

MDG4: The evidence base for health interventions

The ultimate goal is to reduce child mortality



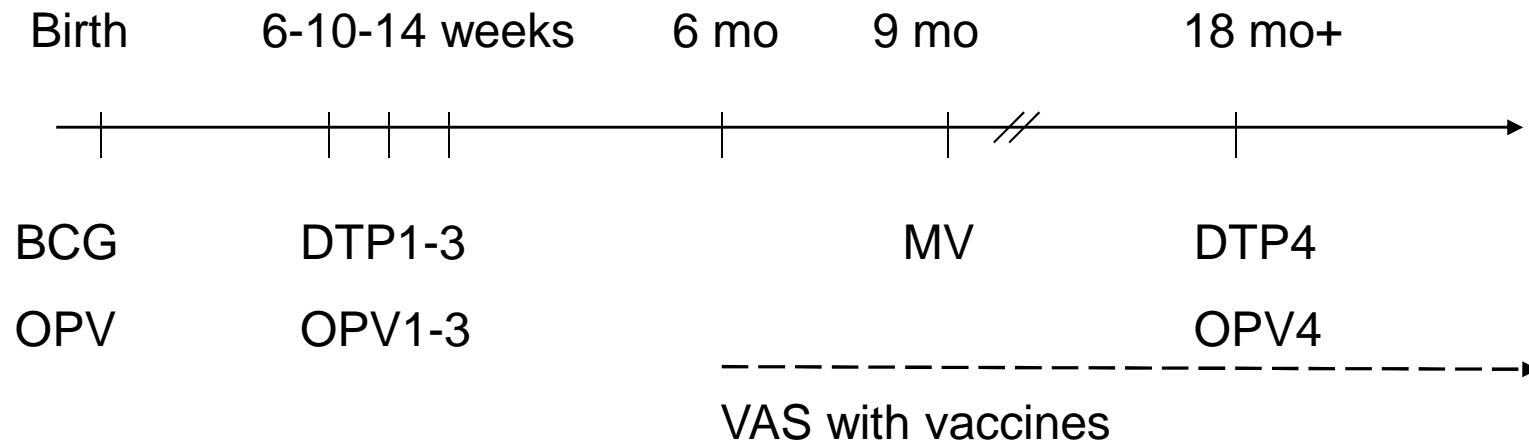
Peter Aaby, Bandim Health Project, Bissau - 1978-2011

Context

- Worldwide an estimated 9.2 million children under the age of five die every year
- Two thirds of the deaths — over 6 million deaths every year — are preventable
- WHO/UNICEF recommend and distribute interventions like vaccines and vitamin A supplements in low-income countries



WHO recommendations for child health interventions



BCG=Tuberculosis vaccine;

DTP=Diphtheria-Tetanus-Pertussis + Hepatitis B+H. Influenza vaccine=Penta;

MV=Measles vaccine; VAS=Vitamin A supplementation

Greetings from Gates: The Value of Vaccines

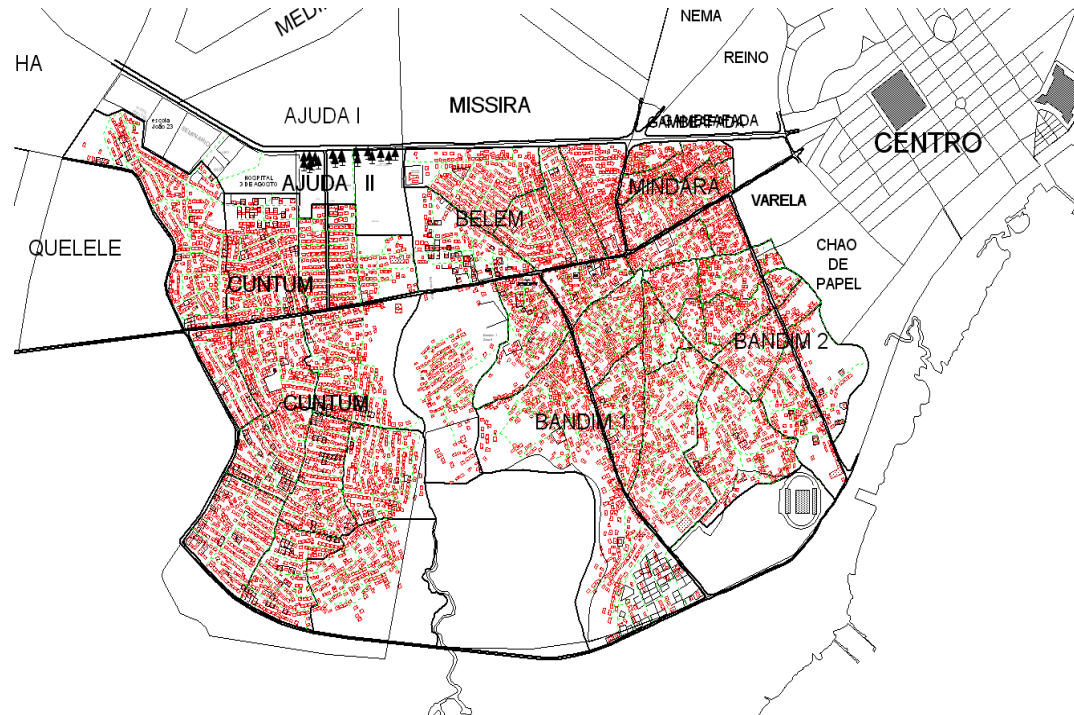
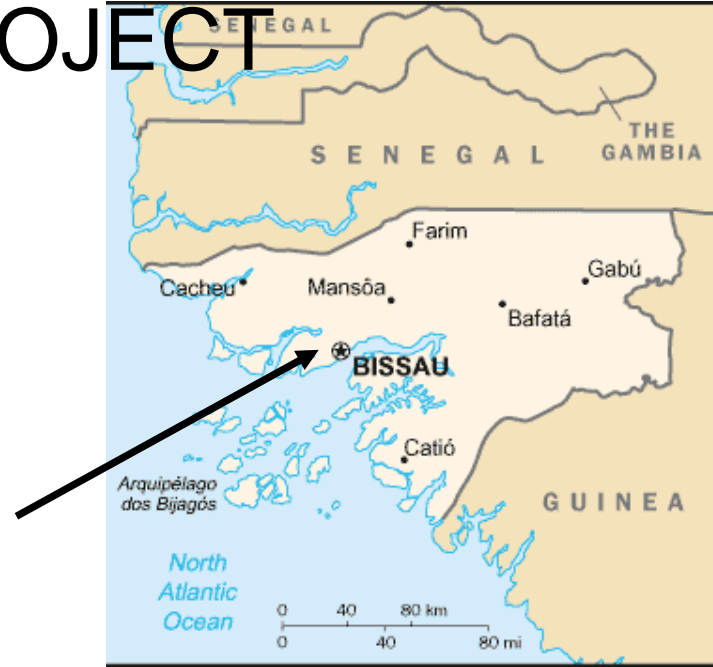


<http://www.gatesfoundation.org/annual-letter/2011/Pages/videos.aspx#video=/annual-letter/2011/Pages/value-of-vaccines-montage.aspx&pager=0&filter=&autostart=true>

Vaccines are miracles

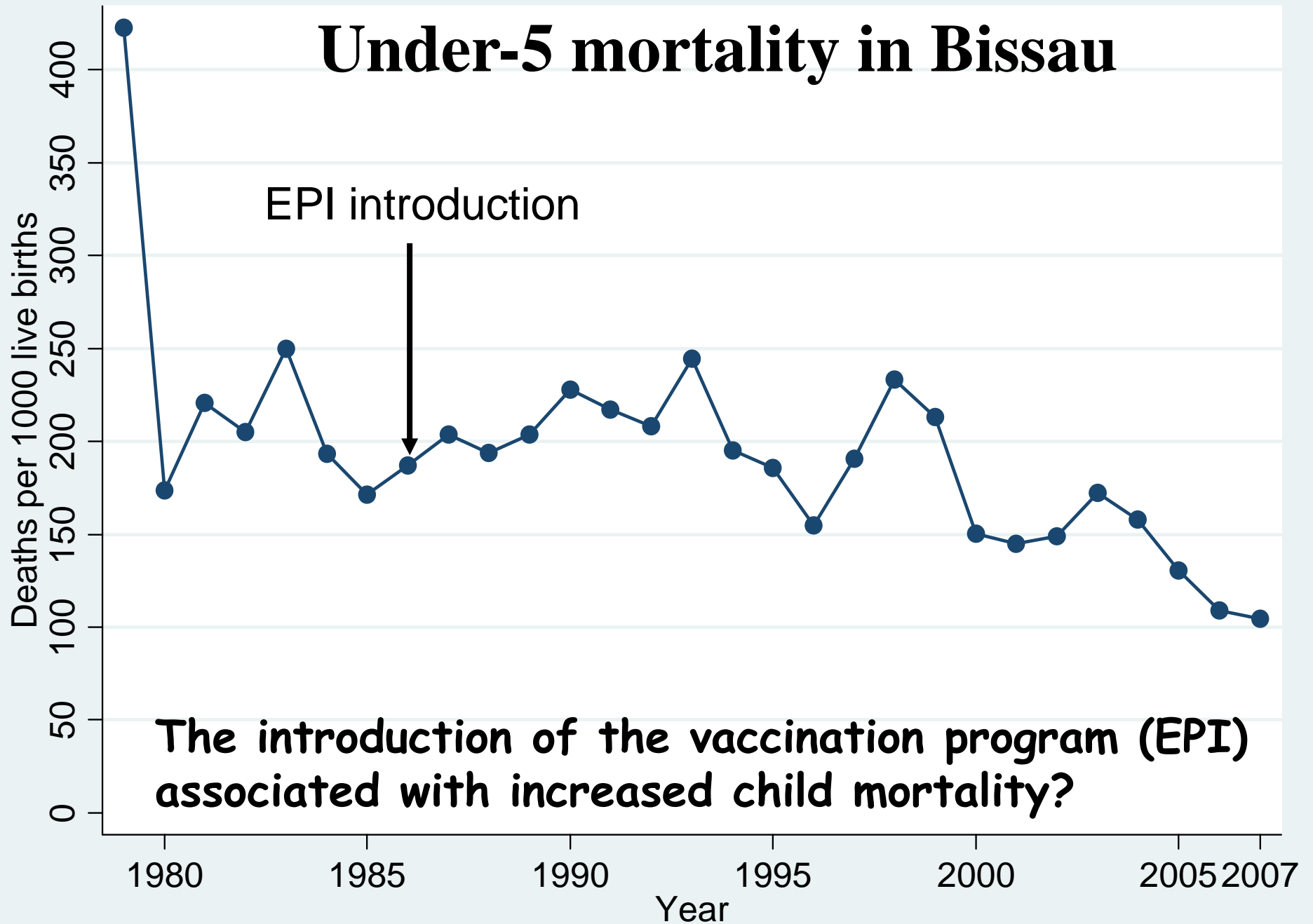
- Main research questions are
 - Deliver the vaccines we have
 - Develop the ones we dont
- I disagree

BANDIM HEALTH PROJECT



1978-2011

Under-5 mortality in Bissau



Example of how vaccination policies are made: Measles vaccine at age 9 months



Measles vaccination at 9 mo of age - established in 1970s

Projected reduction in measles in Kenya - 1974-1981

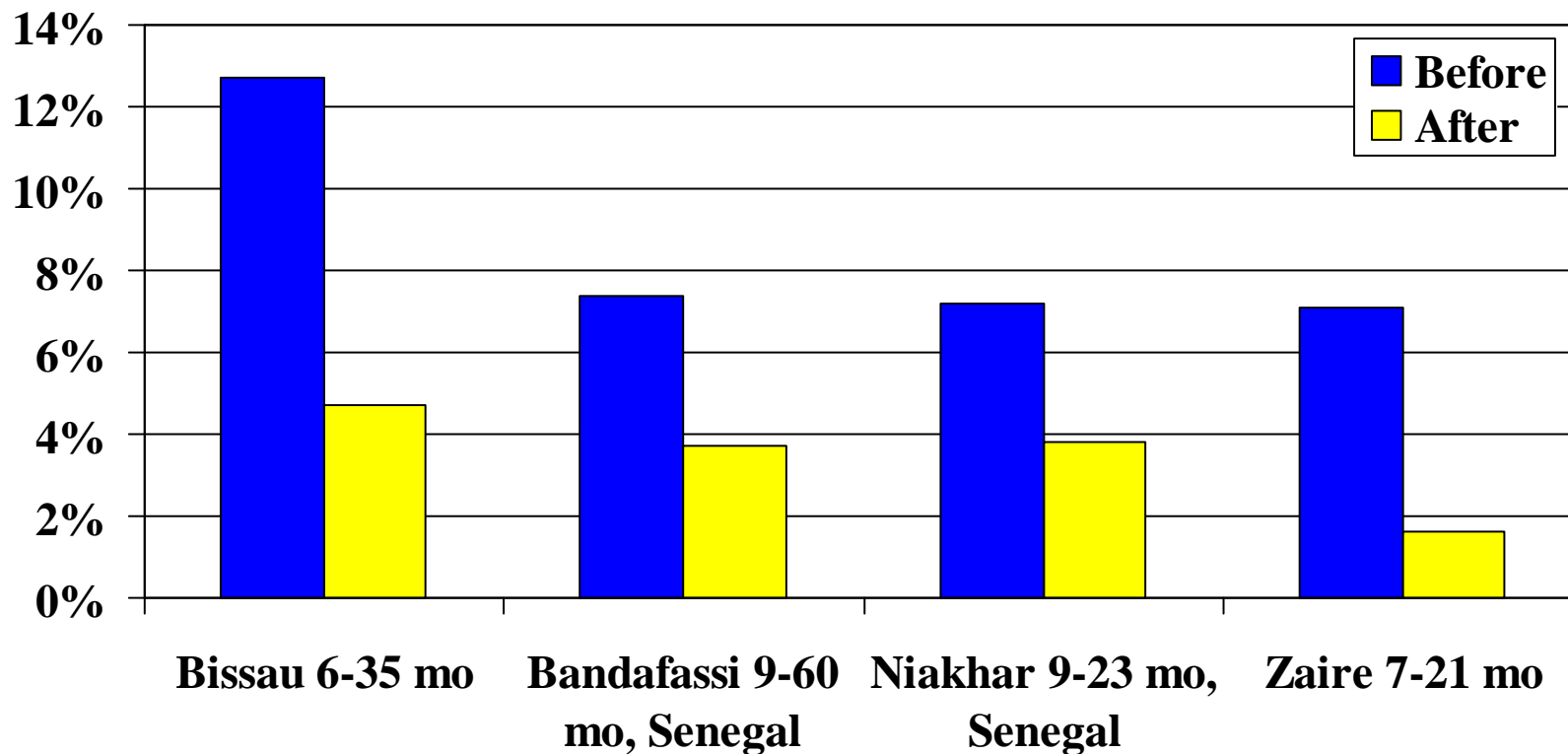
Age	Incidence in unvaccinated	Conversion to measles vaccine	Prevented cases	Unvaccinated Cases	Vaccine Failure	Deaths by measles/1000	Deaths by measles/1000
5	1	35%	35%	0%	65%	26	4.3
6	3	52%	51%	1%	48%	19.6	4.2
7	6	72%	69%	3%	28%	12.4	4.3
8	10	86%	79%	6%	15%	8.4	5.8
9	14	95%	84%	10%	7%	6.8	8.5

Based on 6 assumptions:

- no antibodies are fully susceptible - but 50% protection;
- vaccinated and unvaccinated same severity - but 3-fold difference in mortality;
- same mortality for infants and older children - but 2-fold difference;
- had to be 1-dose policy - but two-dose could have worked

No study of mortality was made to test the assumptions

Introduction of measles vaccination
Before-after measles vaccination (MV):
Annual mortality rates in African community studies



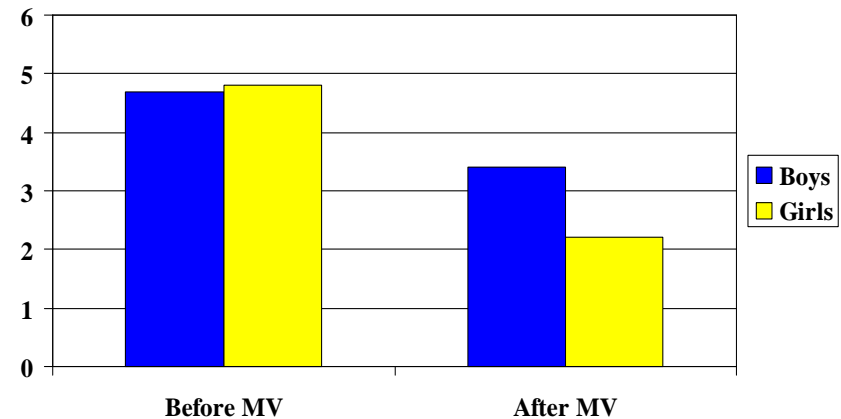
**Bissau: MV at 6 mo introduced 1979 - 3-fold reduction
Measles infection may have caused 10-15% of deaths!
=> A beneficial effect unrelated to measles prevention?**₁₀

Male and female mortality before and after introduction of MV in Senegal

Bandafassi 1981-1988



Niakhar 1985-1988

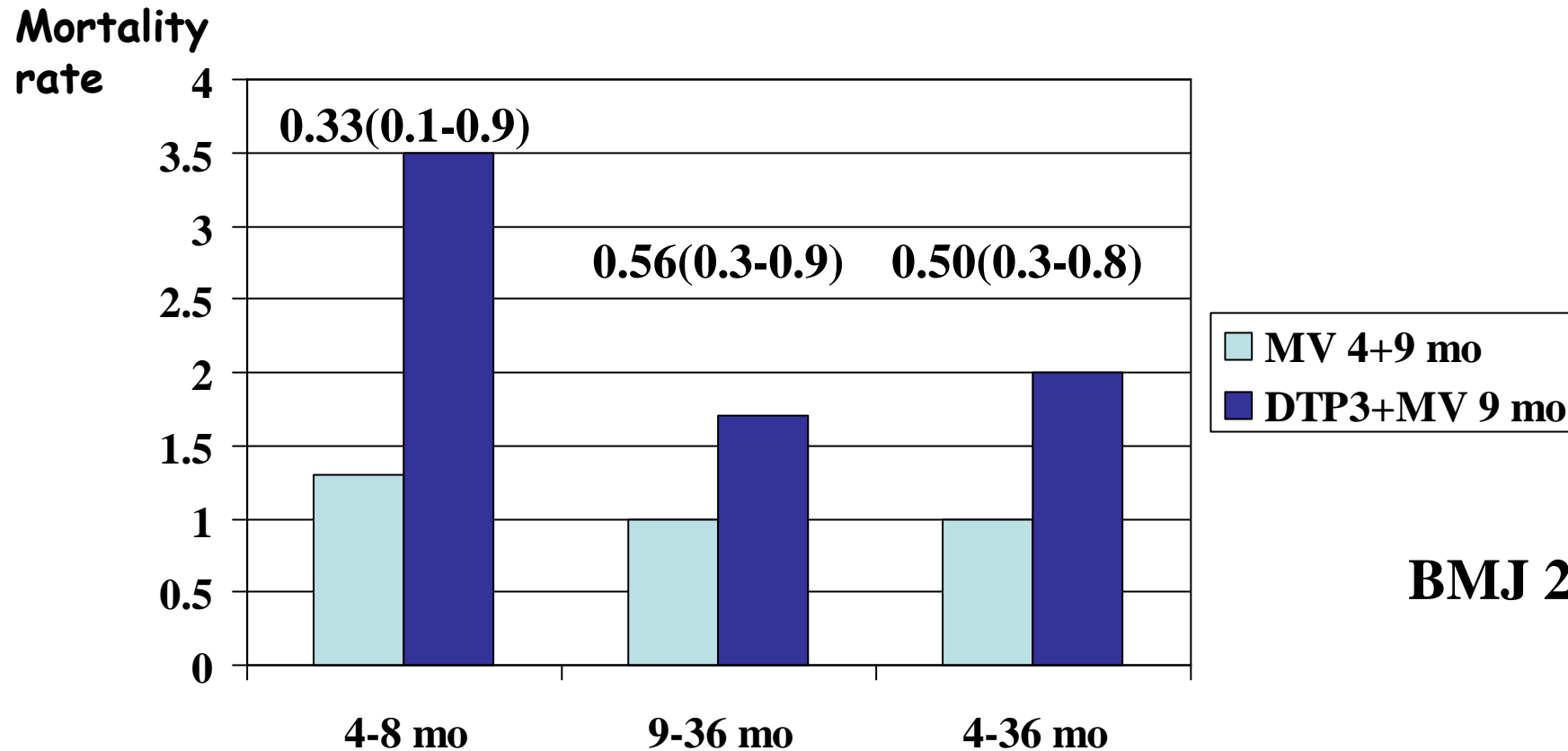


F/M 1.04 (0.9-1.3) 0.65 (0.4-1.0)

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

MV particularly good for girls

Randomised clinical trial(RCT) 2003-09: MV at 4+9mo vs MV at 9mo
(3402 infants with no Vitamin A at birth)



BMJ 2010

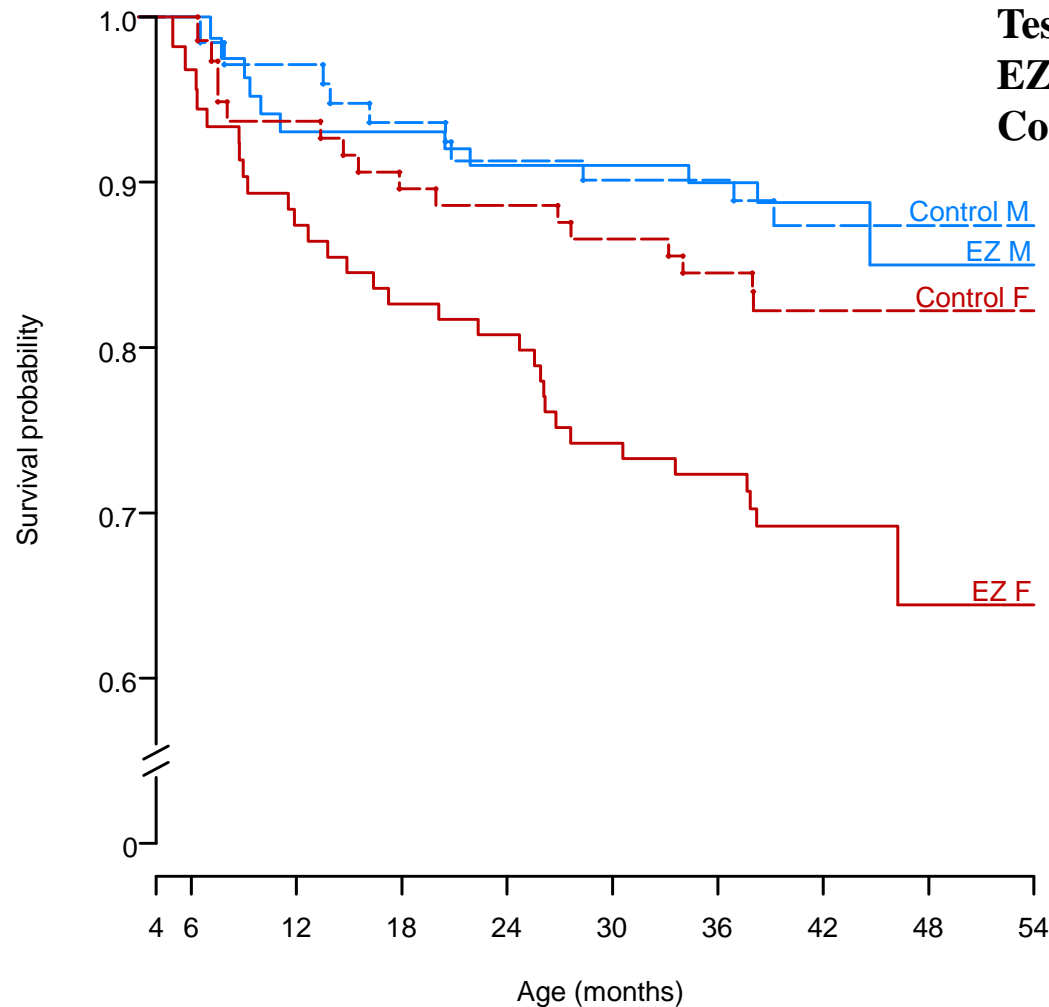
Reduction in overall mortality:

Two MV at 4½ and 9 mo: 50% (22-68) Without measles 45% (14-65)

The best vaccine against child mortality?

=> **Beneficial non-specific effect (NSE)**

But it may go wrong: *Introduction of high-titre MV in 1989 (HTMV)*

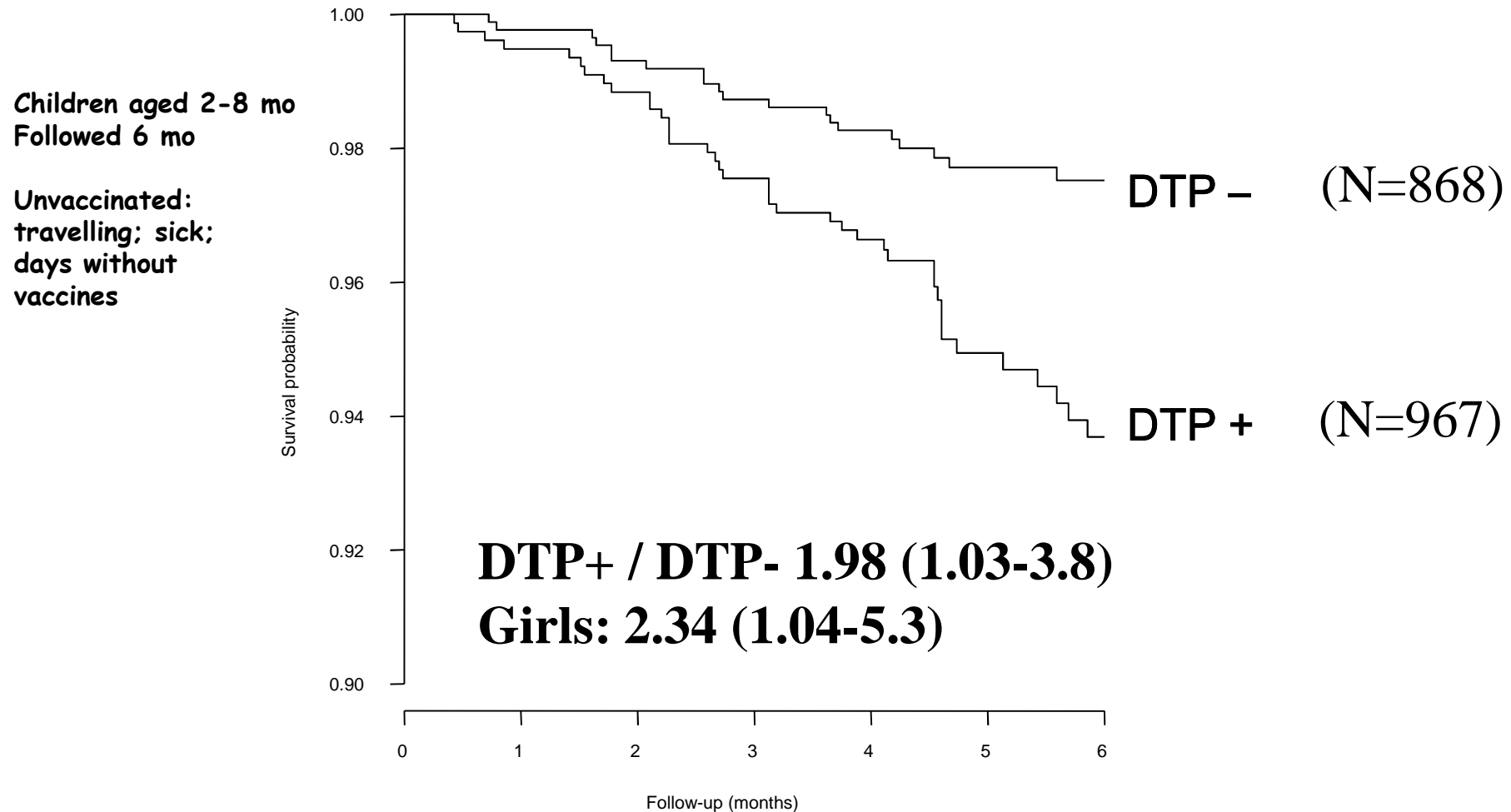


Tested in Bissau, 1986-90
EZ=HTMV at 4 mo; IPV at 9 mo
Control= IPV at 4 mo; MV at 9 mo

The observation was repeated in Senegal and Haiti and WHO had to withdraw the vaccine in 1992

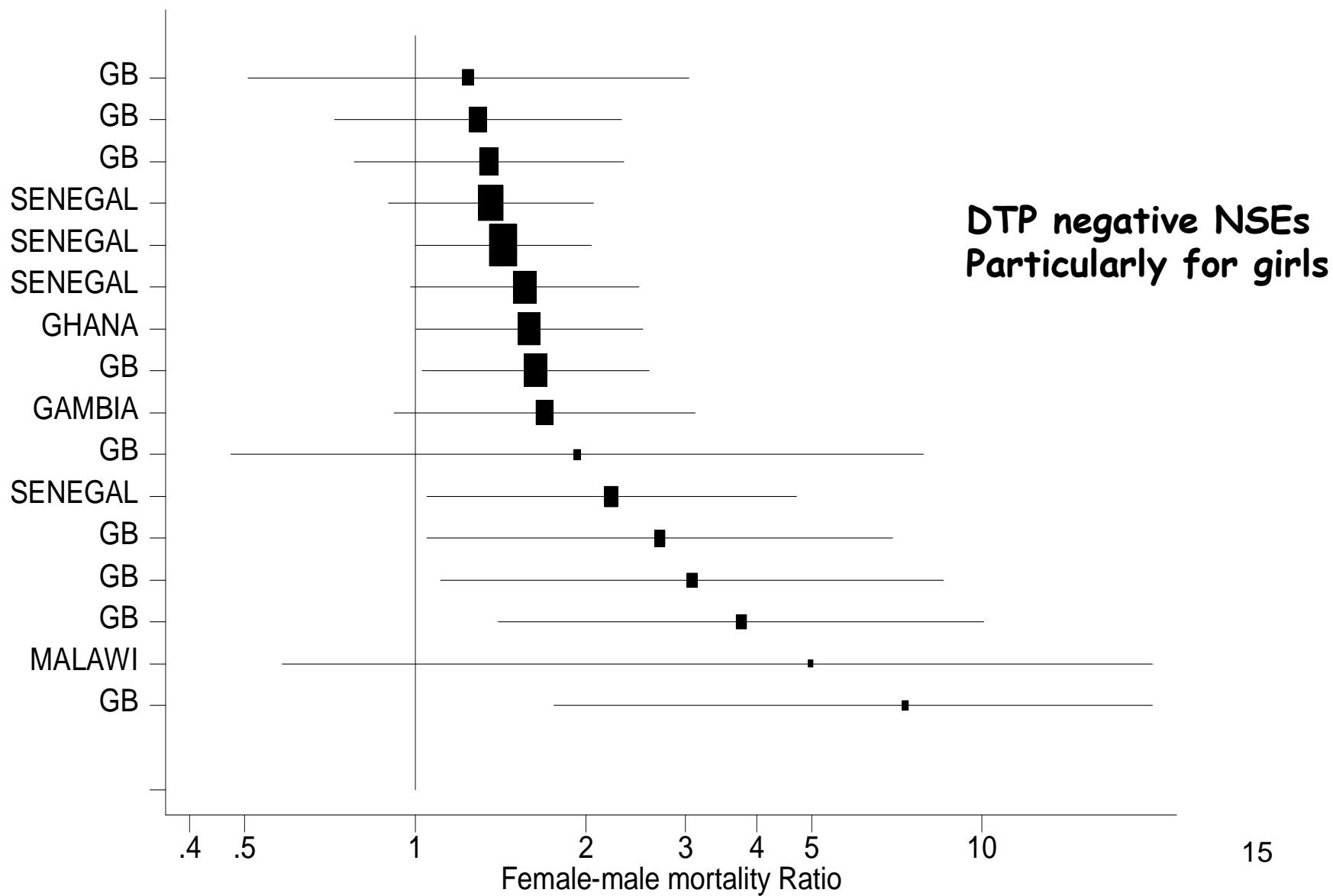
⇒ **HTMV was protective => negative non-specific effect**
(Mortality studies were not planned by WHO)

Introduction of diphtheria-tetanus-pertussis (DTP) Rural areas of Guinea-Bissau 1984-87



Only study of introduction of DTP => negative non-specific effects¹⁴

Female/male MR for DTP-vaccinated children



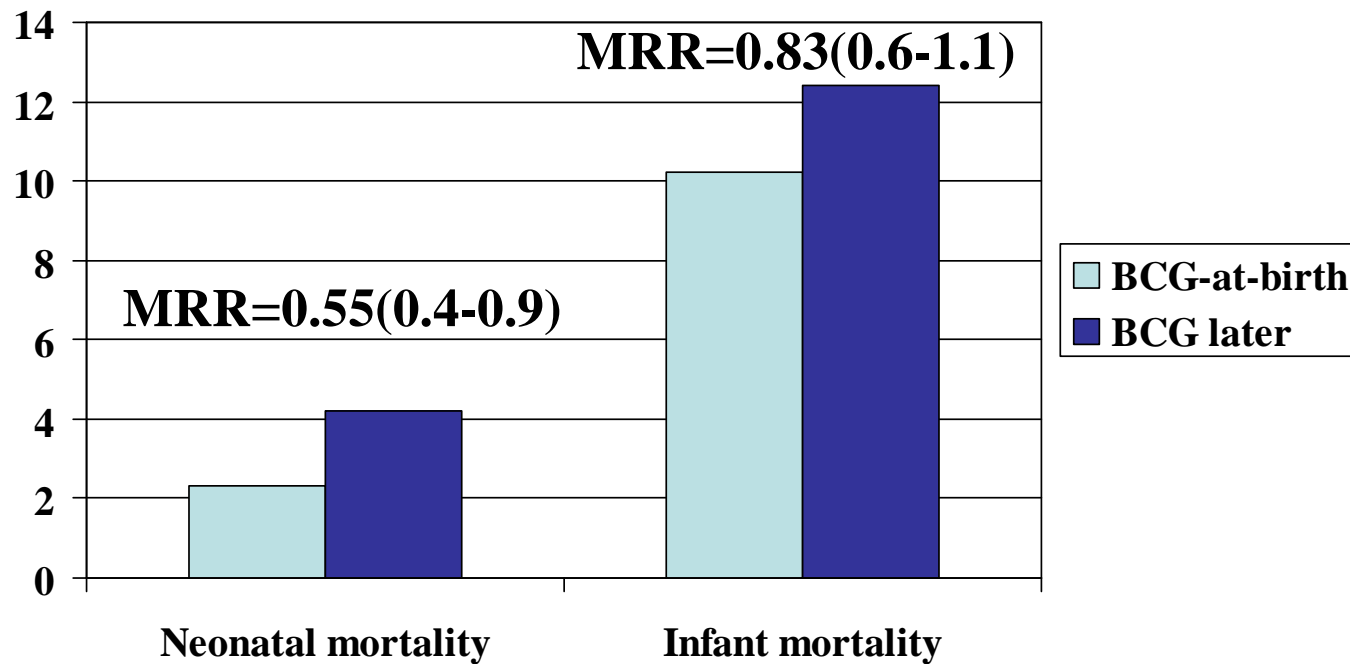


**When BCG developed in the 1920s suggestions of beneficial effect
But BCG not tested in modern time; considered ineffective vaccine
BCG not given to LBW children**

=> RCT justified

- **We recruited LBW children at maternity ward – 11/2004-1/2008**
- **Randomising to BCG-at-birth or later (as normal)**

RCT of BCG-at-birth to LBW children: 2004-2008



45% reduction in neonatal mortality -

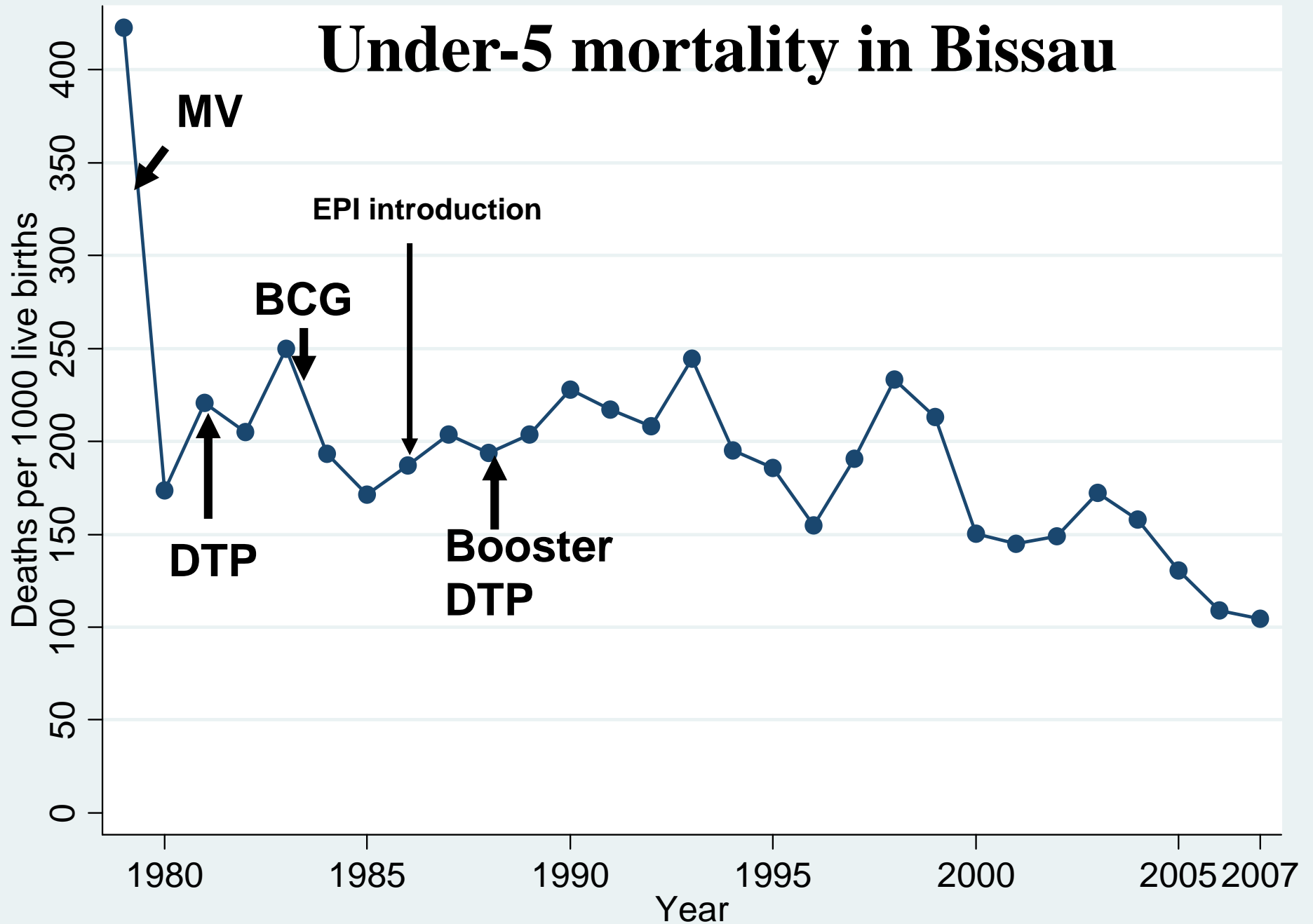
Reduction in neonatal sepsis and respiratory infections

Not prevention of TB => Beneficial NSE of BCG

2008-11: 49% reduction in neonatal mortality

JID 2011

Under-5 mortality in Bissau



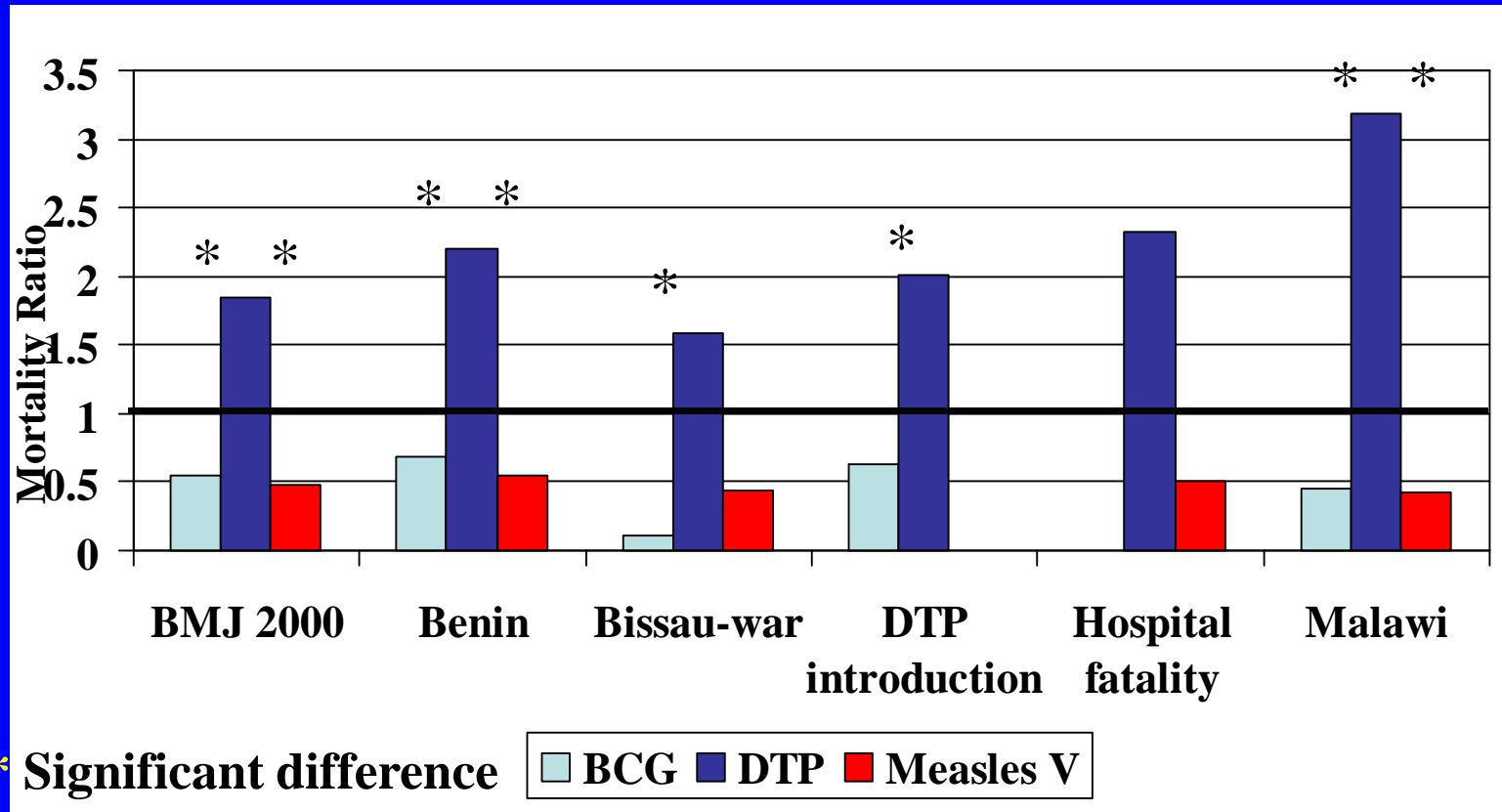
Vaccines are miracles

Studies were not made to test impact on mortality of BCG, DTP, MV in low-income countries. Policy based on assumptions

Global/international health failed 3 major contradictions:

- Vaccines have more general or non-specific immune effects (NSE) affecting susceptibility to unrelated infections - negatively or positively
- The NSE are often different for boys and girls
- Vaccines and other immune interventions may interact

Contradiction I: Contrasting NSE of BCG, DTP, and MV

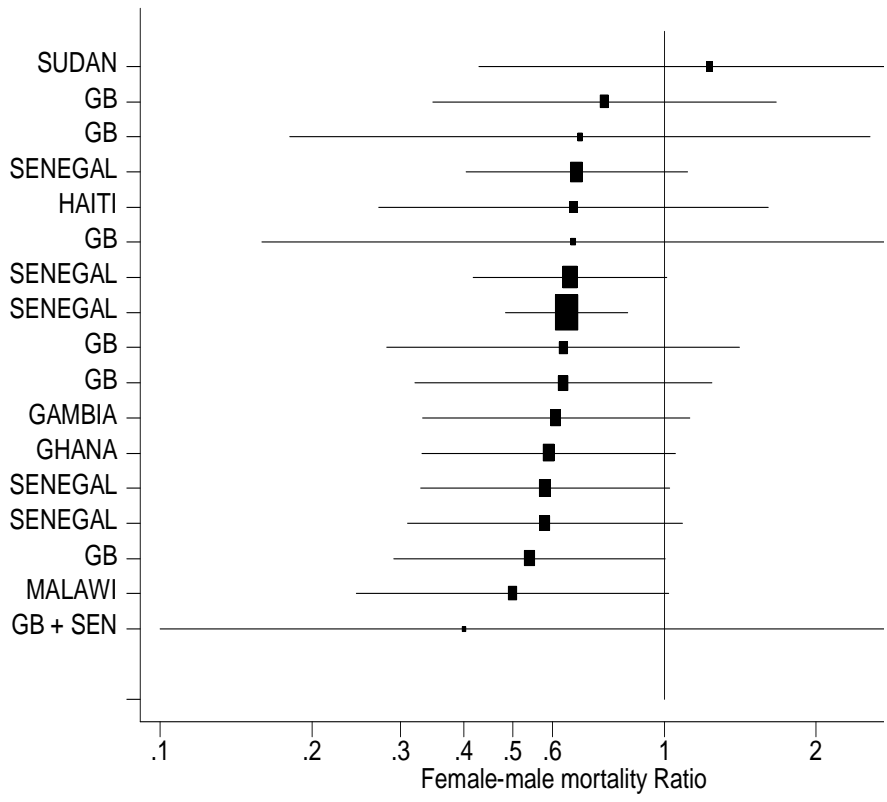


Live vaccines have beneficial NSE: BCG, MV, OPV and Smallpox vaccine

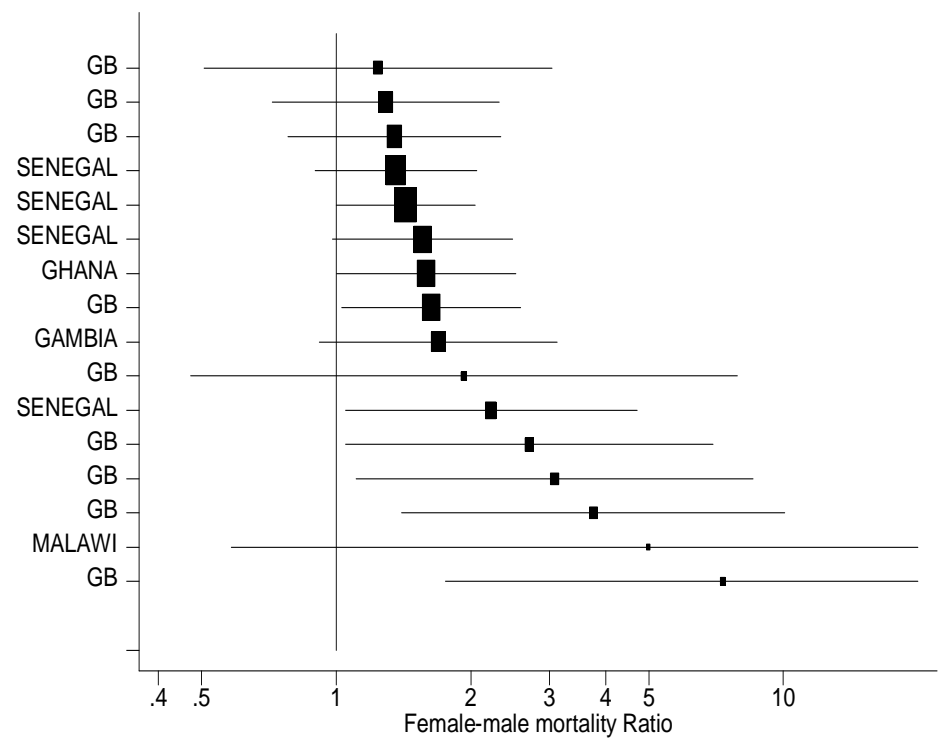
Inactivated vaccines have negative NSE: DTP, HBV, IPV

Contradiction II: NSE differ for boys and girls

F/M mortality ratio Measles-vaccinated

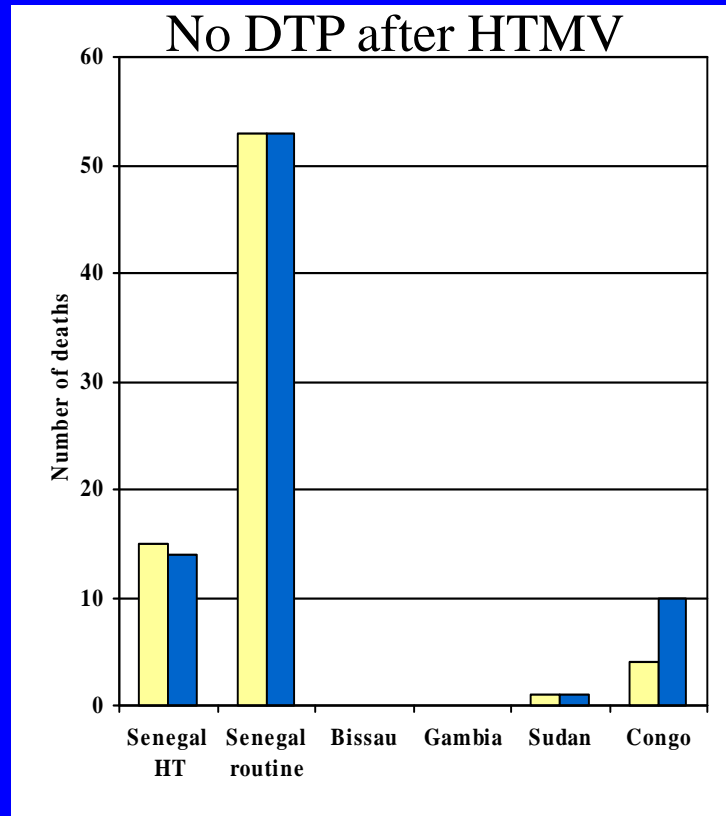


F/M mortality ratio DTP-vaccinated

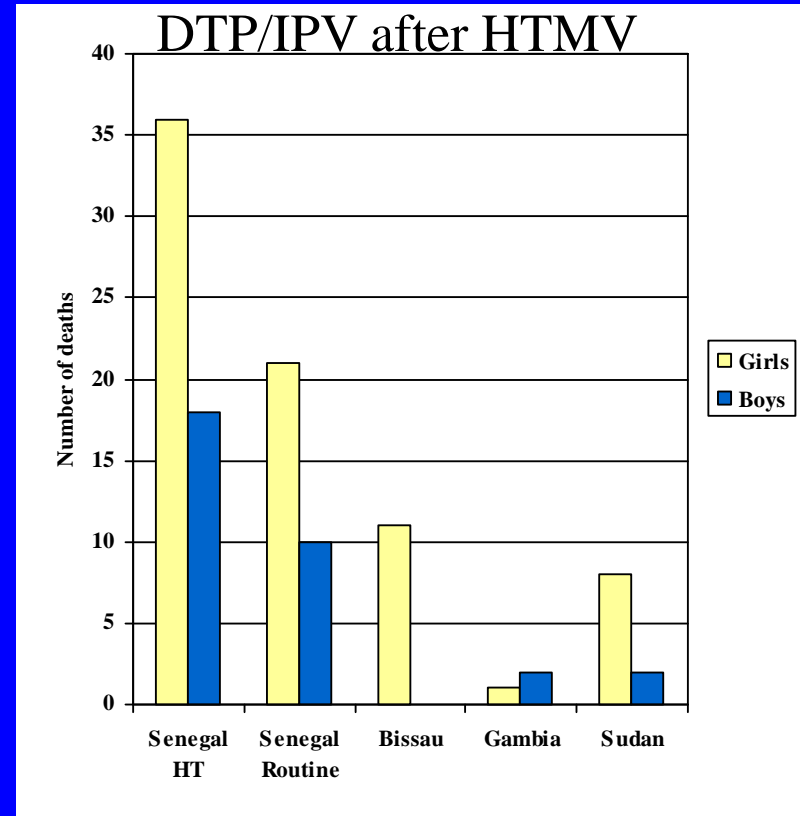


The immune system can be enhanced or be deregulated

Contradiction III: Immune-stimulatory interventions interact - HTMV and DTP!



F/M ratio: 0.96 (0.7-1.3)



F/M ratio: 1.93(1.3-2.8)

**HTMV was withdrawn for the wrong reason.
The real problem was DTP/IPV after MV!**

Lancet 2003

Vaccines are miracles

The millennium goal for child mortality

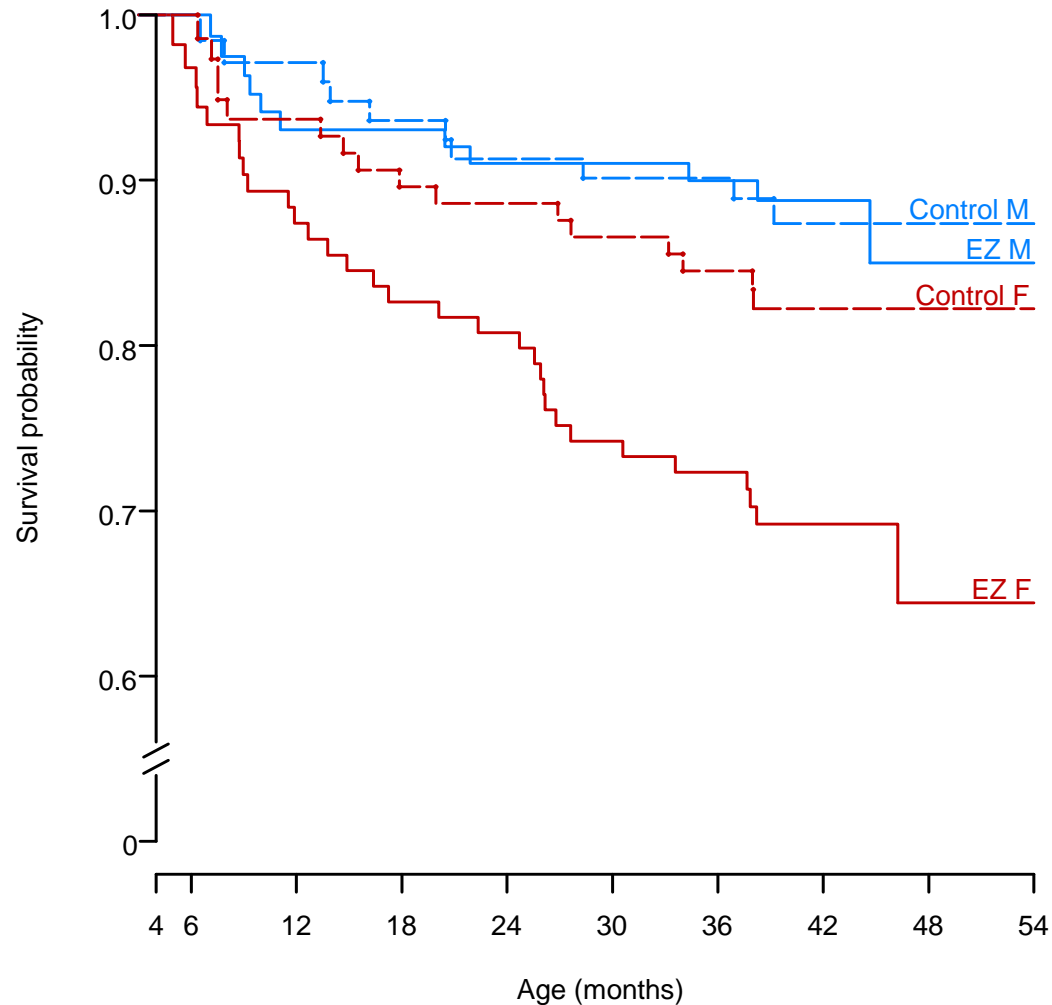
We could have done a much better job if the *beneficial* NSE of vaccines had been considered:

- All children should have received BCG at birth
- not delayed as happens now (median $1\frac{1}{2}$ months)
- Far more could have been saved with early 2-dose MV
-

However, vaccines and vitamin A can also deregulate the immune system and cause increased overall mortality

Catch-22: We can not test what is already policy!

Being wrong I: DTP after HTMV increased mortality

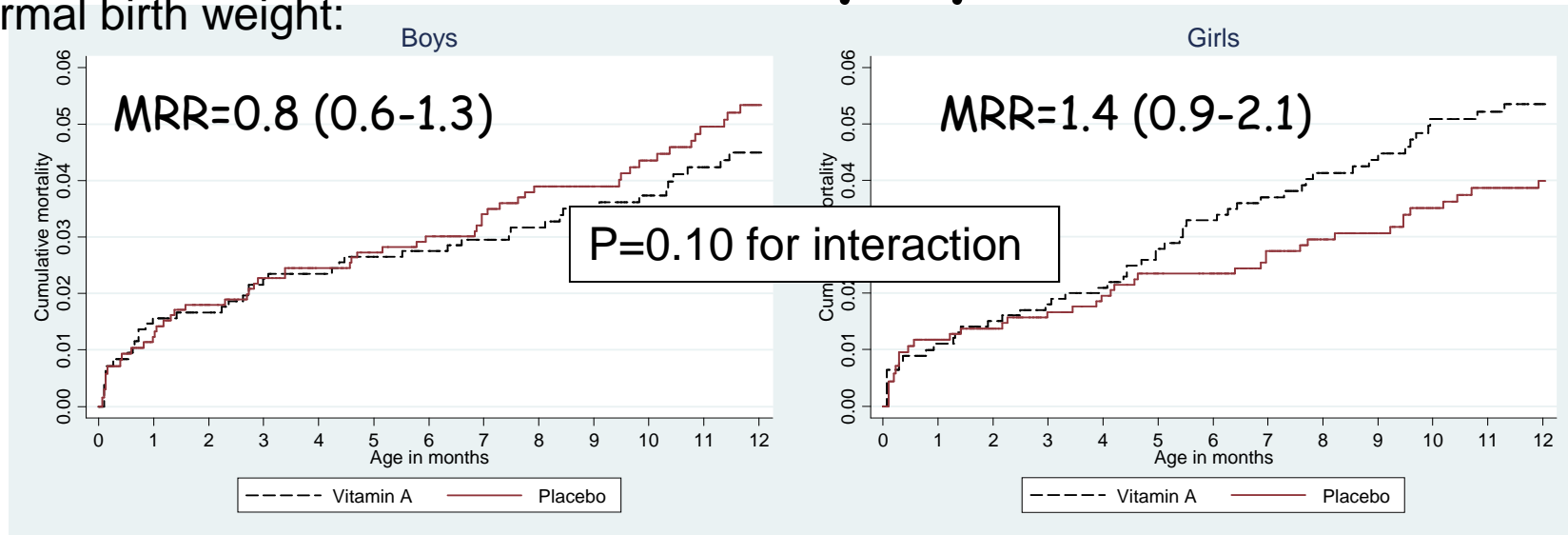


The observation was repeated in Senegal and Haiti and WHO had to withdraw the vaccine in 1992

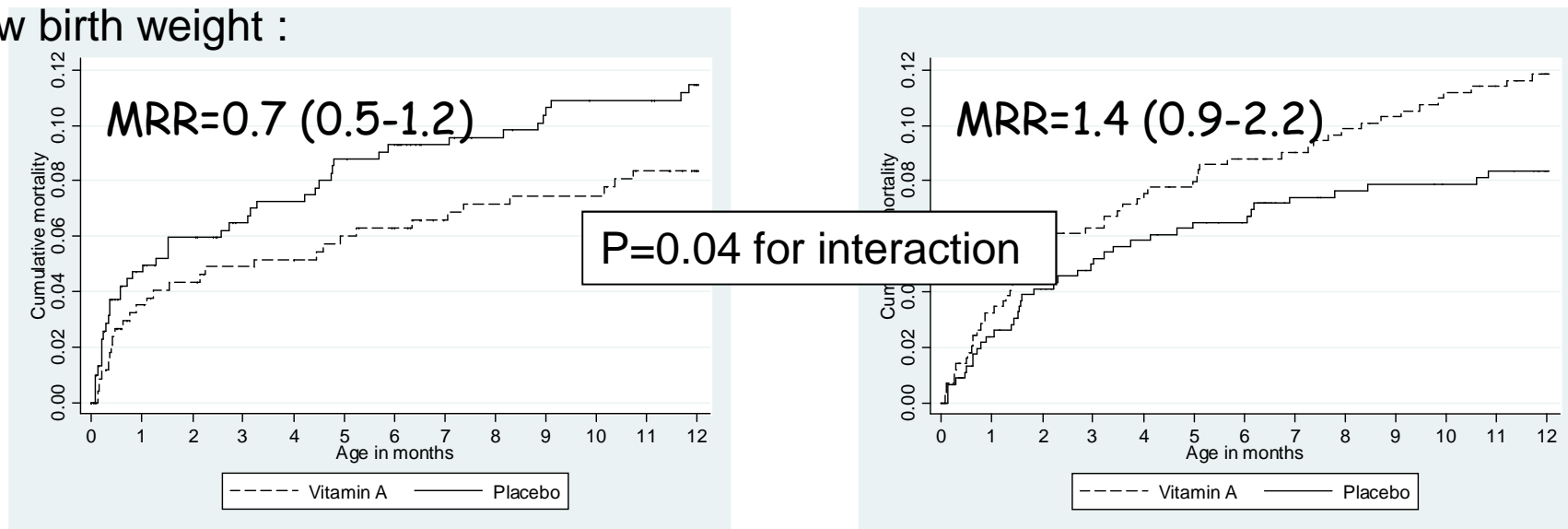
**Meta-analysis of African HTMV studies:
33% increased mortality between 4 mo and 5 years
=> at least $\frac{1}{2}$ mill additional deaths in Africa/year**

Being wrong II: Neonatal Vitamin A vs placebo: mortality by sex

Normal birth weight:

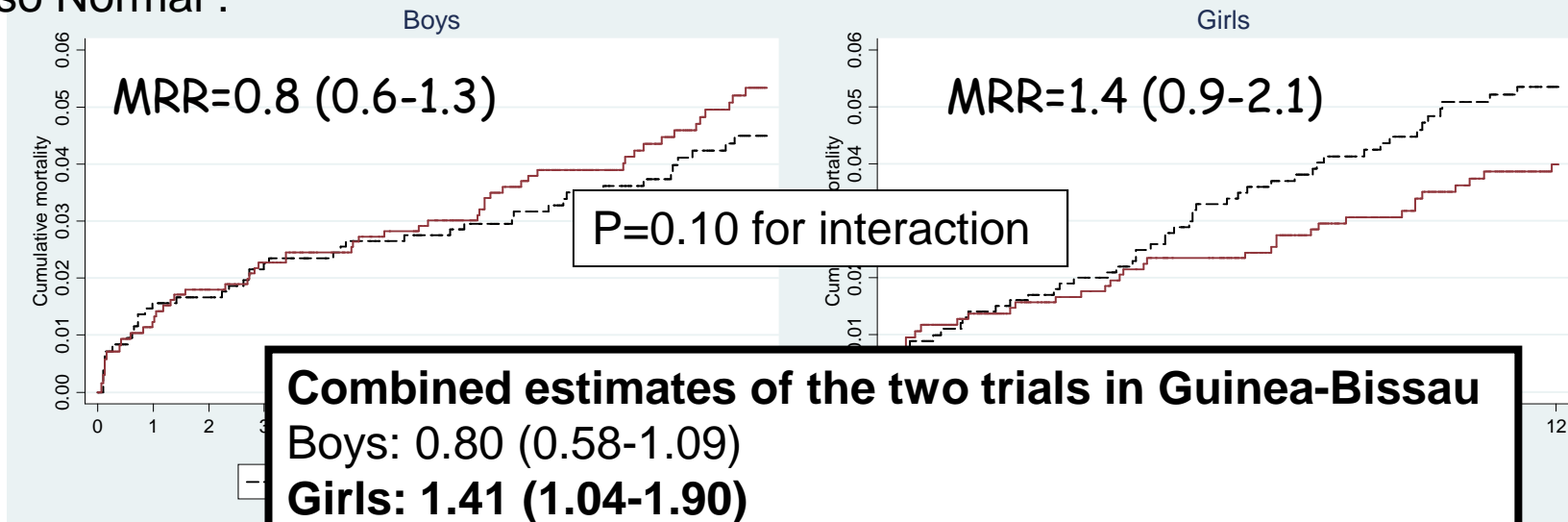


Low birth weight :

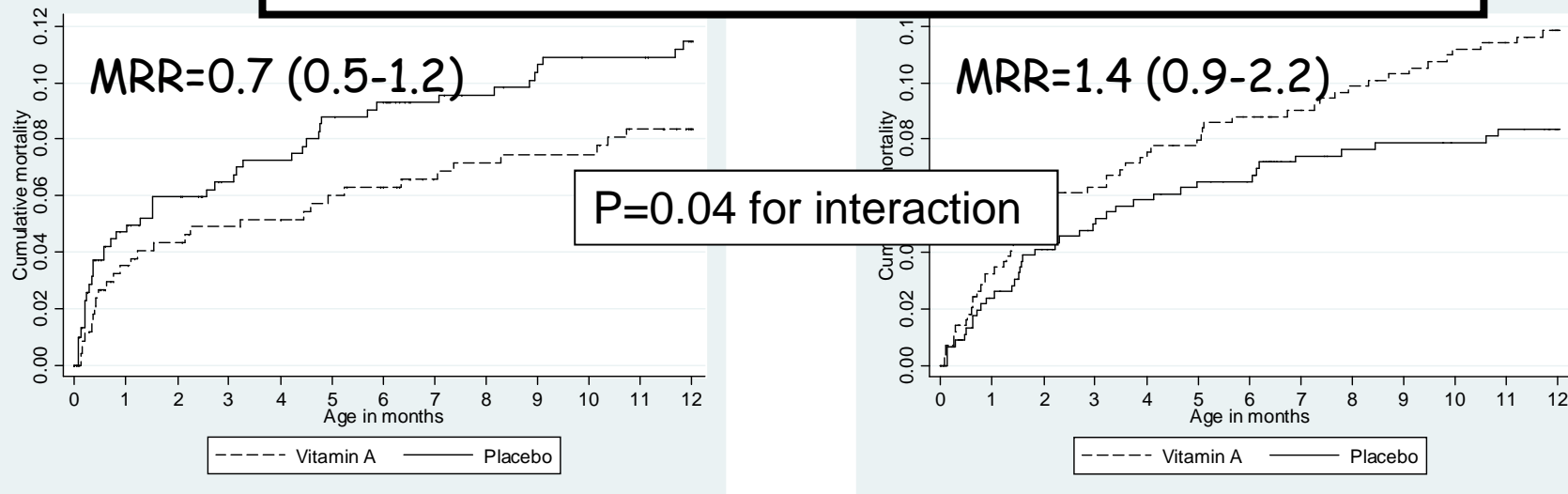


Being wrong II: Neonatal Vitamin A vs placebo: mortality by sex

Peso Normal :



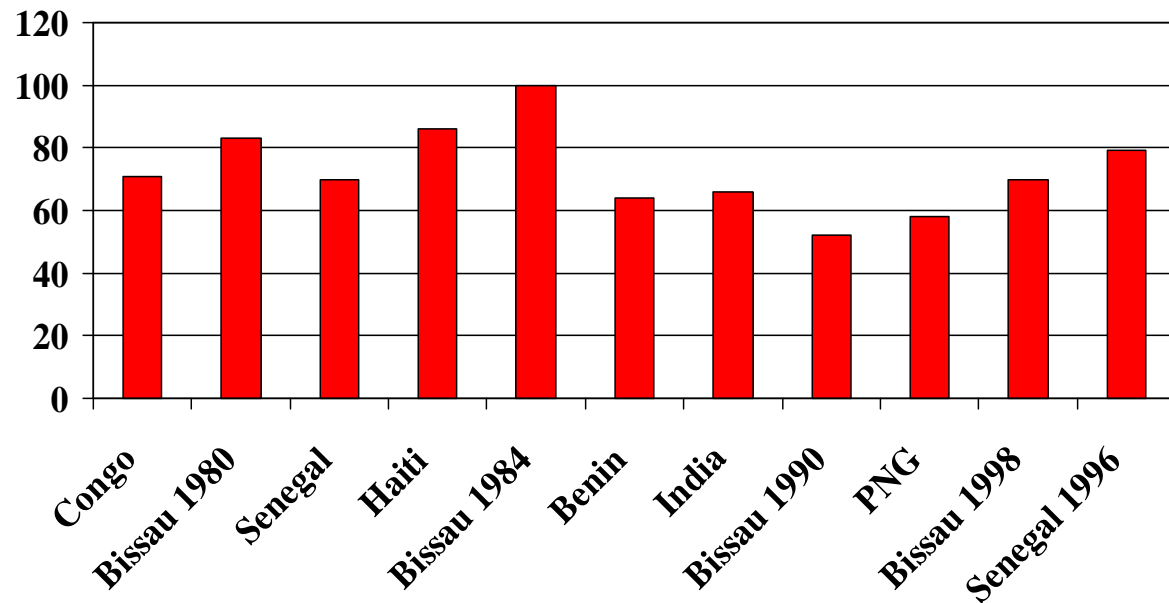
Baixo Peso:



Being wrong III: Eradication of measles will increase mortality

All studies show reduction > 50%

Mortality reduction for MV < 12 mo



If MV has beneficial NSE, reduced vaccination will increase mortality.

Measles eliminated in Latin America in 1996: age of MV increased from 9 to 12 months

The lives lost will be much larger than the lives saved

- but will not be observed

Smallpox? Polio?

Beyond “vaccines are miracles” and MDG4

We have to get beyond policies based on assumptions and beyond the specific-solution paradigm

One disease -> specific vaccine

One deficiency -> micronutrient supplementation

The immune system is a learning system - and susceptibility can be enhanced or misdirected

1. NSE should always be considered
2. Effects should be assessed separately for boys and girls
3. Interactions with existing interventions should be considered

Much more for much less

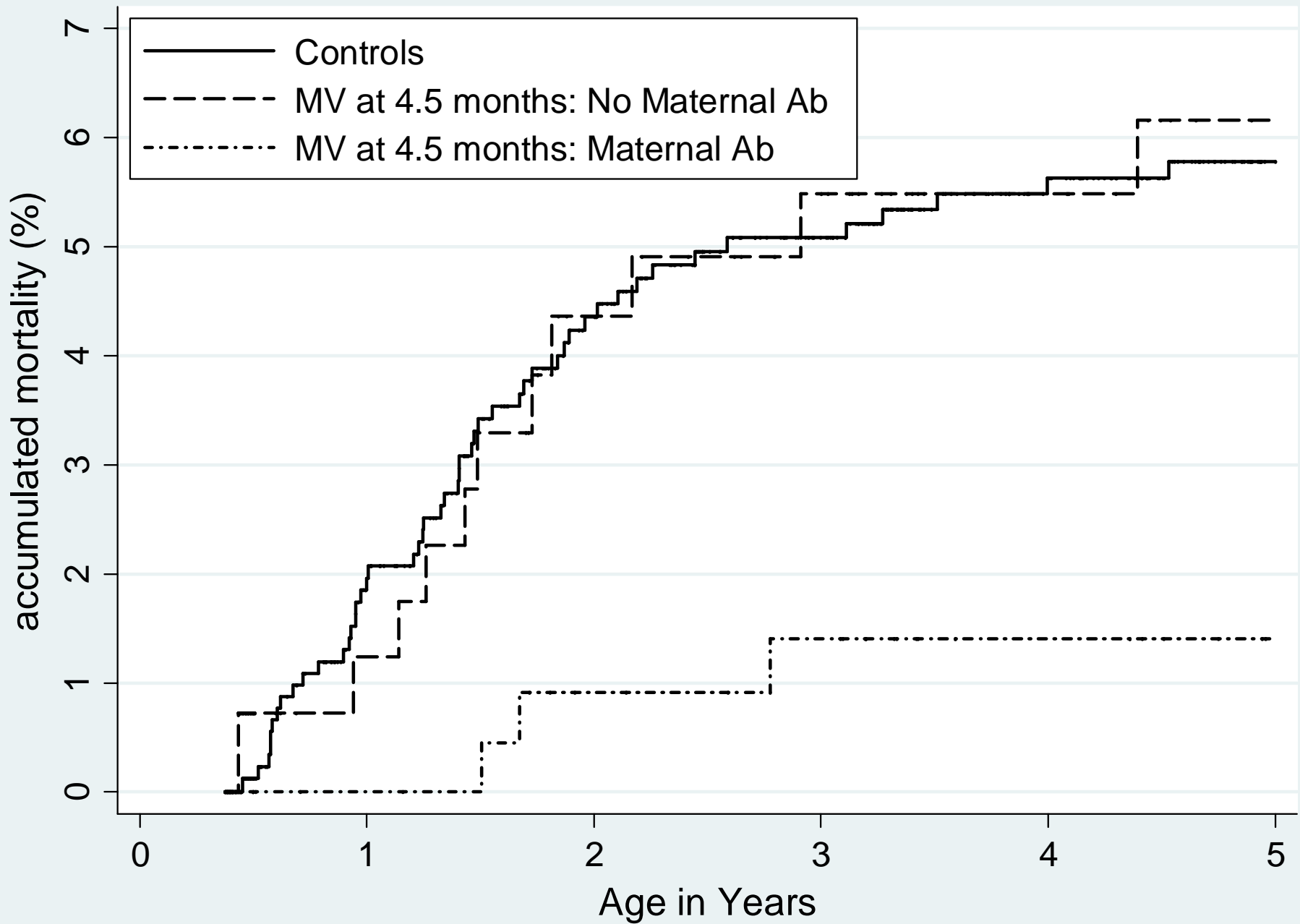
Paradigm shift: Non-specific effects of vaccines

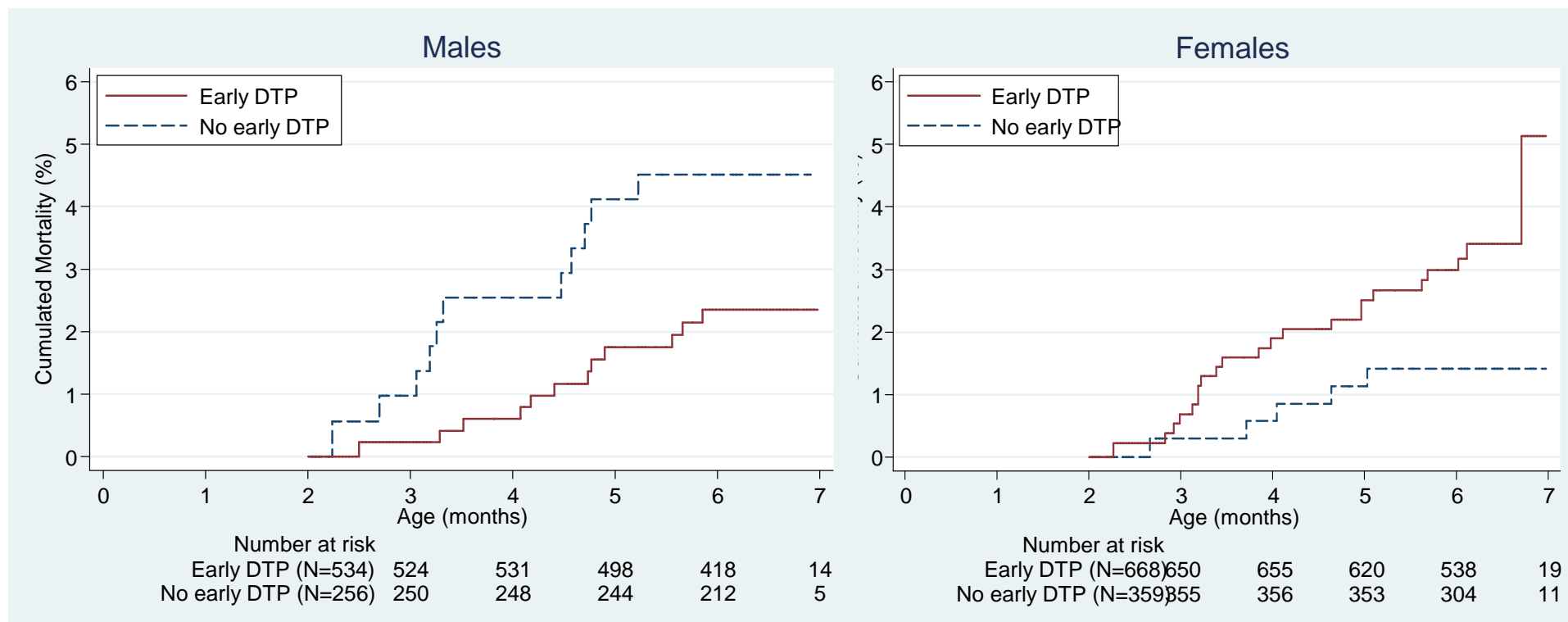
- "Live" vaccines: BCG, Measles vaccine, have non-specific *beneficial* effects on survival
- "Inactivated" vaccines: DTP, Hep B, have non-specific *detrimental* effects on survival

Both effects strongest
for girls!

Numerous references:
www.bandim.org



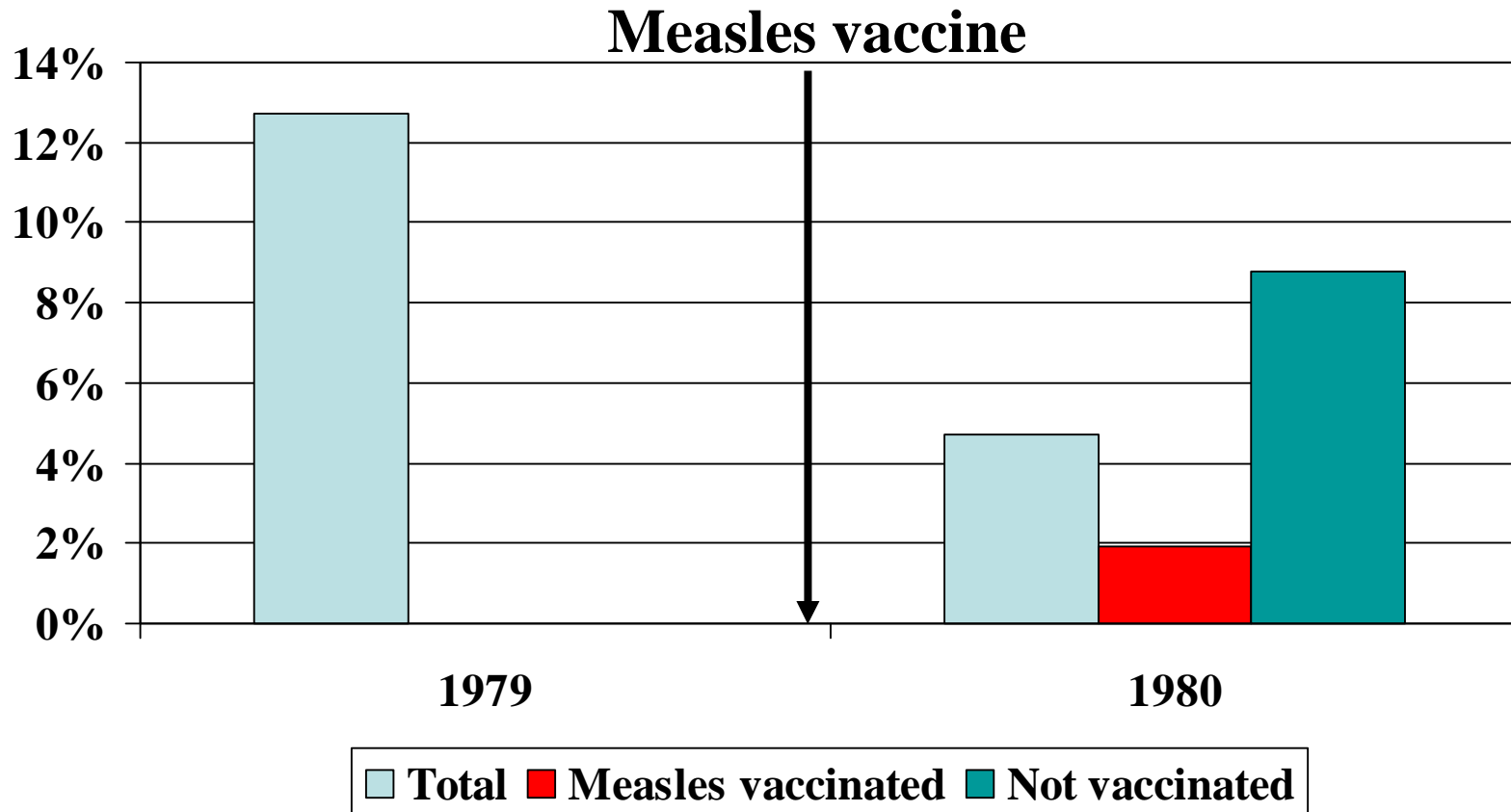




Accumulated mortality curves for DTP vaccinated at 2 months of age and not DTP vaccinated children

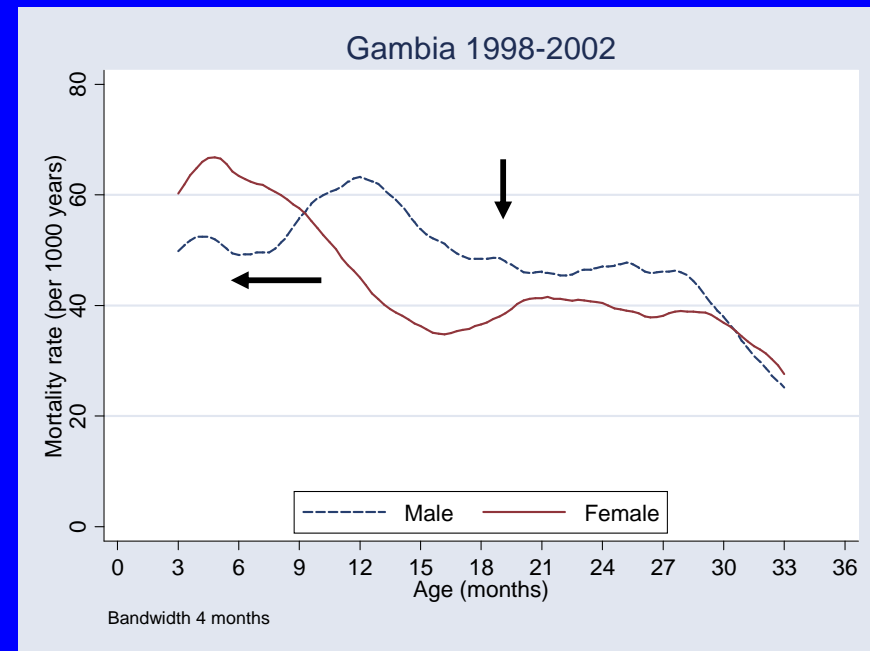
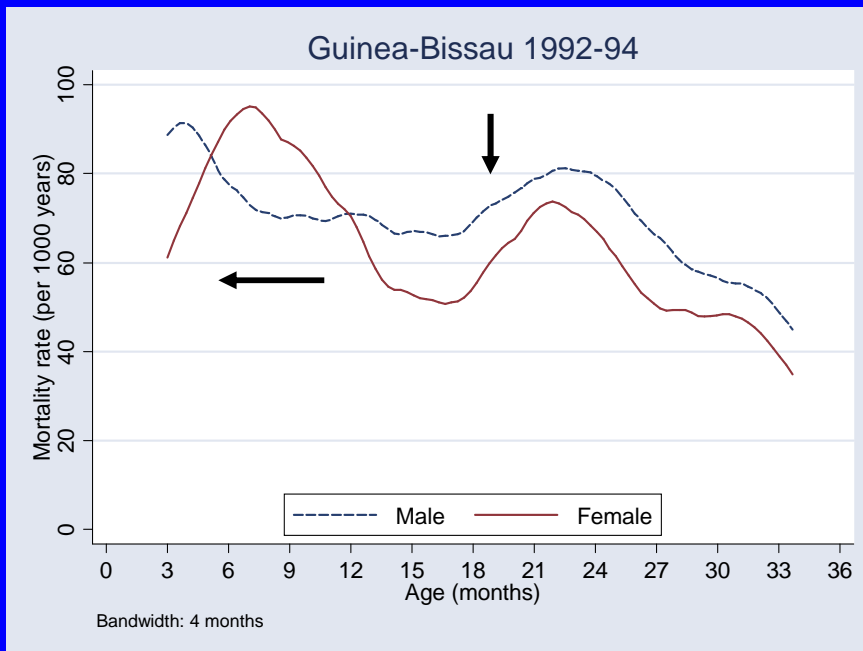
DTP/noDTP	MRR crude	MRR adjusted
Girls	2.5 (0.9-6.5)	5.7 (2.1-16)
Boys	0.5 (0.2-1.2)	1.3 (0.5-3.1)
All		2.6 (1.4-5.1)

**Introduction of measles vaccine in Bissau 1979
Annual mortality rate (6-35 mo) dropped 3-fold**



This made no sense!

Reducing the negative impact of DTP?

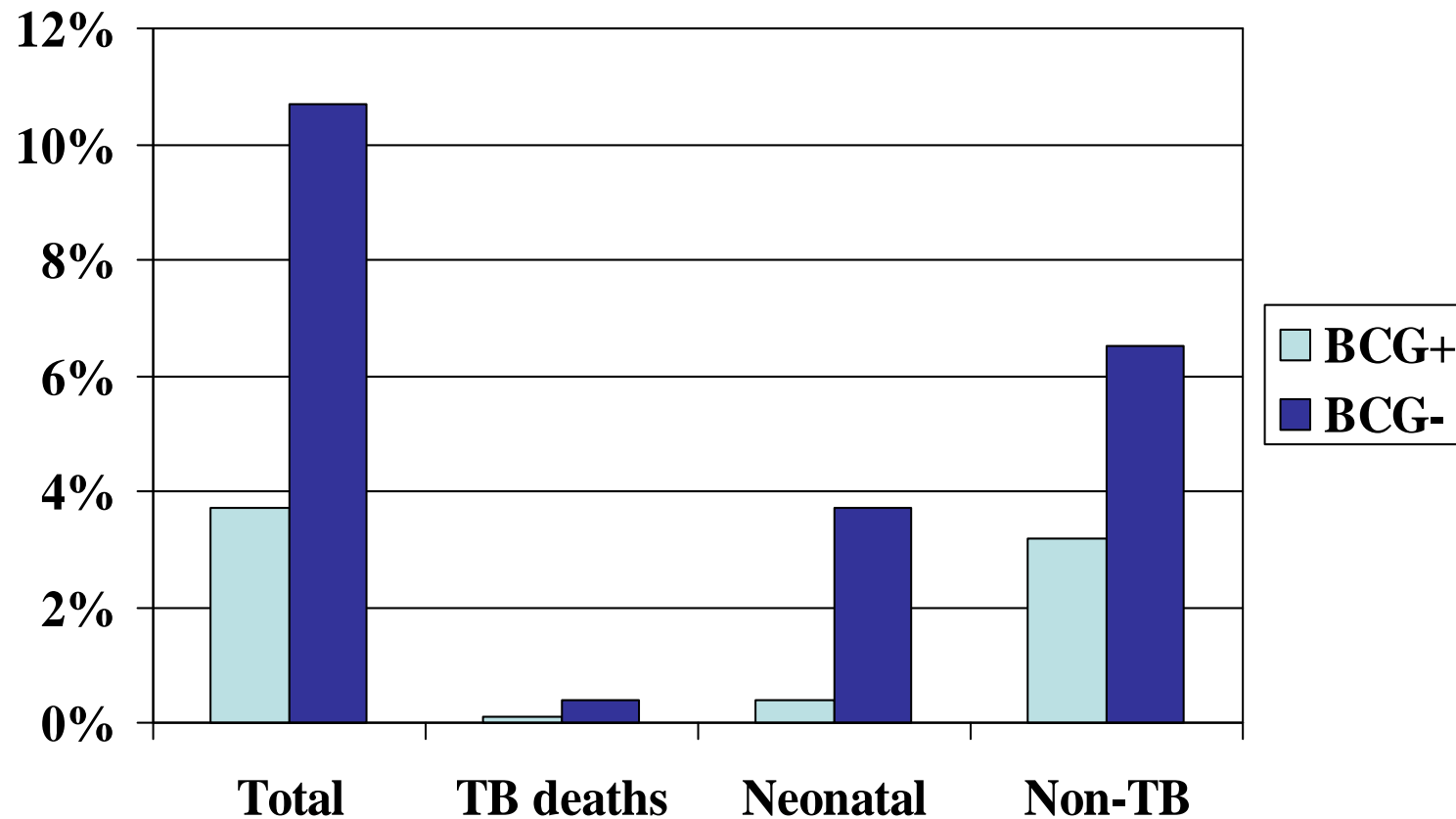


Increased female mortality in the age group of DTP

RCT2: BCG revaccination (19mo)

RCT3: Early MV (4½ mo)

Introducing BCG in Norrbotten, Sweden, 1927-31: Mortality at 0-4 years; 20,000 children



This made no sense: Reduction mostly in infancy but TB deaths occur later³⁴

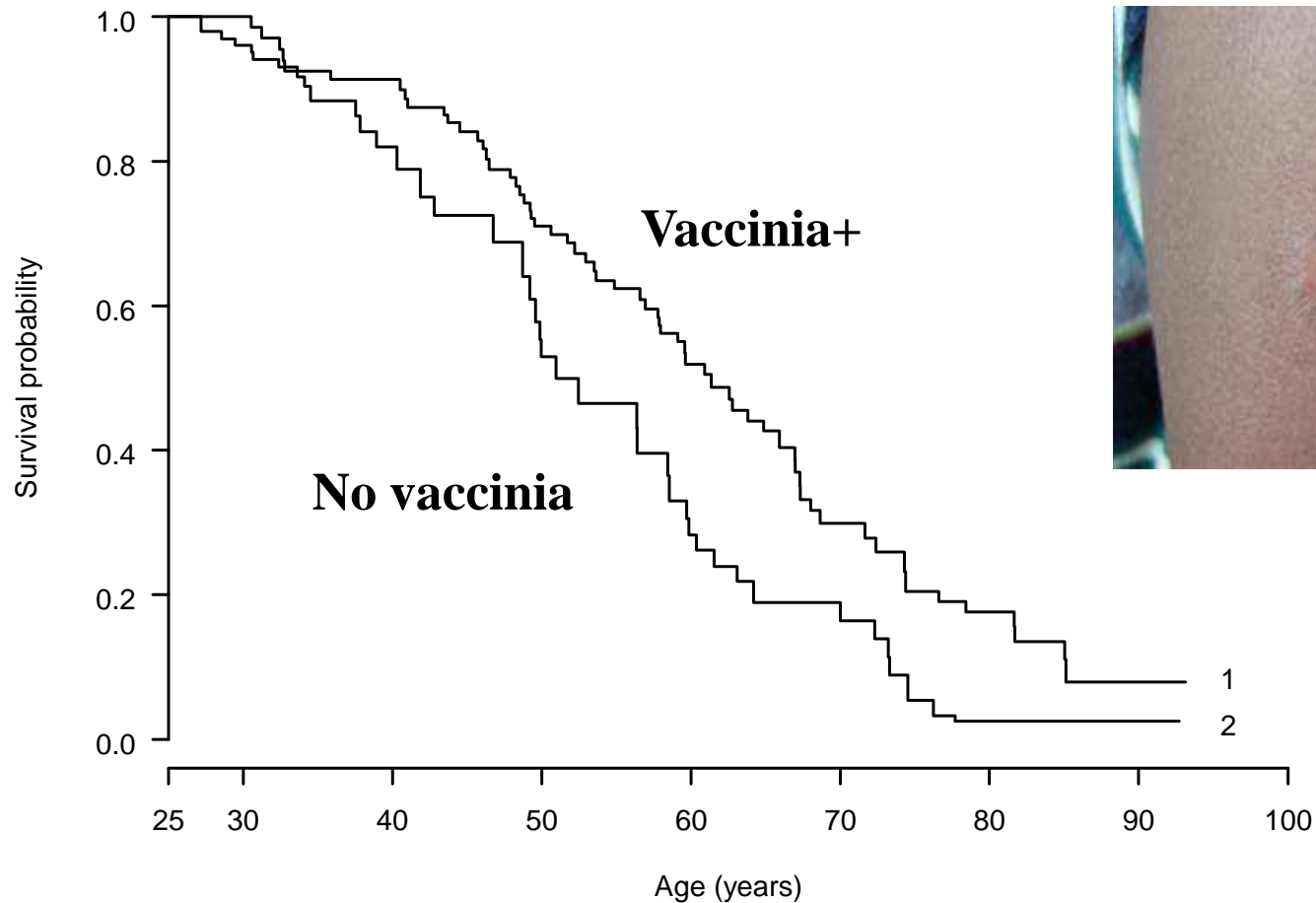
"

One could evidently be tempted to find the explanation of this much lower mortality among BCG-vaccinated children in the idea that the BCG vaccine provokes a *non-specific* immunity"

(Carl Naeslund 1932)

This was only 4 years after the introduction of BCG in northern Sweden

Live vaccines are good – what happens when removed? Measles? Polio? Vaccinia after smallpox eradication?



Guinea-Bissau 1998-2002

MR Scar/no scar 0.60 (0.41-0.87). F 0.51 (0.3-0.8); M 0.72 (0.4-1.2)

Vaccinia scar and mortality in rural area of Guinea-Bissau 2003-6

Adults 30-90 years of age	Adjusted* OR for mortality
Females	0.15 (0.04-0.66)
Males	0.51 (0.03-8.5)
All	0.20 (0.06-0.68)
* Adjusted for age, sex, village, HIV status	

Infant vaccinations in low-income countries Relevant in Europe?

Smallpox and BCG phased out between 1965-1976 in Denmark

We used Copenhagen school health cards with information on vaccinations to link with Danish health registers

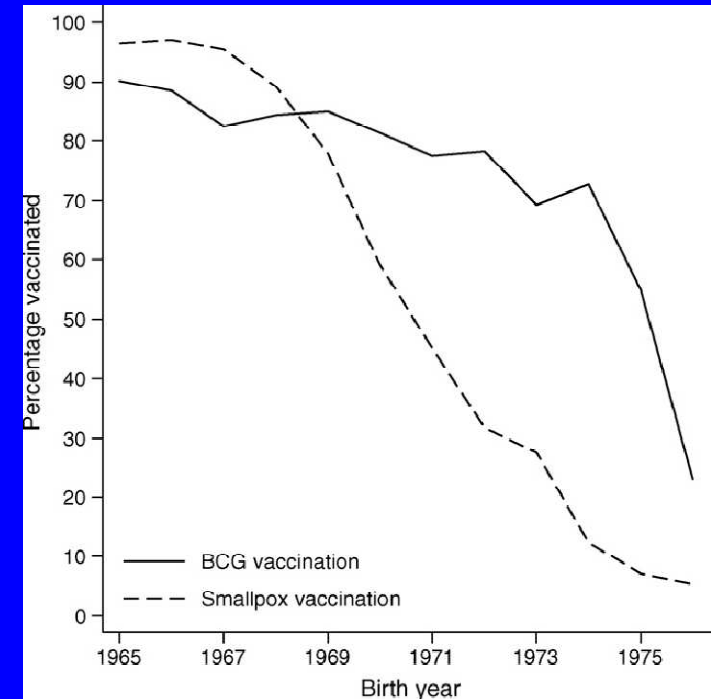
BCG

BCG reduced lymphomas with 51% (7-74%) –
Villumsen et al Vaccine 2009

Smallpox vaccine

Asthma reduced with 45% (0-70%) – *Bager et al J Allergy Clin Imm 2003*

Hospitalisation for infectious diseases reduced with 18% (3-31%) *IJE*



Hypothesis:

Vitamin A amplifies non-specific effects of vaccines

Vitamin A + BCG (birth)

Beneficial

Vitamin A + DTP (1-5 mo)

Not beneficial/Harmful

Vitamin A + MV (6 mo +)

Beneficial

Benn et al, IJE 2003



WHO vitamin A policy

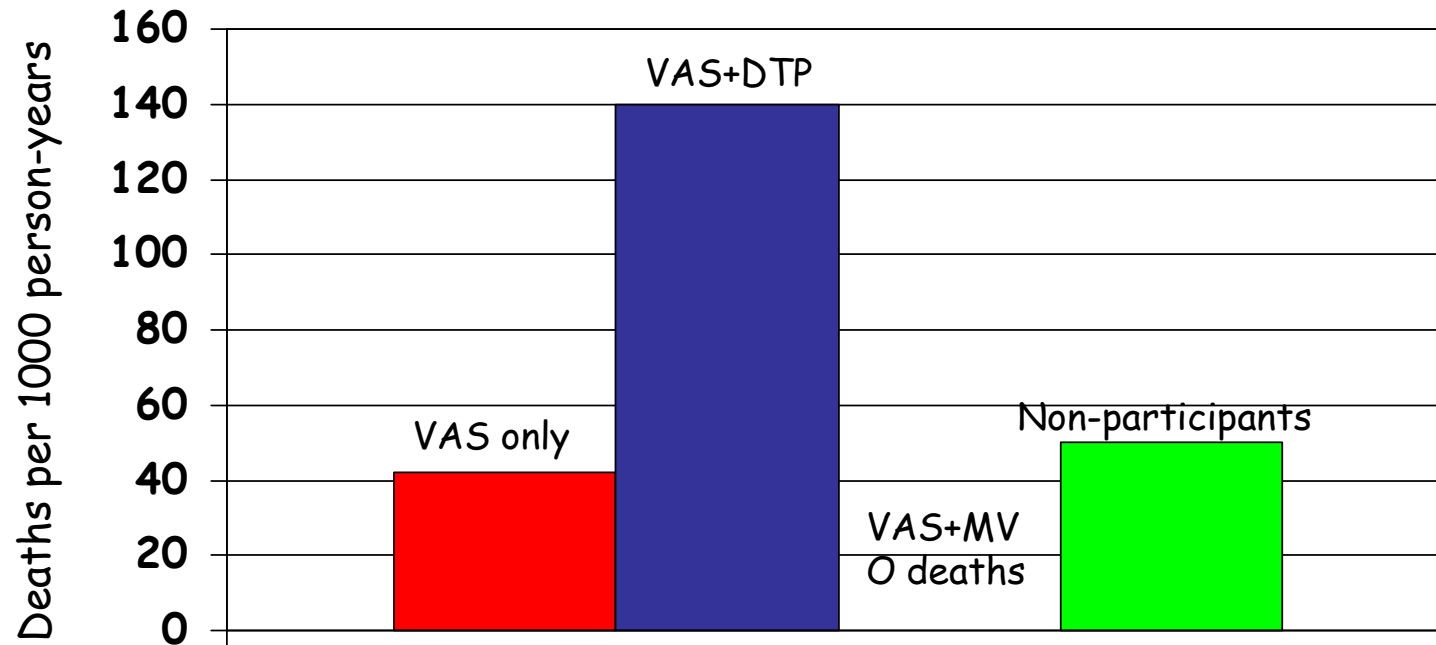
Summary table of target groups and potential immunization contact

Target group	Immunization contact	Vitamin A dose
All mothers, irrespective of their mode of infant feeding, up to six weeks post-partum if they have not received vitamin A supplementation after delivery	BCG, OPV-0 or DTP-1 contact up to six weeks	200 000 IU
Infants 9-11 months of age	Measles vaccine contact	100 000 IU
Children 12 months and older		200 000 IU
Children 1-4 years old	Booster doses* Special campaigns* Delayed primary Immunization doses*	200 000 IU

Never tested in real life!

VAS campaign, Guinea-Bissau 2003

Missing routine vaccines provided at the same time
Children aged 6-17 months



VAS+DTP versus VAS only: adjusted MR=3.4 (1.4-8.6)

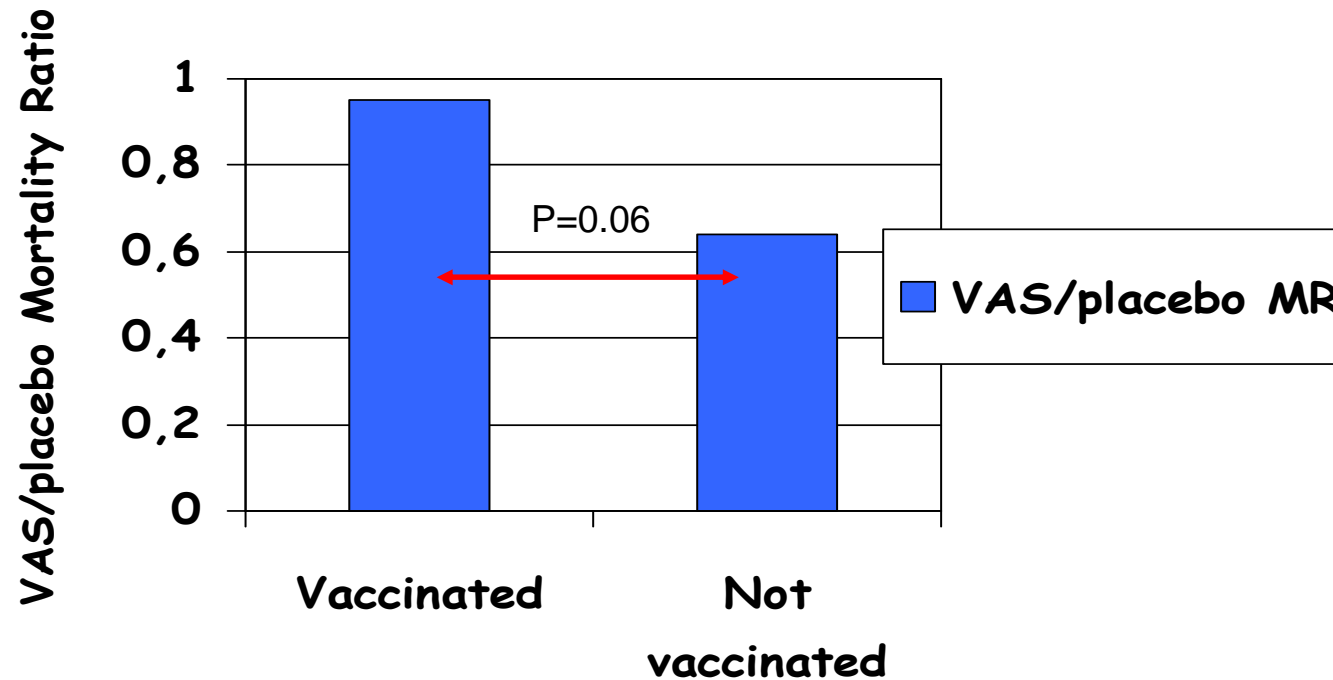
VAS+DTP versus VAS+MV: $P < 0.001$

Benn et al, Int J Epidemiol 2008

Ghana VAST, reanalysis

Original trial conducted in 1989-91; MR=0.81 (0.68-0.98) (Lancet 1993)

Not analysed by vaccination status



The VAS effect tended to differ in children who were vaccinated (N=6,656) and not vaccinated (N=5,066), $p=0.06$

Measles vaccination at 9 mo of age - established in late 1970s

- The policy was based on 6 assumptions:
 - Antibodies are 100% protective
 - If no antibodies after vaccination: fully susceptible
 - No difference in severity between vaccinated and unvaccinated cases of measles
 - No difference in case fatality between infancy or childhood
 - "Vaccine failure" would lead to lack of confidence in the programme - hence better to vaccinate later and have fewer "vaccine failures"
 - Had to be one dose policy

Projected reduction measles in Kenya - 1974-1981

Age	Incidence in unvaccinated	Conversion to measles vaccine	Prevented cases (%)	Unvaccinated cases (%)	Vaccine Failure (%)	Deaths by measles/ 1000	Deaths by measles/ 1000
5	1	35%	35%	0%	65%	26	4.3
6	3	52%	51%	1%	48%	19.6	4.2
7	6	72%	69%	3%	28%	12.4	4.3
8	10	86%	79%	6%	15%	8.4	5.8
9	14	95%	84%	10%	7%	6.8	8.5

All 6 assumptions wrong – if corrected

No study made to substantiate the policy

30 years with measles vaccine at 9 months of age

=> Estimated 30 mill deaths could have been prevented if 6 months of age ⁴⁴