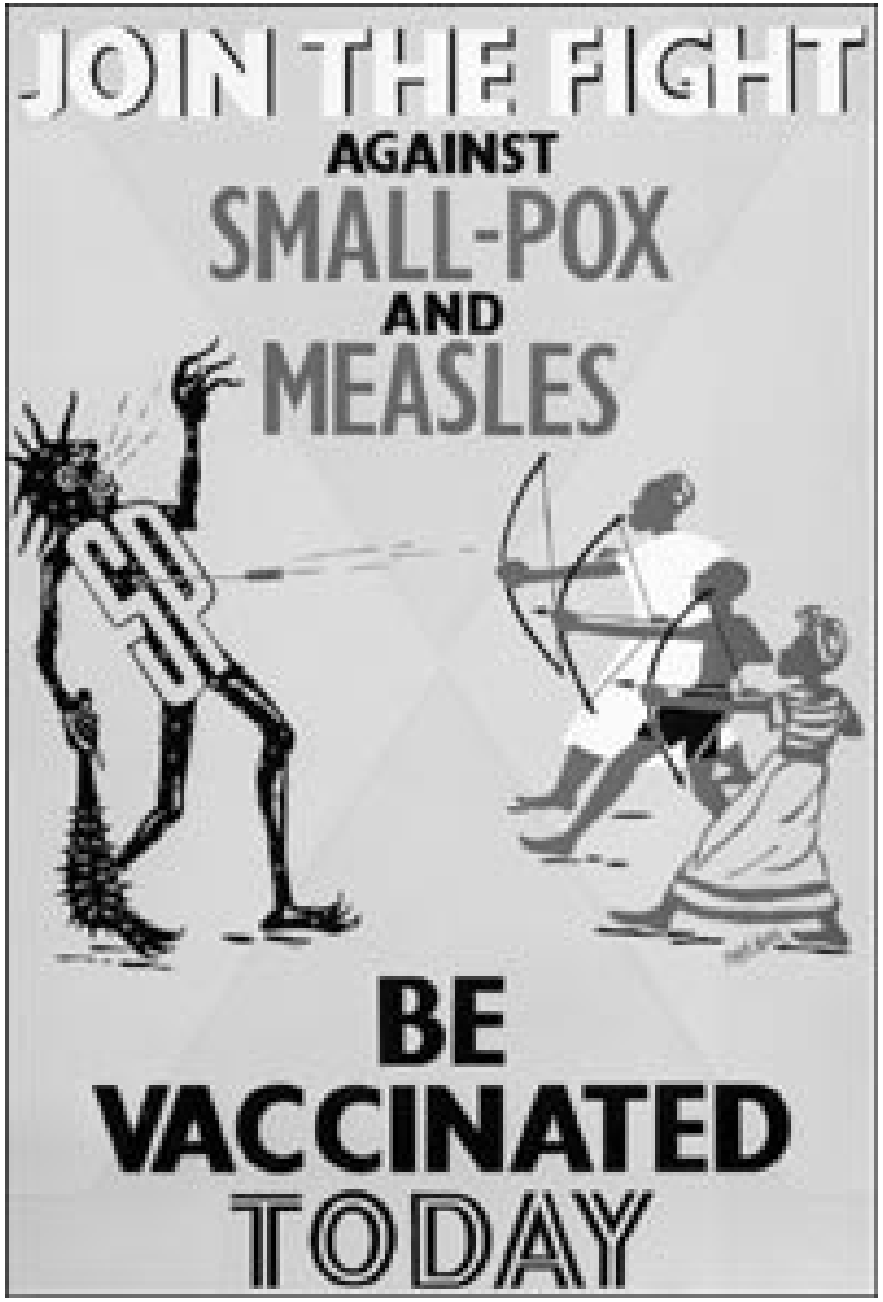
Smallpox gone

Measles within the next 10-15 years



Fra CDC public health images

The eradication of measles infection will increase child mortality in Africa

Peter Aaby
Christine S Benn
Bandim

The eradication scenario

- **The ultimate dream in Public health: eradication**
- **Measles targetted within next 10-15 years**
- **Polio targetted within next 5-10 years**
- **Rubella may be targetted with measles**
- **To quote Gates: Smallpox gone; Polio 99% down; Measles deaths 98% down => Vaccines best buy in Global Health**

- Removing/reducing vaccinations and reduced outbreak control makes eradication efforts cost-effective
- This is clearly beneficial: Saving lives and money ..... .in the current paradigm where the only effect of vaccinations is to prevent against specific diseases
- What will happen if vaccines have other effects?

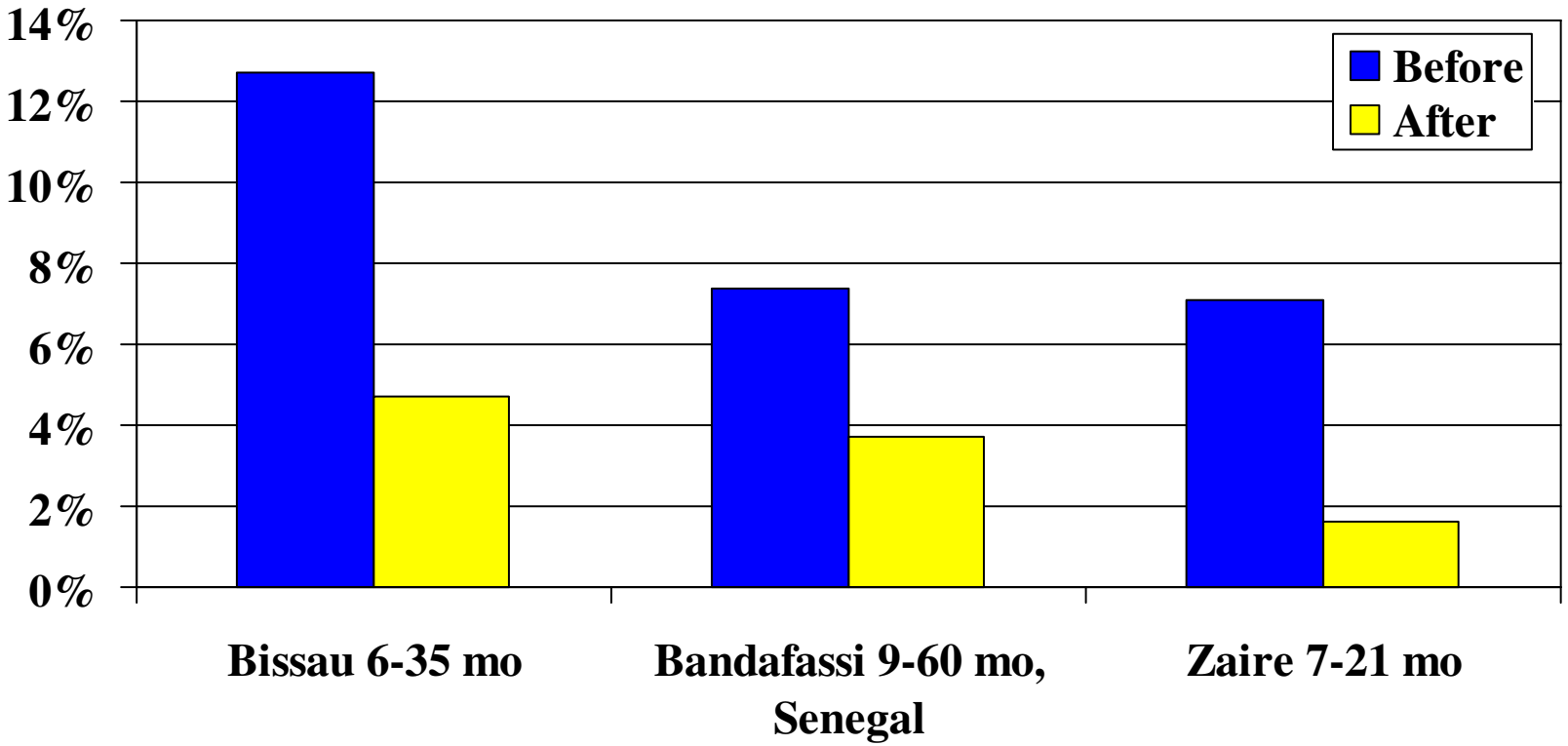
Measles eradication

- The immediate consequences:

1. WHO recommendations: The age of measles vaccination (MV) will be increased from 9 to 12 months – as in Latin America in 1996 when measles was eliminated.
2. It will become increasingly difficult to maintain funding for MV activities
3. The supplementary immunisation activities (SIA) campaigns will be removed to save money
4. DTP/Penta/PCV is likely to be the last vaccinations to profile the immune system

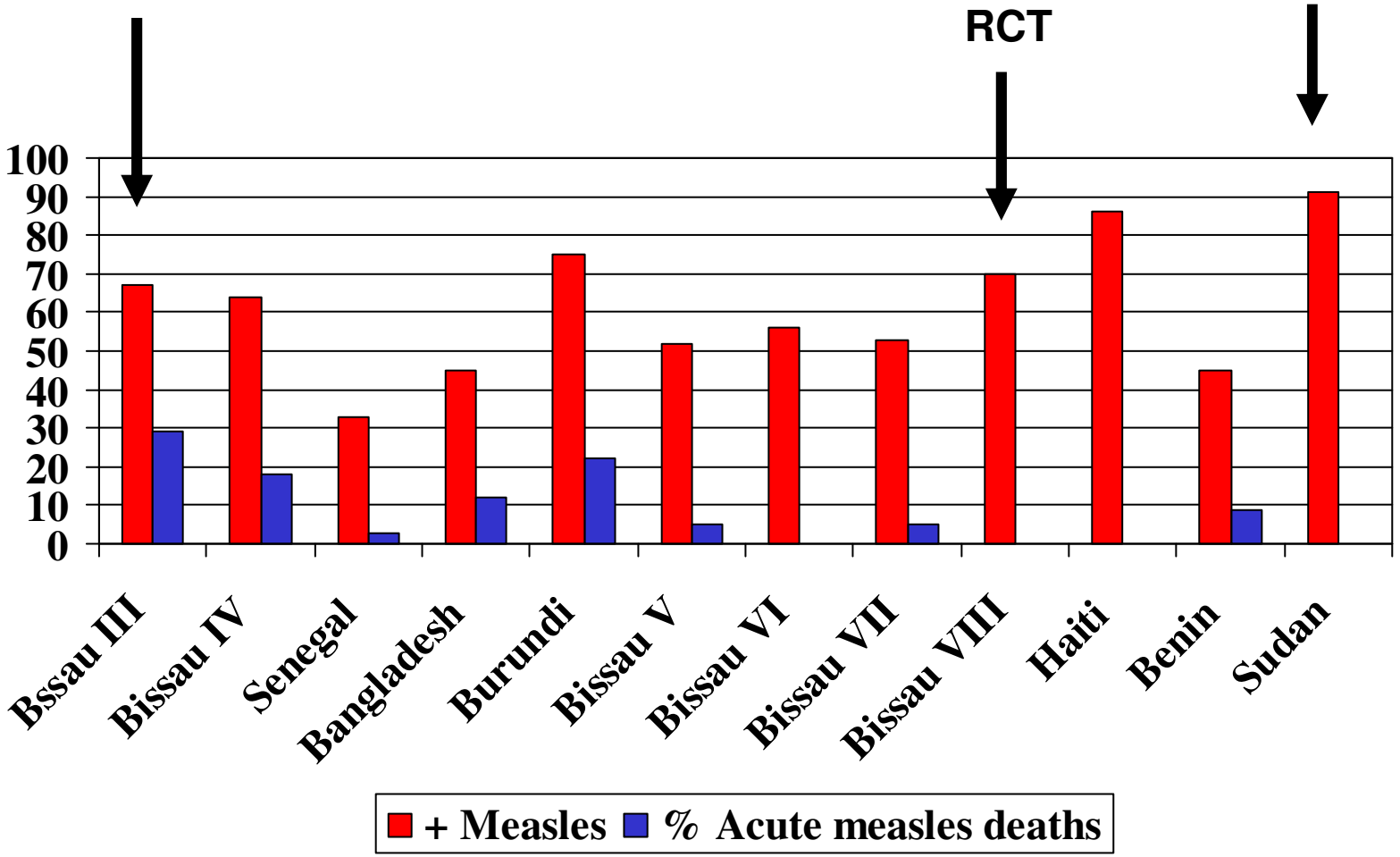
Before-after measles vaccination (MV):

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

Reduction in mortality associated with MV and the % deaths due to measles infection in unvaccinated children

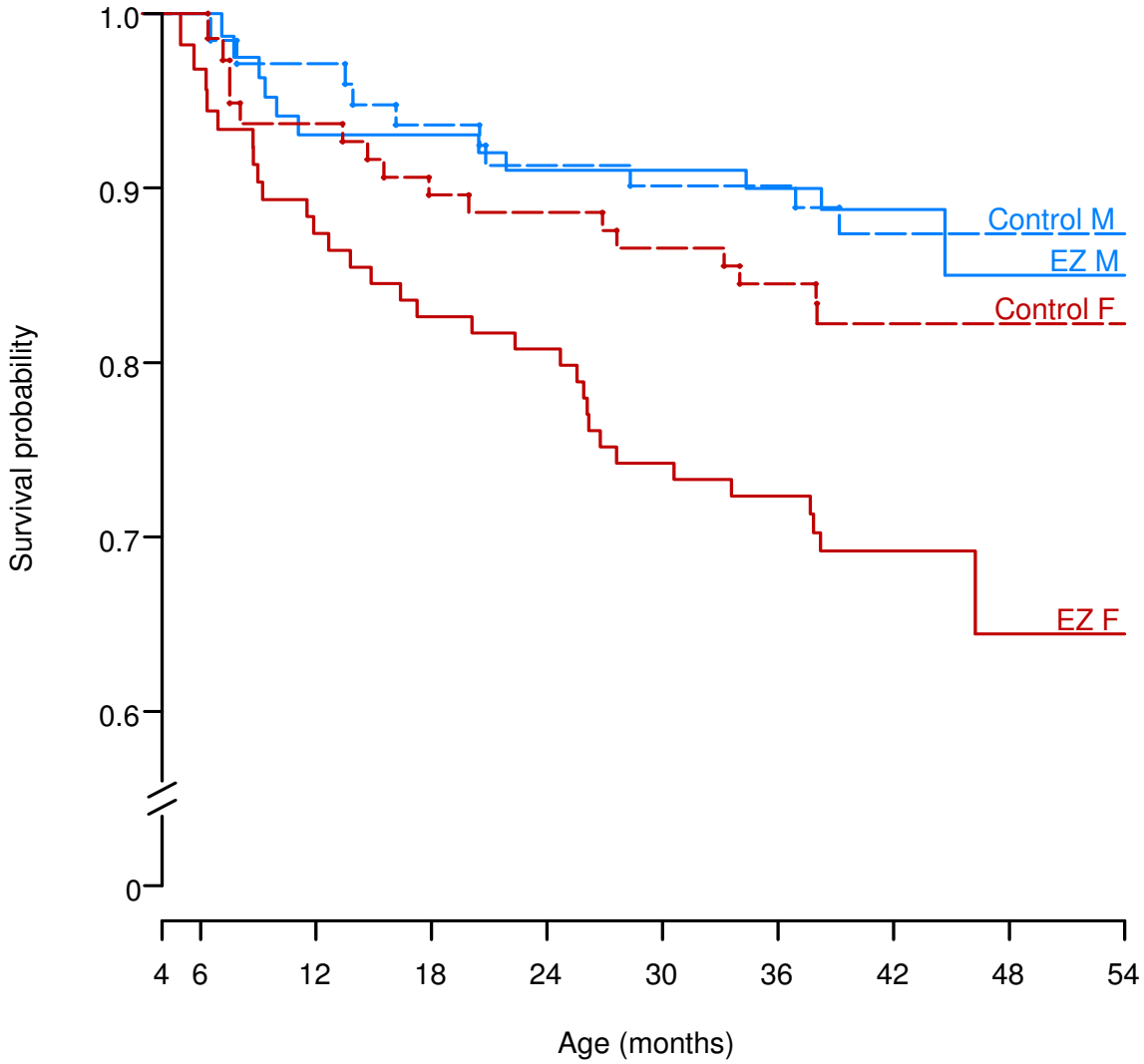


Not explained by prevention of acute (or delayed) measles infection!
Could it be selection bias?

Randomised/blind studies:
Measles vaccinated vs unvaccinated children

Design	Control group	Mortality (deaths/children)		Mortality ratio (MV+/MV-)
		Measles Vaccinated	Not measles vaccinated	
Nigeria: Random, not blind – 18 month follow-up	DTP	0%(0/26)	12%(3/27)	0.00 (0.0-2.5)
Sudan: Random, not blind – 5-9 months	Meningo-coccal A+C	0.3%(1/340)	3.5%(6/170)	0.09 (0.0-0.7)
Bissau: Blind, not random 2-years follow-up	Ineffective measles vaccine	5%(6/124)	13%(7/53)	0.32 (0.1-0.9)
Bissau: Random, not blind – 3 months during war	Inactivated polio (IPV)	2%(4/211)	5%(11/222)	0.30 (0.1-0.9)

High-titre measles vaccine (HTMV), Bissau, 1986-90



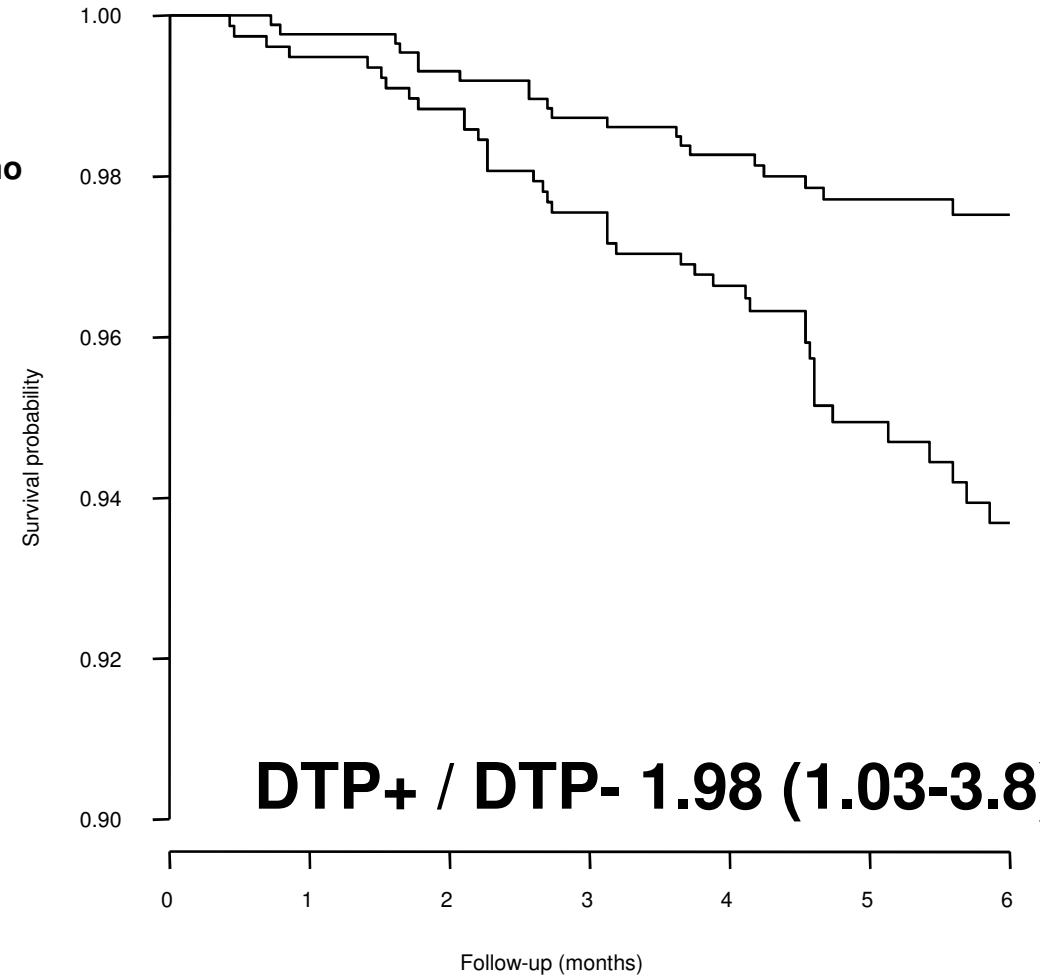
Similar results in Senegal, Sudan and Haiti – HTMV withdrawn 1992

No explanation –but repeatable. How can an effective vaccine do this?

Introduction of DTP: Rural areas of Guinea-Bissau 1984-87

Children aged 2-8 mo
Followed 6 mo

Unvaccinated: travelling; sick; days without vaccines



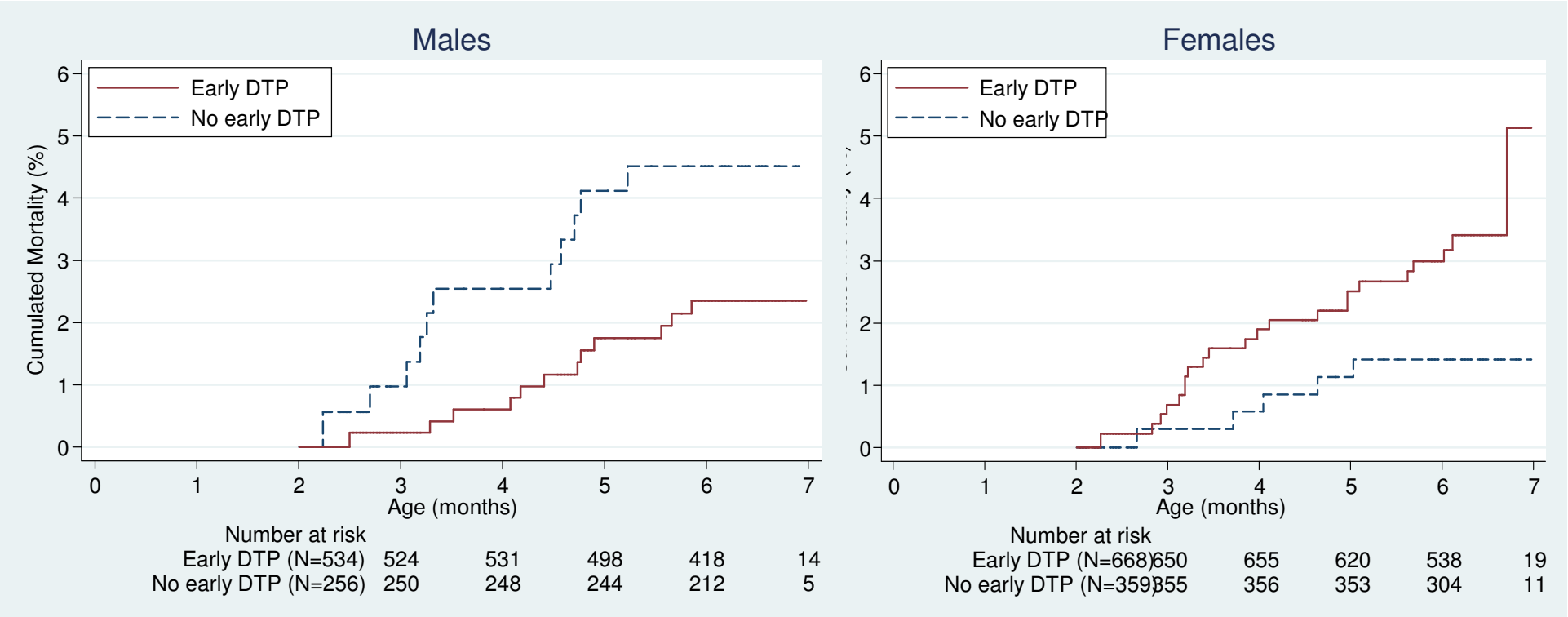
(N=868)

(N=967)

DTP+ / DTP- 1.98 (1.03-3.8)

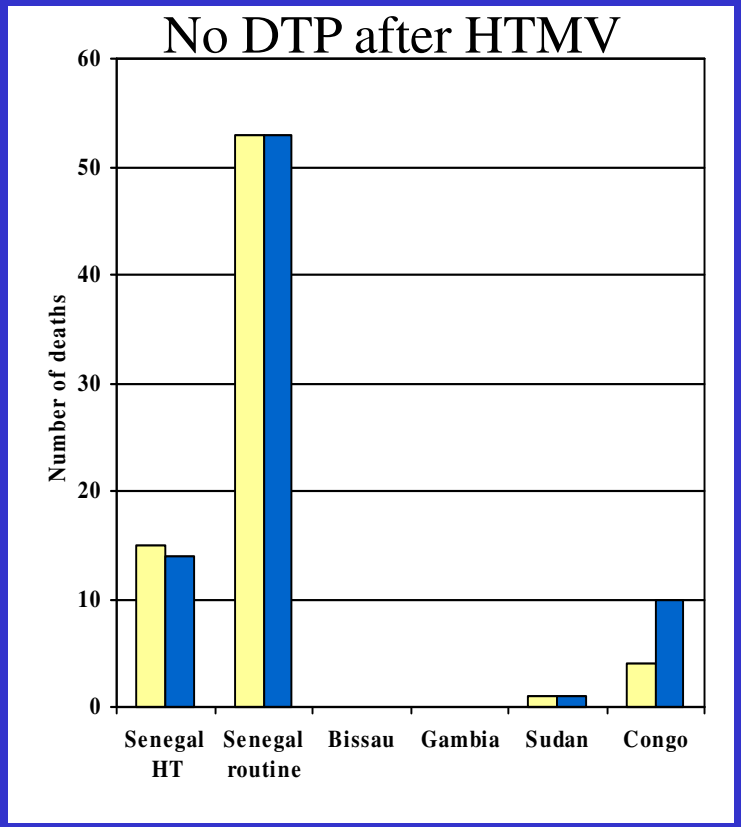
Diphtheria-Tetanus-Pertussis (DTP) effect strongest for girls

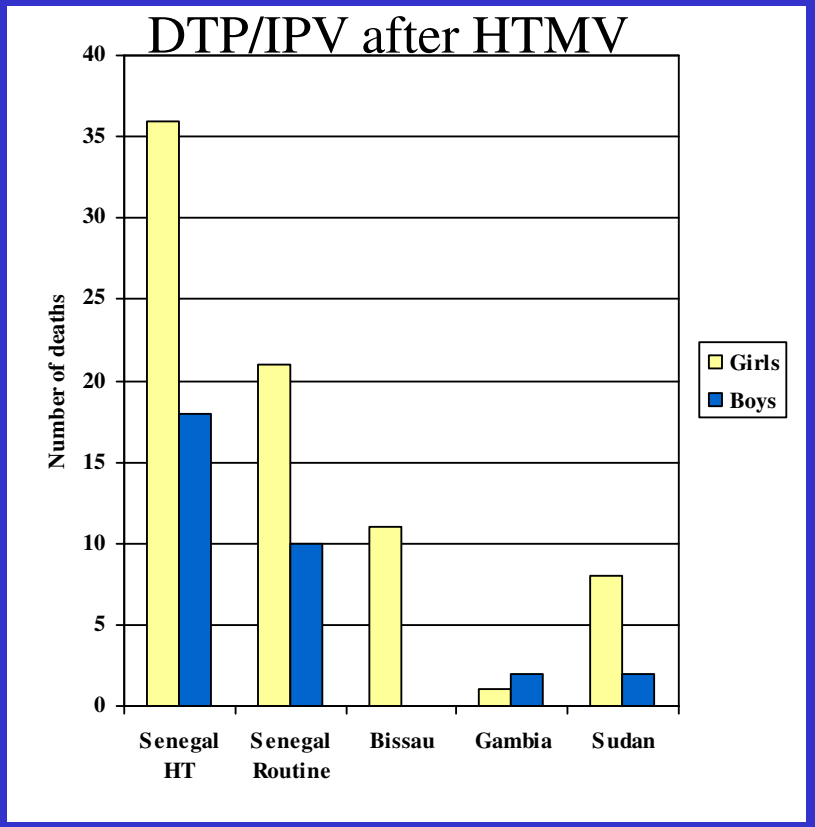
Accumulated mortality curves for DTP-vaccinated vs no DTP at 2 months



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)**

HTMV and DTP?





F/M ratio: 0.96 (0.7-1.3)

F/M ratio: 1.93(1.3-2.8)

Not RCT – but this ”proves” a causal biological process

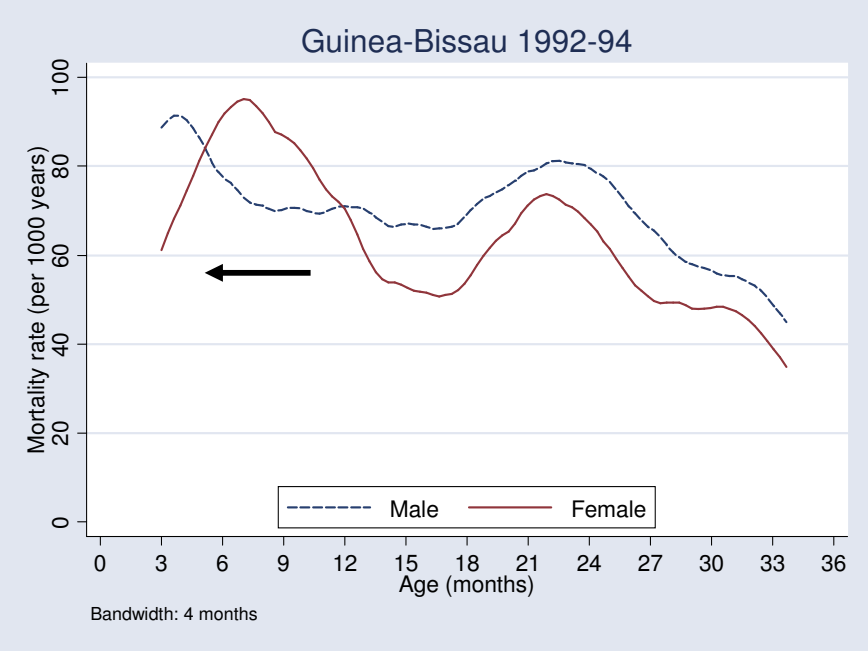
HTMV withdrawn for the wrong reason

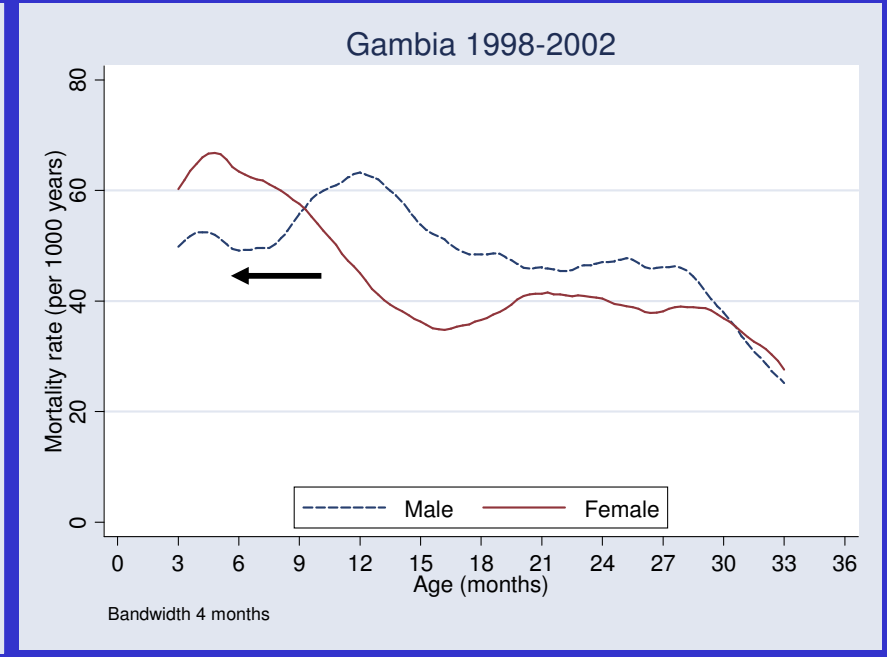
Annual mortality in MV trials depending on DTP status at enrolment

Study	Girls			Boys		
	No DTP3	**DTP3 < MV**	**MR**	**No DTP3**	**DTP3 < MV**	**MR**
2-dose Bissau	7.5%	3.8%	1.97(1.0-3.7)	6.4%	6.0%	1.06(0.6-1.9)
Sudan	6.0%	2.8%	2.16(0.3-17.3)	1.4%	1.9%	0.71(0.1-7.9)
Congo	10.0%	2.8%	3.06(0.6-16.1)	10.6%	5.1%	2.06(0.5-9.22)
Total			**2.10(1.2-3.7)**			**1.13(0.7-1.9)**

DTP after measles vaccine associated with 2 fold higher mortality

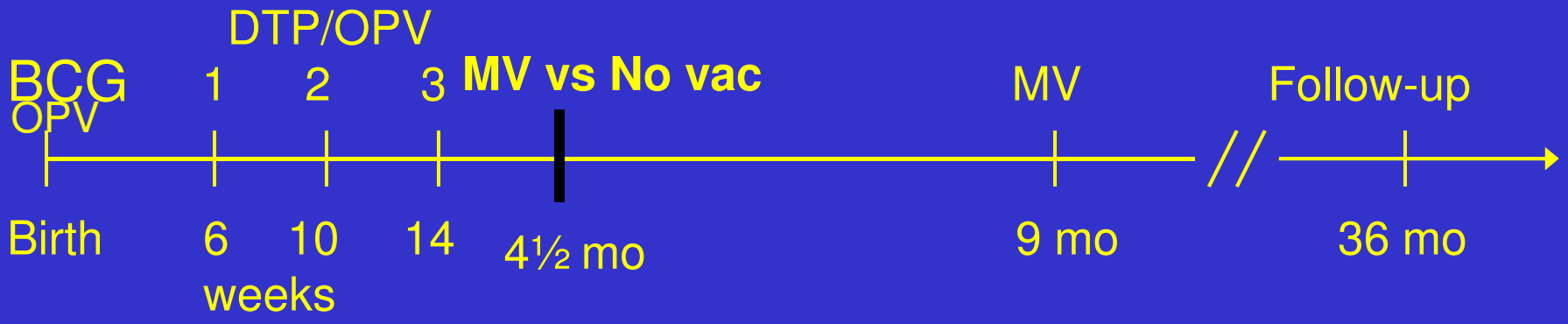
What can be done to reduce the negative effect of DTP?





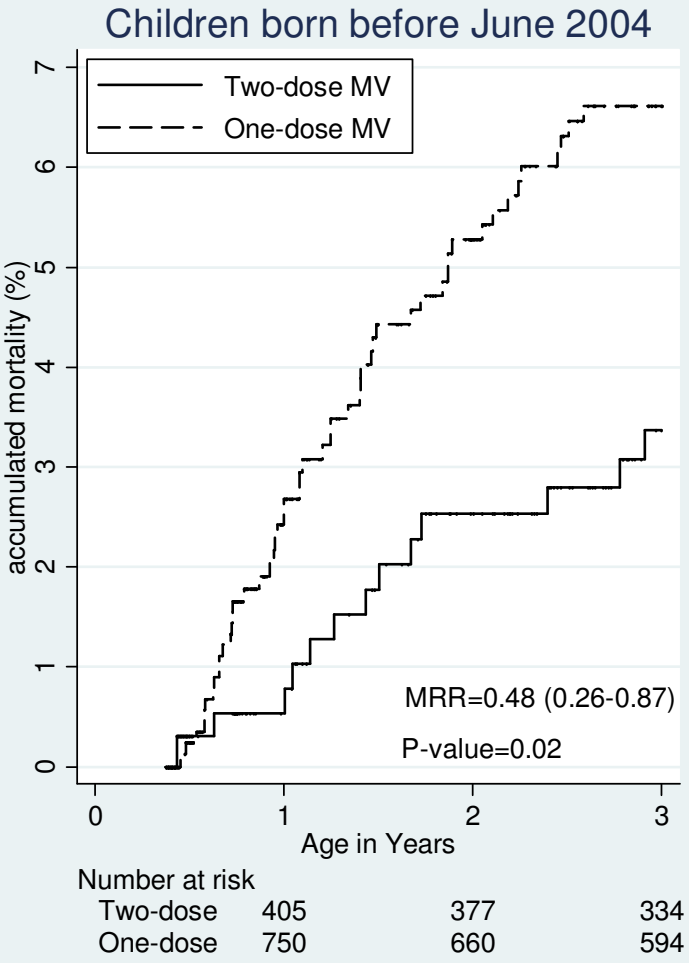
Increased female mortality in the age groups of DTP
=> Change the immunological profile with a live vaccine =>
RCT: Early Measles Vaccine at 4½ m

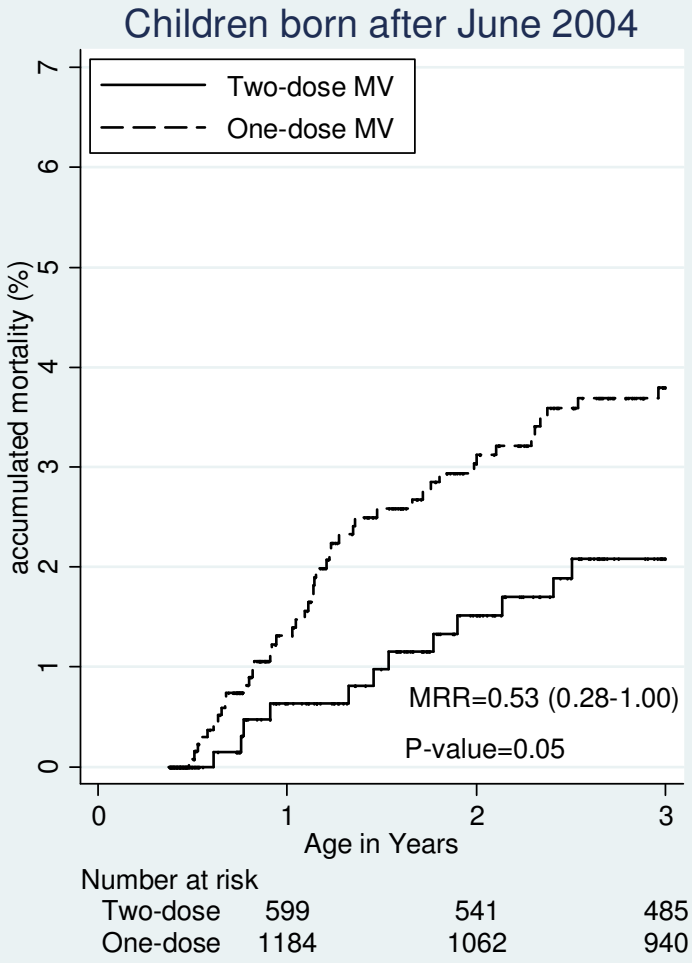
Testing non-specific effects of MV



- **Recruitment 2003-2007 – Follow-up to 2009**
- **6,600 randomised to A) Edmonston-Zagreb (EZ) at 4½+9 mo, or B+C) no vaccine at 4½ mo and EZ MV or Schwarz MV at 9 mo**
- **DTP3 four weeks before enrolment – to prevent the problem of DTP after MV**
- **Study designed to test a 25% difference in mortality**

RCT of two doses of Measles Vaccine



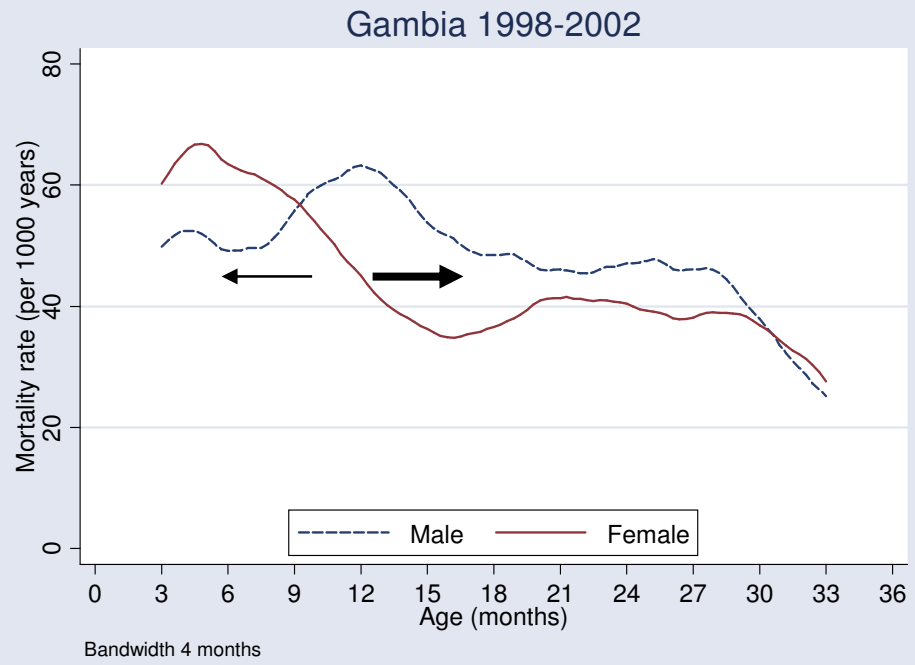


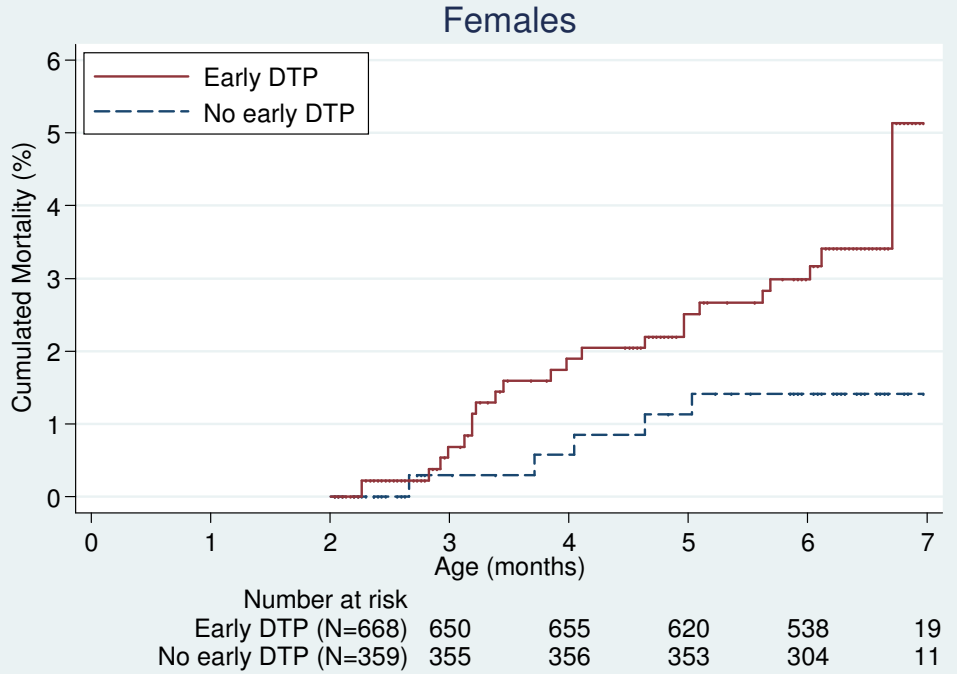
Two-dose standard MV at 4½ and 9 mo was fully protective and reduced mortality with 50% - with 45% if measles was excluded

RCTs of two doses of measles vaccine vs standard policy of one dose at 9 month

Study	Follow-up period	Mortality rate ratio
Sudan, 1989-92 Vaccine 2007	5-36 mo	0.60 (0.3-1.4)
Bissau, 1993-95 IJE 2003	6-18 mo	0.66 (0.2-2.3)
Bissau, 2003-09 BMJ2010	4½-36 mo	0.50 (0.3-0.8)
Combined		0.53 (0.36-0.77)
Observational study campaigns BMJ 1993	9-60 mo 4-8 vs 9-11 mo	0.41 (0.2-0.9)

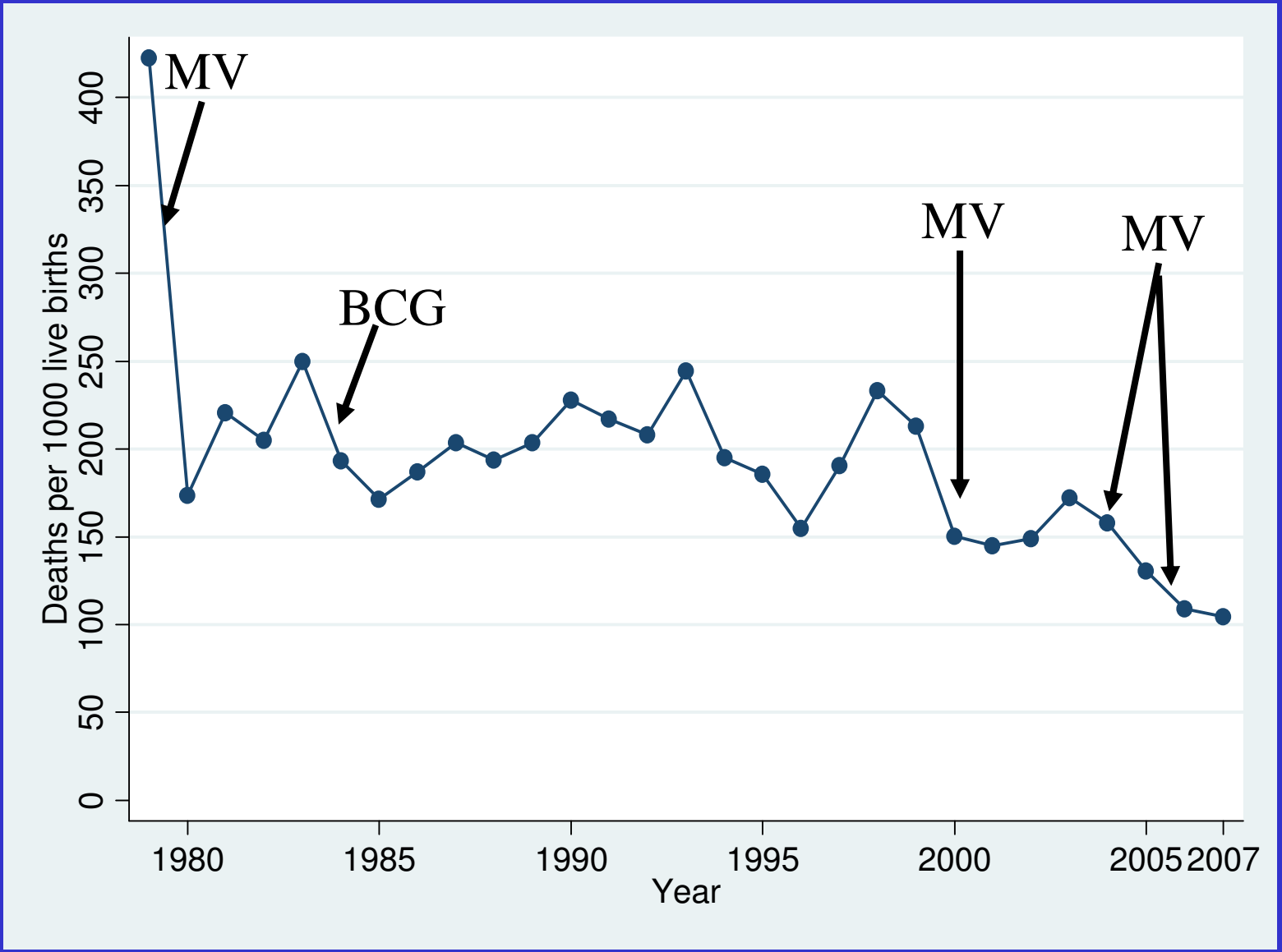
Measles eradication I: age of MV from 9 to 12 months and DTP becomes the last vaccination





Instead of moving the age foreward as done in Bissau it will be moved backwards => increased mortality, particularly for girls

Measles eradication II: Campaigns will be removed



Under-5 mortality in Bandim 1978-2007

Polio eradication

- The immediate consequences:

1. Change from OPV to IPV for fear of OPV related polio cases and revision of OPV strains
2. Removal of OPV

Evidence:

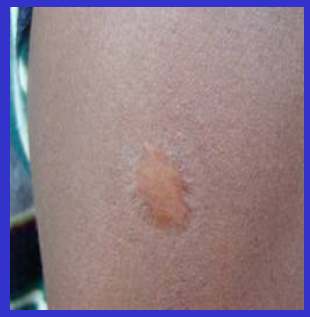
1. OPV may have beneficial effects in natural experiments:

   The hospital case fatality was 3-fold lower when DTP was absent and only OPV given

   Mortality lower among those who received OPV in campaign
2. OPV beneficial effects in RCT (ínterim results)
3. IPV associated with 52% (2-128%) higher female than male mortality in RCT

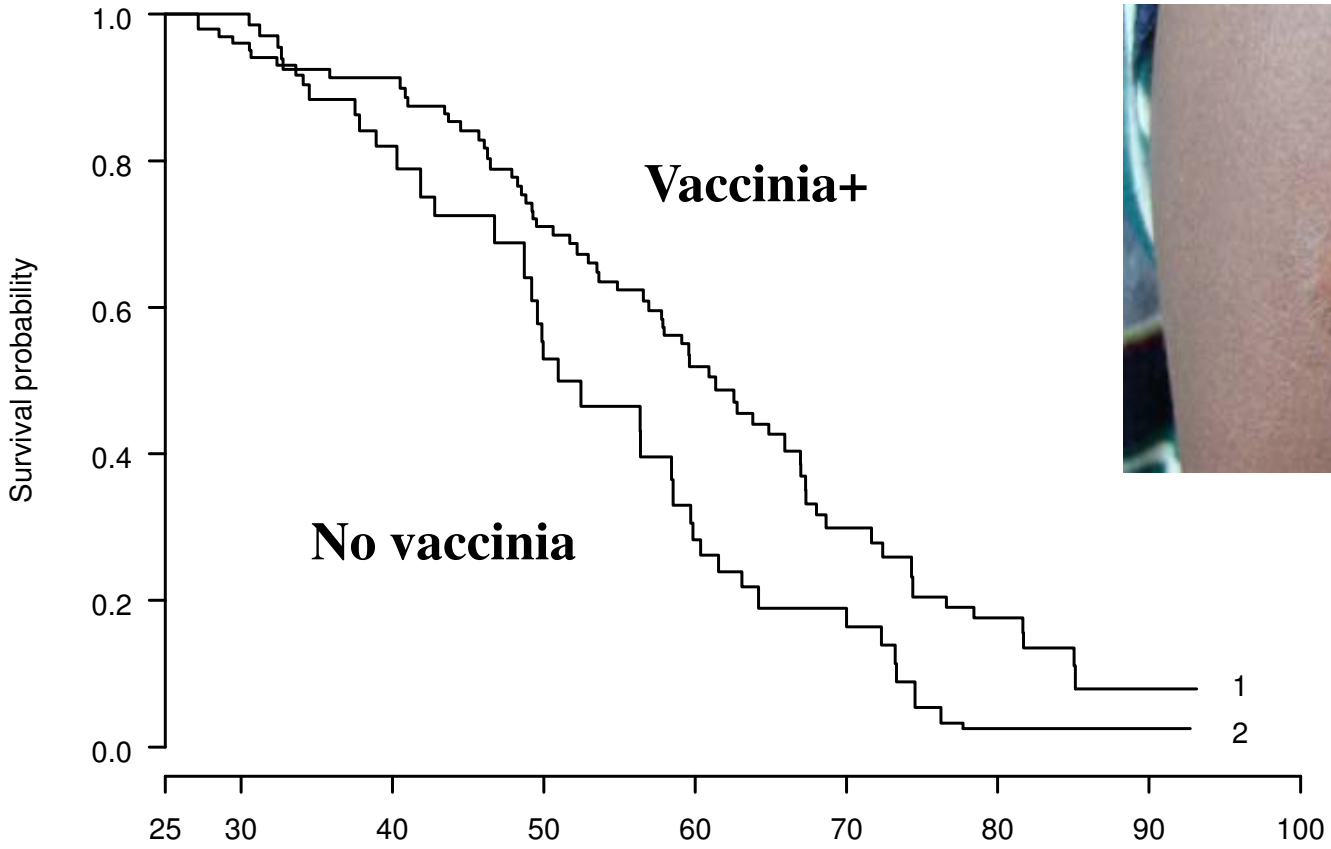
Smallpox and vaccinia eradication

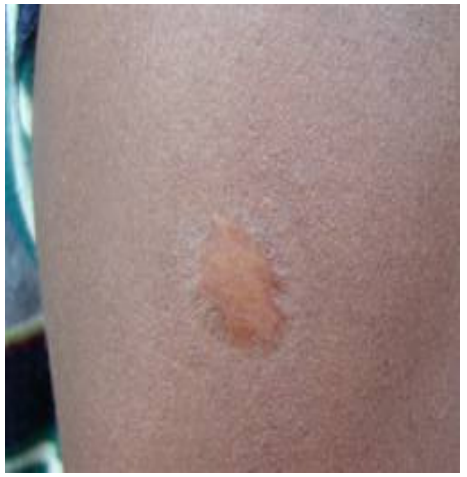
- The first example of eradication of a disease (1977) and removal of a vaccine (1980)
- Due to the fear of what could happen when measles was eradicated we started in 1998 to examine what happened after the removal vaccinia



1. In Bissau: we made scar surveys and followed for mortality
2. In Copenhagen: We used school health cards which had vaccination information and could link to Danish health registers

Live vaccines are good – what happens when removed?
Vaccinia after smallpox eradication in Guinea-Bissau





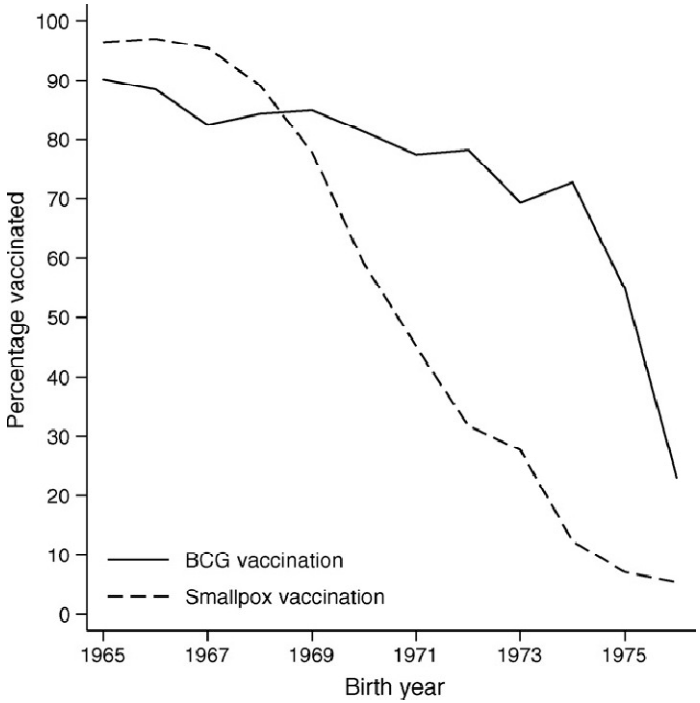
Mortality rate ratio for Scar/no scar:
Study I (1998-2002) 0.60 (0.4-0.9); F 0.51(0.3-0.8); M 0.72(0.4-1.2)
Study II (2003-5) 0.22 (0.1-0.6): F 0.19(0.1-0.6); M 0.40(0.0-3.7)

Protection against HIV for scar/no scar: Female: 46% (0-71%)

Live vaccines are good – what happens when removed? Vaccinia after smallpox eradication in Denmark

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%)
Vaccine 2009

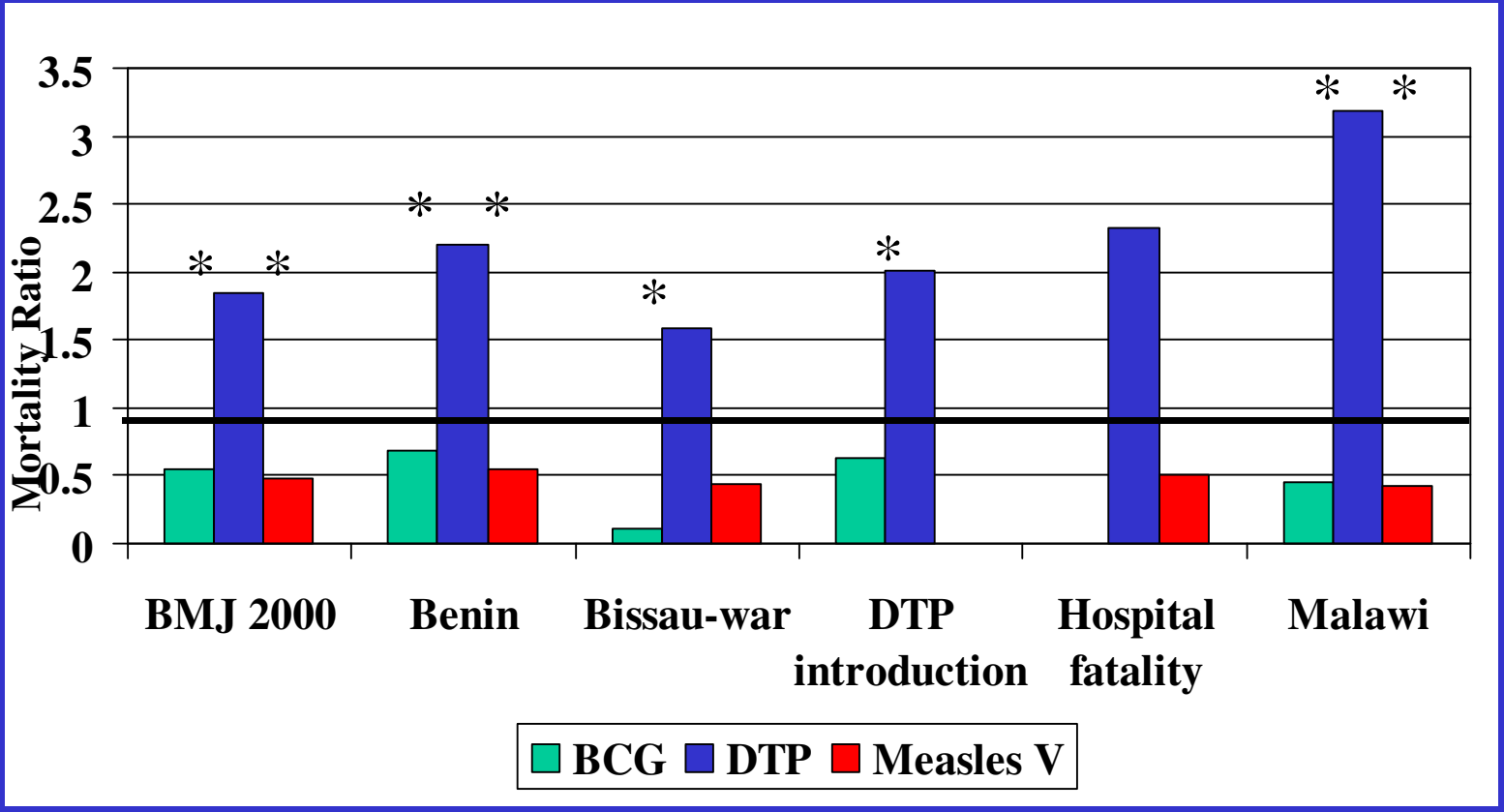
Smallpox vaccine

Asthma reduced with 45% (0-70%) – **J Allergy Clin Imm 2003**
Hospitalisation for inf diseases reduced with 16% (2-28%) **IJE 2011**

BCG and smallpox vaccine

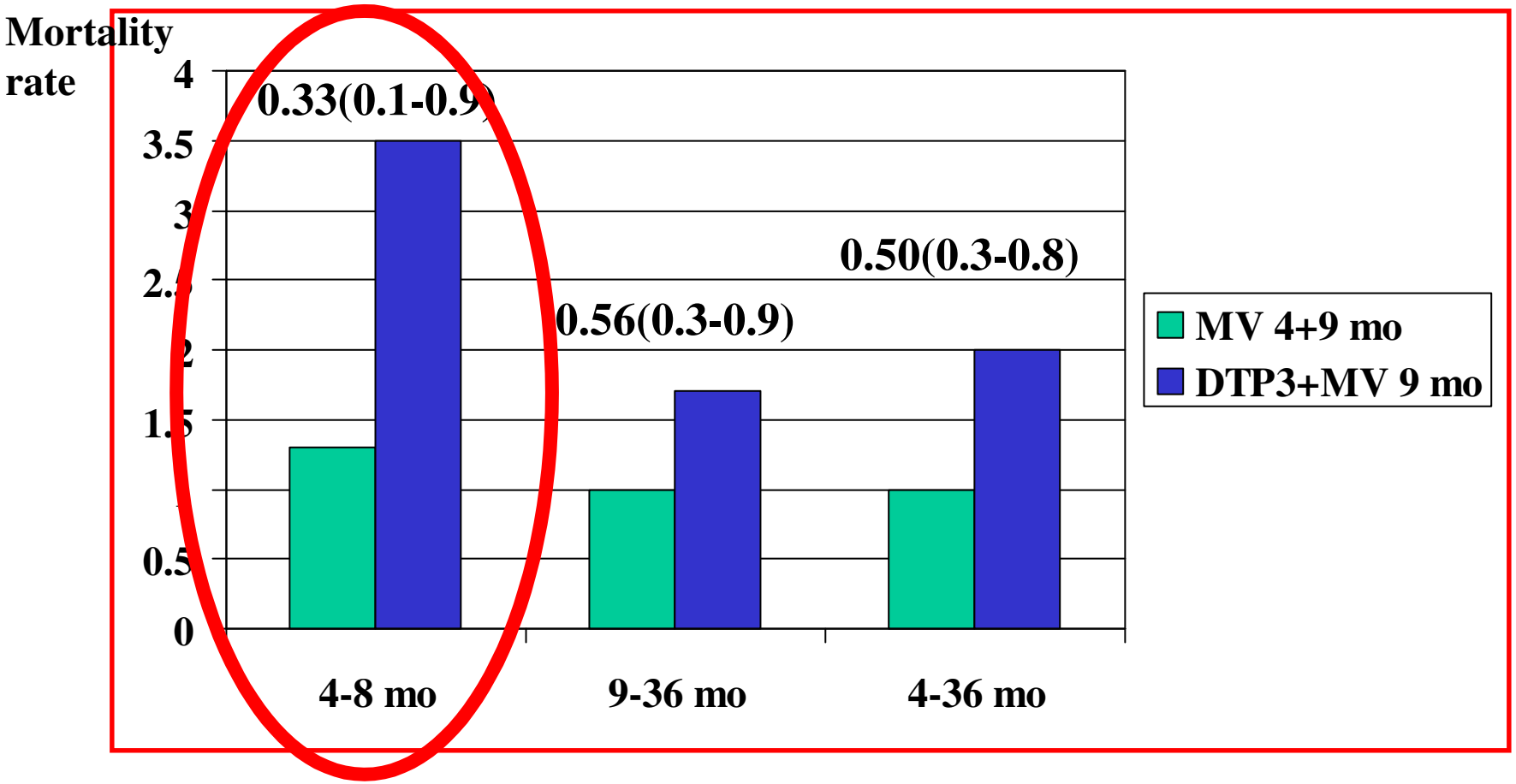
Reduced the risk of hospitalization for HIV-infection by 65% (12-86%)

The eradication of measles will lead to DTP being the last vaccination in childhood



* Significant difference between DTP and BCG or between DTP and MV

MV at 4+9mo vs No vac(DTP3)+MV at 9mo



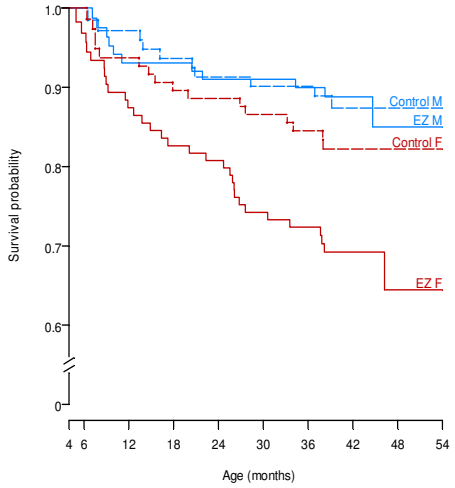
Having DTP as last vaccination
The only RCT suggests 3-fold higher mortality in infancy for DTP =>
Globally this would mean 100,000s of children every year

The eradication scenario:What can be done?

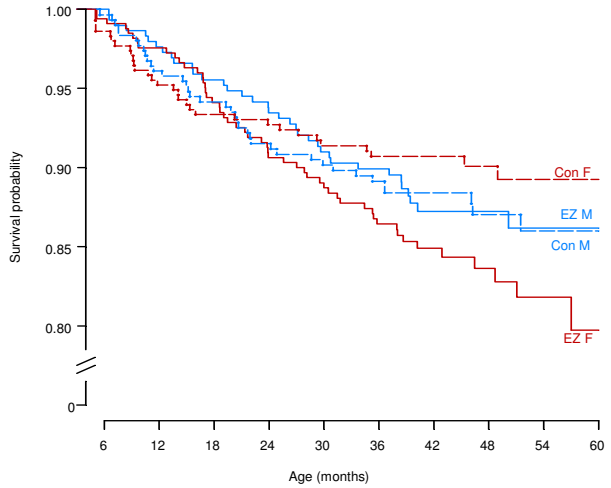
- Global health's eradication strategy is contradicted by all data
- INDEPTH sites are in best situation to resolve these contradictions: ***are there or are there not non-specific beneficial effects of vaccines***
- Polio - OPV
  - Test IPV vs OPV in RCT
  - Document effect of OPV campaigns –
    - Maybe have a phased implementation of a trial
  - Gradual phasing out of OPV
- Measles vaccine
  - Test 12 mo vs 9 mo in RCT
  - Document effect of MV campaigns (SIA) of children aged 9-60 months
    - Maybe phased implementation
    - Comparison of effects above and below 9 months
  - Gradual change in age of vaccination or phasing out
- Smallpox vaccine
  - More surveys

High-titre measles vaccine: 2-fold higher female mortality

BISSAU 1986-90, EZ-HT



SENEGAL 1987-92, EZ-HT



Lessons from high-titre measles vaccine (HTMV) trials:

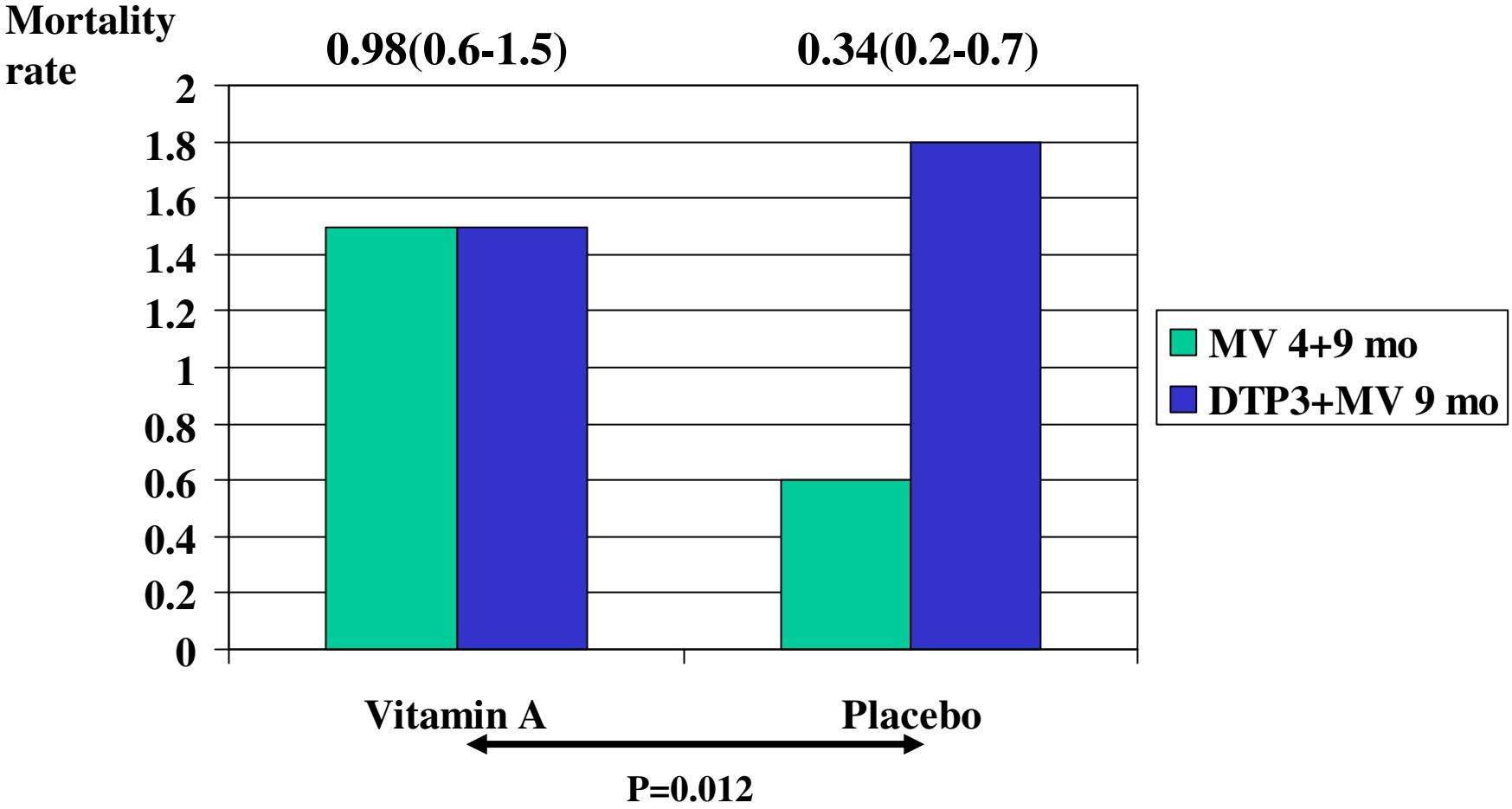
- **EZ HTMV was fully protective against measles => negative non-specific effect**
- **Sex-differential effect**
- **Public health effects: 35% excess mortality from 4 to 60 months => at least ½ mill annual deaths in Africa**

WHO introduced HTMV 1989 and withdrew it in 1992 =>

Interpretation: Too much of a good thing => Major donors: Money for new vaccines!

=> We looked for important NSEs of other vaccines

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

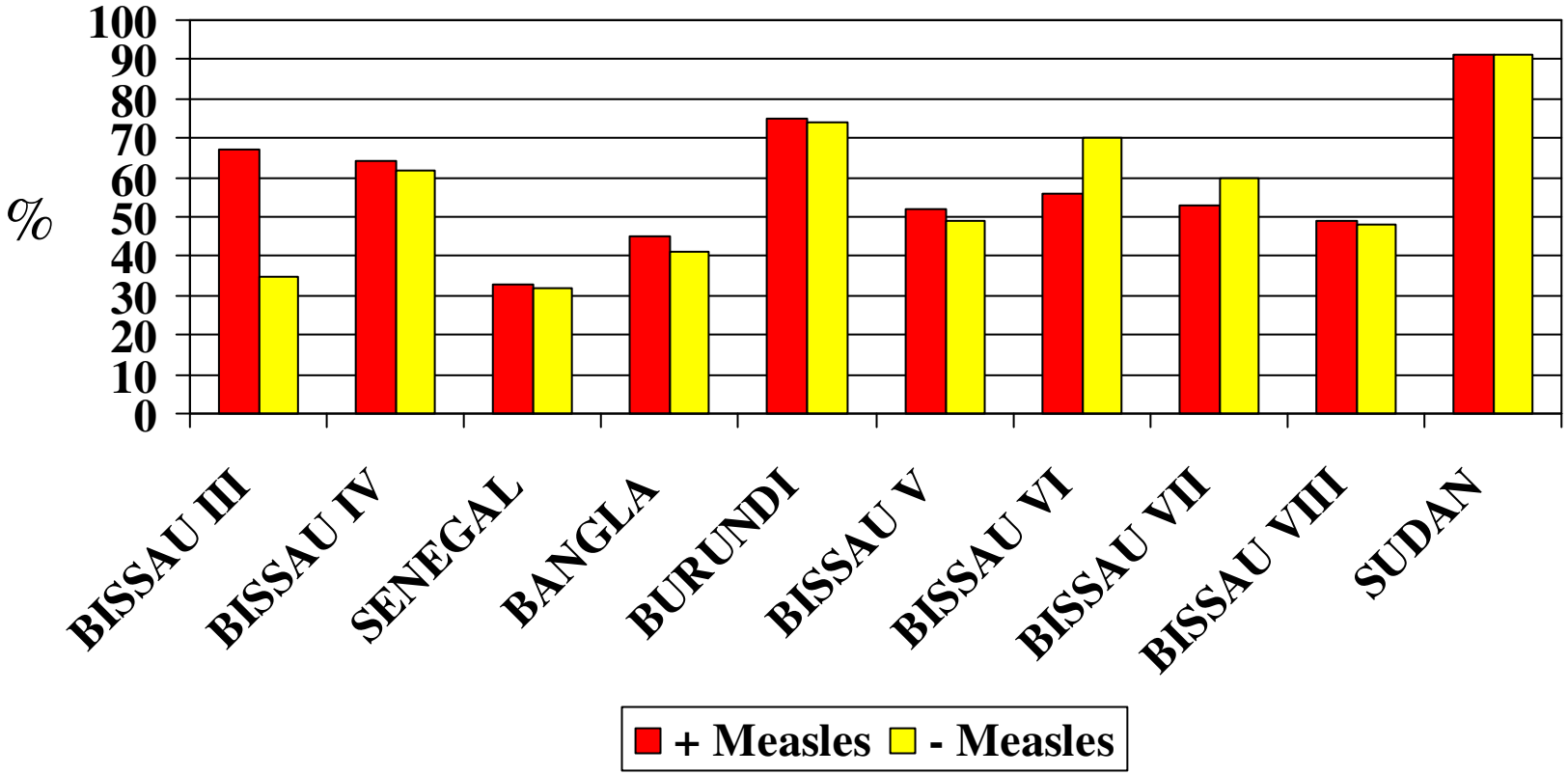
=> Only those who did not receive VAS-at-birth

Non-specific effects (NSE) of standard MV at 4½ and 9 months of age:

General reduction in childhood mortality

- Vaccines stimulate the immune system affecting susceptibility
- The NSE are often more important than specific effects
- Vaccination programmes should take the NSE into consideration: age at vaccination, number of vaccinations, sequence of vaccinations
- Reconsider assumptions –
    - Focus: specific diseases or immune deviations
    - Effects may differ for boys and girls
    - Interventions interact
- INDEPTH in a unique position to pursue these problems
- => EU is (hopefully) going to fund a multicentre trial of early MV

Impact of preventing measles infection: Reduction in mortality with or without measles cases in the survival analysis



Hypothesis: Non-specific beneficial immunestimulation