Vaccinations and child survival WG

Focus: monitoring childhood interventions including routine services and campaigns => changes in policy

Why is that necessary?

Current focus in International Health is

- 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
- Effects assumed to be the same for girls and boys
- Effects assume to be independent

Vaccinations and child survival WG

Focus: monitoring childhood interventions including routine services and campaigns => changes in practice

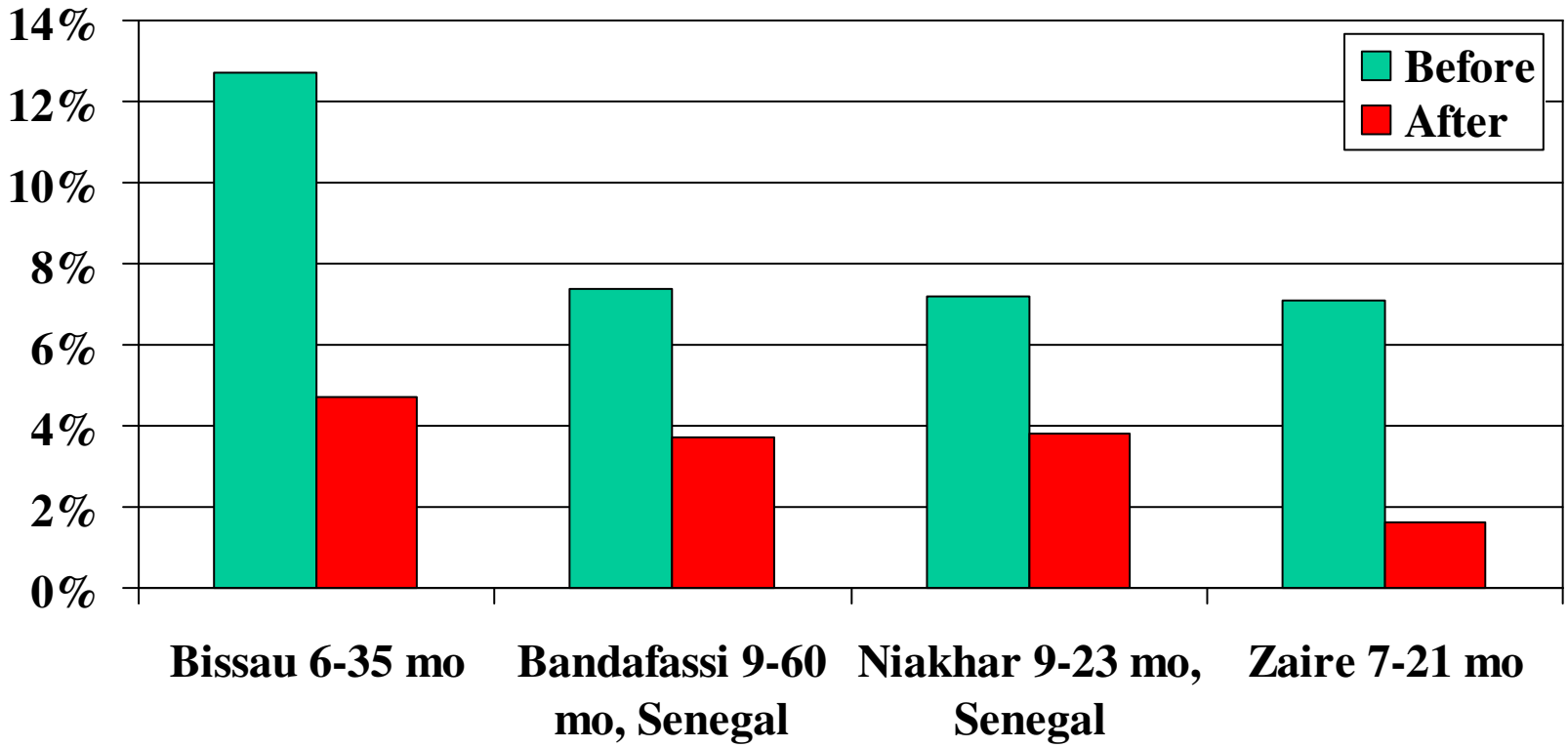
However, current interventions in International Health:

- Effects on mortality can be far better than they should
- Effects on mortality can be negative – increasing mortality
- Effects often differ completely for girls and boys – suggesting that to treat girls and boys optimally you may have to treat them differently
- Interventions often interact – neutralising or reversing effects of other interventions

INDEPTH is in a unique position to document the ”real effect” and turn them into policy

Before-after measles vaccination:

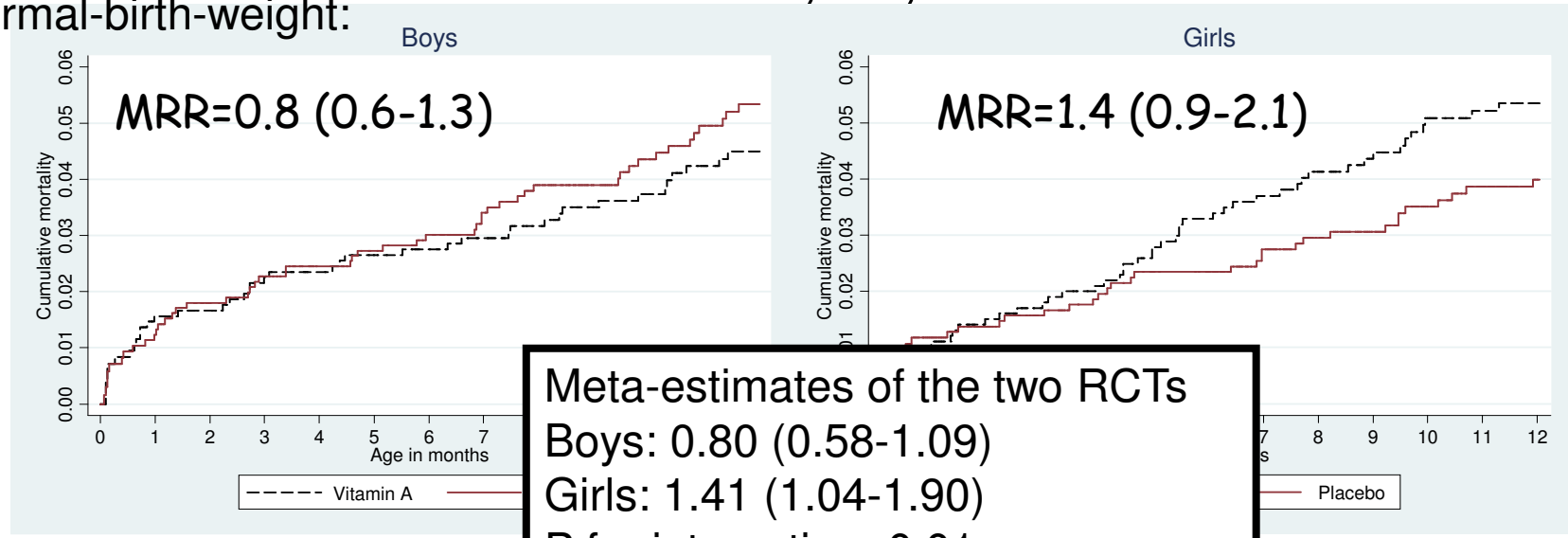
Annual mortality rates in African community studies in the 1970s and 1980s



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

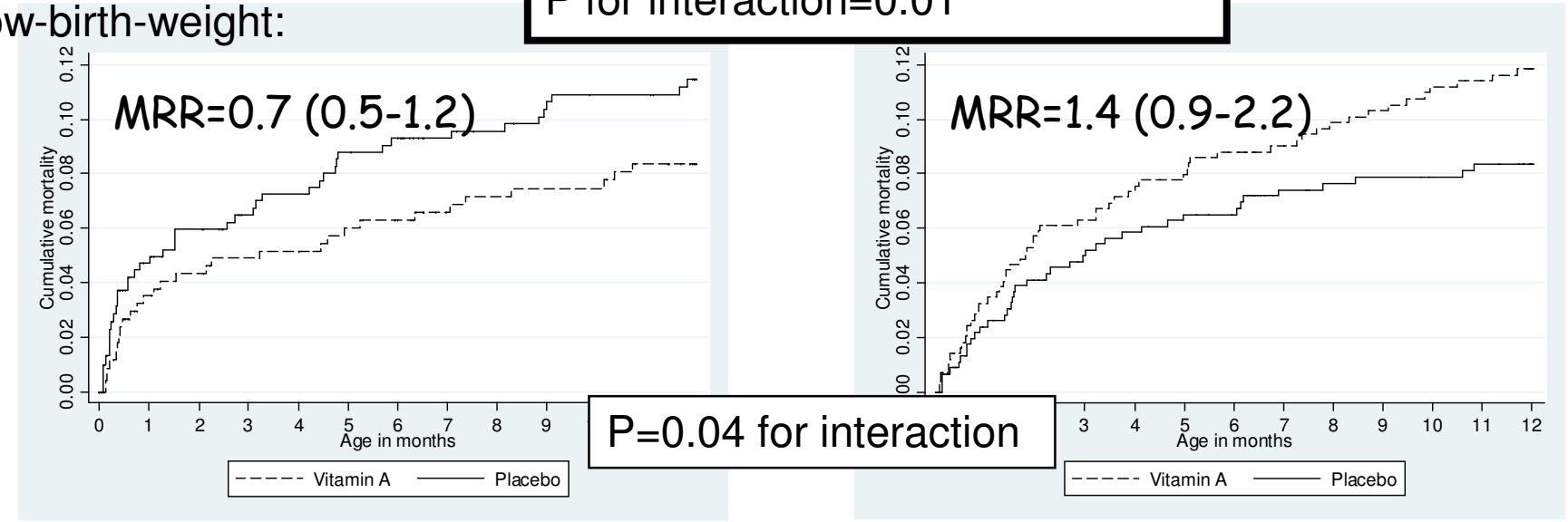
Vitamin A supplementation at birth and infant mortality by sex

Normal-birth-weight:



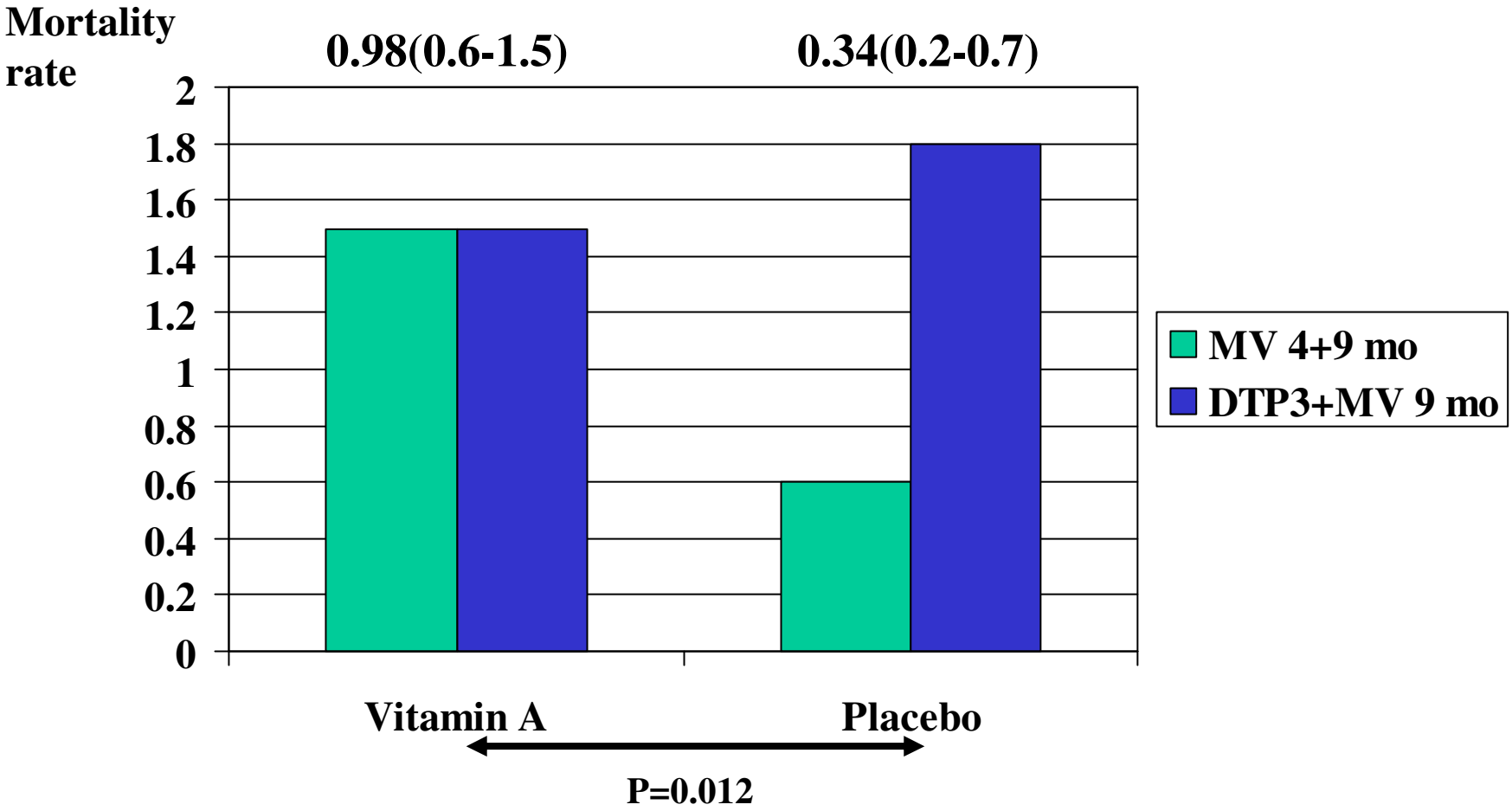
Meta-estimates of the two RCTs
Boys: 0.80 (0.58-1.09)
Girls: 1.41 (1.04-1.90)
P for interaction=0.01

Low-birth-weight:



P=0.04 for interaction

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

Vaccinations and child survival:

These effects may be unbelievable!

But they are there and we better face them:

- High-titre MV 2-fold increased mortality for girls
- Vitamin A interact negatively with DTP in Bissau and Ghana
- 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

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

Vaccinations and child survival: What is required?

We need ***better data*** on vaccination and other childhood inventions and campaigns

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

We need ***young scientists*** at the centres who can collect and analyse such data

=> These needs have defined the WG agenda

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

Vaccinations and child survival: 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: special teams for data collection; children under 2 or 3 years of age, 3-4 yearly rounds, birth form, verbal autopsy, SES and nutritional status, and documenting other interventions (vitamin A etc) and campaign

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

(we can come back)

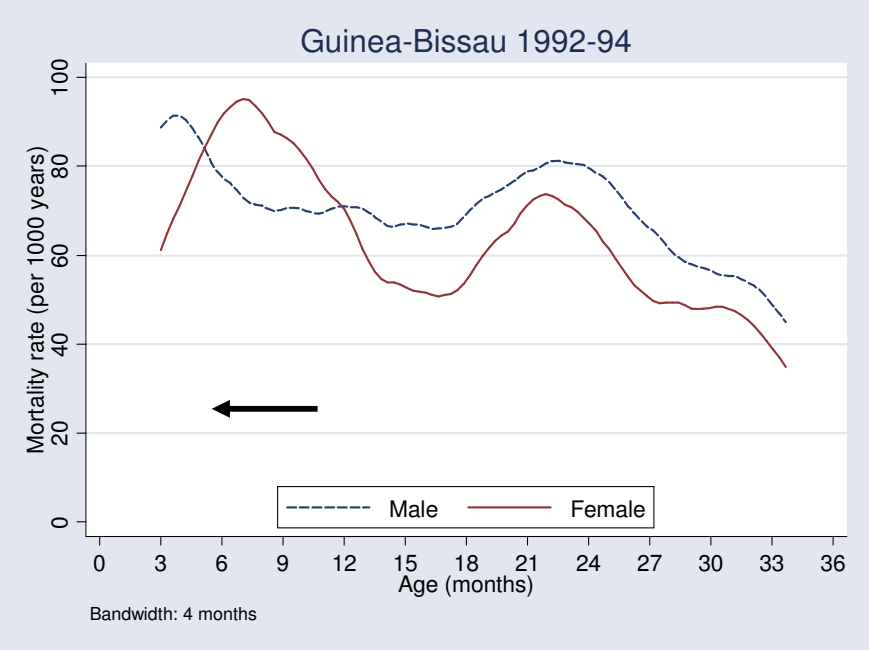
Vaccinations and child survival: EU: Multicentre study

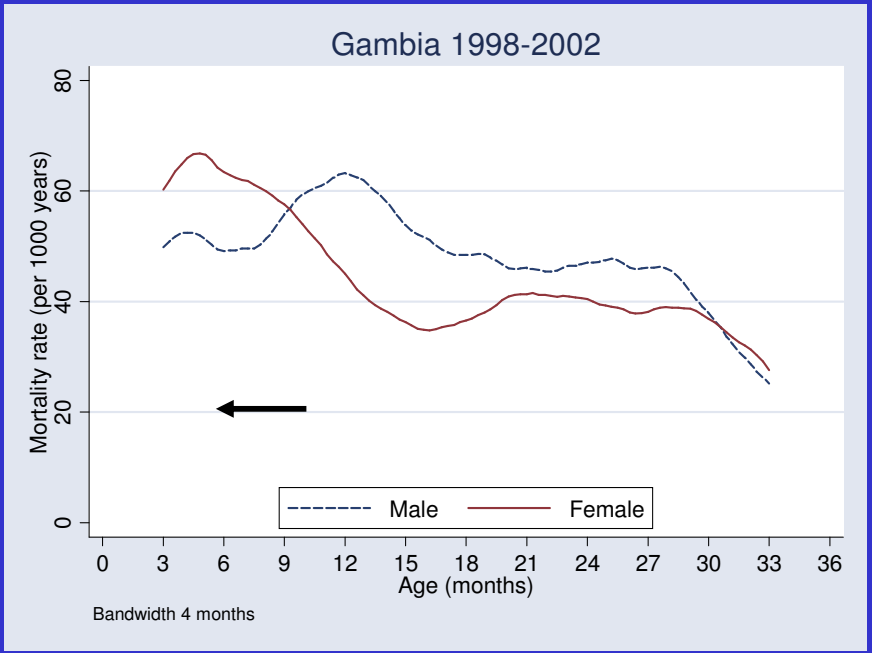
- **EU proposal: ”Optimising the impact and cost-effectiveness of existing child health intervention programmes for vaccines and micronutrients in low-income countries” (Navrongo, Nouna, Bandim)**
- **To support common data collection methodology and analysis of the impact of routine vaccinations and 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**

WG:Vaccinations and child survival

- **Analysis of existing data 2007-2010**
  - **Farafenni => Routine vaccinations and child mortality (Vaccine 2007)**
  - **Navrongo => Vaccines and vitamin A (Am J Clin Nut 2009)**
  - **Draft: Paul Welaga: Non-specific of routine vaccinations: testing the hypothesis with data from Navrongo**
  - **Started analysis of the first cross site paper : The impact of nutritional status on time to vaccination (Vadu, Bissau, Malawi)**
  - **Been promissed more data from Vadu, Matlab, Rufiji – (hope to report next year)**

Analysis from Farafenni (Vaccine 2007)





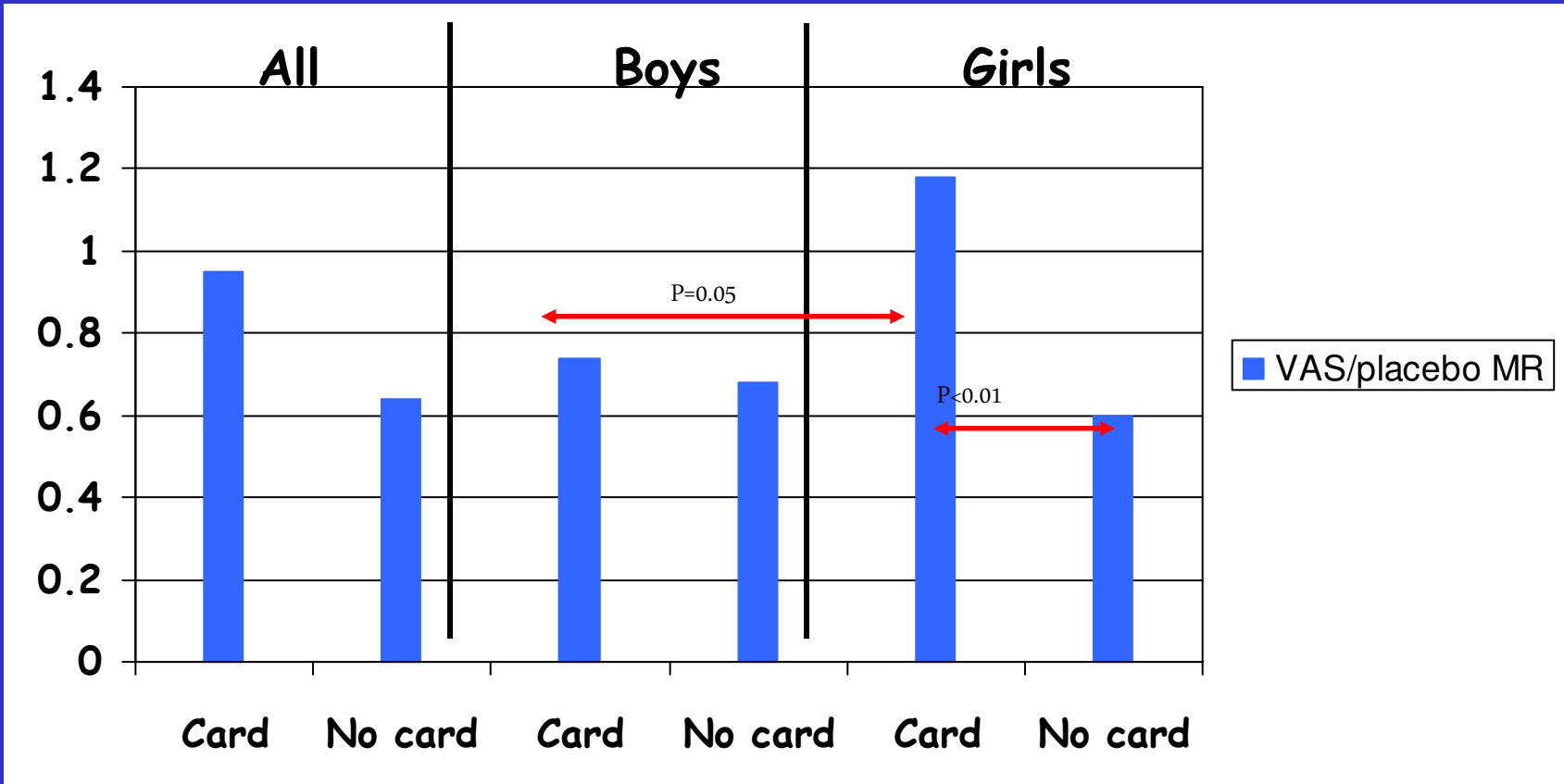
Showed the same changes in relative female-male mortality as in Bissau

DTP age (3-8 months) – higher female than male mortality

MV age (9-17 months) – lower female than male mortality

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

WG:Vaccinations and child survival

PhD network: Ballabgarh, Navrongo, Nouna, Nairobi, Kintampo, Bandim

Multi-centre trial: Navrongo, Nouna, Bandim

Analysis of existing data: Navrongo, Vadu, Matlab, Rufiji – we can do a lot more with existing data

Interested parties: Iganga, Gambia, Dodowa, Ifakara?

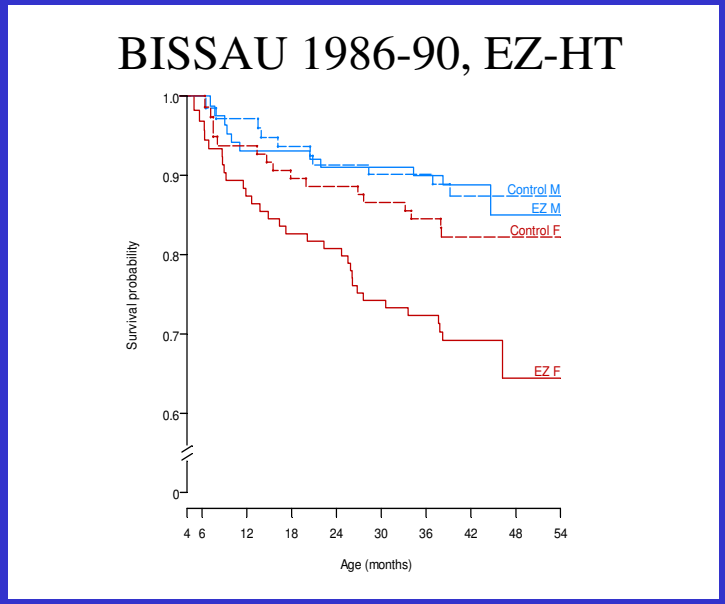
Other initiatives?

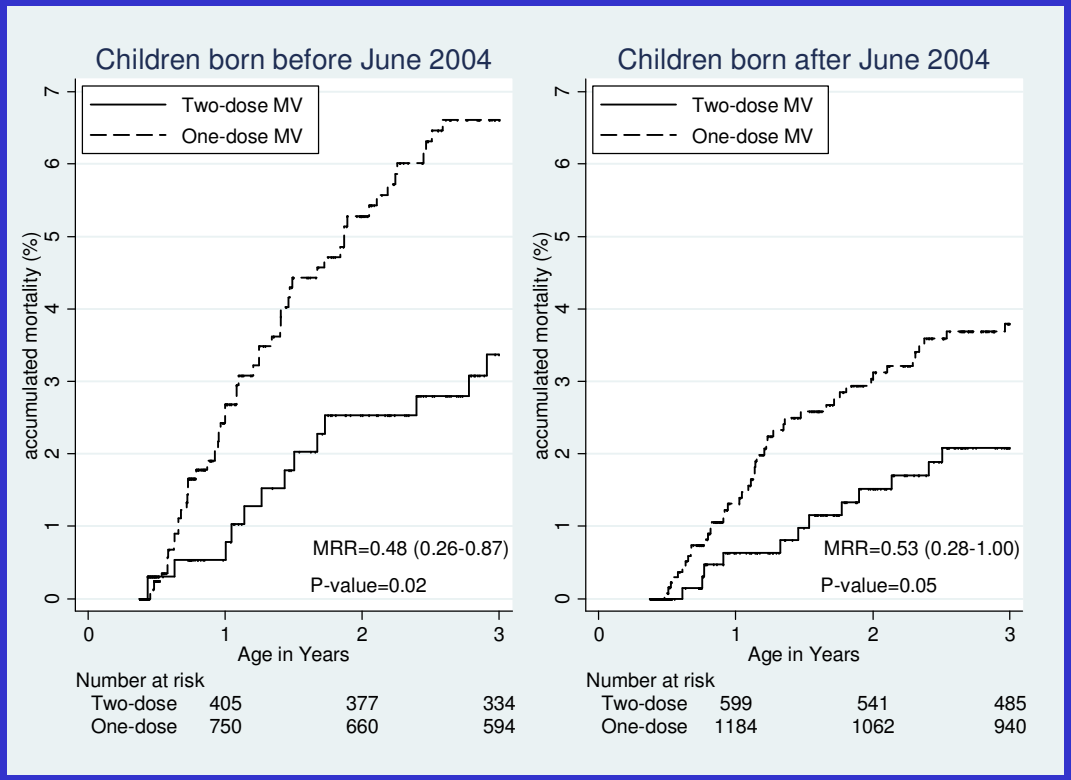
Working group meeting Wedn 16-17.30

Vaccinations and child survival:

- The area is obviously controversial because it questions many of the current assumptions
- However, it also has huge potential for improving child survival
- I hope more INDEPTH centres will pursue the area

1986-90 RCT High-titre MV 2003-2009 RCT two-doses MV





- **EZ high-titre MV was fully protective against measles => negative non-specific effect**
- **Two-dose standard MV at 4½ and 9 mo was fully protective against measles => beneficial non-specific effect**

Non-specific effects of vaccine on child survival

Vitamin A and early measles vaccination:

Morality 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