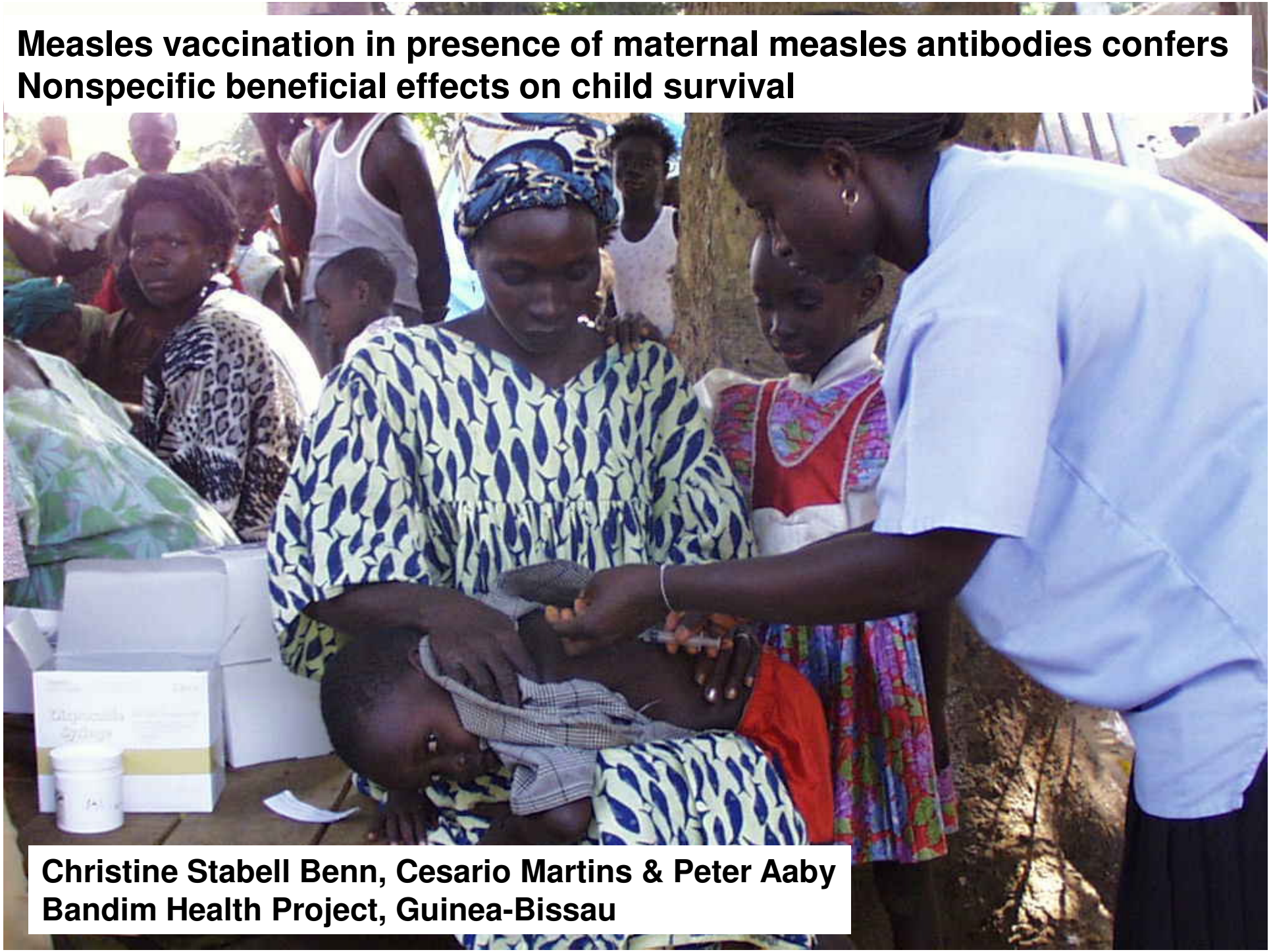
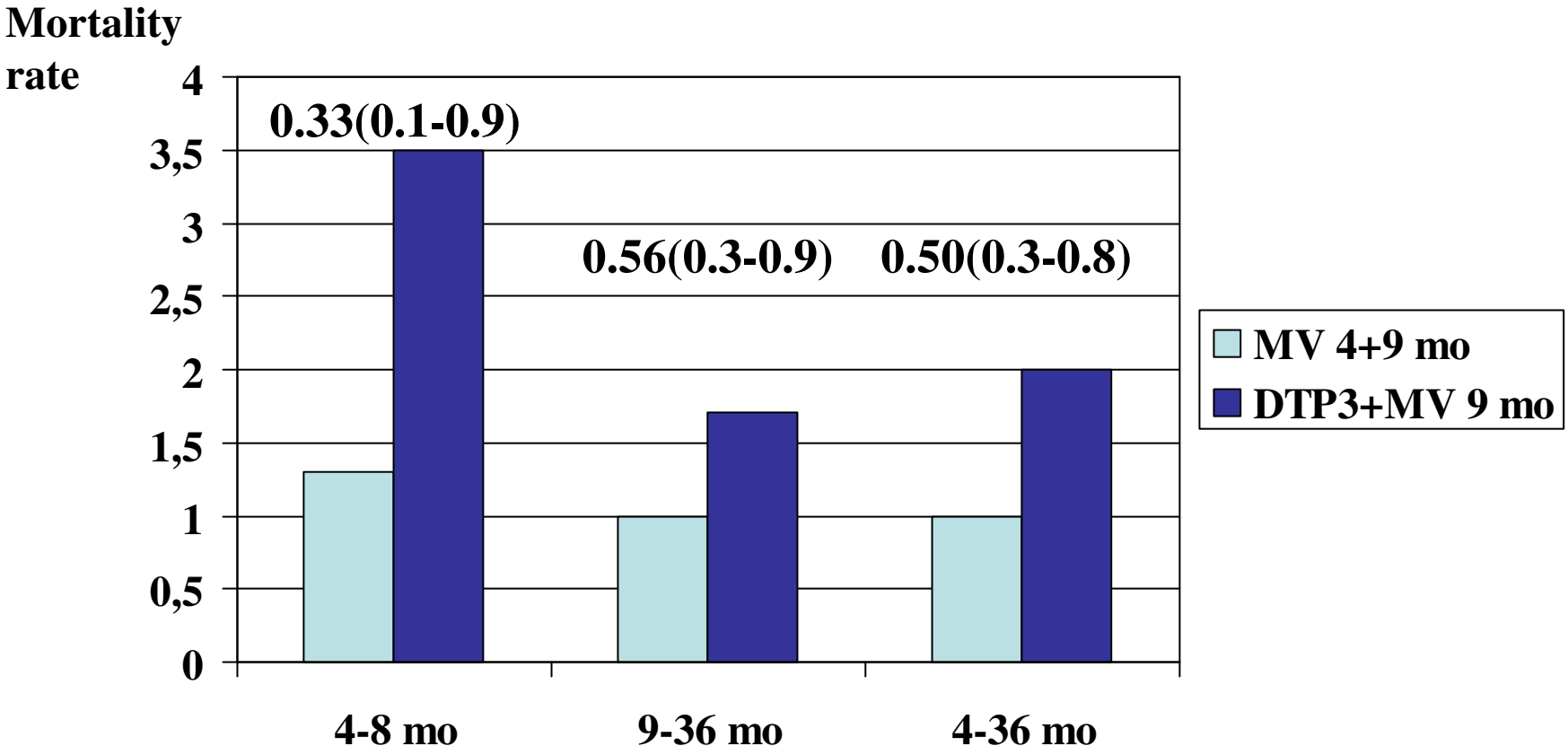
Measles vaccination in presence of maternal measles antibodies confers Nonspecific beneficial effects on child survival



Christine Stabell Benn, Cesario Martins & Peter Aaby
Bandim Health Project, Guinea-Bissau

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



Reduction in overall mortality:

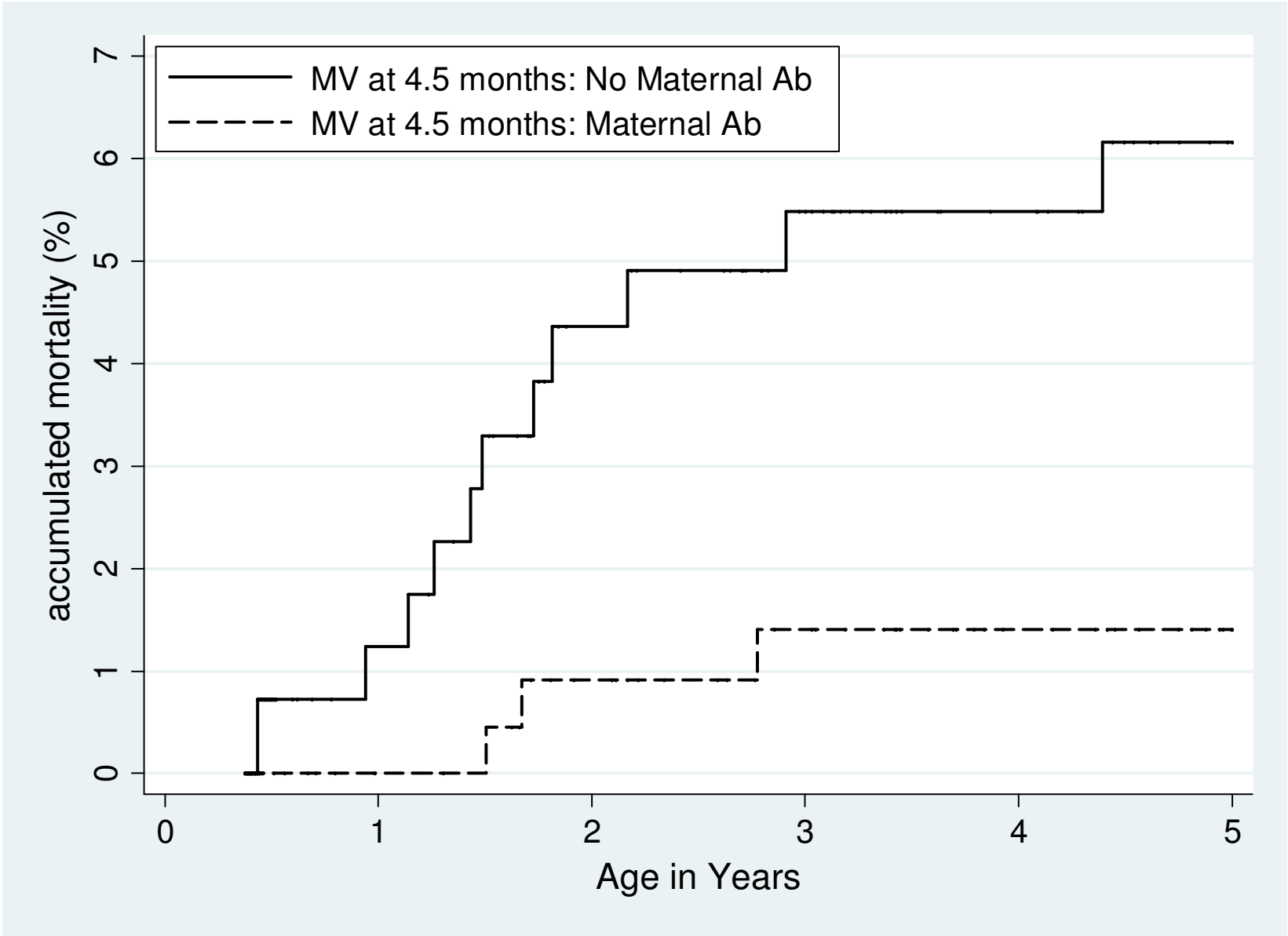
Two MV at 4½ and 9 mo:	**50% (22-68)**	**(F: 53%(14-74); M: 44%)**
Measles inf censored	**45% (14-65)**	

BMJ 2010

Development of hypothesis

- Zinkernagel: One should meet the pathogens in the presence of maternal antibodies

- Beneficial to receive measles vaccine in the presence of maternal measles antibodies?

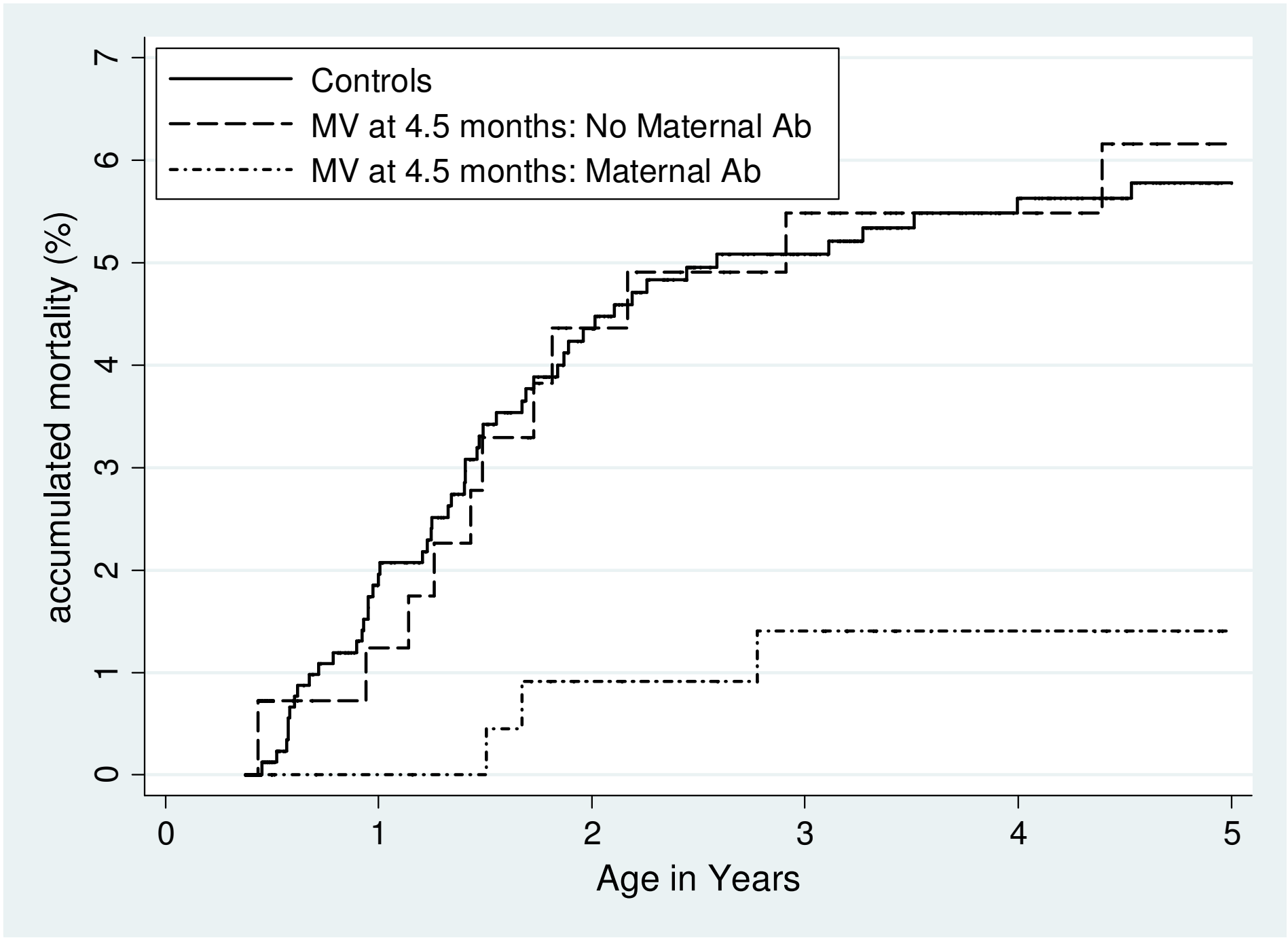


N=450
60% had MatAb

16>= Mother´s level

Mortality ratio from 4 to 60 mo

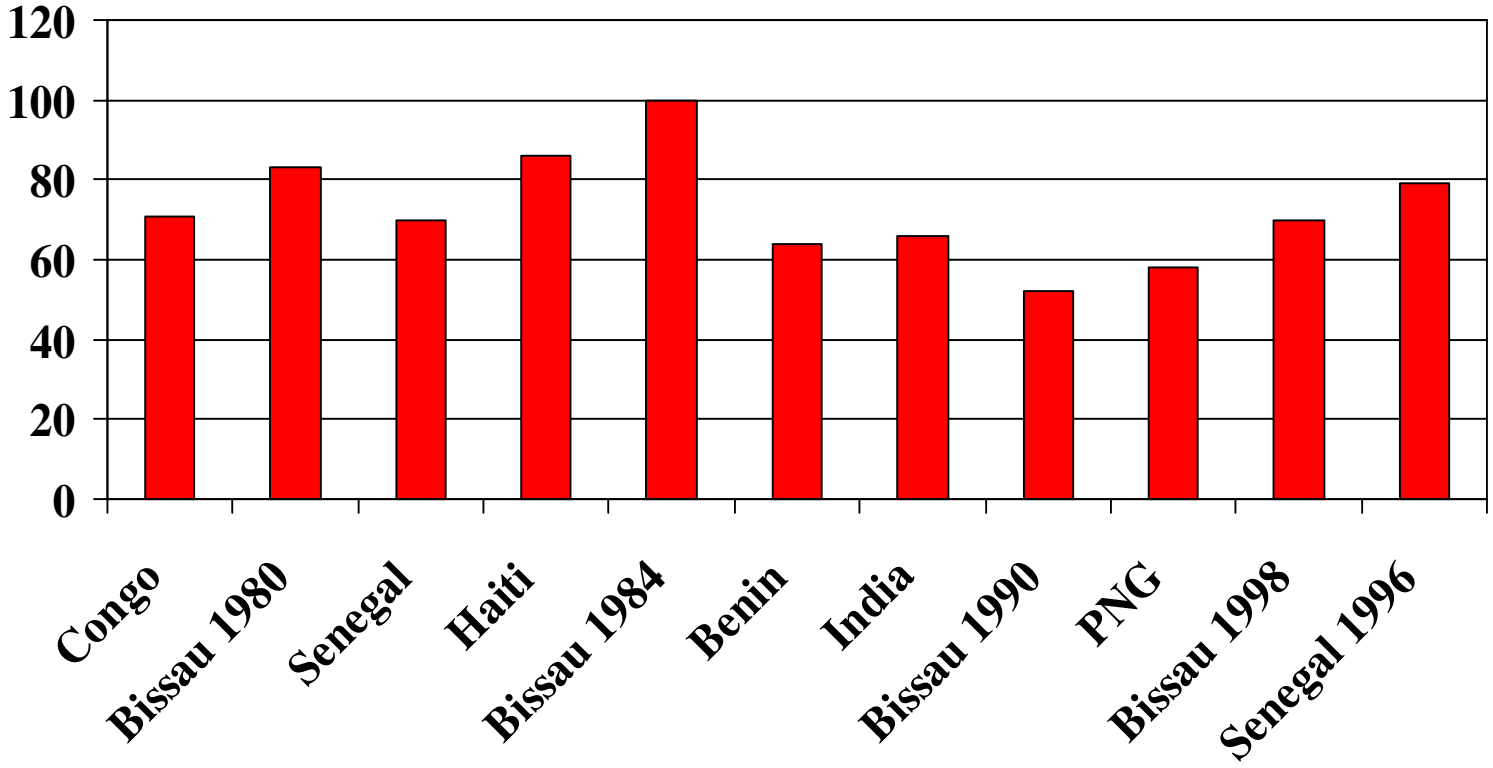
MV4mo+MatAb vs MV4mo+No MatAb	**0.23 (0.1-0.8)**
Effect after 2nd MV (9-60 mo)	**0.26 (0.1-0.9)**


Controls
MV at 4.5 months: No Maternal Ab
MV at 4.5 months: Maternal Ab
accumulated mortality (%)
0
1
2
3
4
5
6
7
0
1
2
3
4
5
Age in Years

MV in presence or absence of MatAb: Effect on survival in RCTs in Guinea-Bissau

Study	Period	Age MV	MatAb+ (deaths/ pyrs)	No MatAb (deaths/ pyrs)	Mortality Ratio
DTP not given after MV					
2-dose MV	2003-09	4½ mo	3/908	11/760	**0.23 (0.1-0.8)**
DTP given with or after MV					
Medium-titre EZ MV	1985-90	4 mo	17/568	15/266	0.53 (0.3-1.1)
2-dose MV	1993-98	6 mo	0/75	11/339	0 (0-2.0)
Combined					**0.45 (0.2-0.9)**

Reduction in mortality %) associated with measles vaccination (MV):
Comparing MV before 12 months versus MV unvaccinated children



MV before median age of MV is better for child survival than later MV: Mortality ratio <median/>median: 0.49(0.3-0.8)
(No difference among controls)

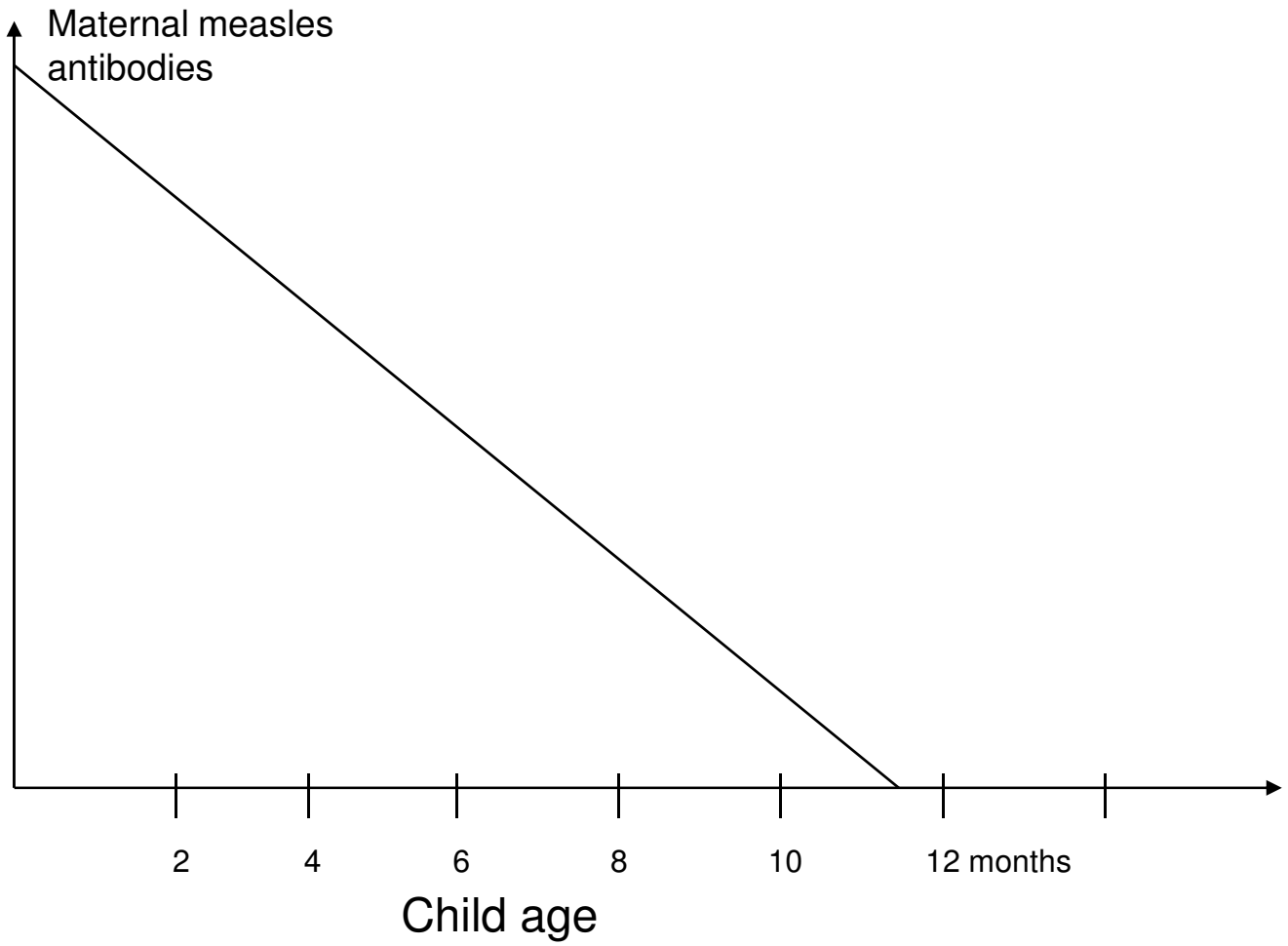
MatAb likely explanation

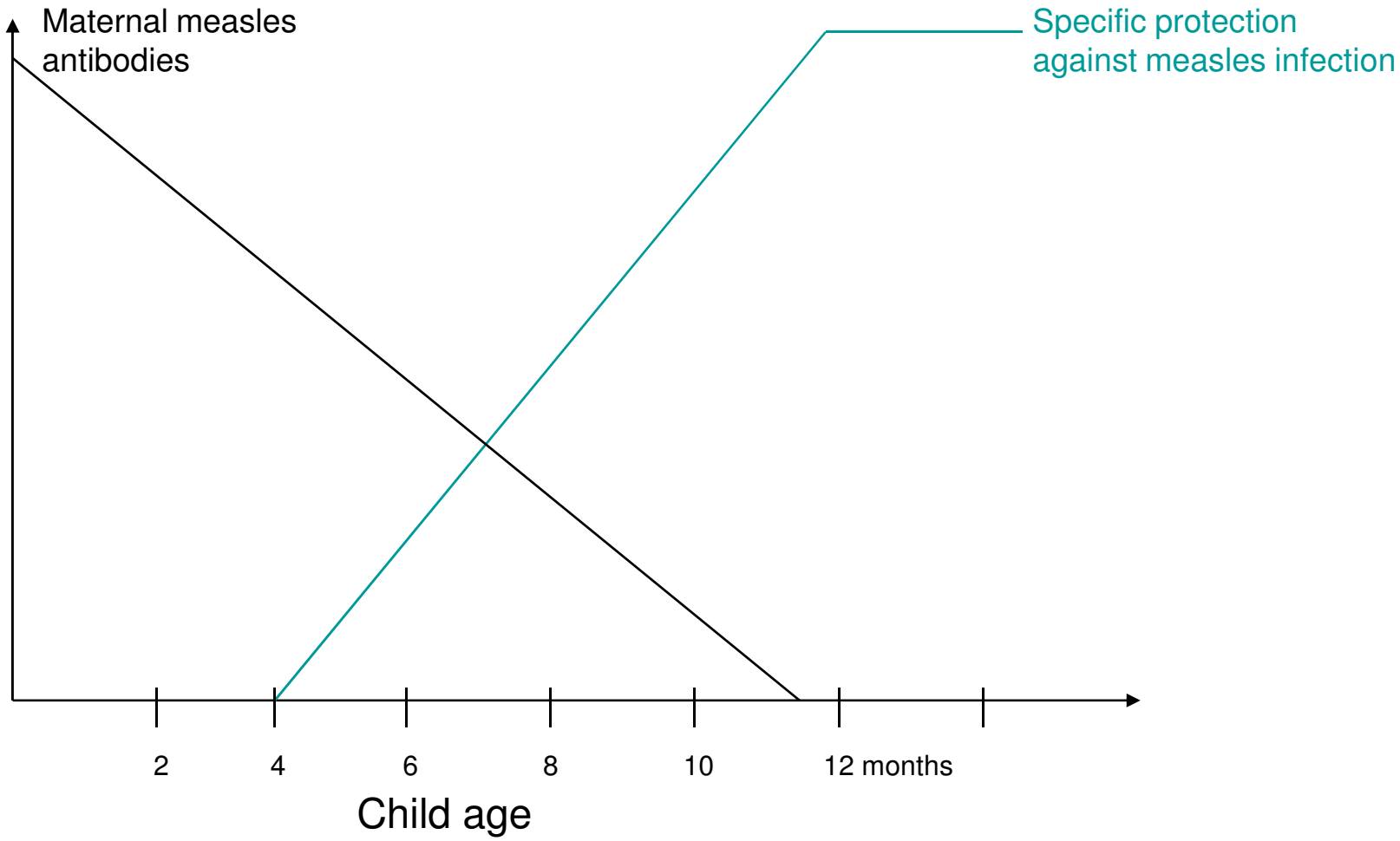
Biological mechanisms?

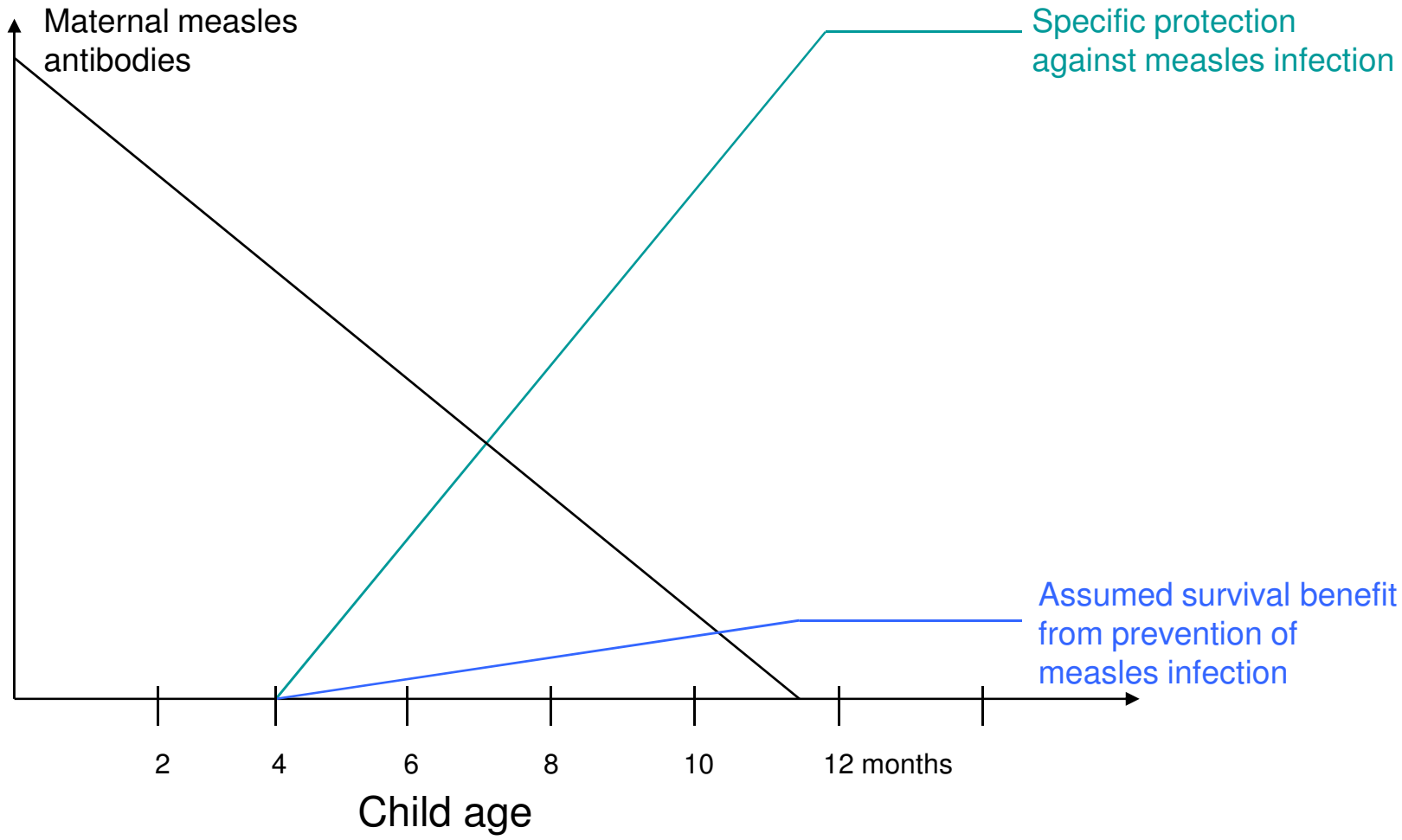
- Animal studies: vaccines induce heterologous protection against unrelated antigens through cross-reaction of T-cell epitopes
- The beneficial non-specific effects of measles vaccine could be caused by heterologous immunity due to cross-reactive epitopes

- In the presence of maternal antibodies, the child may respond more to subdominant epitopes, leading to a more diverse T- and B-cell repertoire and increased heterologous protection against other pathogens

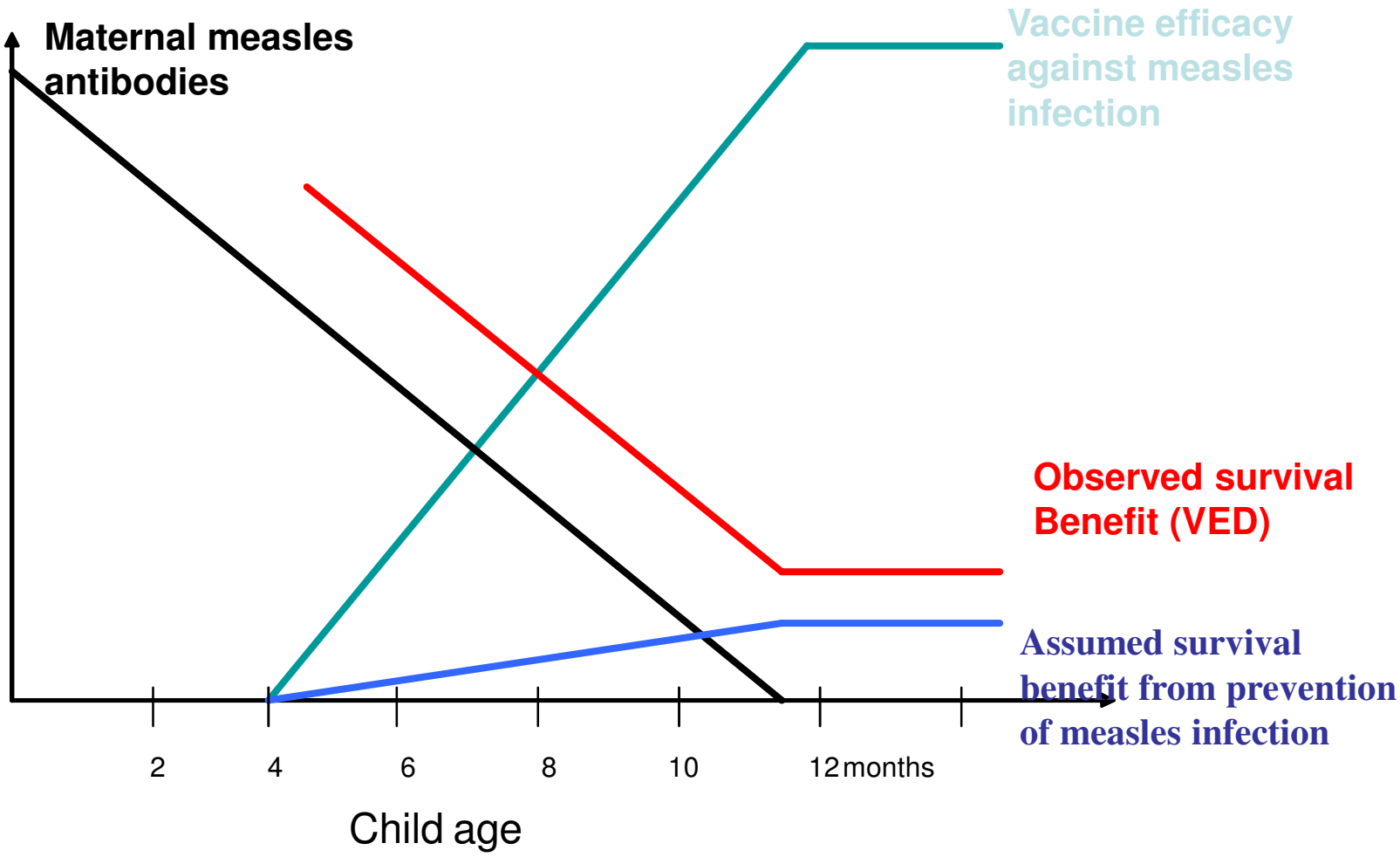
- Furthermore, maternal antibody-antigen complexes are powerful immunogens, and this could result in enhanced T-cell responses in infants immunised in the presence rather than in the absence of maternal antibodies


Maternal measles
antibodies
2
4
6
8
10
12 months
Child age


Maternal measles antibodies
Specific protection against measles infection
2
4
6
8
10
12 months
Child age



Latin America in 1996: age of MV increased from 9 to 12 months
SAGE recommends to increase MV from 9 to 12 months with improved control



Eradication of measles vil increase child mortality?

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

SAGE recommends to increase MV from 9 to 12 months with improved Measles control

Prediction: Infants will be deprived of beneficial effects of MV

=> Child mortality will increase

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)

Conclusions and implications

- The current MV programme assumes that the efficacy of MV against measles infection and the effect on survival increases with age as maternal antibodies wane.
- However, in total contradiction of these assumptions,
  - the beneficial effect of MV was found only among children who had maternal antibodies at the time of vaccination
  - MV at 4.5 months of age in the presence of maternal antibody reduced all-cause mortality 4-fold between 4.5 months and 5 years of age compared with controls who received the recommended MV at 9 months of age
- Implications:
  - we would need to understand how maternal antibodies generate a beneficial immune profile following early measles vaccination
  - current MV policies should be reconsidered; we should vaccinate earlier rather than later

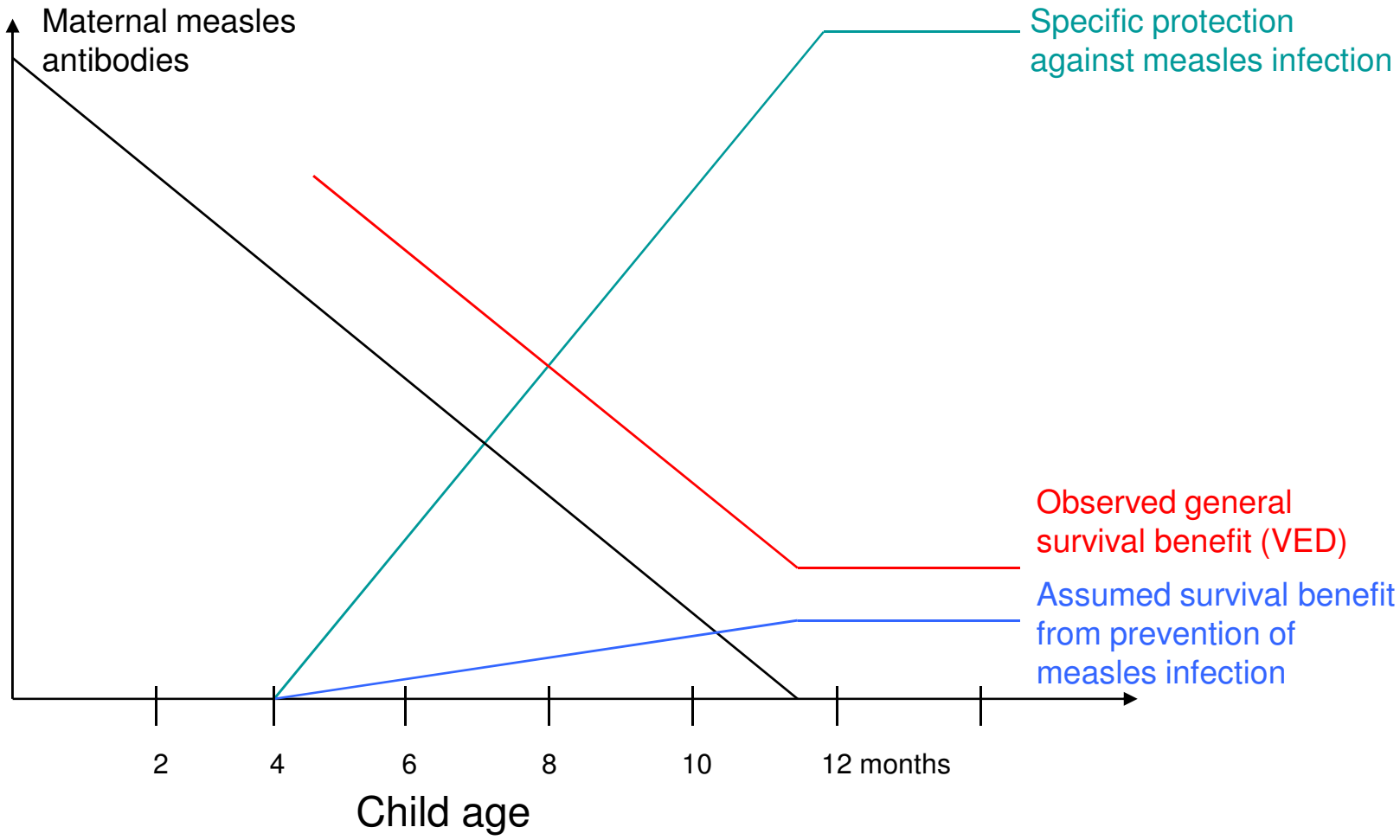

Maternal measles antibodies
Specific protection against measles infection
Observed general survival benefit (VED)
Assumed survival benefit from prevention of measles infection
2
4
6
8
10
12 months
Child age

Table 1. Mortality between 4.5 and 60 months of age in relation to the presence of maternal HAI antibodies at the time of measles vaccination (4.5 months of age)

Maternal antibody concentration	Deaths/children having lower level than mother	Deaths/children having same or higher level than mother	Deaths/all children
< 31.25 miU (minimum detectable level)	11/201		11/201
31.25 miU*	0/84	0/1	0/85
62.50 miU*	1/44		1/44
125	1/45	0/1	1/46
250	0/31	1/1	1/32
500	0/14	0/1	0/15
1000	1/9	0/2	1/11
2000	0/4	0/3	0/7
4000	0/2	0/4	0/6
8000		0/2	0/2
16000		0/1	0/1
31.25-16000 miU	3/233	1/16	4/249

Note: Titres of <125 miU are usually considered non-protective; antibodies were measured with the HAI (haemagglutination inhibition) test.

MRR for antibody+MV/no antibody+MV: 0.23 (0.06-0.82)