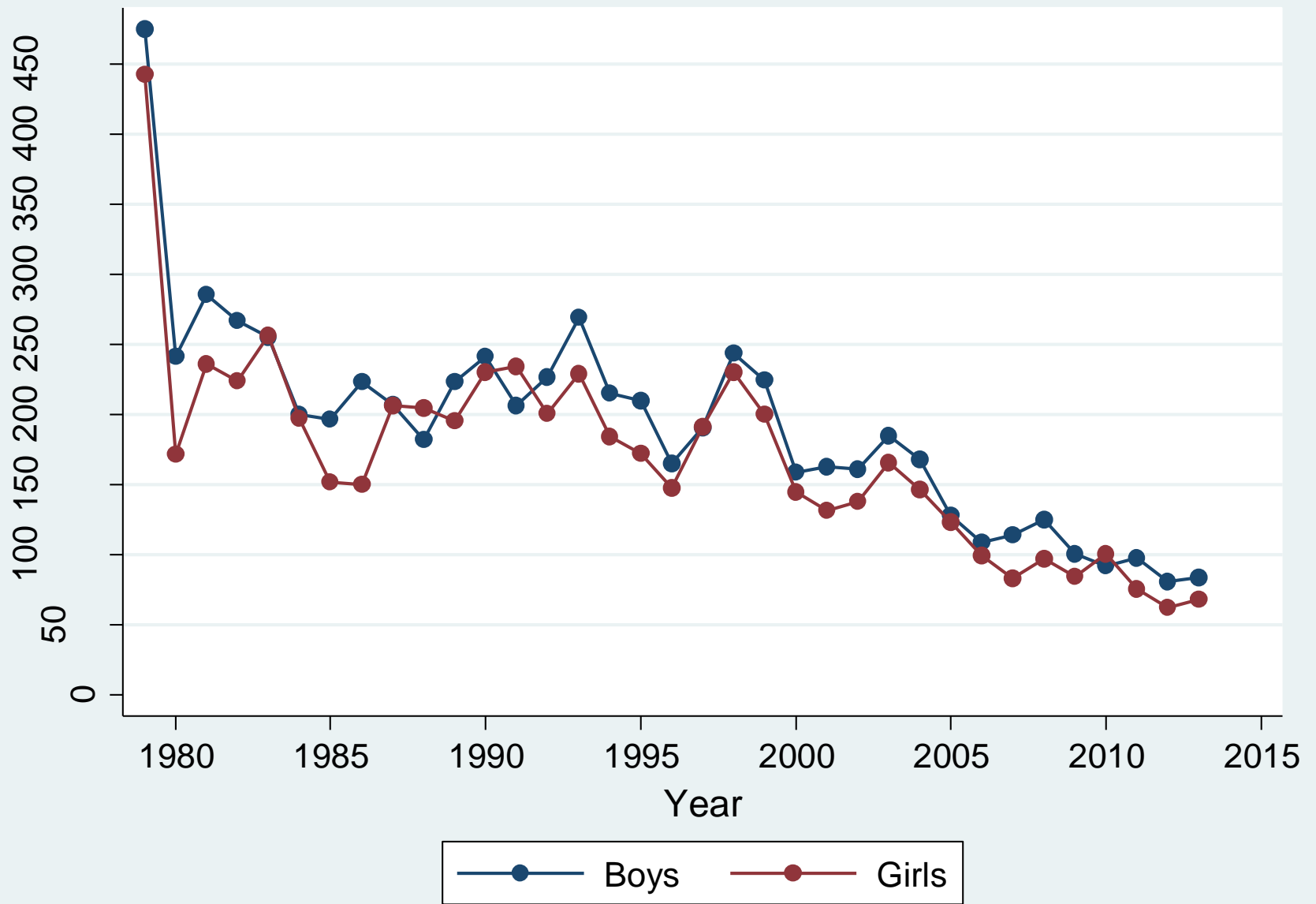
Randomised Trials	Age-adjusted MRR after-OPV vs before-OPV	MRR without censoring for OPV campaigns	MRR with censoring for OPV campaigns
<b>3 trials of neonatal Vit A</b>	<b>0.67 (0.53-0.85)</b>	<b>1.13 (0.94-1.34)</b>	<b>1.15 (0.80-1.65)</b>
<b>Early MV at 4½ +9 mo</b>	<b>0.72 (0.48-1.07)</b>	<b>0.70 (0.52-0.94)</b>	<b>0.42 (0.19-0.96)</b>
<b>BCG at birth I</b>	<b>0.91 (0.65-1.26)</b>	<b>0.83 (0.63-1.08)</b>	<b>0.78 (0.45-1.38)</b>
<b>OPV at birth</b>	<b>0.88 (0.60-1.30)</b>	<b>0.83 (0.61-1.13)</b>	<b>0.68 (0.45-1.00)</b>
<b>BCG at birthII</b>	<b>0.84 (0.62-1.13)</b>	<b>0.70 (0.47-1.04)</b>	<b>0.66 (0.44-1.00)</b>
<b>All</b>	<b>0.78 (0.68-0.90)</b>		



**H1N1 campaign has not been evaluated in low-income countries**

<b>Randomised Trial</b>	<b>Age-adjusted MRR after-H1N1 versus before-H1N1</b>	<b>Vitamin A group</b>	<b>Placebo</b>
<b>RCT of vitamin A versus placebo</b>	<b>1.68 (1.00-2.85)</b>	<b>2.83 (1.51-5.30)</b>	<b>0.76 (0.28-2.09)</b>

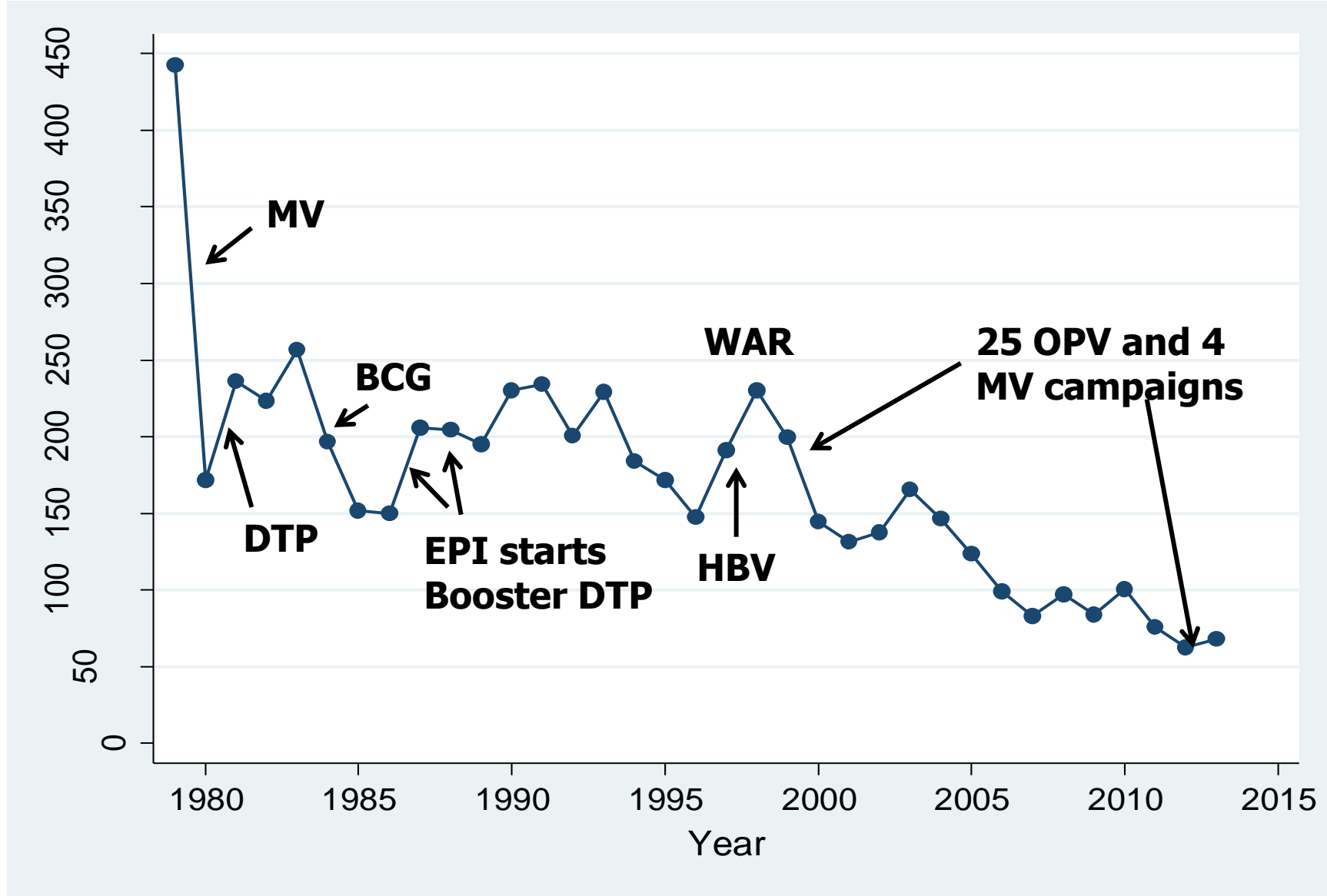
**This methodology could be used to evaluate campaigns at other INDEPTH centres**



**INDEPTH Network**  
Better Health Information for Better Health Policy

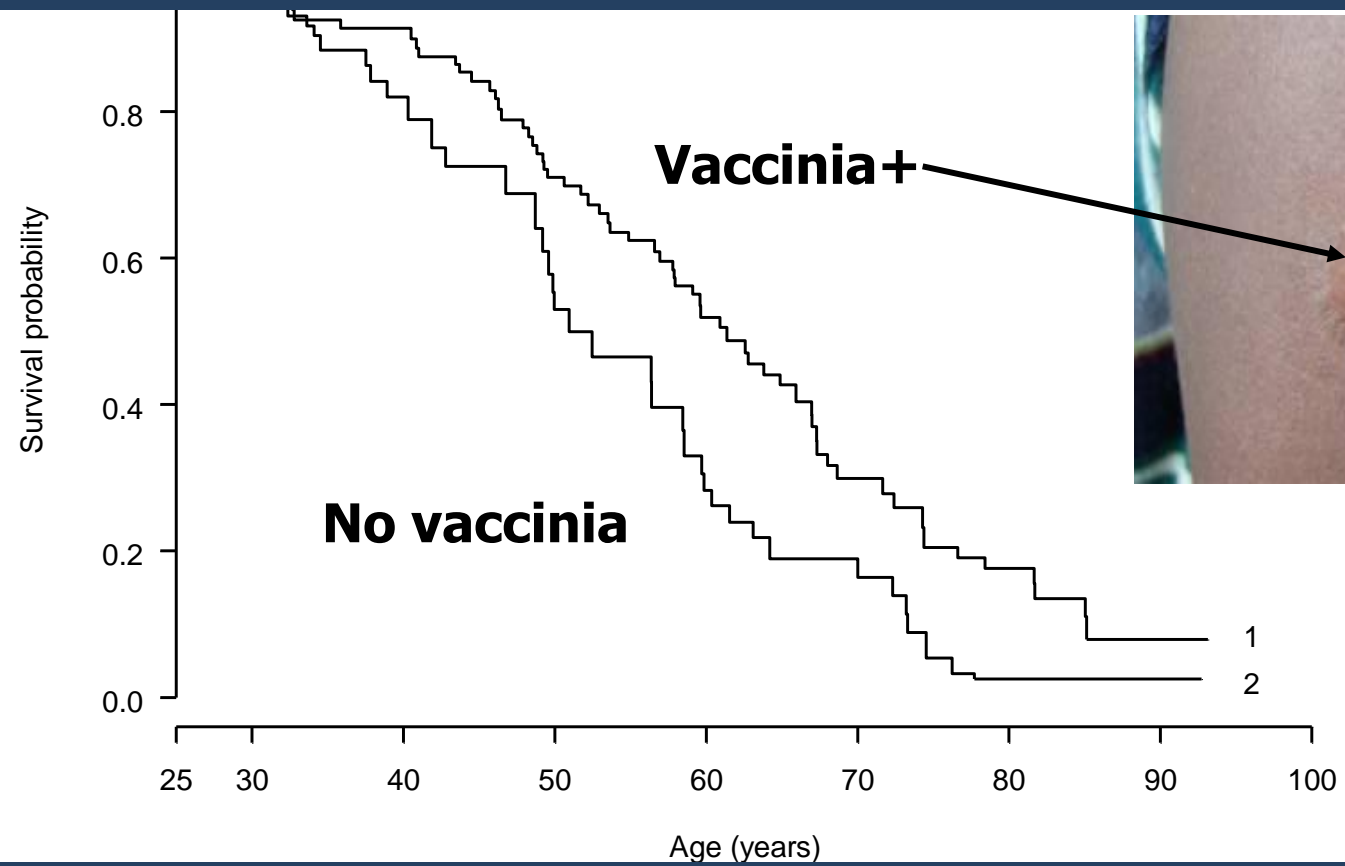
**Urban Bissau**  
**MDG4 236/1000 to 68/1000 => 68%**

# Resolving the paradigm contradictions: The road to MDG4 is paved with OPV and measles vaccine (MV) campaigns



**MDG4 236/1000 to 68/1000 => 68%**

# Measles and polio to be eradicated – OPV and MV? Live vaccines have beneficial effects – when removed? Eradication paradigm: Smallpox vaccination in Guinea-B?



**Study I Scar/no scar: Reduction 40% (13-59%) (Vaccine 2006)**  
**Study II Scar/no scar: Reduction 78% (39-92%) (PLoS ONE 2006)**  
**Protection against HIV-1 for scar/no scar: Female 55% (9-78%)**  
**Denmark: Admissions for infections reduced by 16% (2-28%) (Int J Epidemiol)**  
**BCG+vaccinia 43% (17-61%) reduction in mortality**  
**Protection against HIV-1: Female 71% (7-91%) (not drug addicts)**

# **INDEPTH and the NSEs of vaccines**

## ***New research opportunities and priorities for INDEPTH: SAGE/WHO has recommended further research into NSEs***

- ***IMMEDIATE ACTIONS BY WG on VACCINES and interested centres***
  1. ***Promote measles vaccination - ask GAVI for funding to improve coverage for MV ; assure that MV and BCG are used to monitor the vaccination programme***
  2. ***Study determinants of neonatal mortality and promote better BCG vaccination has strong beneficial effects on neonatal mortality***
  3. ***Workshop on the impact of different campaigns (MV, OPV, Influenza, VAS)***
  4. ***Workshop on the road to MDG4 in centres with long follow-up***
  5. ***INDEPTH call for data on the introductions of routine vaccinations, in particular DTP (diphtheria-tetanus-pertussis ) has strong negative effects on child survival***
  
- ***LONGTERM PLANS FOR INDEPTH***
  1. ***INDEPTH to promote data collection on routine interventions – e.g. included collection of such information in connection with verbal autopsies***
  2. ***Confront the irrational DTP3 policy***
  3. ***Confront the eradication paradigm – in relation to the eradication of polio and measles***
  4. ***The vitamin A supplementation policy has failed – consider new strategies for Vitamin A supplementation***

# 2014 an important year for the non-specific effects (NSE) of vaccines

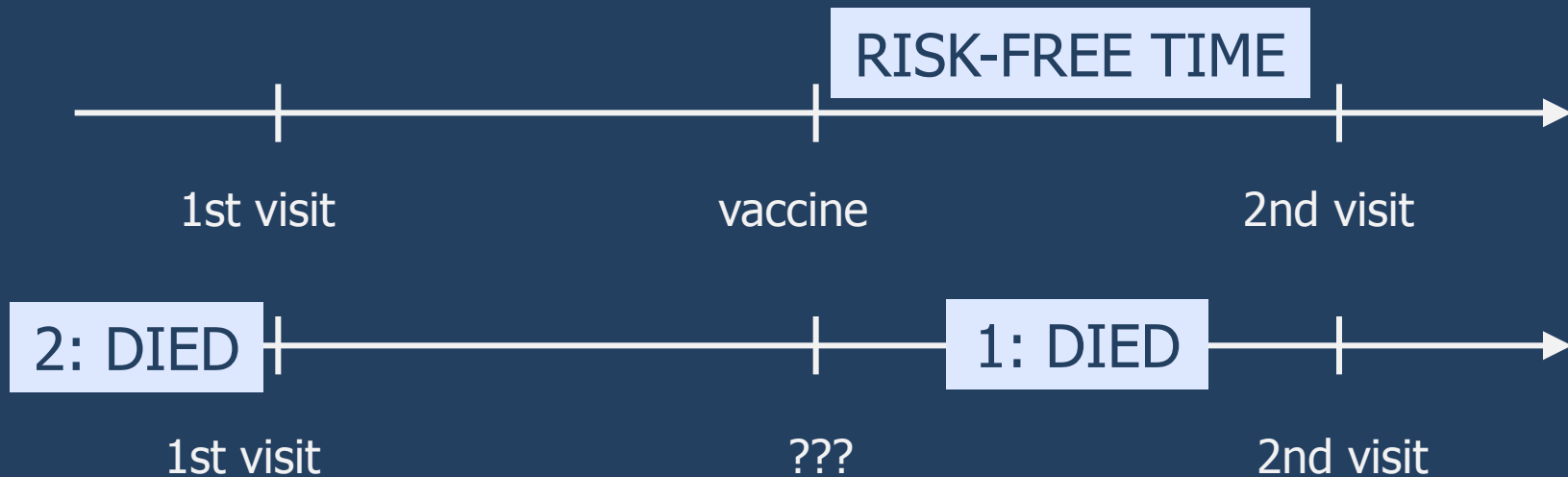
## ***INDEPTH Vaccine network***

- ***EU Trials progressing to end Dec 2015***
- ***GAVI contract***
- ***PhD enrolment at Danish university***

## ***New NSEs research opportunities and priorities***

- ***GAVI collaboration – measles vaccine (MV) is de-emphasised but MV associated with much better survival***
- ***BCG has strong beneficial effects on neonatal mortality***
- ***DTP (diphtheria-tetanus-pertussis ) has strong negative effects on child survival***
- ***The vitamin A supplementation policy has failed***
- ***Oral polio vaccine (OPV) has major beneficial NSEs***
- ***Campaigns with live vaccines have major impact on child survival***
- ***Bandim has reached MDG4 in both urban and rural areas***
- ***SAGE/WHO has recommended further research into NSEs***
- ***INDEPTH should make NSE a major priority***

# WHO: No DTP problem or sex-differential effect (WER 2004) However, the WHO-sponsored studies had survival bias



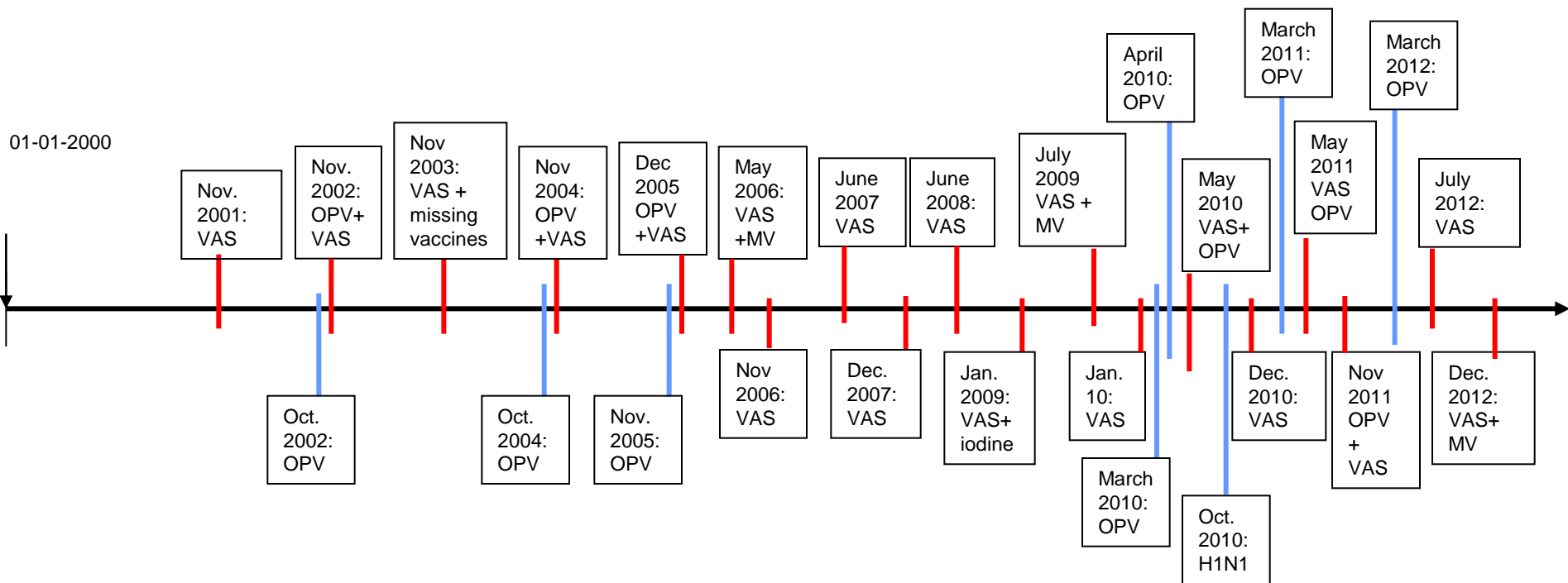
**1: Retrospective updating - dead children have no vaccine information**

**2: Children with no vaccine information assumed to be unvaccinated**

**=> Time after vaccination goes to vaccinated group; unknown deaths goes to unvaccinated group => too high mortality in "unvaccinated" group => Examine MRR for unvaccinated versus vaccinated children**



# Decade of national campaigns: 2000-2014



**VAS= vitamin A supplementation**

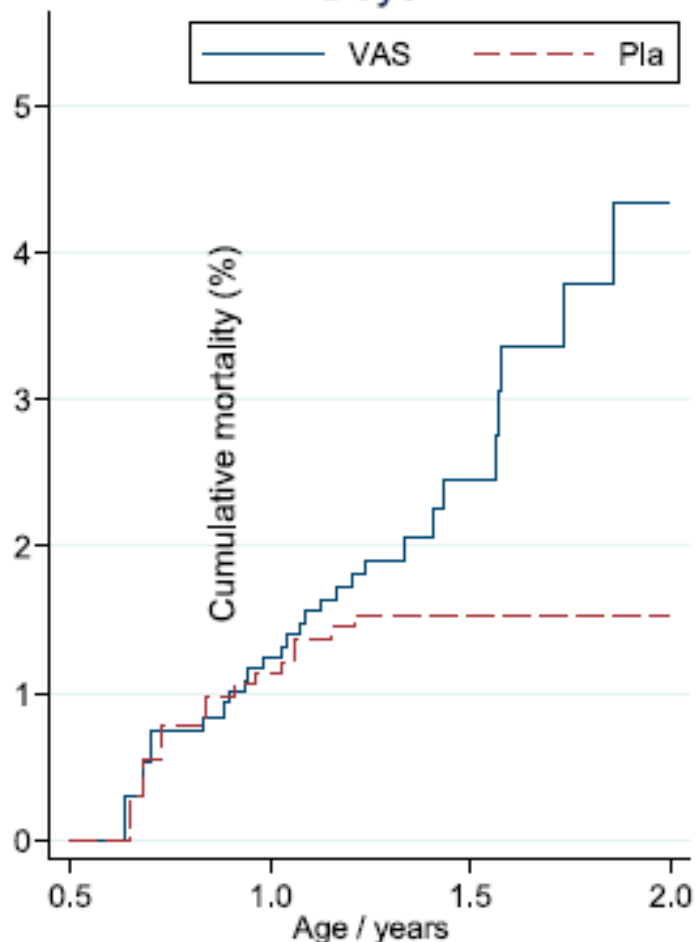
**OPV=oral polio vaccine**

**MV=measles vaccine**

**H1N1= influenza vaccine**

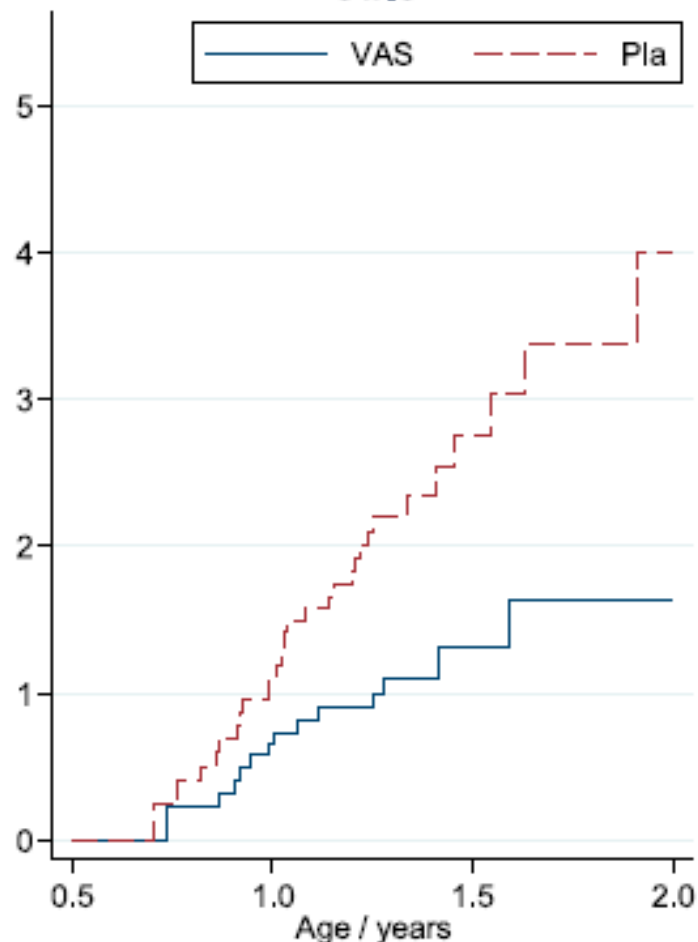
# INDEPTH and vitamin A supplementation (VAS)

Boys



Number at risk				
VAS	142	1354	378	128
Pla	138	1333	416	129

Girls



Number at risk				
VAS	129	1282	391	143
Pla	119	1290	393	128

**The first RCT of VAS with Vaccines**

**Neonatal VAS also failed in Tanzania and Kintampo**

**Time for new studies Of VAS**

**FIGURE 2**

Cumulative mortality according to gender and randomization to VAS/placebo. Note: Follow-up censored after 6 months of follow-up.



**No polio in Bissau: OPV campaigns should have no effect on mortality**

**First OPV campaign in Bissau 1998: Mortality March-Dec**

1998

OPV campaign in 1998 – age groups	1-2 doses of OPV	No OPV	Mortality rate ratio (MRR)
0-5 months	5%(28/553)	8%(19/238)	0.56 (0.3-1.0)
0-4 years	4%(143/3898)	6%(46/798)	0.67 (0.5-0.9)

Vaccine 2005



**INDEPTH Network**

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**Campaigns have not been assessed for impact on survival**



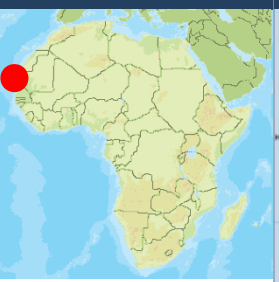
**INDEPTH Network**  
Better Health Information for Better Health Policy



# Bandim Health Project

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

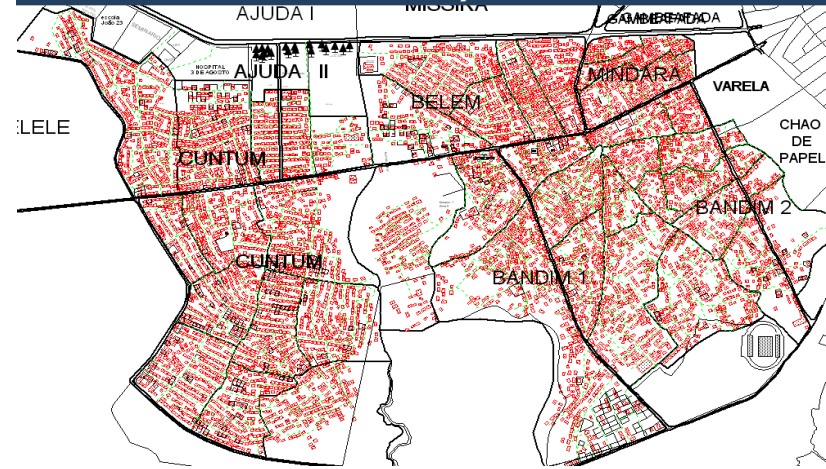
**Guinea-Bissau**



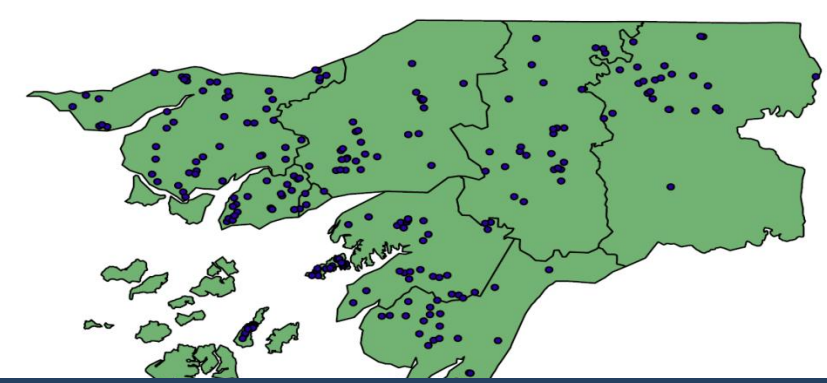
**Bissau City**



**Urban study area**



**Rural study area**



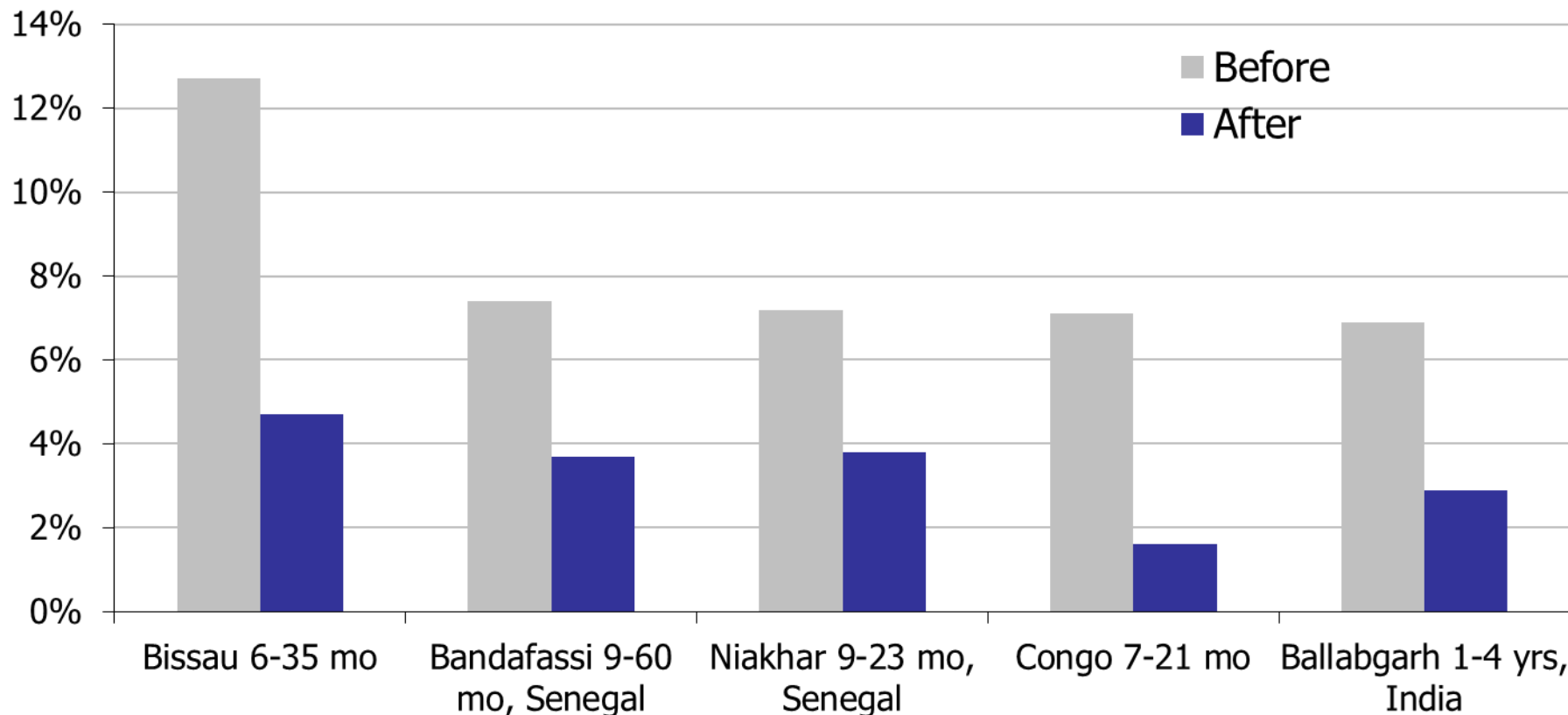
**Urban study area > 100,000 persons**  
**Rural study area > 100,000 persons in 180 villages**

# INDEPTH Working Group on Child survival – the impact of interventions in childhood

# MV introduced mid-1970s based on antibody studies

## Before-after measles vaccination:

*Annual mortality rate in (INDEPTH) community studies*



**>50% reduction – how possible? Measles was 10-15% of deaths (WHO)**

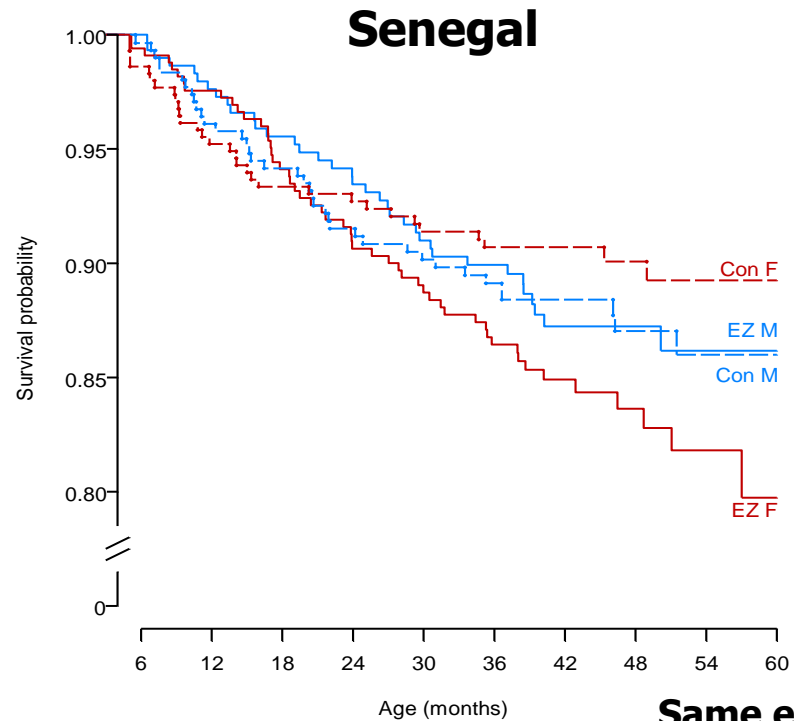
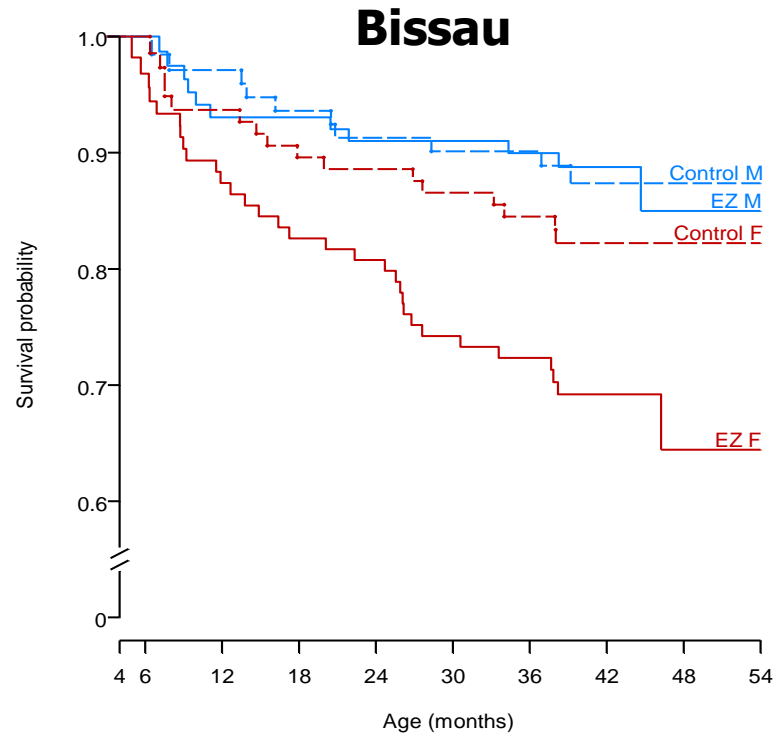
J Infect 1984; AJE 1993; AJE 1995; Kasongo Lancet 1981; Kapoor Ind J Pediatr 1991



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# High-titre Measles Vaccine at 4-5 mo, 1986-92



J Pediatr 1993 and Bull WHO 1994

Same effect in  
Haiti and Sudan

High-titre measles vaccine introduced 1989-withdrawn 1992 by WHO  
HTMV was protective against measles

- A protective vaccine had **negative non-specific effects**
- **vaccines interact with sex** – HTMV 2-fold higher mortality for girls
- **33% excess mortality 4 mo-5yrs** – If not withdrawn ½ mill deaths/year in Africa

→ **Effect due to DTP after MV**

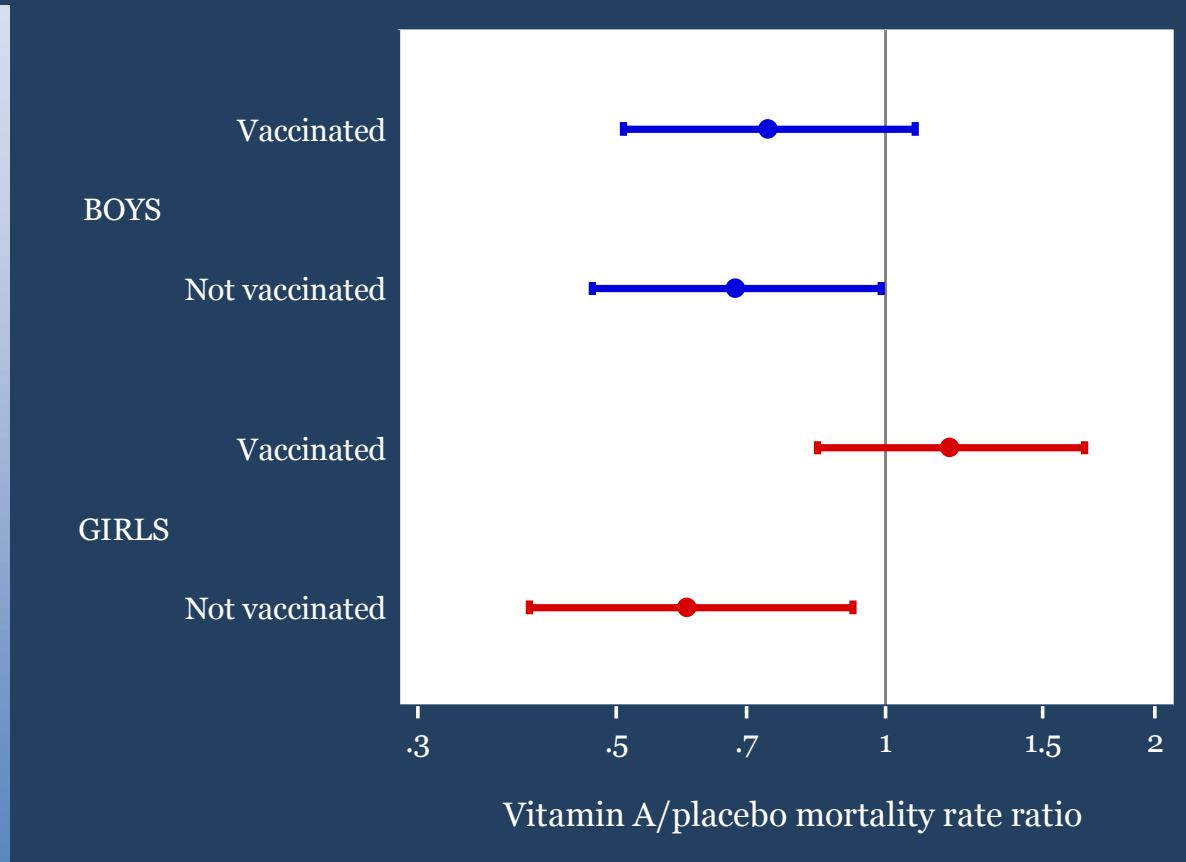


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*Vitamin A assumed to reduce mortality by 25% based on trials  
However, recommended to be given with vaccines: Never tested!*

**Navrongo, Ghana, 1989-91; Mortality reduced by 19%(2-32%) (Lancet 93)**

**Not analysed by vaccination status**



Mortality reduction in unvaccinated: 36% (12-53%); in vaccinated: 5%(-26-28%)

Random trial of VAS with vaccine in Bissau **no effect**

# **Global Health Interventions and the INDEPTH Network**

*Global Health has inherited a specific-disease-specific-intervention model with additive effects -*

*Contradictions identified by INDEPTH centres:*

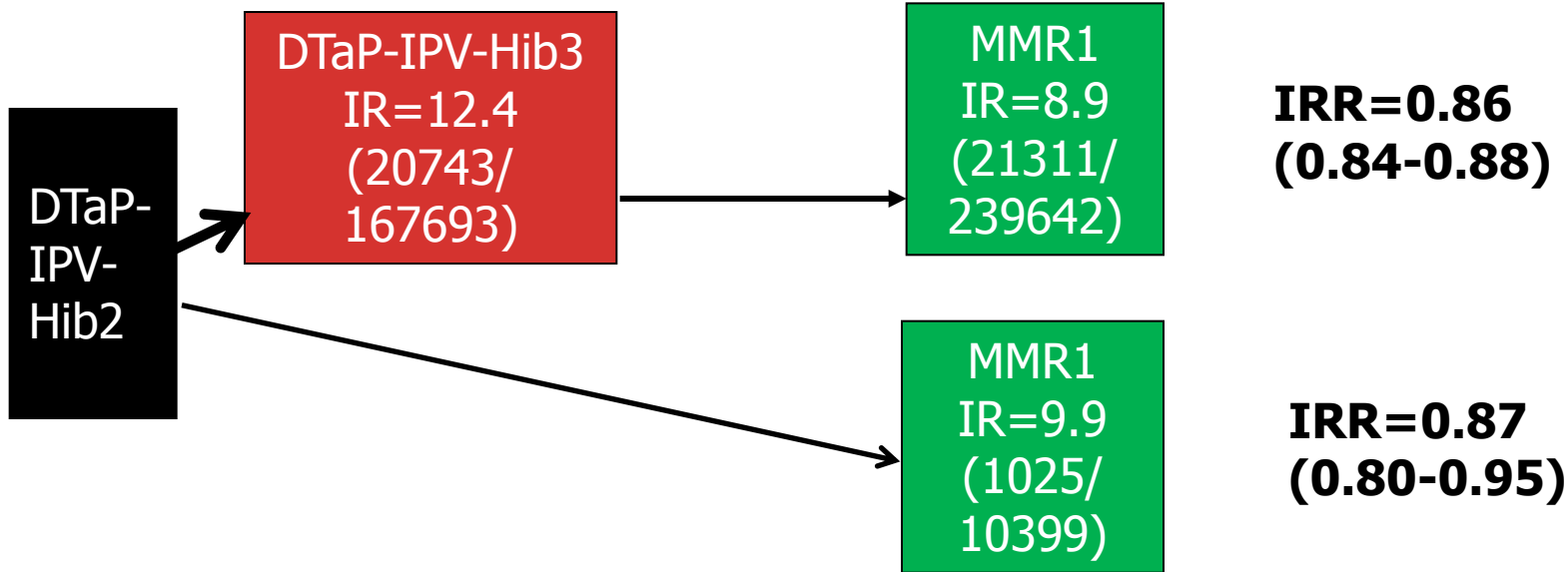
- Live vaccines reduce mortality more than expected*
  - Measles vaccine reduce mortality by >40%*
  - BCG reduce neonatal mortality by >40% in trials*
- Inactivated vaccines increased mortality for girls*
- Effects are very often sex-differential*
- Interventions very often interact:*
  - Vitamin A amplifies the non-specific effects of vaccines*
  - Sequence or combination of vaccines is important*

*The immune system is a learning entity which can be enhanced or misdirected – if we controlled the system we had reached MDG4*

*WHO is currently reviewing the non-specific effects of vaccines (BCG, DTP, measles vaccine)*



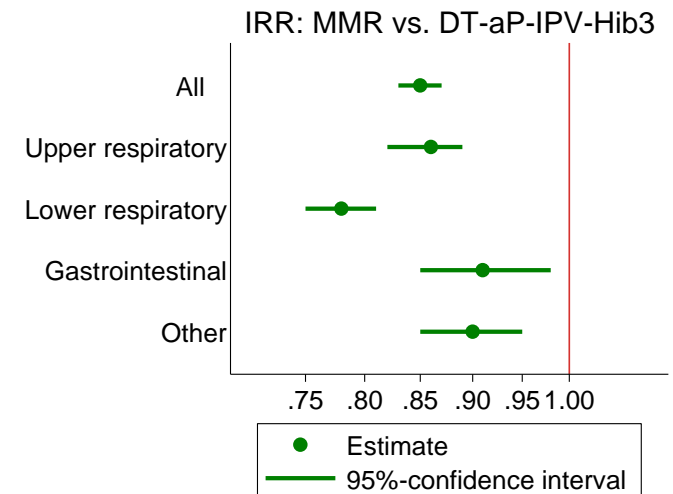
# High-income: Infectious hospital admissions MMR vs. DTaP-IPV-Hib3 in Denmark



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

**DTP after MMR IRR=1.62 (1.28-2.05)**

**Sørup JAMA 2014;311:826-35**





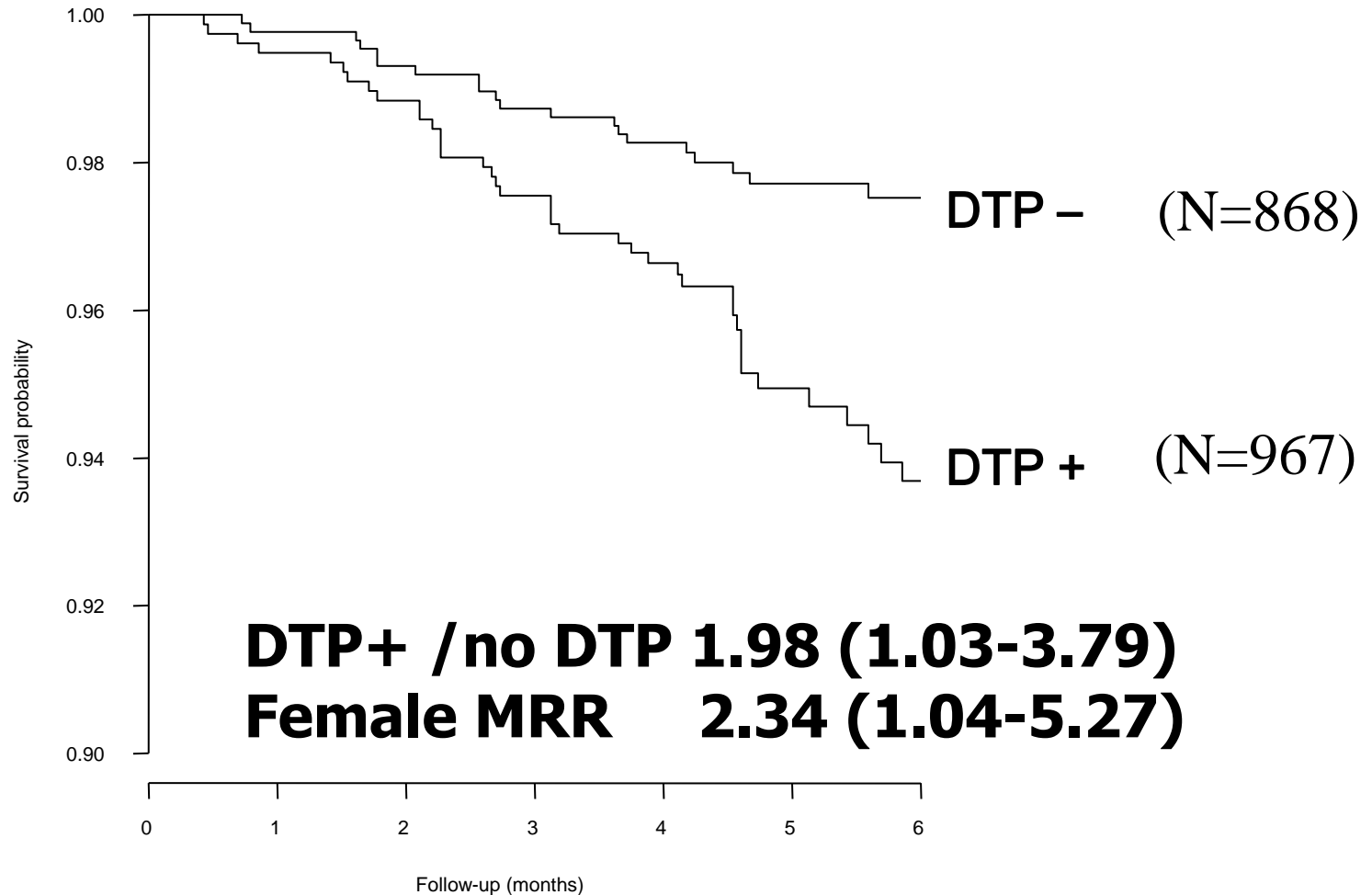


# Introduction of DTP

*Rural areas of Guinea-Bissau 1984-87*

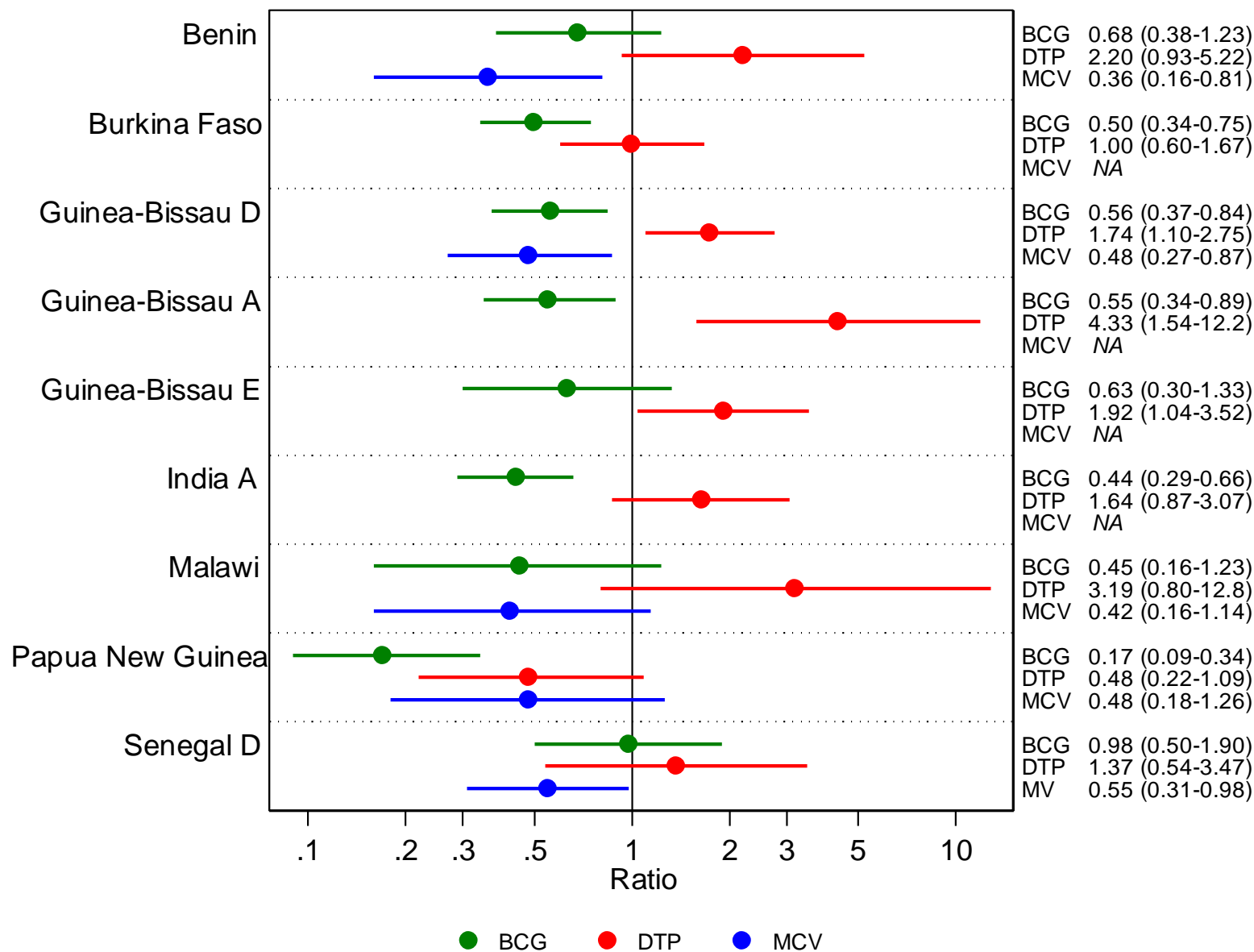
**Children  
aged 2-8 mo**

**Unvaccinated:  
travelling; sick;  
days without  
vaccines**



The only study in the global literature of effect on mortality of introduction of DTP

# Differential effects of BCG, DTP and MV



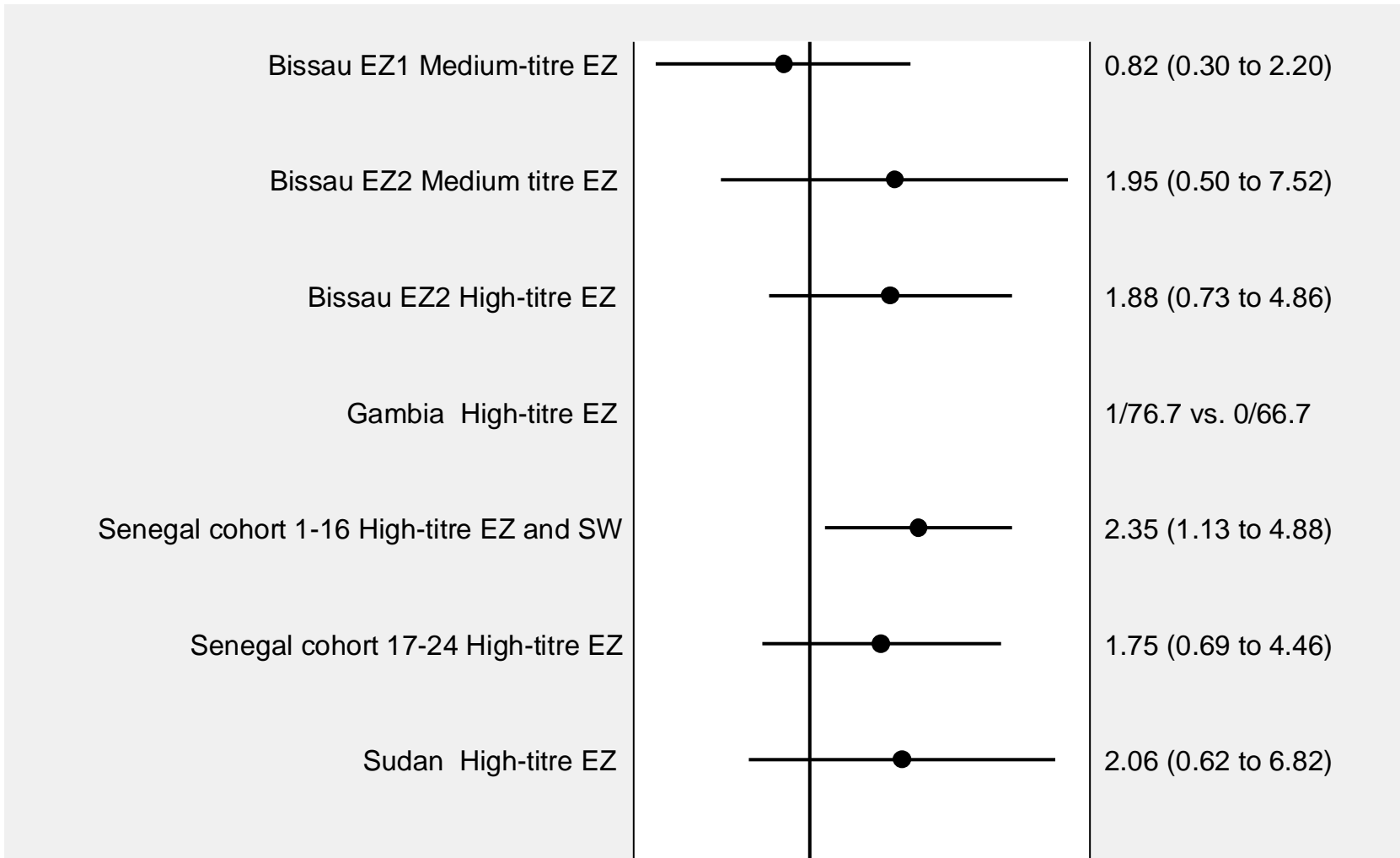
## Early MV trials with cross-over

Age	Early MV	Controls
4-5 months	Medium/ High titre MV	Inactivated Vaccine
9-10 months	Inactivated Vaccine	Standard MV



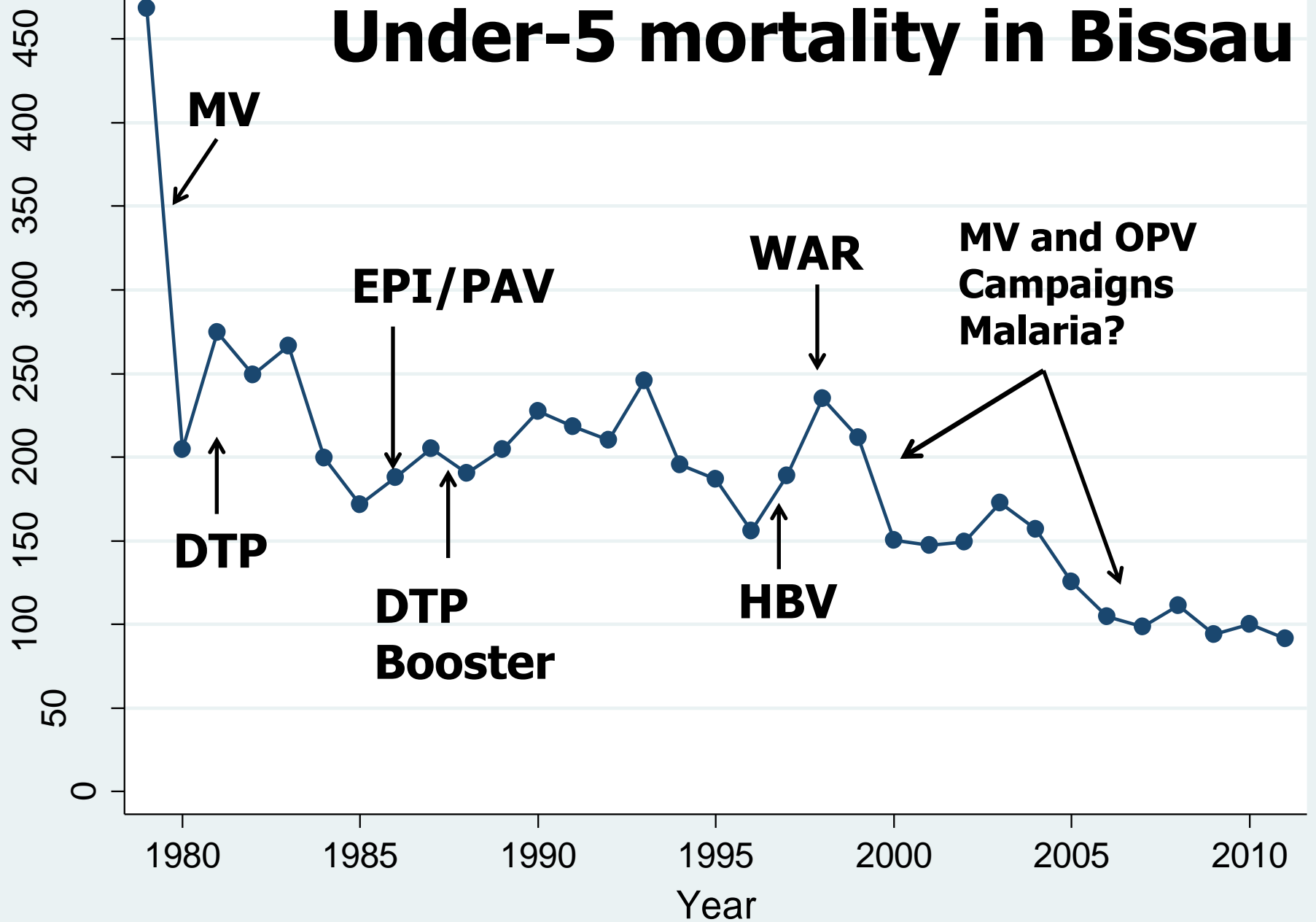
**5 RCTs of early MV before 9 month had a cross-over design with the two groups getting a 2<sup>nd</sup> vaccination after 9 months and followed to 3-5 years of age:**

**Mortality R. Ratio for inactivated vs MV 1.38 (1.05-1.80)**



**5 RCTs inactivated versus MV = 89% (27-180%) higher mortality for girls**

# Under-5 mortality in Bissau

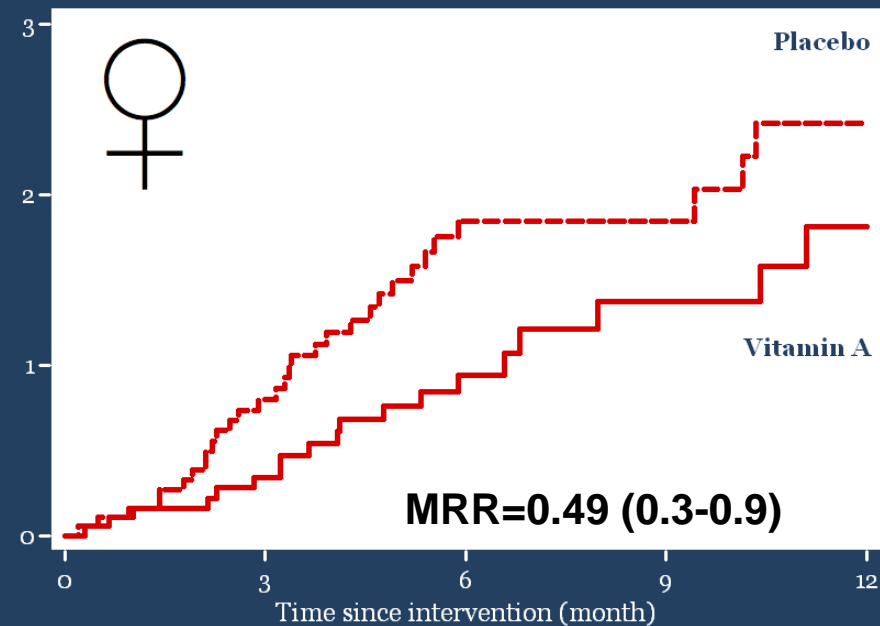
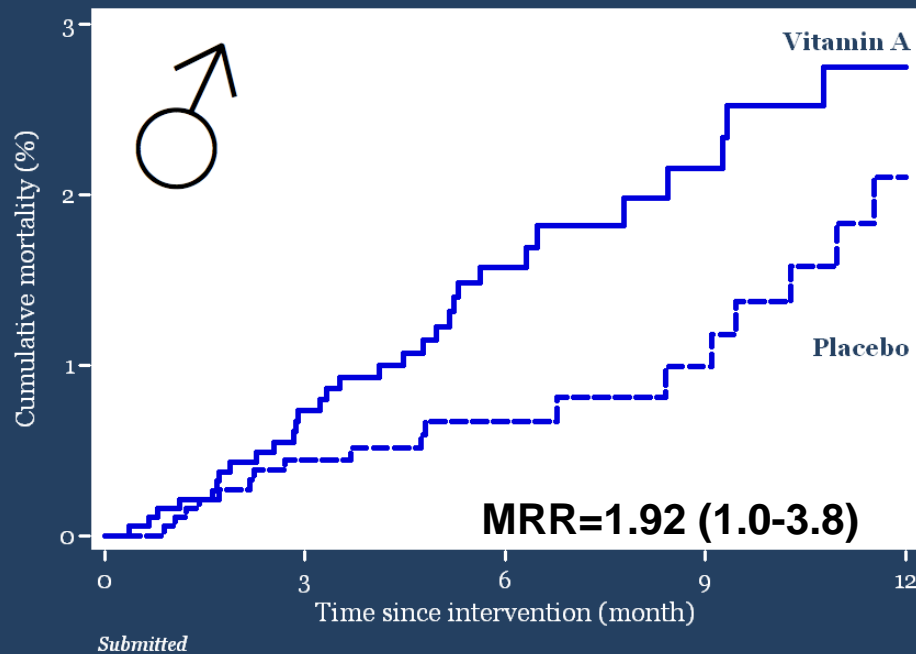




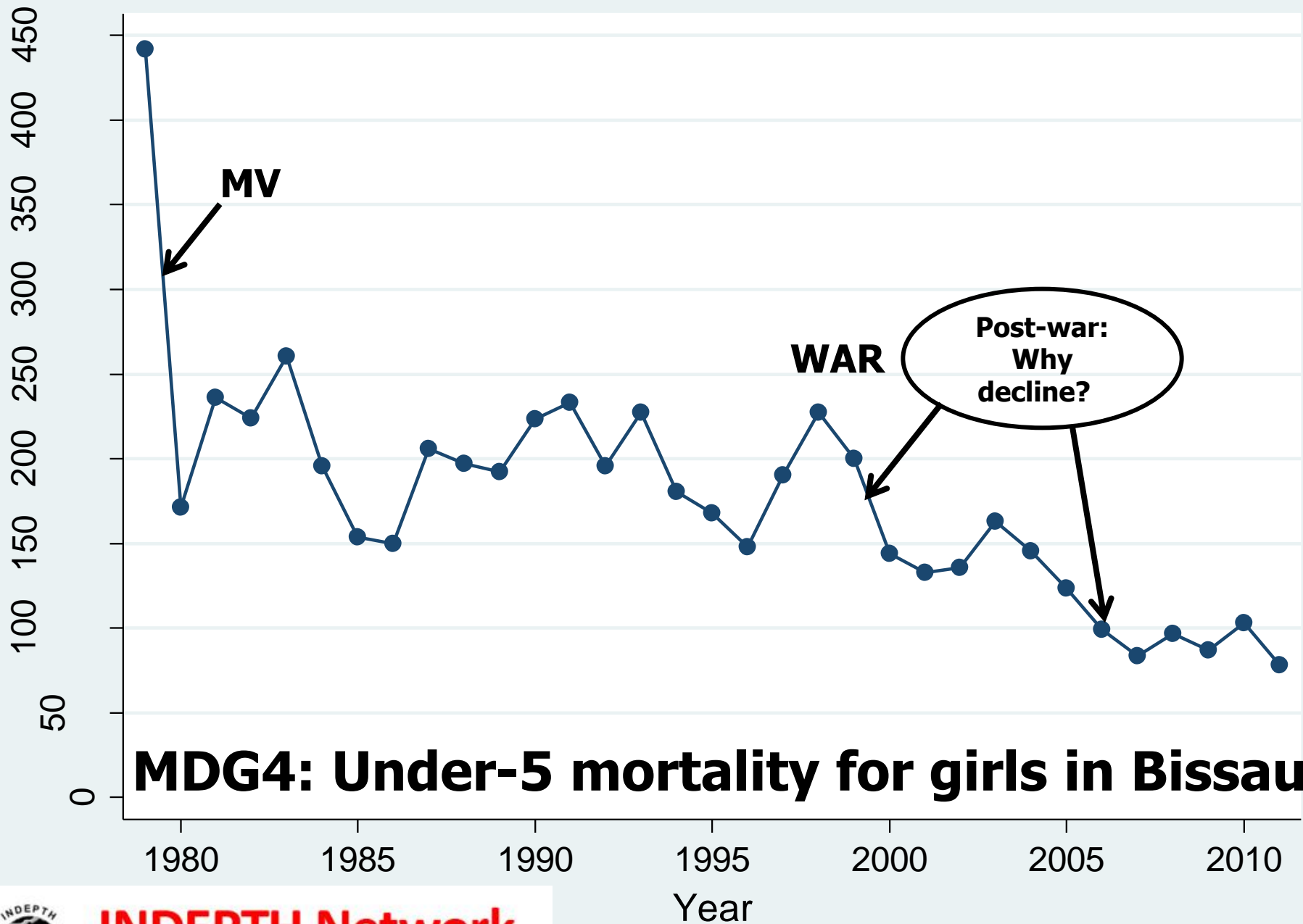
# Interactions: RCT of VAS with vaccines after 6 months

## 7585 children in urban and rural Bissau (2007-10)

Overall effect VAS vs placebo MRR = 0.93 (0.6-1.4)



P for same effect in boys and girls=0.004



**MDG4: Under-5 mortality for girls in Bissau**

