Randomised trial to test the non-specific effects of standard measles vaccine at 4½ and 9 months of age: General reduction in childhood mortality

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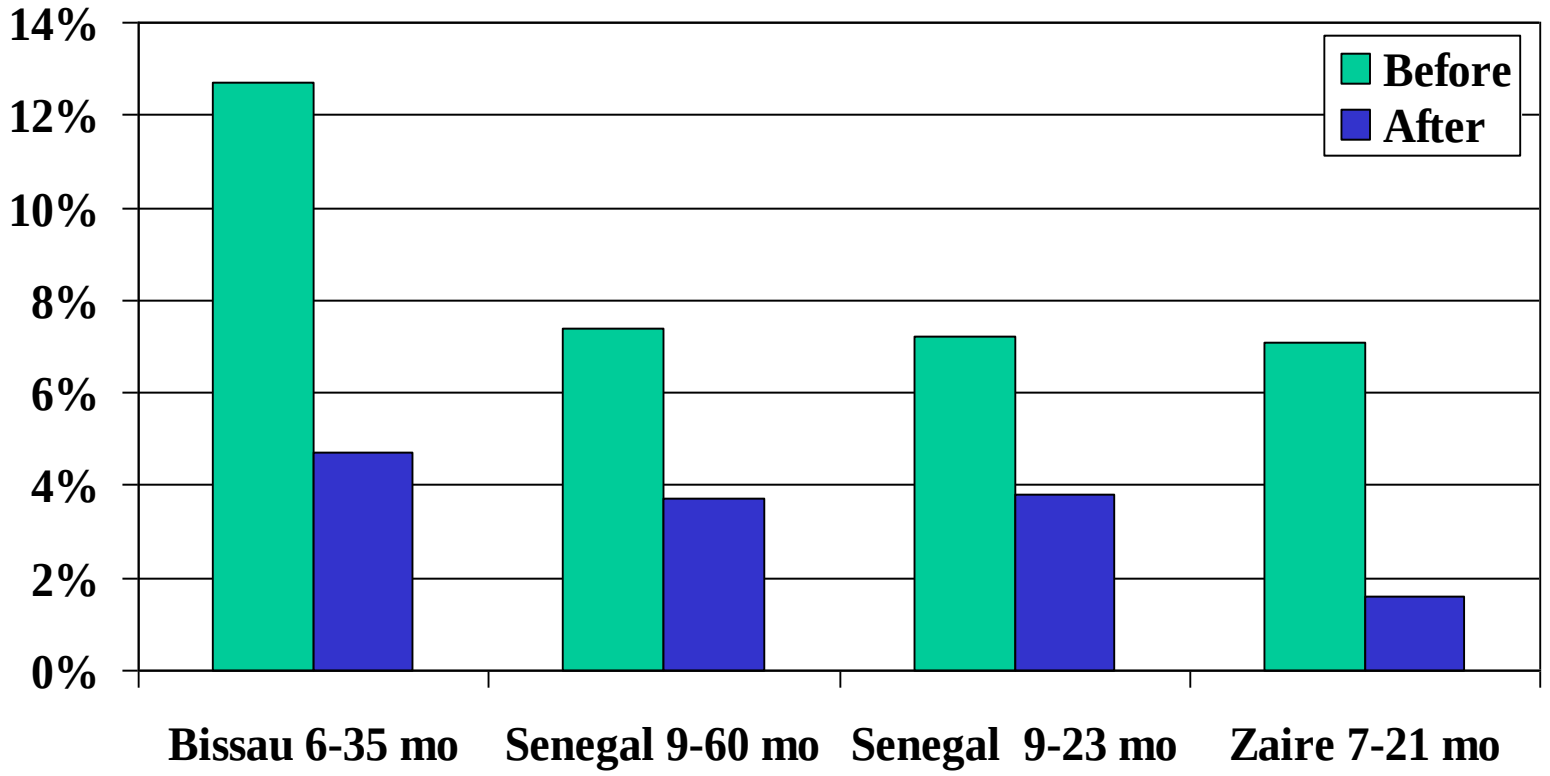
Introduction of measles vaccination in African communities: Annual mortality before and after



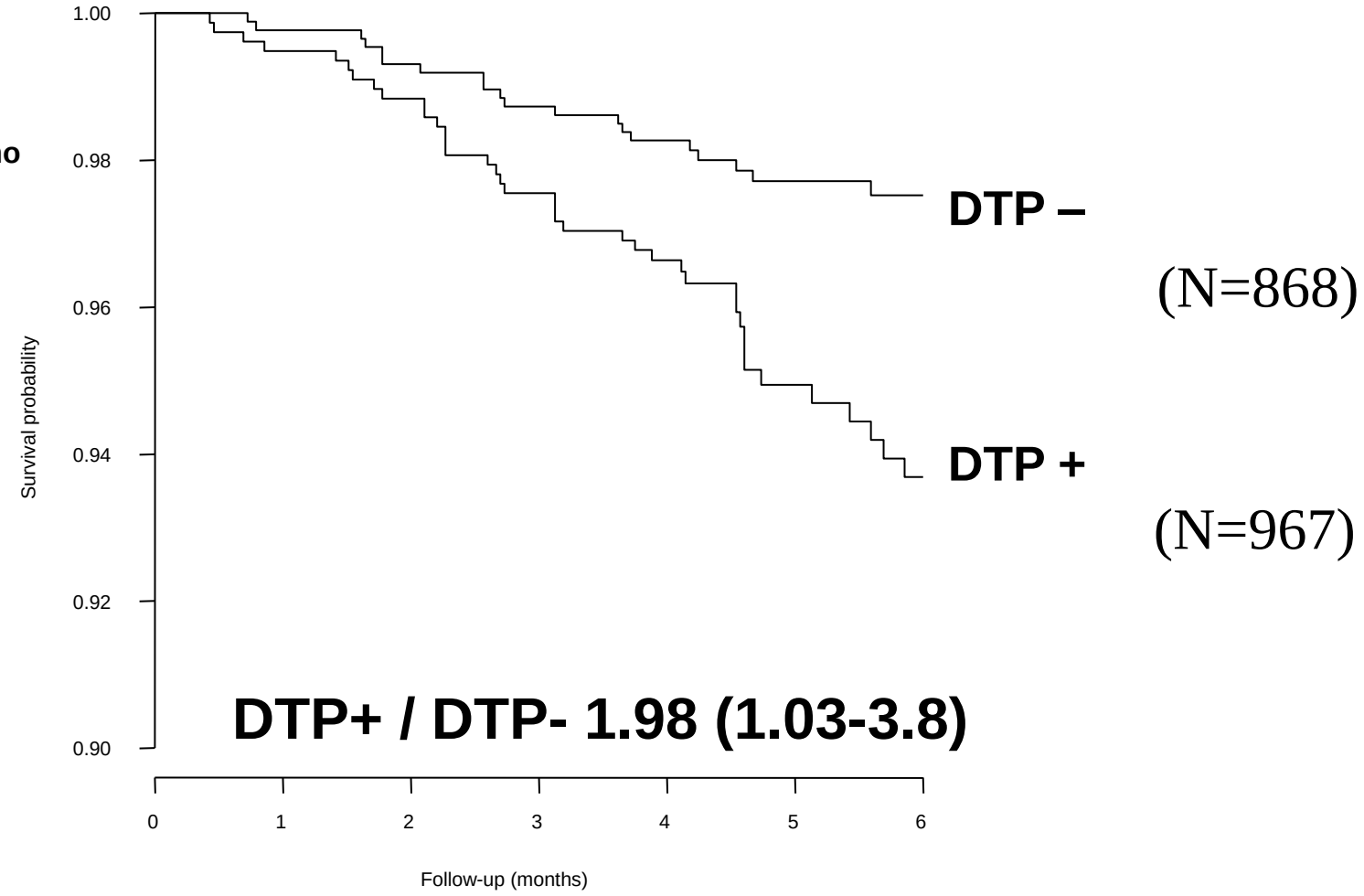
Measles not more than 10-20% of deaths. Reduction in mortality not due to prevention of acute and long-term effects of measles infection

Measles vaccine (MV) - beneficial non-specific effects (NSE)

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

Children aged 2-8 mo
Followed 6 mo

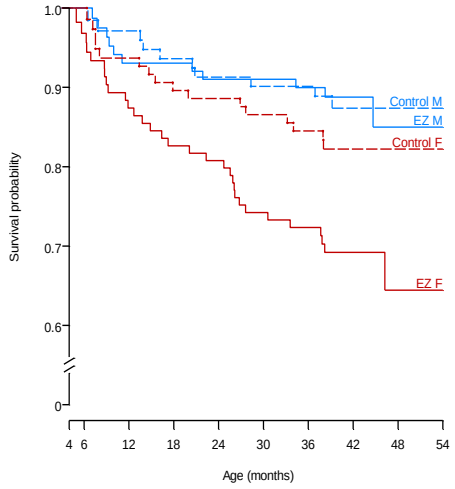
Unvaccinated: travelling; sick; days without vaccines



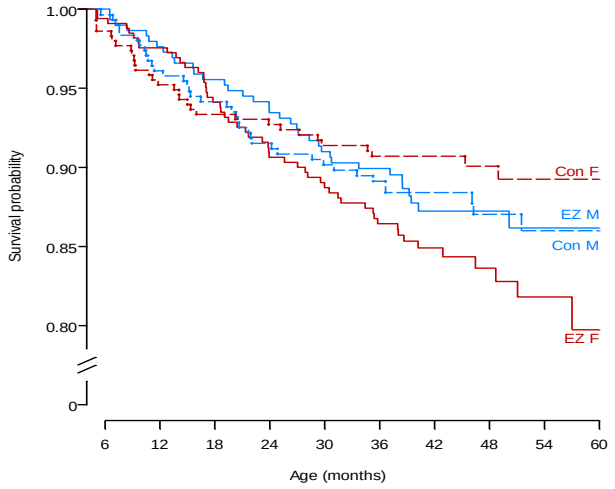
Diphtheria-Tetanus-Pertussis has negative effects for girls

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:

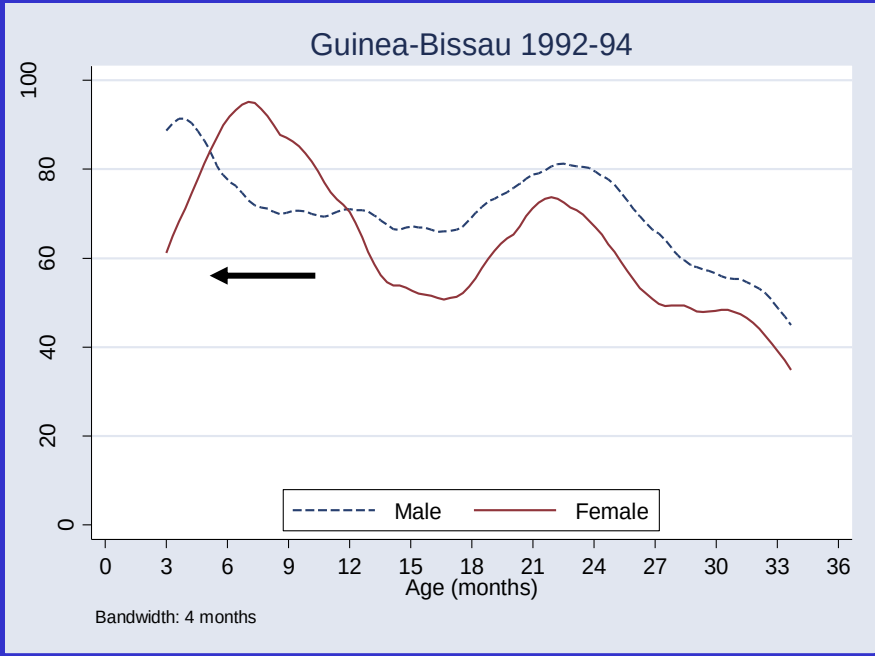
- **EZ HTMV was fully protective against measles => negative non-specific effect**
- **Sex-differential effect**
- **Public health effects: 35% excess mortality from 4 to 60 months => at least ½ mill annual deaths in Africa**

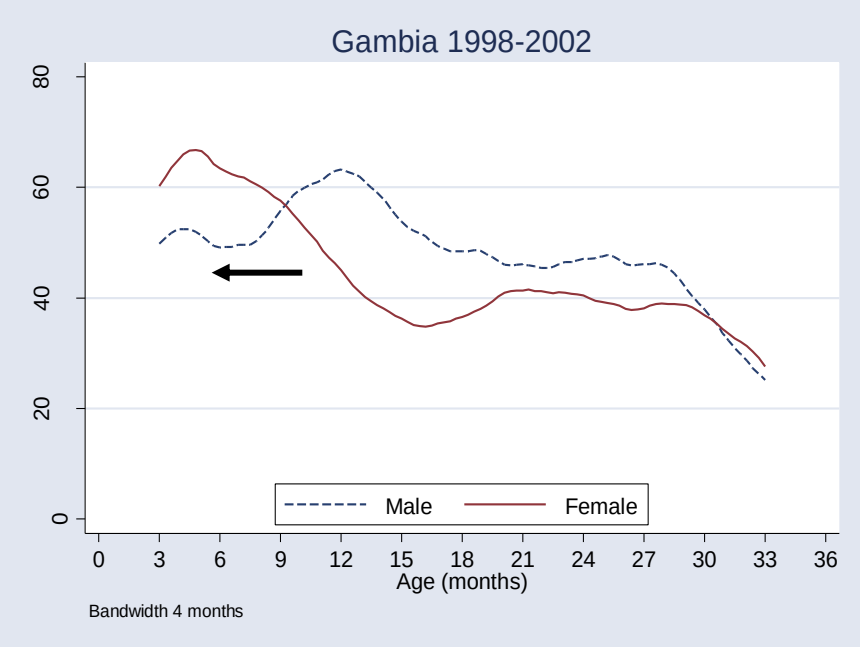
WHO introduced HTMV 1989 and withdrew it in 1992 =>

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

=> We looked for important NSEs of other vaccines

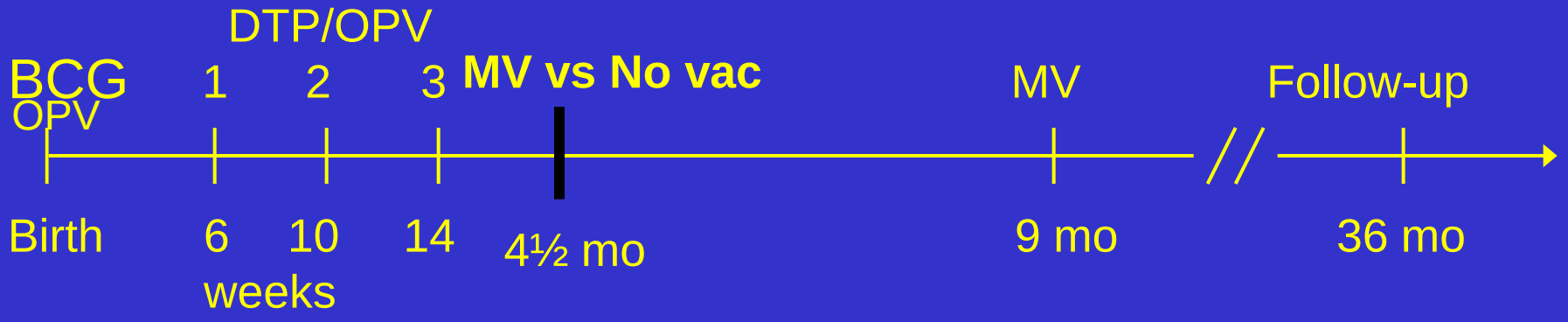
What can be done to reduce the negative effect of DTP?





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



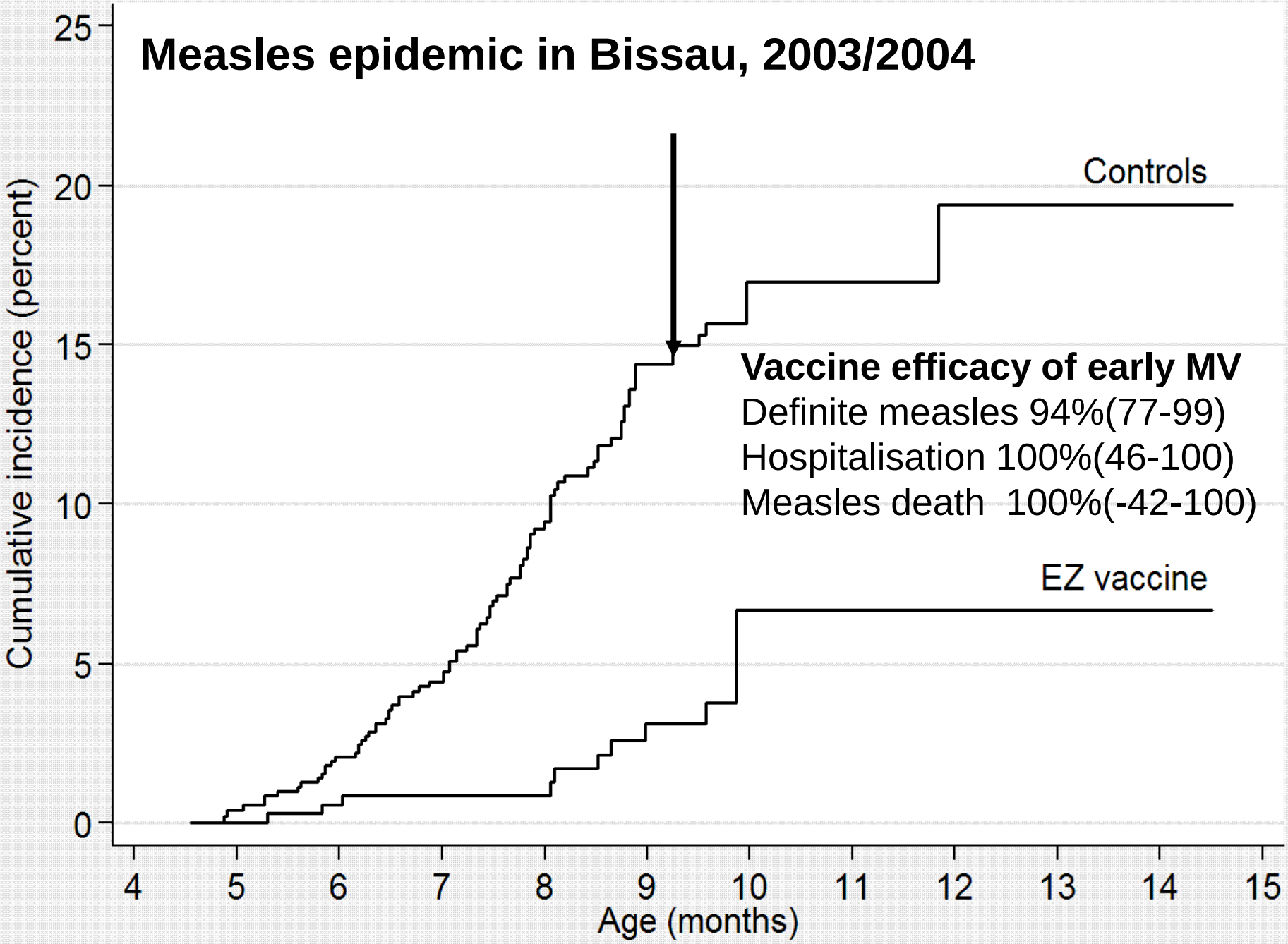
- **Recruitment 2003-2007 – Follow-up to 2009**
- **6,600 randomised to A) Edmonston-Zagreb (EZ) at 4½+9 mo, or B+C) no vaccine at 4½ mo and EZ MV or Schwarz MV at 9 mo**
- **DTP3 four weeks before enrolment – to prevent the problem of DTP after MV**
- **Study designed to test a 25% difference in mortality**

Comparisons

- **MV versus DTP3 between 4 and 8 months**
- **MV at 4+9 mo versus MV at 9 mo between 9-36 mo**

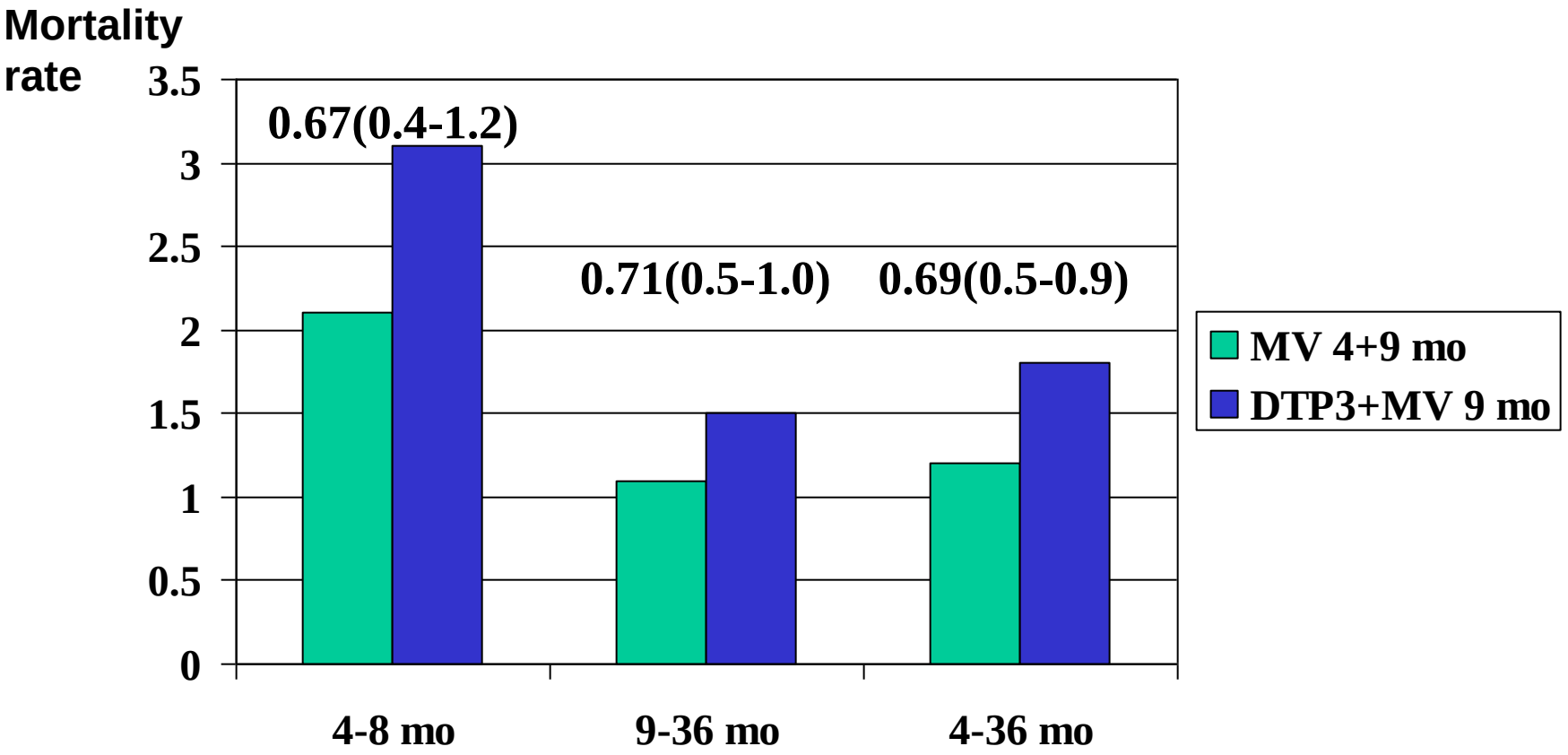
Procedures

- Newborns were identified in database of Bandim HDSS
- Before inclusion, mothers reminded to complete the OPV/DTP vaccination schedule at 6,10, and 14 wks
- The formal inclusion in the study was carried out at 4½ months of age


Measles epidemic in Bissau, 2003/2004
Cumulative incidence (percent)
0
5
10
15
20
25
4
5
6
7
8
9
10
11
12
13
14
15
Age (months)
Controls
EZ vaccine
Vaccine efficacy of early MV
Definite measles 94%(77-99)
Hospitalisation 100%(46-100)
Measles death 100%(-42-100)

MV at 4½+9mo vs No vac(DTP3)+MV at 9mo

Follow to 3 yrs for all children (2003-2009)

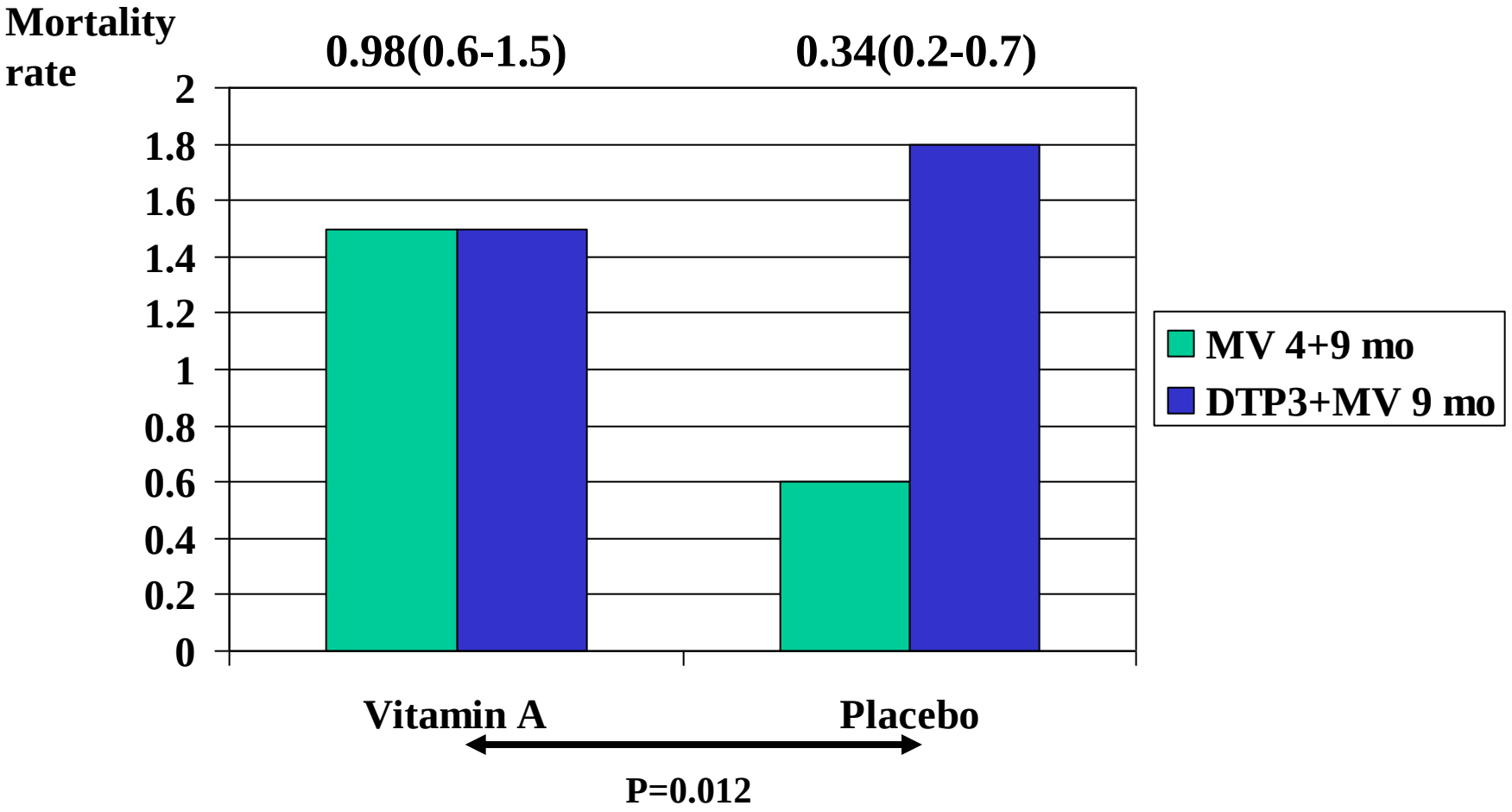


Two MVs at 4 and 9 mo: **31% (6-49%)** **(F: 41 %(9-62); M: 18%)**

Measles inf censored **26% (0-46%)**

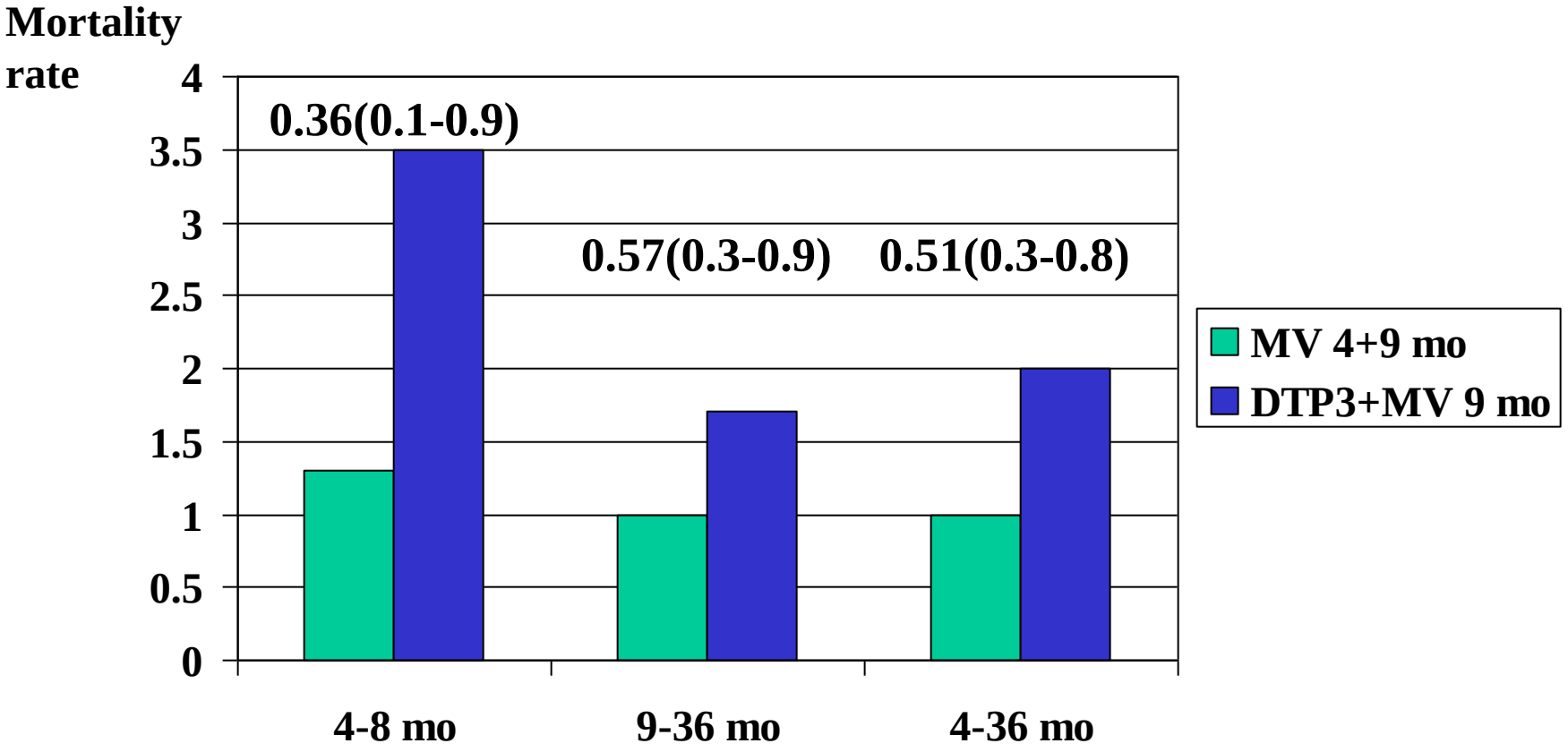
(NB not against unvaccinated)

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

MV at 4+9mo vs No vac(DTP3)+MV at 9mo (3402 infants with no Vitamin A at birth)

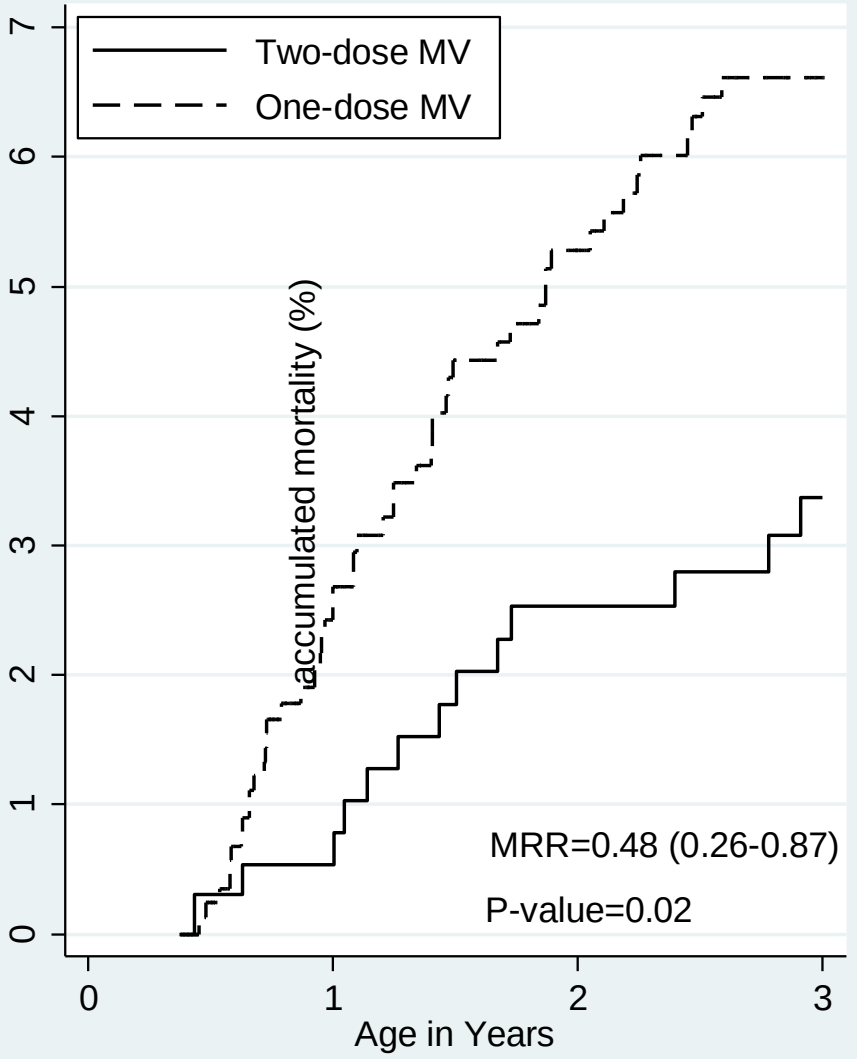


Reduction in overall mortality:

Two MV at 4½ and 9 mo: 49% (22-68) (F: 53%(14-74); M: 44%)

Measles inf censored 45% (14-65)

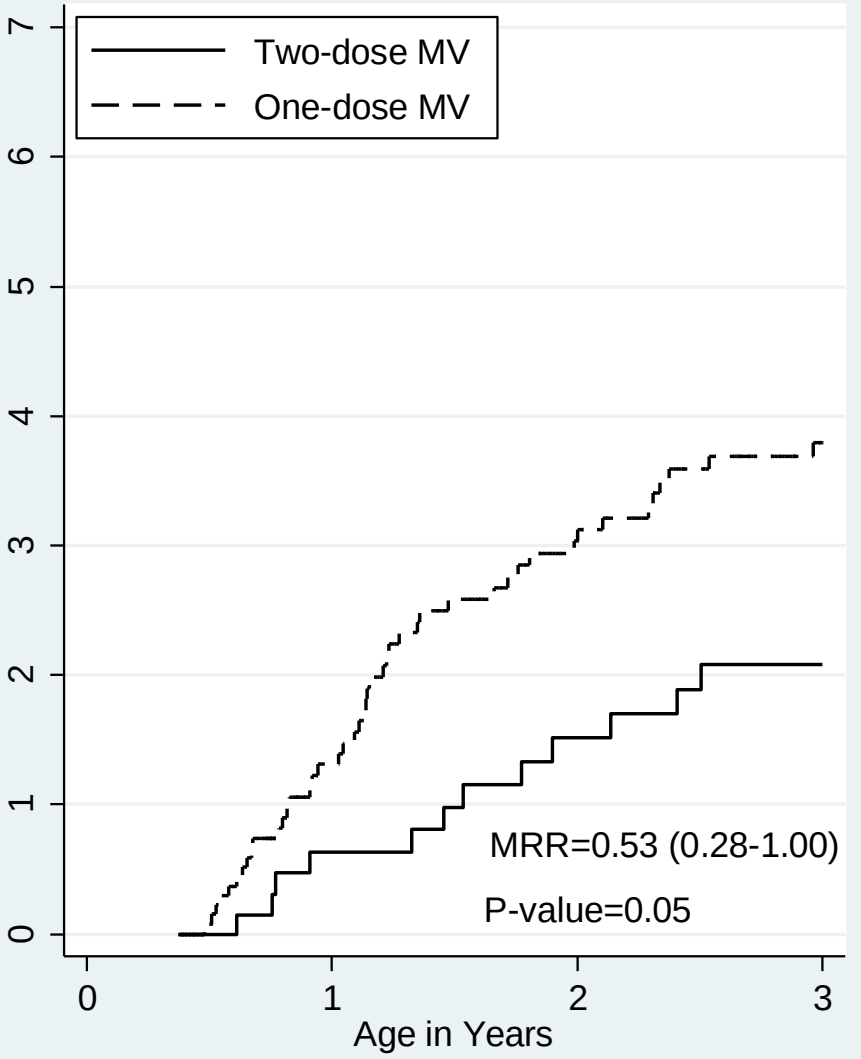
Children born before June 2004



Number at risk

Two-dose	405	377	334
One-dose	750	660	594

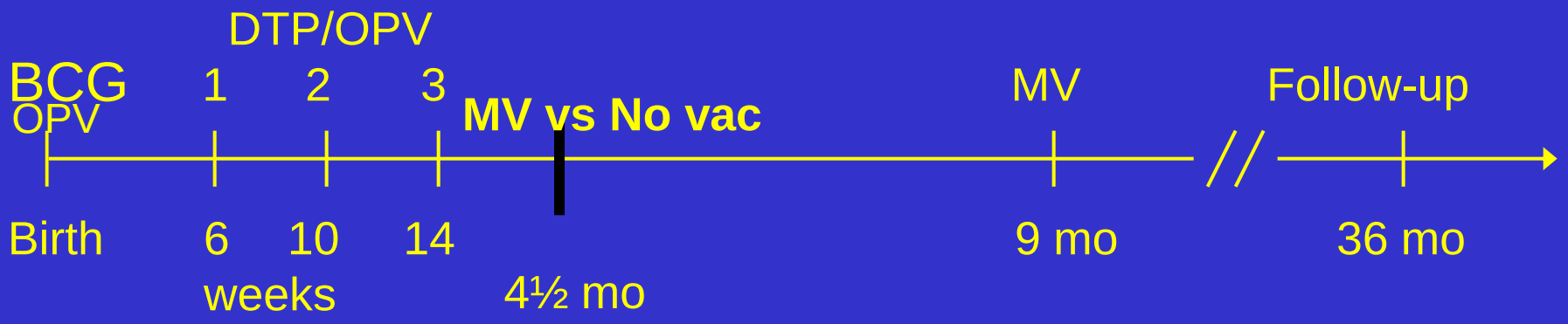
Children born after June 2004



Number at risk

Two-dose	599	541	485
One-dose	1184	1062	940

Testing non-specific effects of early measles vaccination: Conclusions



Key features

- **Low maternal antibody levels**
- **Edmonston Zagreb (EZ) measles vaccine**
- **All had DTP3 before measles vaccine**

Conclusions

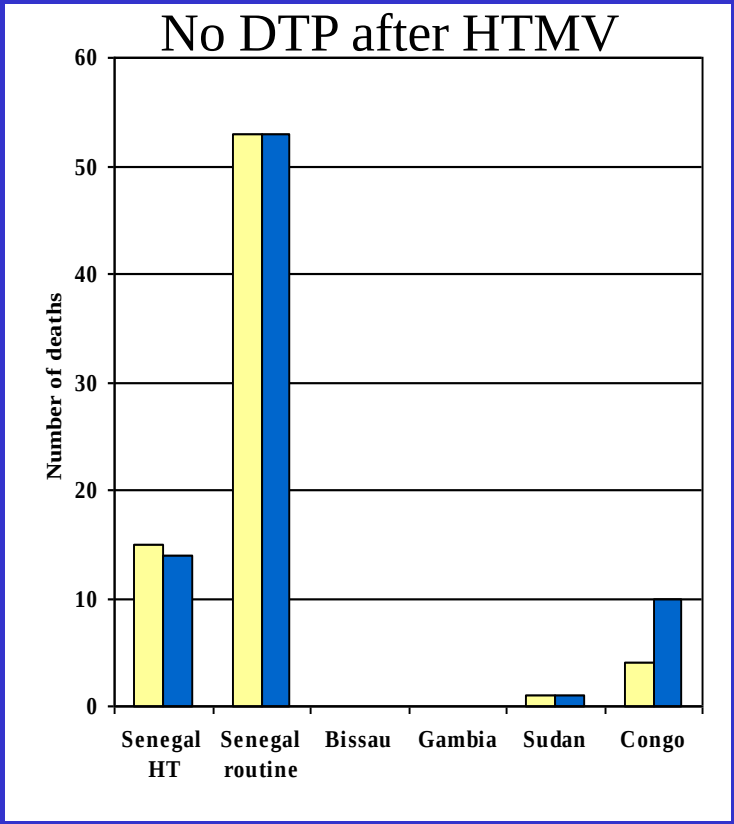
- **EZ at 4½ mo is protective against measles infection**
- **MV affects non-measles morbidity - 49% (15-69) reduction in hospitalisations for girls – 16% for boys**
- **MV vs DTP3 between 4-8 mo: 64% (8-86) reduction in mortality**
- **MV at 4½+9 mo vs MV at 9 mo between 9-36 mo: 43% (7-66)**

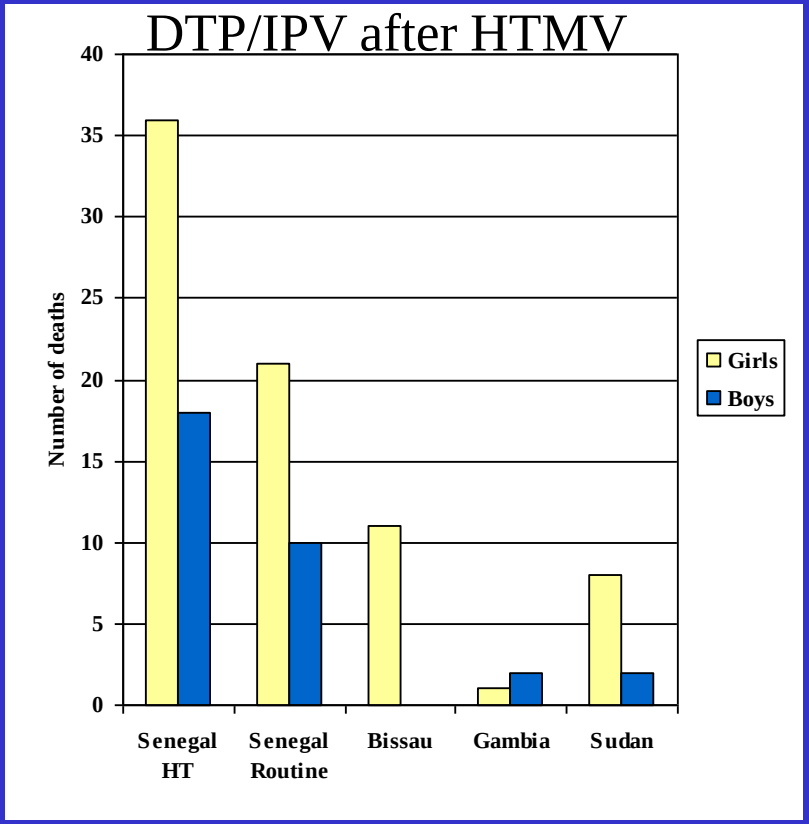
Non-specific effects (NSE) of standard MV at 4½ and 9 months of age:

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

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