

WG: Vaccinations and child survival

Focus:

Monitoring childhood interventions including routine services and campaigns

=> To find possible changes in policy

Why is that necessary?

Paradox:

**All interventions justified by their impact on mortality
but the impact on mortality has not been studied**

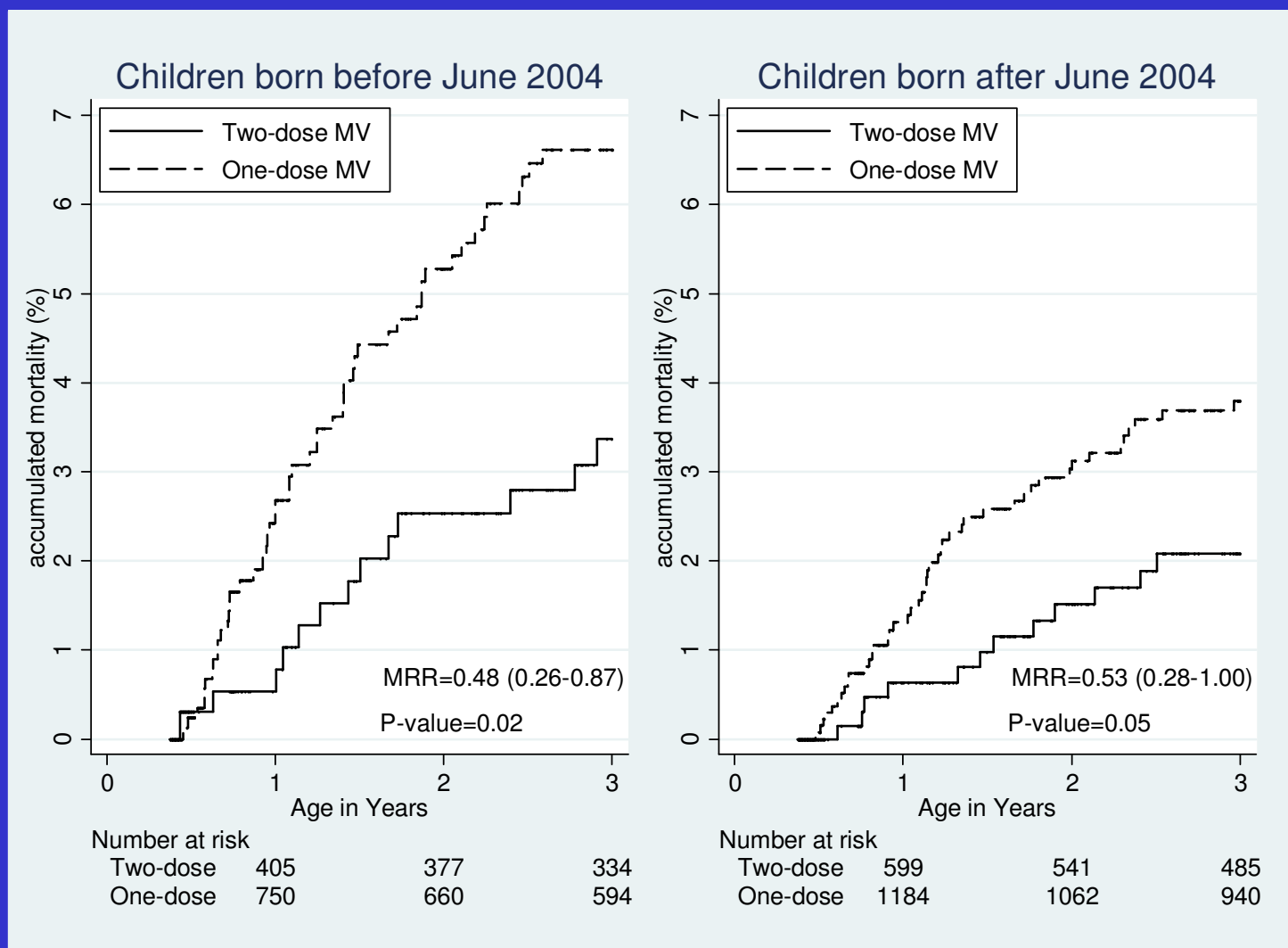
WG Vaccinations and child survival

Current paradigm in Global Health: **Specific solutions**

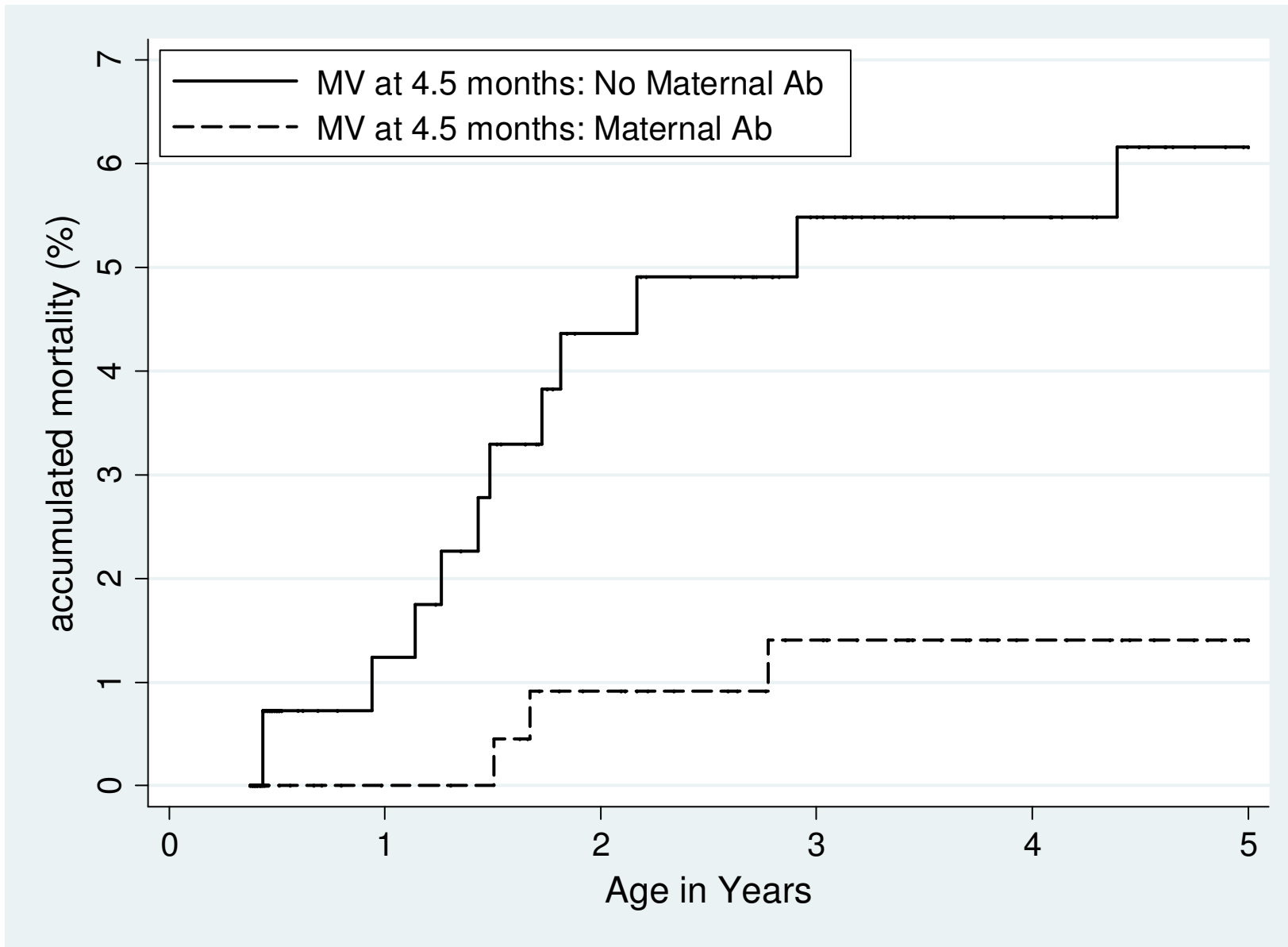
- Prevention of specific diseases (malaria, rota, measles etc) and deficiencies (vitamin A, iron etc)
- Effects assumed to be good and proportional to the burden of disease/deficiency
- Effects assumed to be the same for girls and boys
- Effects assume to be independent

If impact on mortality of childhood interventions is considered a different pattern emerge:

RCT of two doses of Measles Vaccine



Two-dose standard MV at 4½ and 9 mo was fully protective and had beneficial non-specific effect on mortality



N=450
 60% had
 MatAb
 16 ≥
 Mother's
 level

Mortality ratio from 4 to 60 mo

MV4mo+MatAb vs MV4mo+No MatAb

0.23 (0.1-0.8)

2 RCTs of BCG at birth to LBW infants

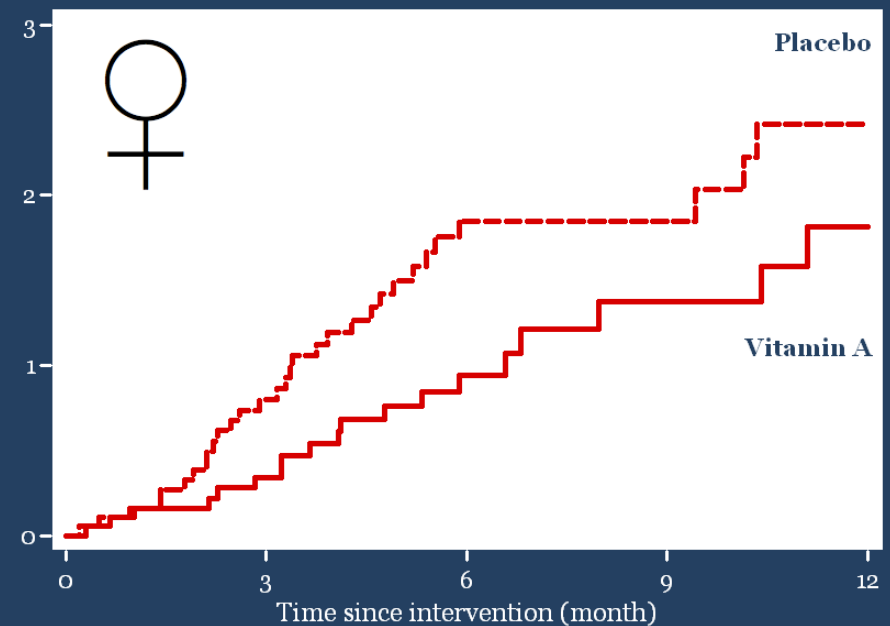
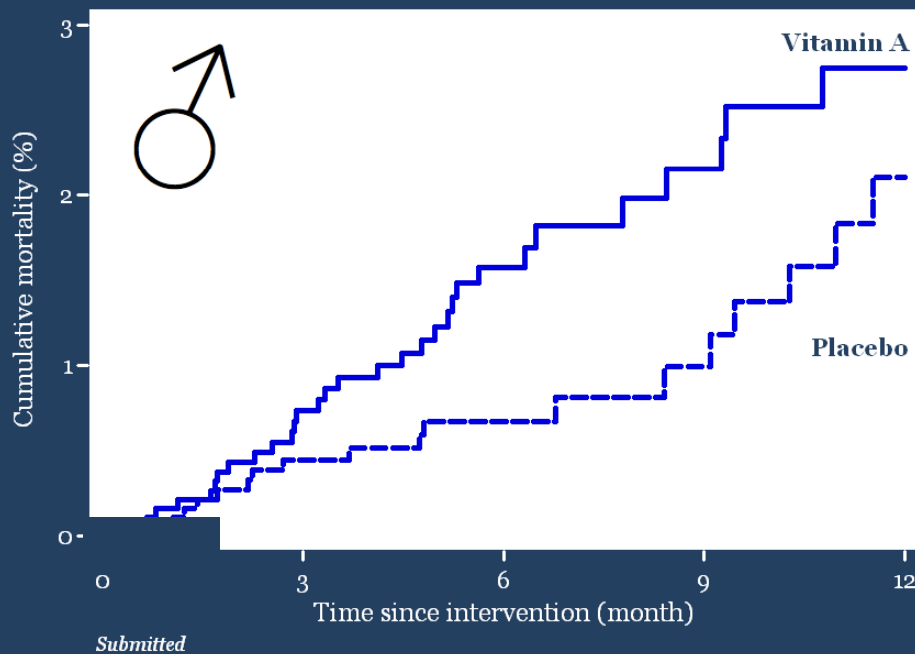
	Mortality rate ratio for BCG vs controls	
Trial	Effect within 3 days	Effect within 1st mo
2002-2004	0.17 (0.02-1.35)	0.28 (0.06-1.37)
2004-2009	0.49 (0.21-1.15)	0.55 (0.34-0.89)
Combined	0.42 (0.19-0.92)	0.52 (0.33-0.82)

Due to prevention of neonatal sepsis and respiratory infections
Nothing to do with prevention of TB

2011: Some very recent results

*Randomized trial testing the effect of vitamin A with vaccines to children > 6 months
Enrolling 7585 children in urban and rural Guinea-Bissau between 2007-2010*

Overall effect: MRR=1.02 (0.69-1.51)



P for same effect in boys and girls=0.01

Ane Fisker, PhD thesis

Vaccinations and child survival:

These effects may be hard to believe!

But the current paradigm is contradicted

- *High-titre MV 2-fold increased mortality for girls*
- *RCT of BCG 45% reduction in neonatal mortality*
- *RCT of BCG revaccination after DTP booster 3-fold reduction*
- *RCT of MV at 4+9 months 50% reduction in mortality between 4 mo and 3 years of age*
- *RCT: Vitamin A interact negatively with DTP in Bissau and Ghana*
- *RCT Vitamin A with vaccines has sex-differential effects*

This is a huge opportunity for INDEPTH – we are the only ones who can measure “real life” effects for current interventions and all the new vaccines in the pipeline

Vaccinations and child survival: What is required?

Better data on vaccination and other interventions

- Few sites have regular data on routine interventions and campaigns
- Data have often been analysed wrongly => we need better analytical methods

Young scientists at the centres who can collect and analyse such data

Develop generalisations and make them believable and inevitable for *policy change*

=> These needs have defined the WG agenda

Vaccinations and child survival: I: Research training network

PhD proposal to Danida: Monitoring the impact of childhood interventions on child survival and morbidity (Ballabgarh, Navrongo, Nouna, Nairobi, Kintampo, Bandim)

To support data collection and analysis of impact of routine vaccinations and other interventions in childhood

Common data collection methodology: Improve routine data collection on vaccinations => to facilitate observational studies and decide on priority trials

Money from September 2010.

First workshop held in February 2011 in Bissau

Data collection is ongoing

Site visits

Vaccinations and child survival:

II. Multicentre study

EU proposal: "Optimising the impact and cost-effectiveness of existing child health intervention programmes for vaccines and micronutrients in low-income countries" (Navrongo, Nouna, Bandim)

To support common data collection methodology and analysis of the impact of routine vaccinations and other interventions in childhood

Conduct a multicentre trial of early measles vaccination at 4 months

Develop a methodology to assess "real life" effects of health programmes and evaluate the cost effectiveness and suggest possible modifications => conduct new trials

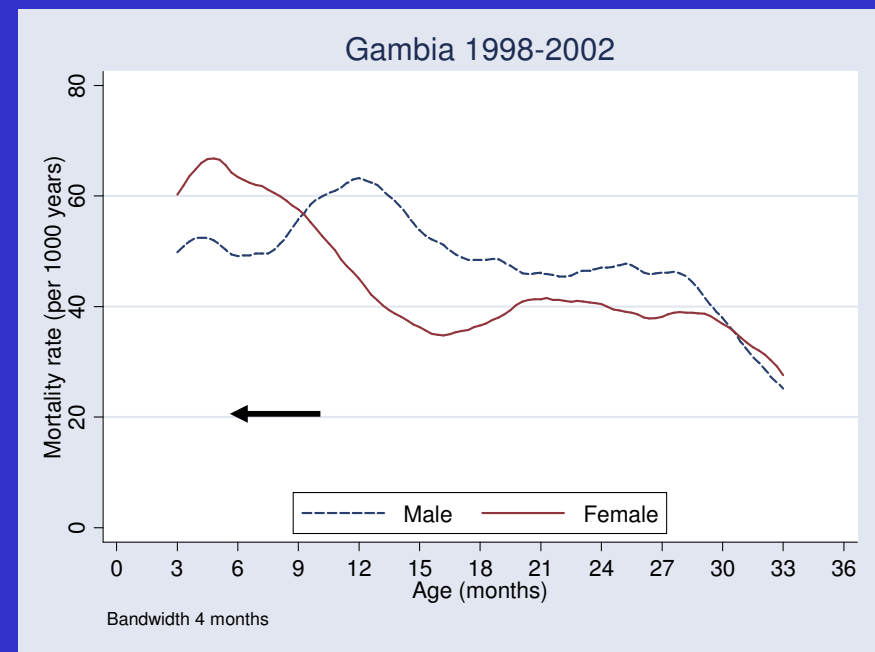
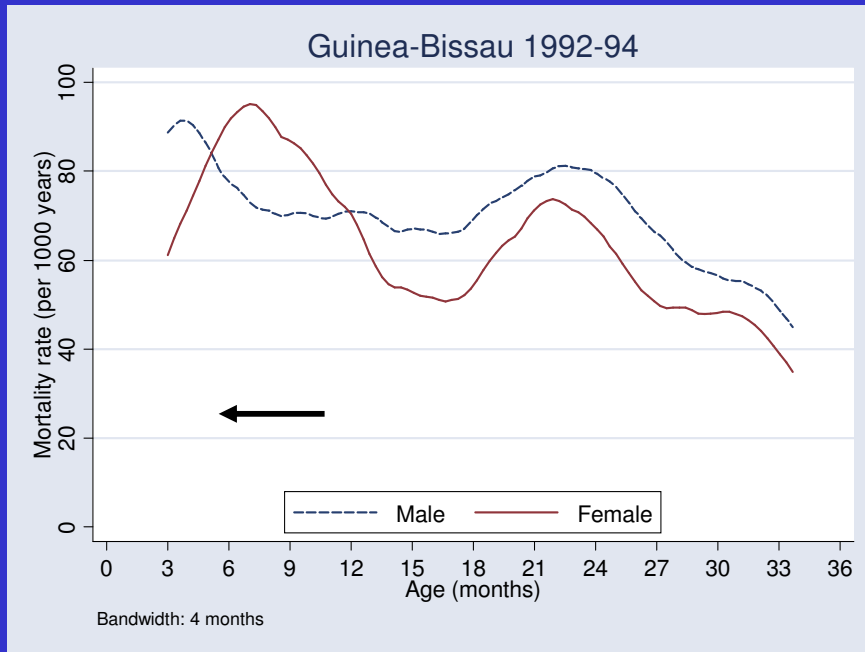
First consortium meeting in Navrongo in April 2011

Trial protocol under development

Vaccinations and child survival

- **III. Analysis of existing data 2007-2011**
 - **Farafenni => Routine vaccinations and child mortality (Vaccine 2007)**
 - **Navrongo => Vaccines and vitamin A (Am J Clin Nut 2009)**
 - **Vadu: Siddhi: Non-specific and sex-differential effects of vaccinations on child survival in rural western India (submitted)**
 - **Navrongo: Paul Welaga: Non-specific of routine vaccinations: testing the hypothesis with data from Navrongo (to be submitted)**
 - **Draft: cross site paper : The impact of nutritional status on time to vaccination (Vadu, Bissau, Malawi)**
 - **Data from Matlab and Rufiji has also been discussed**

Analysis from Farafenni (Vaccine 2007)



Same changes in relative female-male mortality as in Bissau
DTP age (3-8 months) – higher female than male mortality
MV age (9-17 months) – lower female than male mortality

These observations led to RCT of early MV

WG: Impact on public health policy

Global impact

- **Bandim and Niakhar: high-titre measles vaccine => increased female mortality – withdrawn by WHO 1992**

Current topics:

- **Bandim, Nouna, Navrongo: Early MV in RCT**

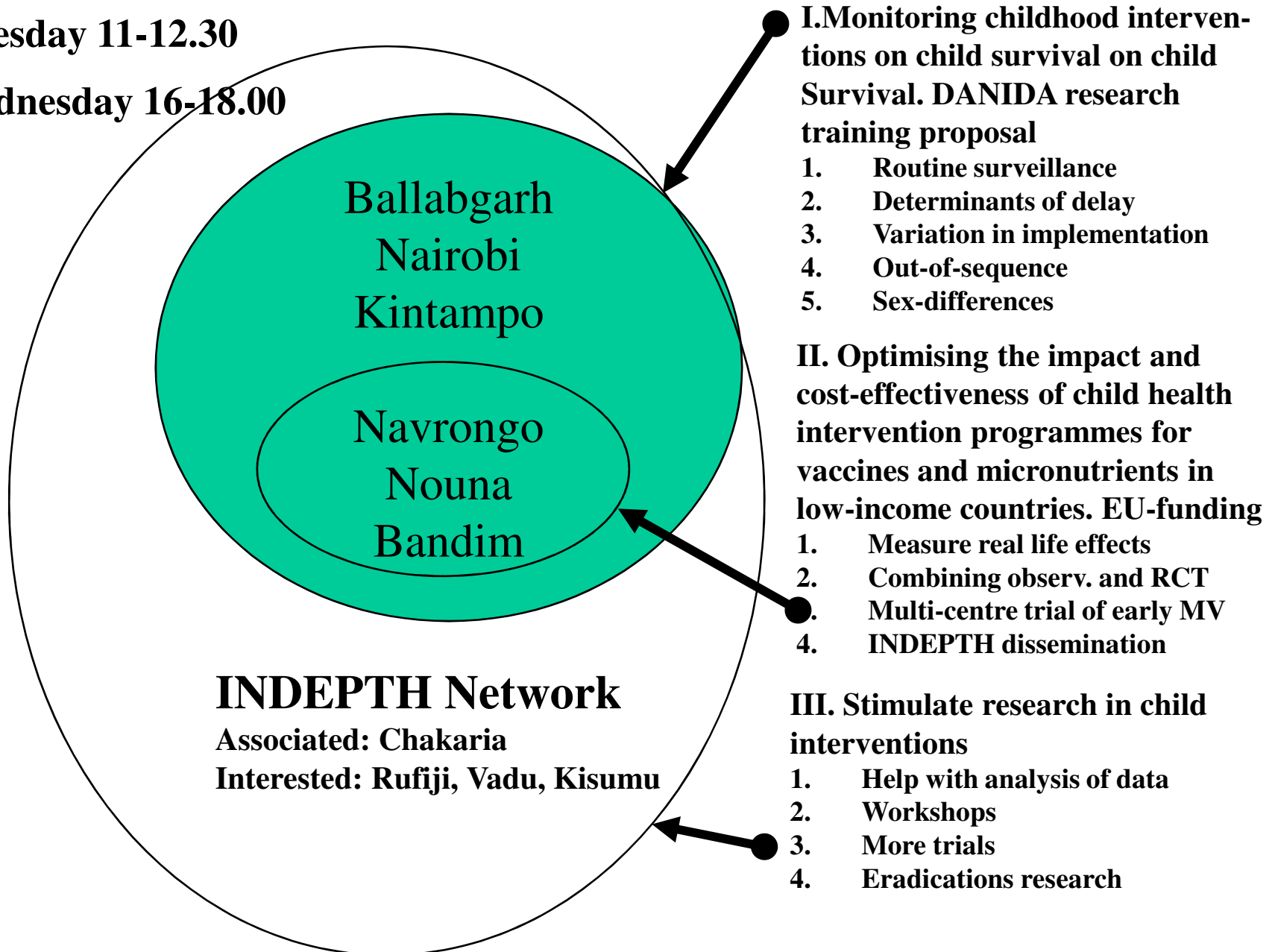
Potential topics

- **Early BCG**
- **Not give DTP after MV**
- **Not give vitamin A with DTP**
- **Consequences of eradication**

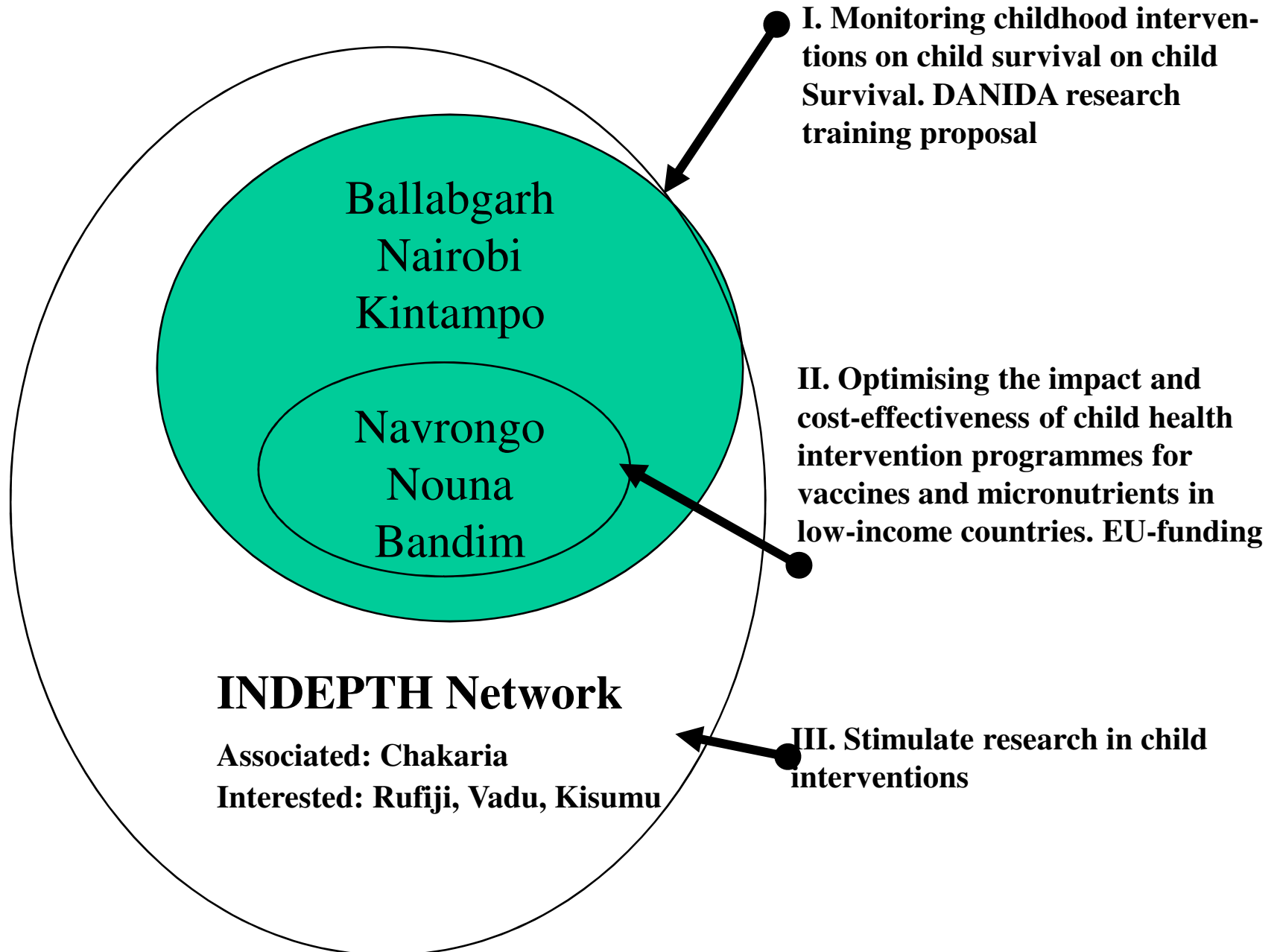
WG Vaccinations and child survival: Where we are now!

6.3 Tuesday 11-12.30

13.6 Wednesday 16-18.00



WG Vaccinations and child survival: Where are we now?



WG: Vaccinations and child survival:

The area questions many current assumptions:

Specific solutions vs Immunity as a learning system

It has huge potential for child survival with both beneficial and negative effects:

- MV has beneficial effects. When measles is eradicated and vaccinations are reduced child mortality will increase again.

More INDEPTH centres should pursue this area

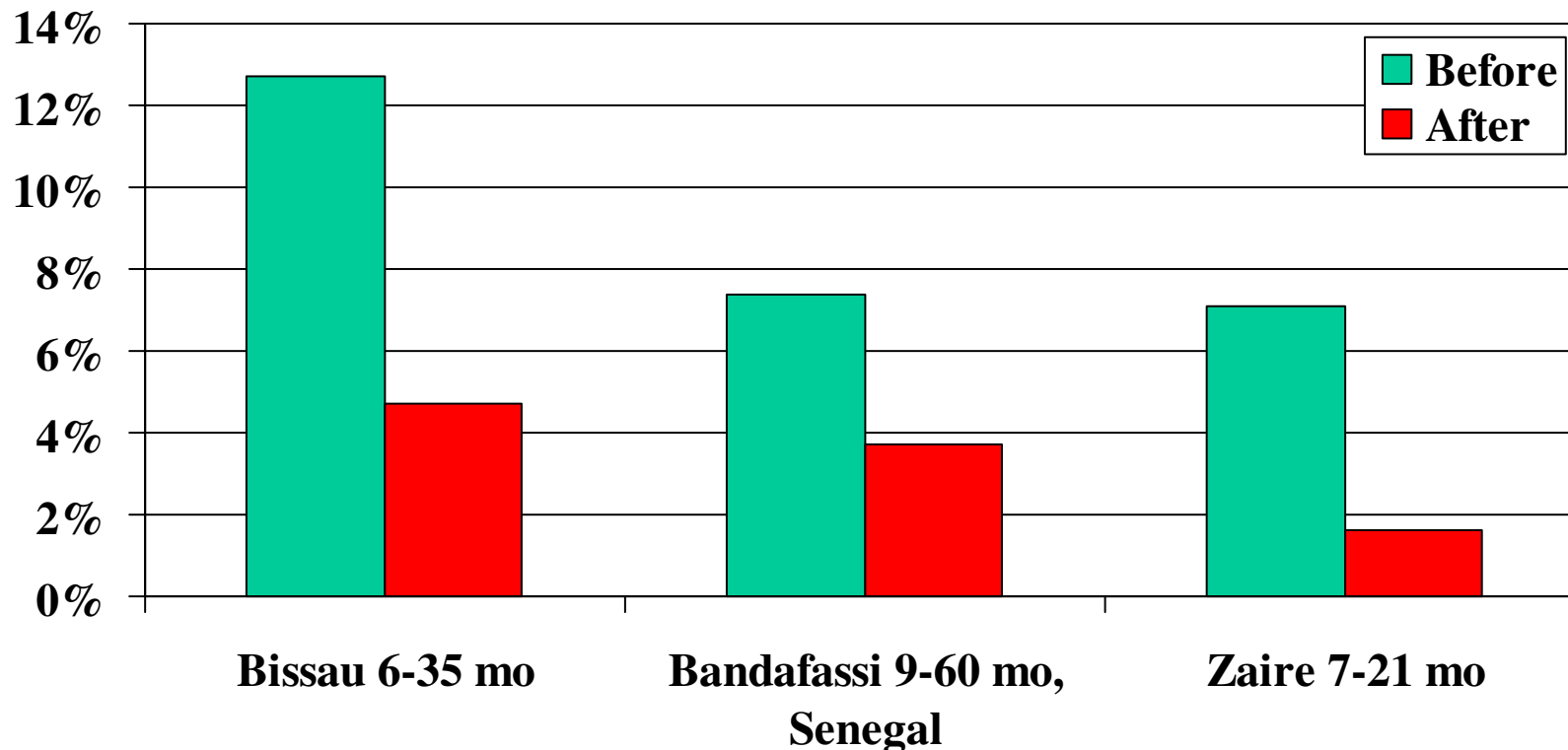
Non-specific effects of vaccine on child survival



**Real
life?**

Before-after measles vaccination:

Annual mortality rates in African community studies in the 1970s and 1980s



**Measles is not 50% of deaths – Why this effect of Measles vaccine?
Does not fit current concepts => *a beneficial non-specific effect***

Vitamin A and early measles vaccination: Mortality between 4 and 36 months after measles vaccination at 4 months

	Deaths/N		Mortality rate ratio
	Vitamin A at birth	Placebo	
Boys	20/526	4/350	3.33 (1.2-9.7)
Girls	13/496	5/329	1.72 (0.6-4.8)
All	33/1022	9/679	2.44 (1.2-5.1)

Beneficial nonspecific effects: Early MV at 4+9 mo vs MV at 9 mo

Morality rate between 4 and 36 months (deaths/pyrs)			Mortality rate ratio
	MV at 4 + 9 months	MV at 9 months	
Boys	1.0 (12/1254)	1.7 (40/2300)	0.56 (0.29-1.06)
Girls	1.1 (13/1199)	2.3 (56/2402)	0.47 (0.26-0.86)
All	1.0 (25/2453)	2.0 (96/4703)	0.50 (0.32-0.78)

Only 10% due to prevention of measles infection; censoring for measles the MRR is 0.55 (0.35-0.87)

Vaccinations and child survival: Campaigns for a cohort born 2003-6

- BCG vaccination for all children born at the national hospital since 2002
- Vitamin A and missing vaccination campaign in 2003
- OPV campaigns in 2004 and 2005
- Vitamin A campaigns every year 2004, 2005, 2006 twice, 2007 twice, 2008 twice, 2009 twice
- Measles vaccination campaign in 2006 for all children aged 6 months to 15 years
- Measles vaccination campaign in 2009 for all children aged 9 months to 5 years of age
- Bed net distribution 2006 and 2007
- Bed net impregnation 2006 and 2007
- De-worming every year 2006-2009

**WG: Vaccinations and child survival
DANIDA application for 3 mill \$ for this
network**

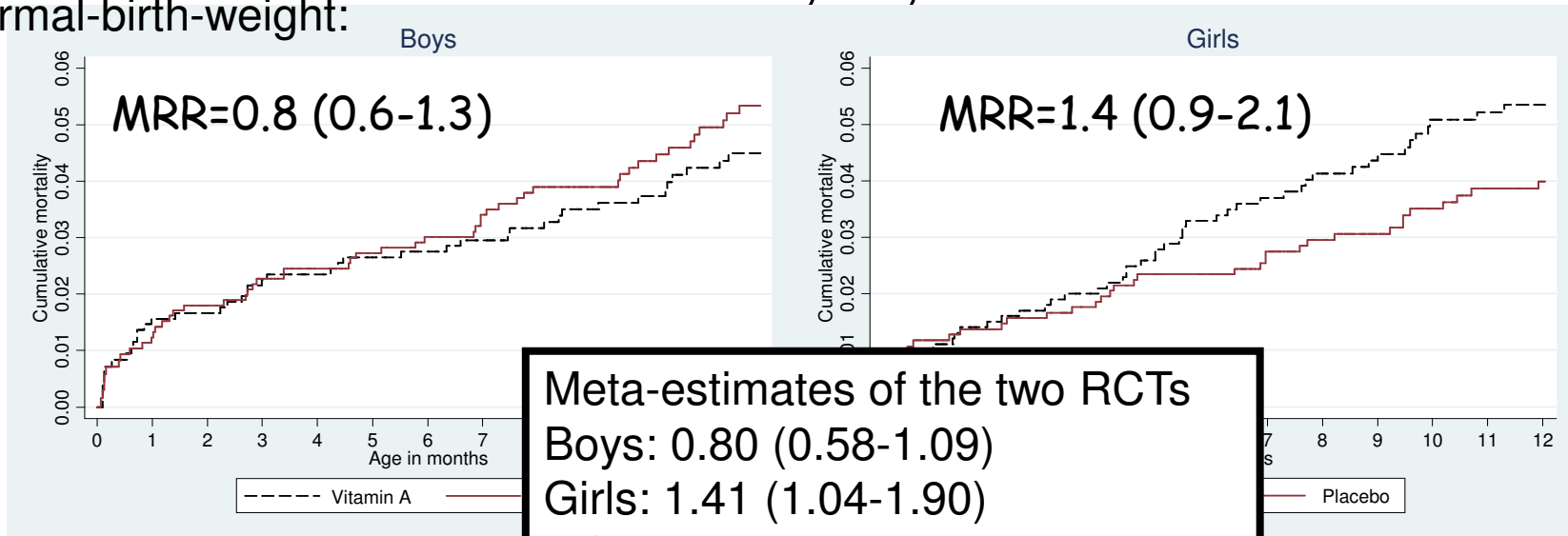
**Response: Science okay – you can get 2 mill if
you can get the last mill elsewhere**

**We are trying to apply to EDTCP together
with Heidelberg**

**If this is not feasible we have to have an
alternative "low cost" solution**

Vitamin A supplementation at birth and infant mortality by sex

Normal-birth-weight:



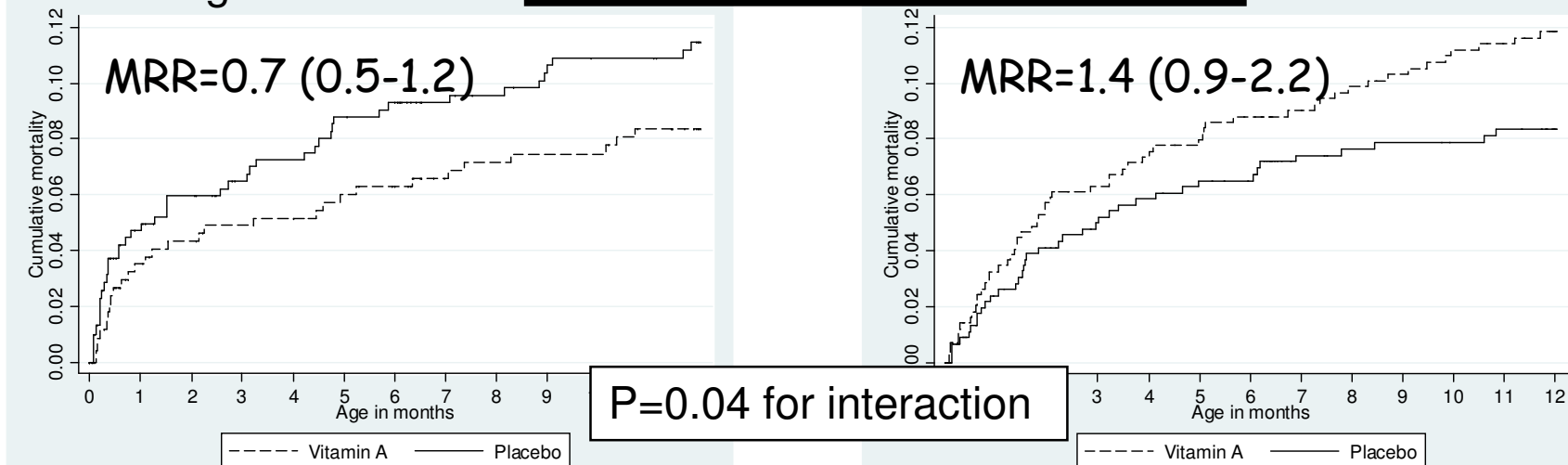
Meta-estimates of the two RCTs

Boys: 0.80 (0.58-1.09)

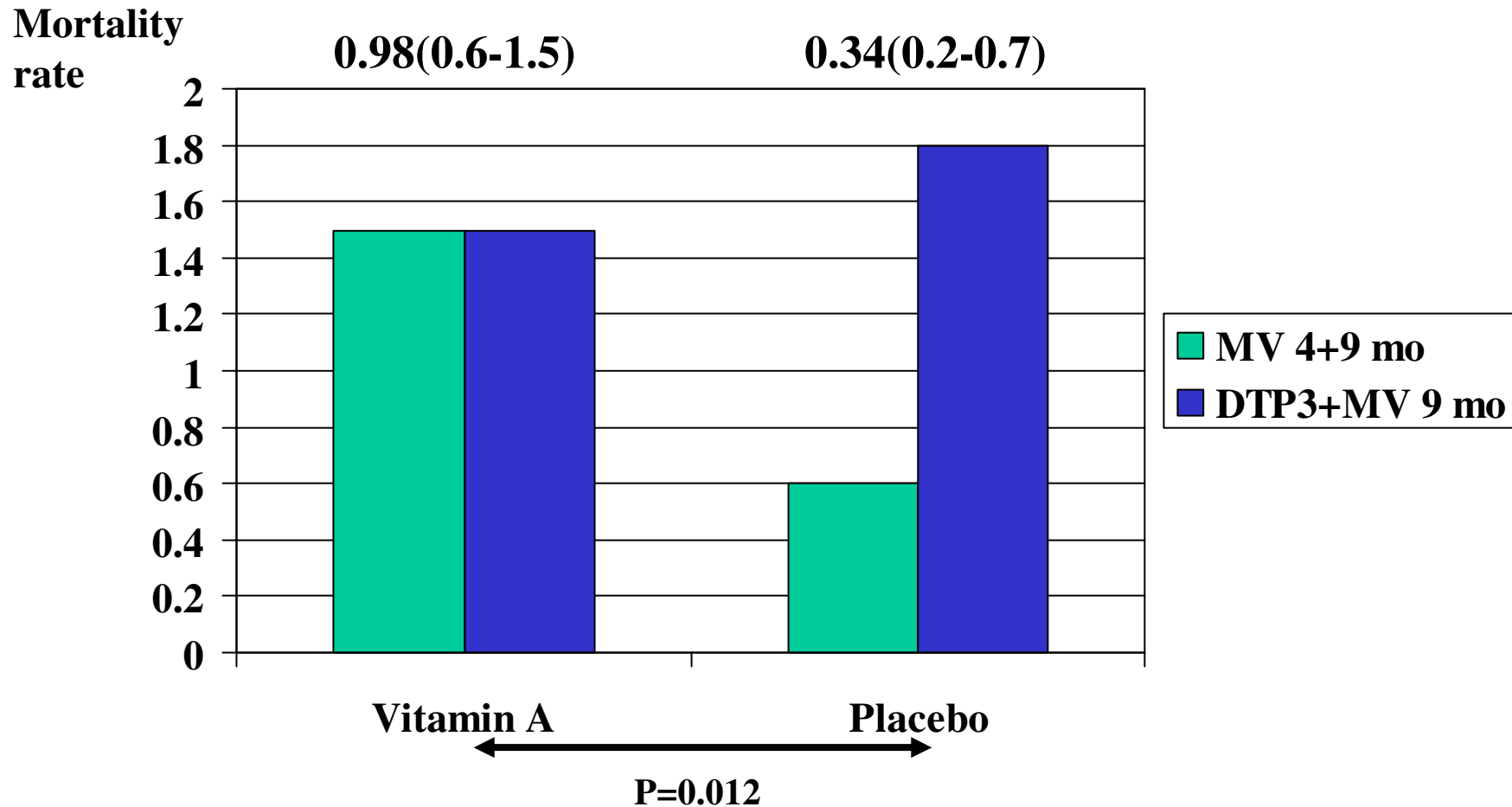
Girls: 1.41 (1.04-1.90)

P for interaction=0.01

Low-birth-weight:



MV at 4+9mo vs No vac(DTP3)+MV at 9mo by Vitamin A-at-birth status



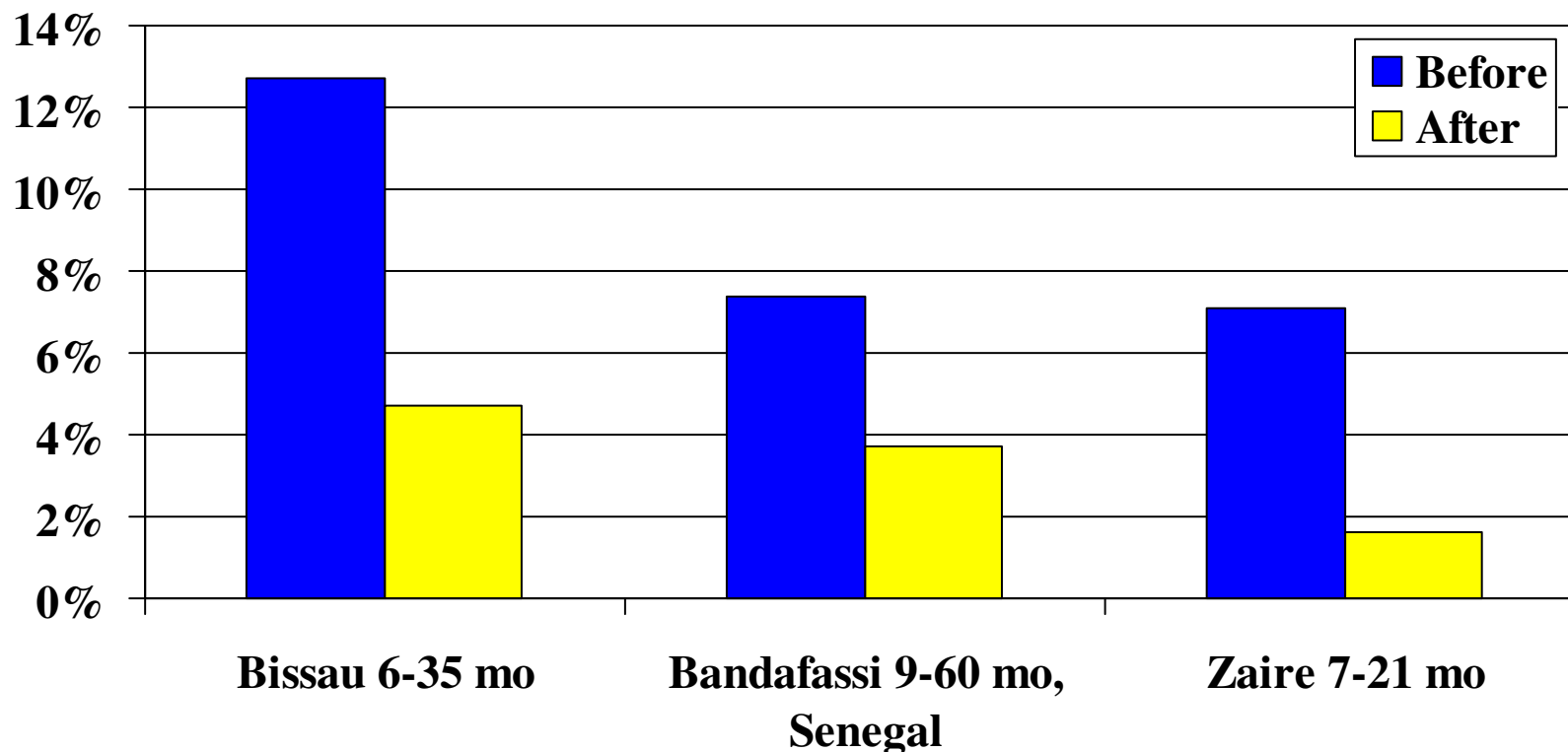
Vitamin A may have a fundamental impact on the NSEs

WG: Vaccinations and child survival

- What has happened 2007-2009
 - Centre visits – Nouna; Kilifi; Navrongo; Ballabgarh, Vadu, Rufiji
 - 2008: Small grants from Indepth/DANIDA =>
 - April 2008: Workshop on non-specific effects of vaccines in London (organised by Peter Smith). Resulted in 3 papers =>
 - Data Collection (TMIH)
 - Analytical issues (TMIH)
 - Potential randomised trials of non-specific effects (PIDJ)
 - 2009 Applications to DANIDA, EDCTP, EU-FP7
 - 2010: Danida – 1.3 mill € for research training network and EU-FP7 possibly 3 mill € for multisite study; EDCTP: 0

Before-after measles vaccination (MV):

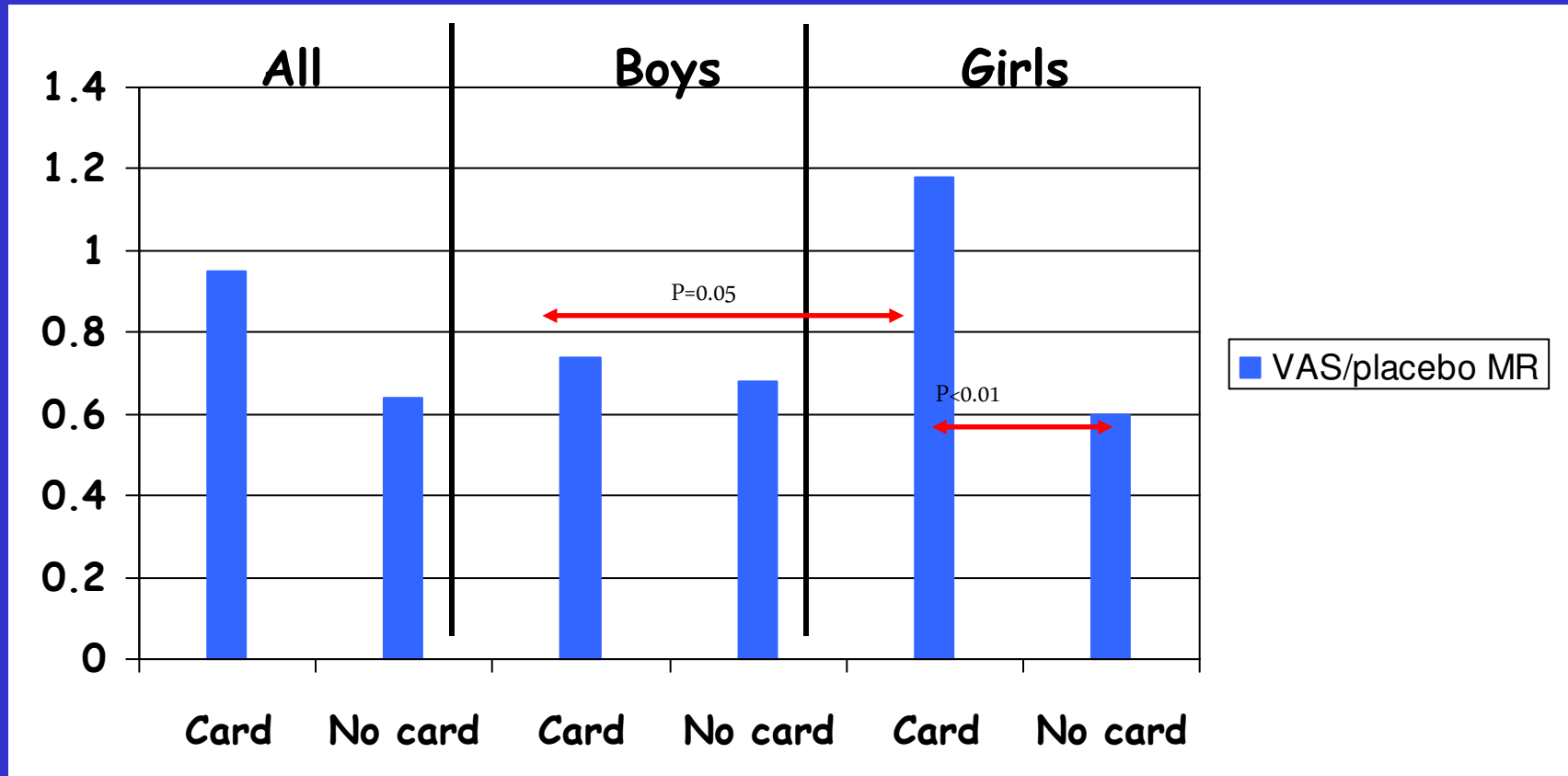
Annual mortality rates in African community studies



**Bissau: MV at 6 mo introduced 1979 - 3-fold reduction
Measles infection may have caused 10-20% of deaths!
=> A beneficial effect unrelated to measles prevention**

Navrongo RCT, reanalysis

Mortality Ratio for VAS vs placebo



The VAS effect differed in children with (N=6,656) and without (N=5,066) a health card - due to differential effect of VAS in girls (P<0.01)

Benn et al, Am J Clin Nut 2009