



Vitamin A, Immune modulation and Mortality

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Current Assumptions

- Observation: Vitamin A deficiency associated with increased mortality
- Several randomised trials in late 80's-early 90's: Vitamin A supplementation associated with decreased overall mortality
- Assumption: Vitamin A supplementation acts by preventing vitamin A deficiency



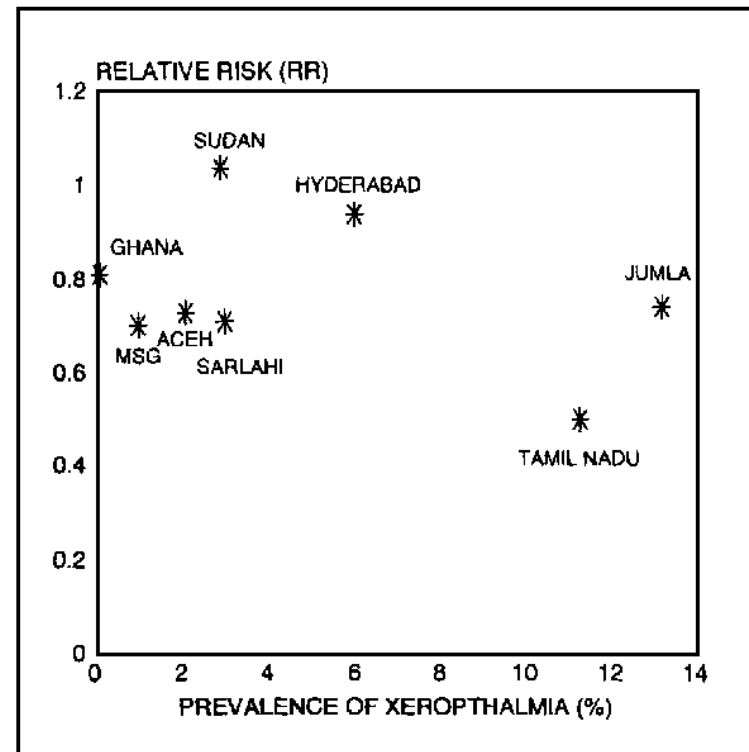
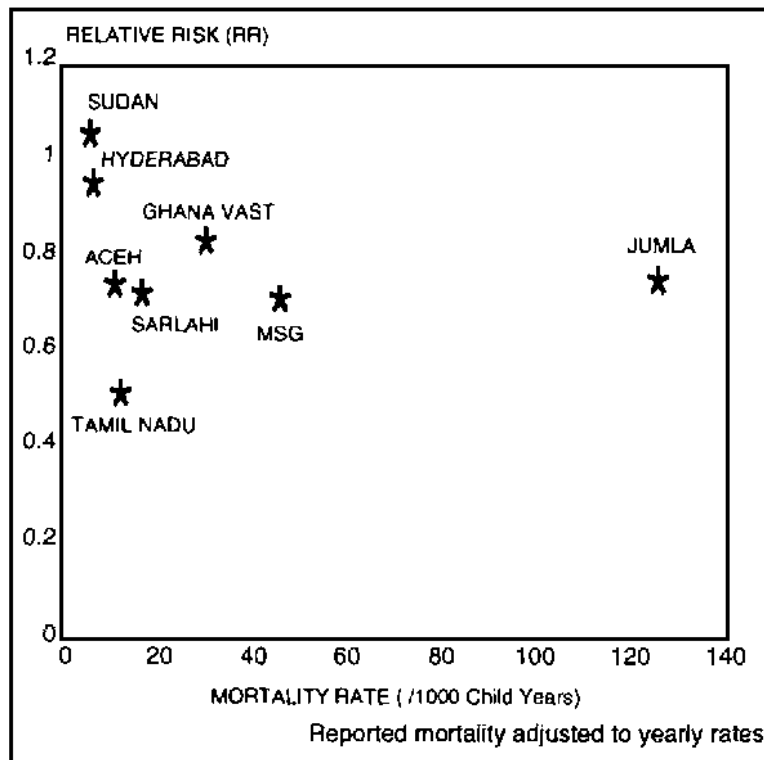
Challenging Current Assumptions

- Vitamin A is an immunomodulator => At times beneficial, at times harmful
- Three main illustrations:
 - Vitamin A and vitamin A deficiency
 - Vitamin A and infectious diseases
 - Vitamin A and vaccines
- Taken together the data show that vitamin A supplementation does more than treat vitamin A deficiency



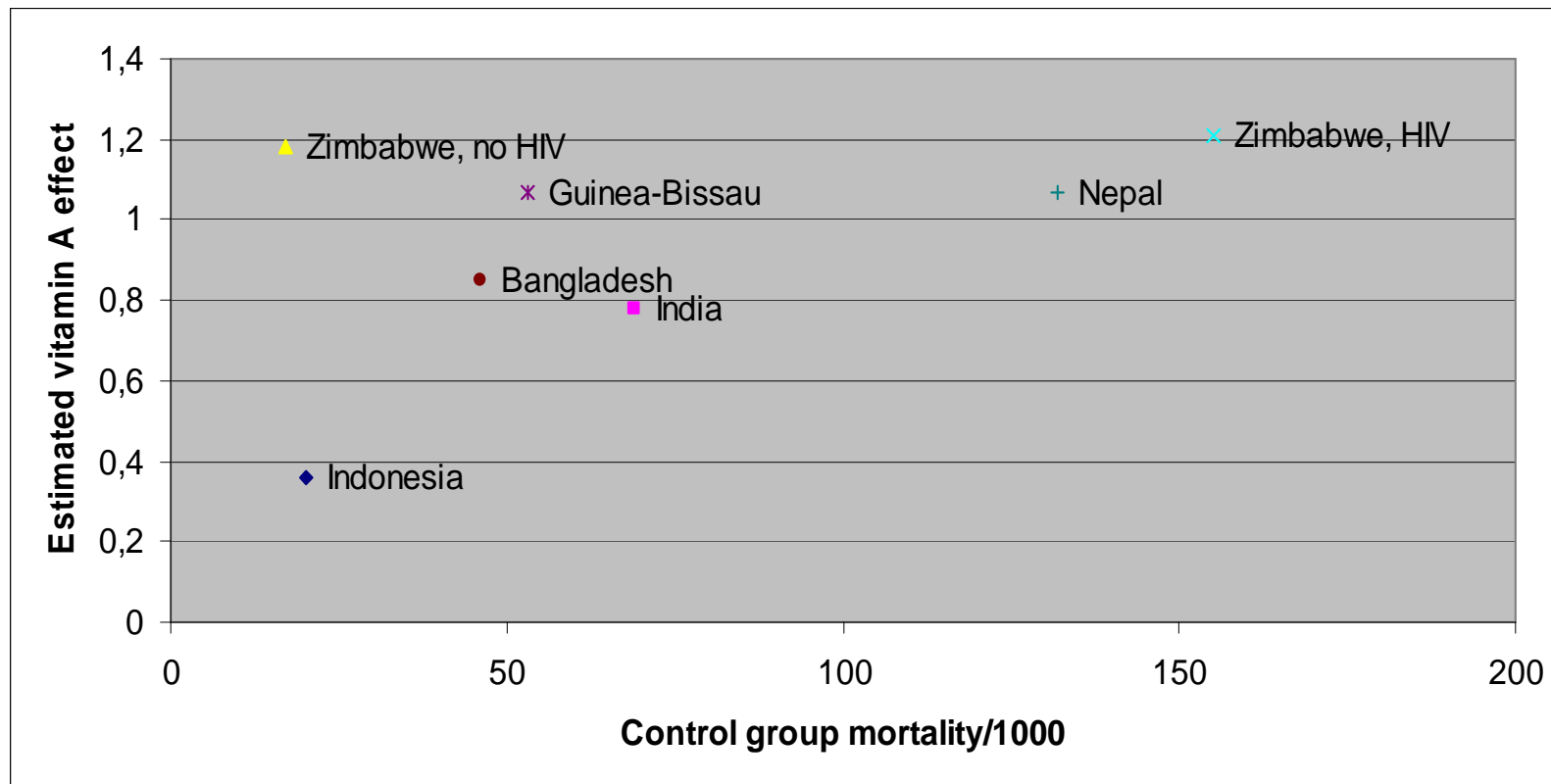
Vitamin A and vitamin A deficiency

- Beaton's meta-analysis 1993: No correlation between mortality/xerophthalmia (markers of vitamin A deficiency) and effect of vitamin A supplementation



Vitamin A and vitamin A deficiency

- Recent data on neonatal supplementation: No correlation between mortality and effect of vitamin A supplementation



Vitamin A and age groups

- Most trials found beneficial effect after 6 months of age
- Some trials found beneficial effect at birth
- All trials providing vitamin A supplementation between 1-5 months of age did not find beneficial effect in spite of widespread vitamin A deficiency

For instance WHO multicenter trial, Landet 1998:

Vitamin A indicator	First dose	
	Vitamin A (n=318)	Control (n=312)
Mean (SD) retinol ($\mu\text{mol/L}$)	0.67 (0.33)	0.68 (0.32)
Retinol \leq 0.35 $\mu\text{mol/L}$	21 (6.92%)*	24 (8.34%)
Retinol \leq 0.70 $\mu\text{mol/L}$	197 (63.02%)	193 (62.16%)
A2:retinol ratio \leq 0.06	242 (77.95%)	230 (75.56%)

RR=0.96
(0.73-1.27)

Vitamin A and infectious diseases

- Vitamin A deficiency => increased risk of infections => increased loss of vitamin A
- If vitamin A supplementation merely treated vitamin A deficiency the effect should be beneficial in spite of infectious diseases
- This is not the case



Vitamin A and infectious diseases

Two examples:

Treatment with vitamin A:

- Measles infection: Meta-analysis: Two doses of vitamin A on two consecutive days: RR 0.18; 95% CI 0.03 to 0.61
Respiratory infections: OR=1.29; 95% CI 0.62 to 2.69 (Cochrane reviews 2005)

Prophylactic vitamin A:

- Shorter durations of EPEC-associated diarrhea, longer durations of *G. lamblia*-associated diarrhea
- Vitamin A-supplemented children infected with EPEC had reduced IL-4 levels (OR= 0.3, 95% CI 0.13-0.67)
- Vitamin A-supplemented children infected with *A. lumbricoides* had increased IL-4 levels (OR=12.1, 95% CI 0.95-154) (Long 2006)



Vitamin A and vaccines

We have proposed that vitamin A acts as an immune enhancer, amplifying the non-specific effects of vaccines (Benn 2003)

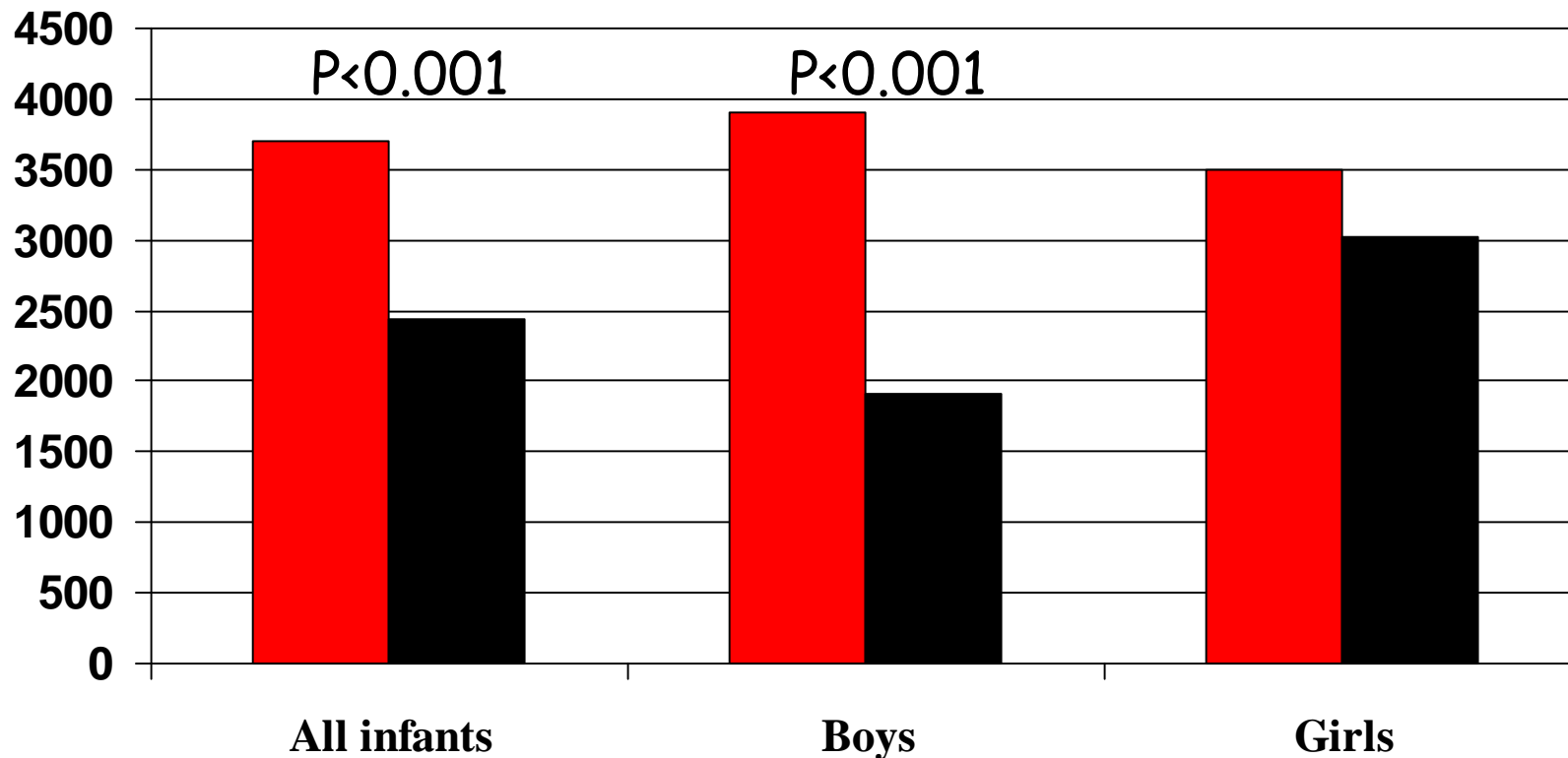
Based on

- 1) observations of non-specific effects of vaccines
 - BCG at birth and measles vaccine at 9 months reduce mortality more than can be explained by prevention of TB and measles
 - Diphtheria-tetanus-pertussis (DTP) given between 1-5 months of age associated with increased mortality, particularly in girls (Aaby et al, numerous papers)
- 2) Age group pattern



Specific vitamin A-vaccine interactions

Measles-specific antibody titres at age 18 months after VAS and measles vaccine at age 9 months. Guinea-Bissau 1993-95 (Benn 1997)



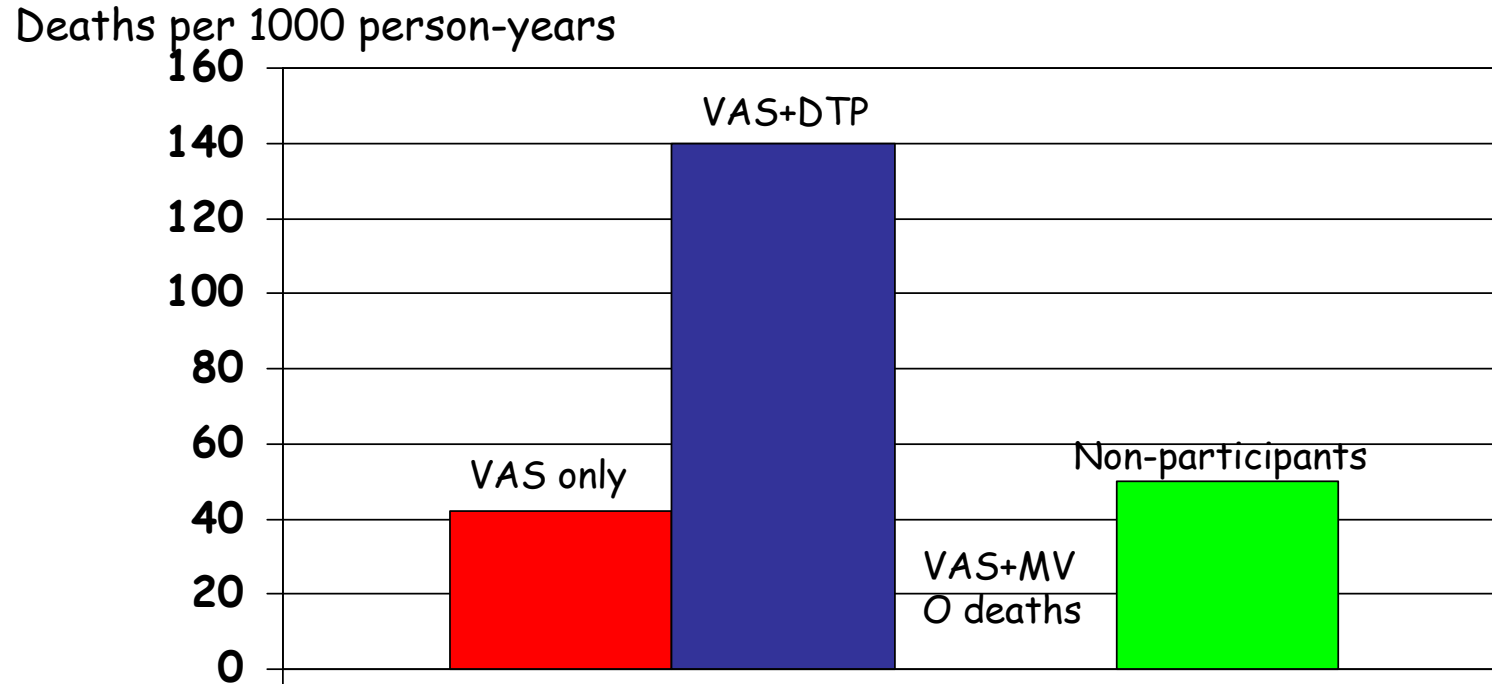
■ Vitamin A

■ Placebo



VAS campaign, Guinea-Bissau 2003

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



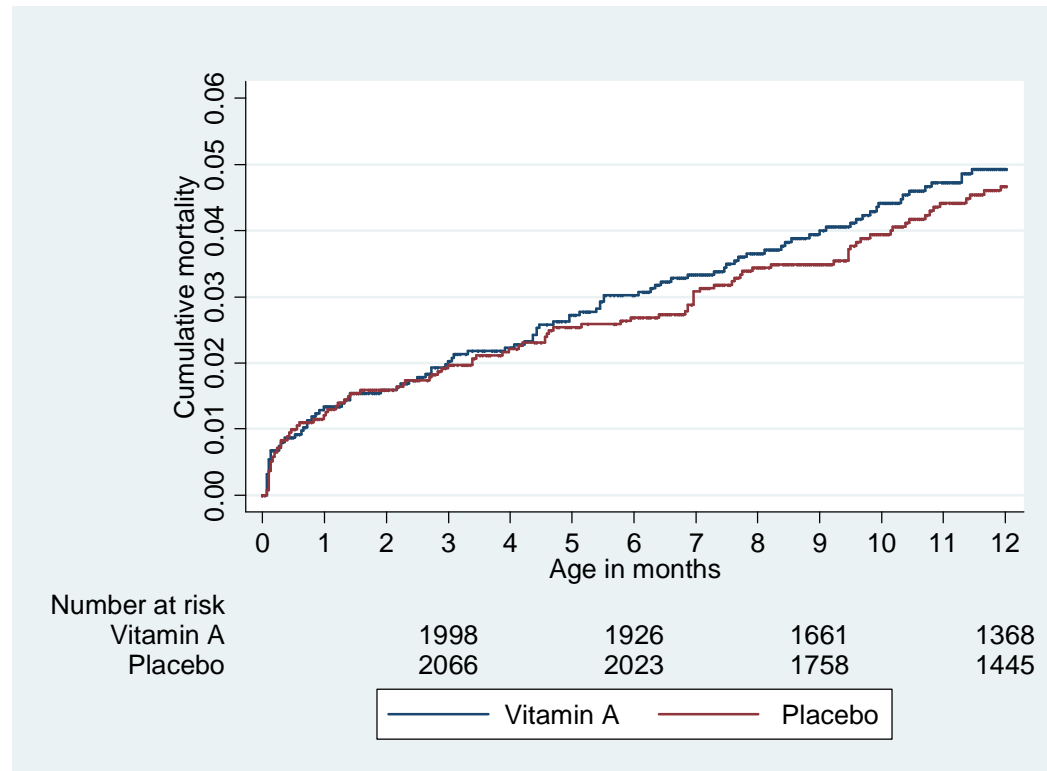
VAS+DTP versus VAS only: adjusted MR=3.4 (1.4-8.6)

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

Benn et al, Int J Epidemiol 2008



Vitamin A supplementation given with BCG vaccine to normal-birth-weight newborns

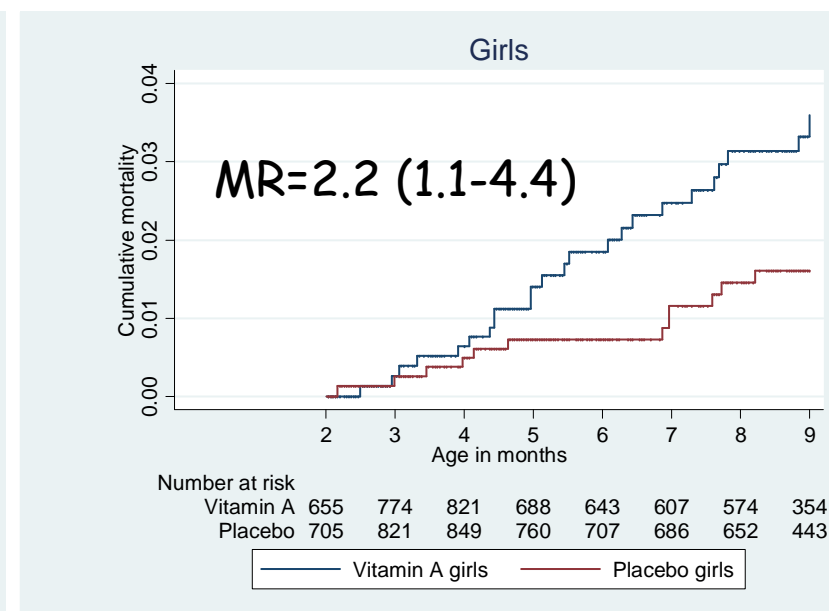
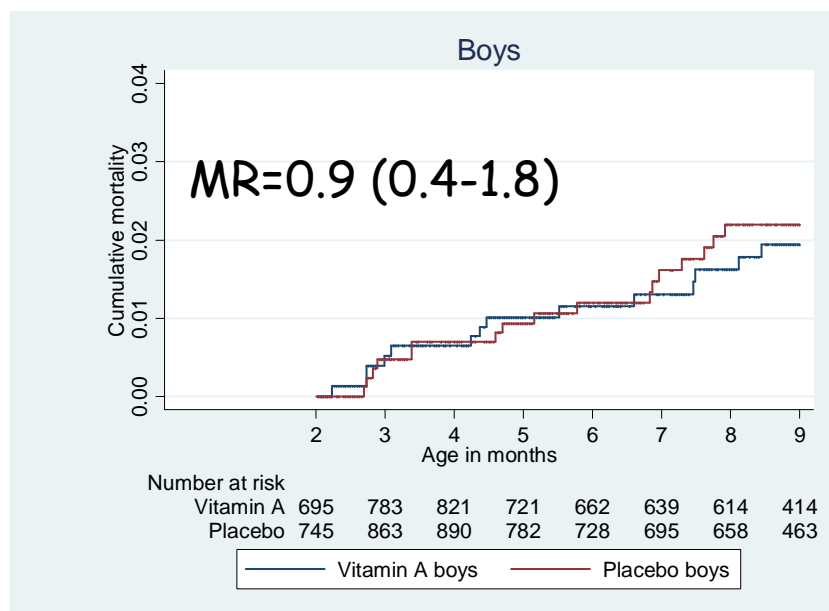


Result: VAS/placebo MR=1.07 (0.79-1.44)

Benn et al. BMJ 2008



VAS at birth and mortality by vaccination status



Vitamin A/placebo MR

BCG (0-5 weeks)

DTP (6 weeks-8 months)

All

0.9 (0.5-1.5)

1.4 (0.9-2.3)

Boys

0.9 (0.4-1.9)

0.9 (0.4-1.8)

Girls

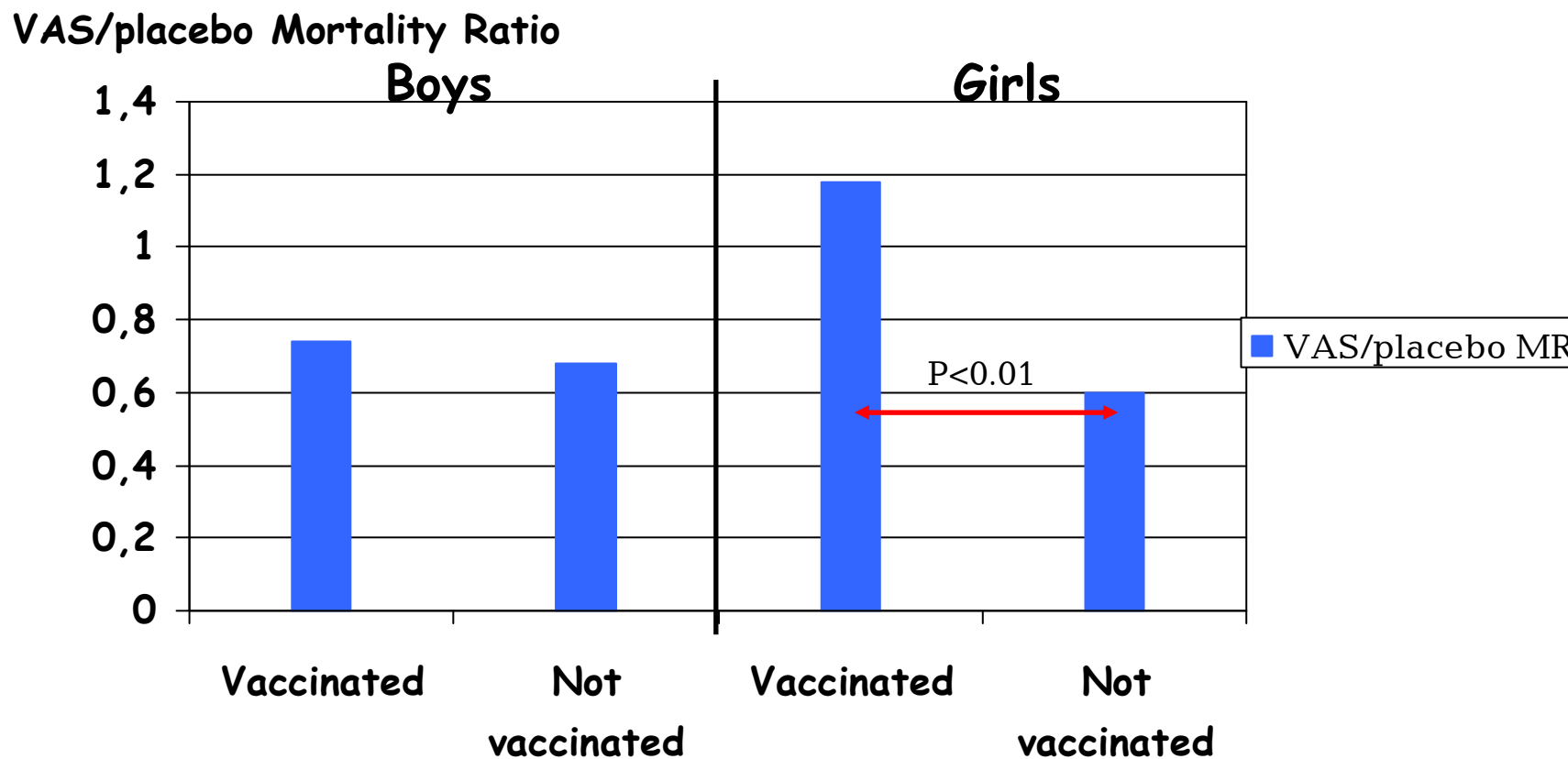
0.8 (0.3-2.1)

2.2 (1.1-4.4)

Benn et al. IJE 2009



Ghana VAST, reanalysis



The VAS effect differed in girls with and without vaccinations



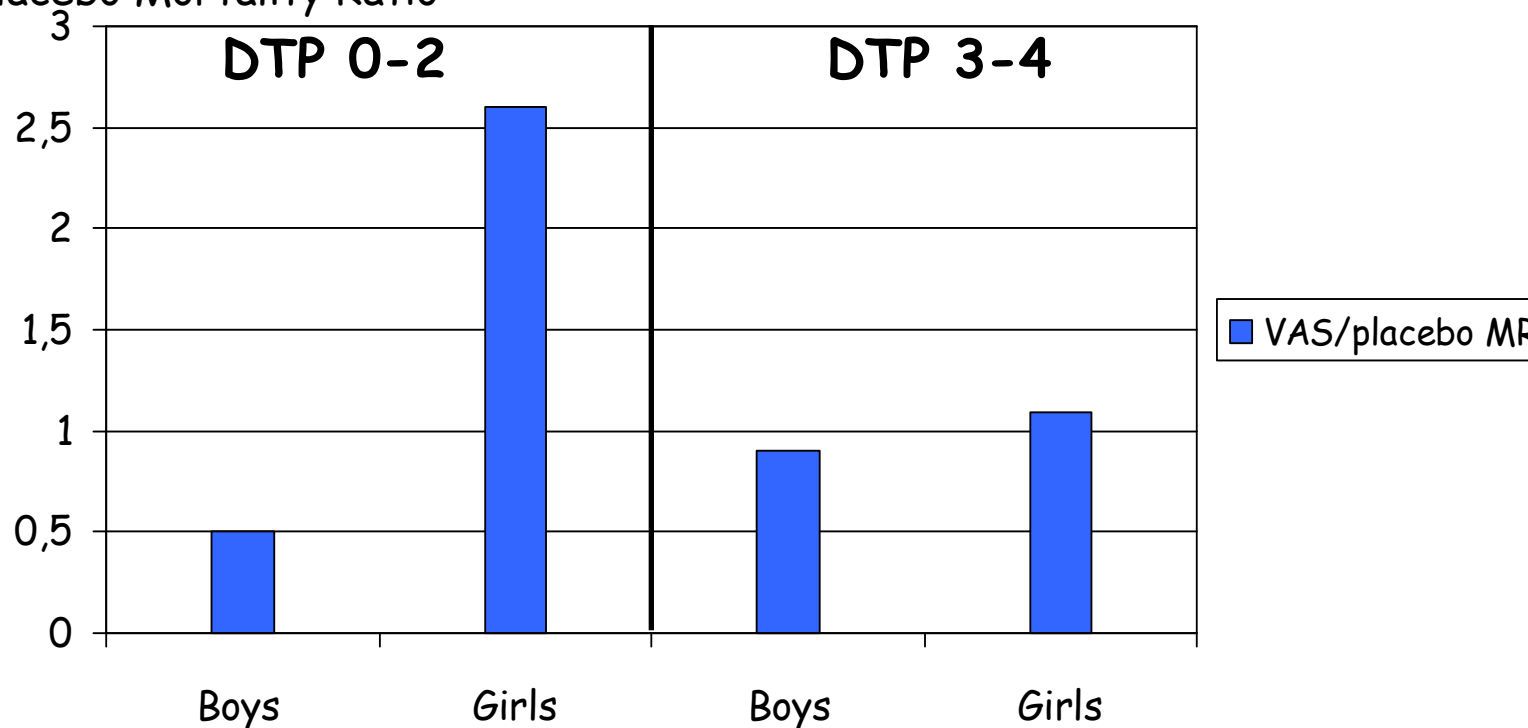
Benn et al, Am J Clin Nutr 2009



Ghana VAST, reanalysis

Children with a health card and measles vaccine

VAS/placebo Mortality Ratio



Girls with DTP 0-2: VAS/placebo MR=2.6 (1.4-4.8)

Interpretation: Negative interaction btw VAS and subsequent DTP in girls



Benn et al, Am J Clin Nutr 2009



Independent Ghana trials

- 25,000 IU with 3 DTP vaccines (Newton, J Nutr 2005)
 - 7 versus 3 deaths in VAS/placebo groups
- 50,000 IU with 3 pentavalent vaccines (Newton, Vaccine 2008)
 - 5 vs. 1 deaths in VAS/placebo groups
- MH-weighted relative risk of dying after vitamin A (25,000 IU or 50,000 IU) administered together with DTP/pentavalent vaccine: 2.96 (0.95-9.19) (p=0.048) (Newton, Vaccine 2008)



Conclusions

- Vitamin A protects against vitamin A deficiency and thereby against mortality
- Vitamin A is **also** an immuno-modulator and the effect on mortality depends on what is going on in the immune system
- Vitamin A may be harmful in certain situations: 1-5 month-old-children, respiratory infections, girls, DTP vaccine
- We can optimise the use of vitamin A supplementation if we take the immuno-modulatory effects into account



Shift in Paradigm

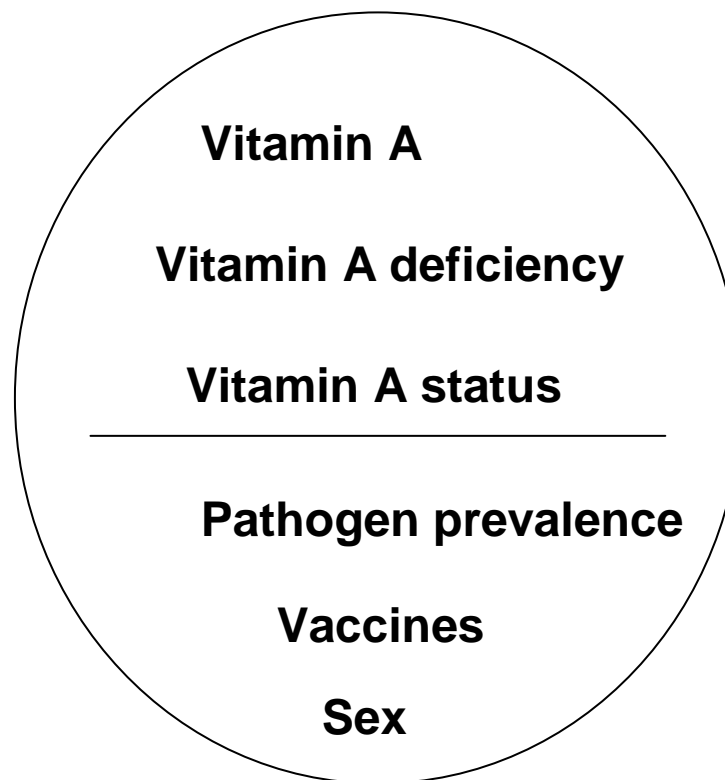
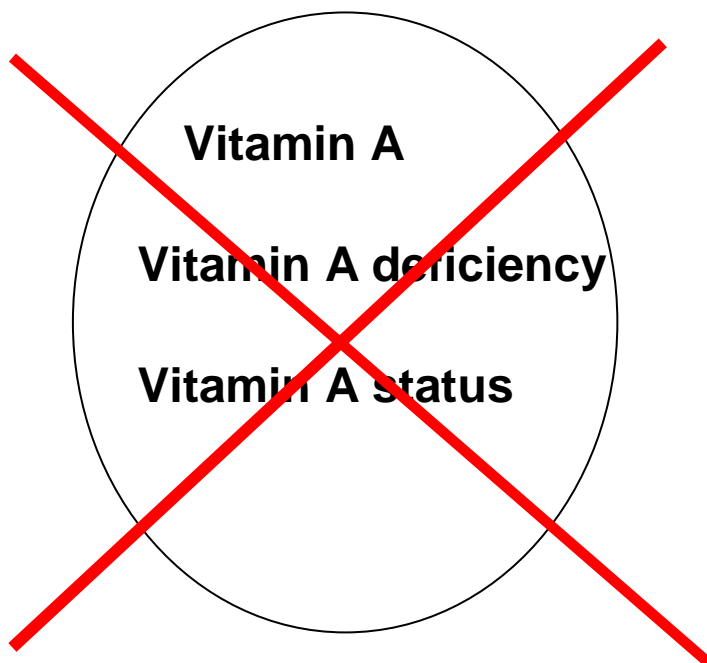
Vitamin A

Vitamin A deficiency

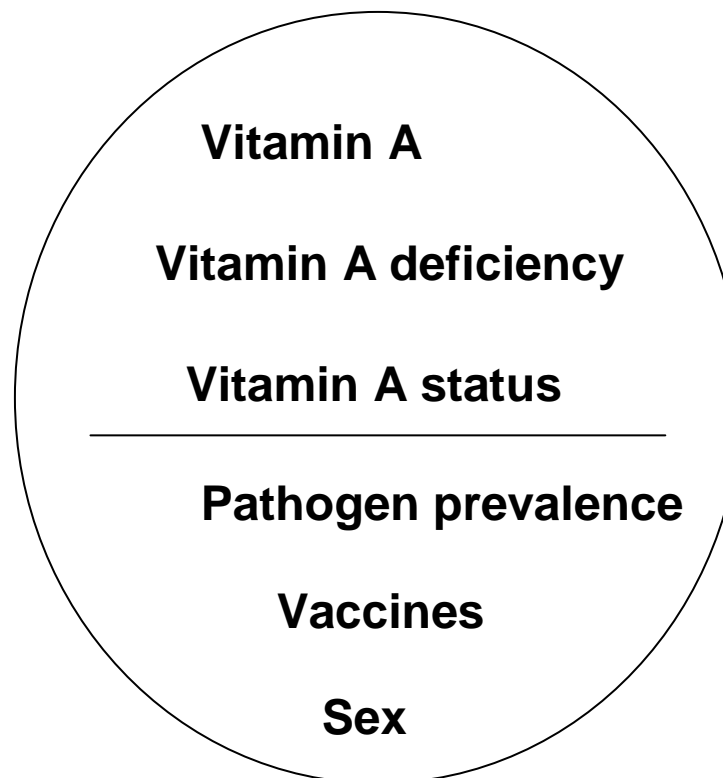
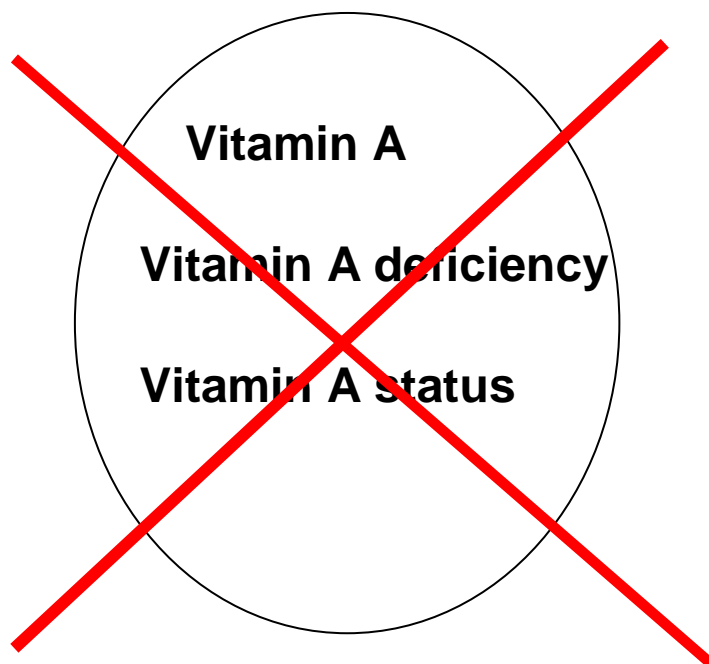
Vitamin A status



Shift in Paradigm



Shift in Paradigm



It can no longer be considered sufficient to evaluate the effect of vitamin A on indicators of vitamin A status alone - a good status is not necessarily any good.

