



Neonatal vitamin A supplementation interacts with routine immunizations in infancy - with consequences for mortality

Christine Stabell Benn, MD, PhD
Peter Aaby, Ane Fisker, Carlitos Balé, Amabelia Rodrigueus,
and many more

Bandim Health Project
INDEPTH Network
Statens Serum Institut
Guinea-Bissau & Denmark



Disclosure: No competing financial interests

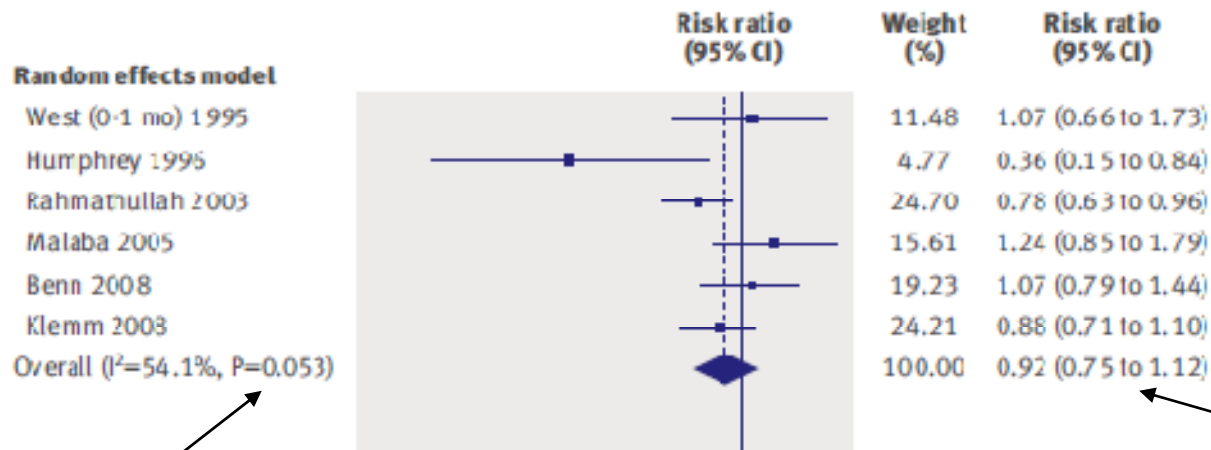
Background

- Vitamin A deficiency associated with increased mortality
- Randomised trials in late 80's-early 90's: Vitamin A supplementation associated with 23-30% reduction in overall mortality in children > 6 mo of age
- **WHO policy:** High-dose vitamin A supplements every 4-6 months to all children 6 mo- 5 yr in low-income countries - preferably linked to the immunization program (EPI) for logistic reasons
- Overall effect of WHO policy never tested in randomised trial
- **Our hypothesis:** Vitamin A supplementation beneficial when given with the live **BCG** and **measles vaccine**, but harmful with inactivated **diphtheria-tetanus-pertussis (DTP)** vaccine



Neonatal vitamin A supplementation

- **Seven trials** have been conducted:
 - Asia: Nepal (West 1995), Indonesia (Humphrey 1996), India (Rahmathullah 2003), and Bangladesh (Klemm 2008)
 - Africa: Zimbabwe (Malaba, Humphrey 2005/6), Guinea-Bissau (Benn 2008 and Benn, 2010)



Heterogeneity

Gogia BMJ 2009

No effect

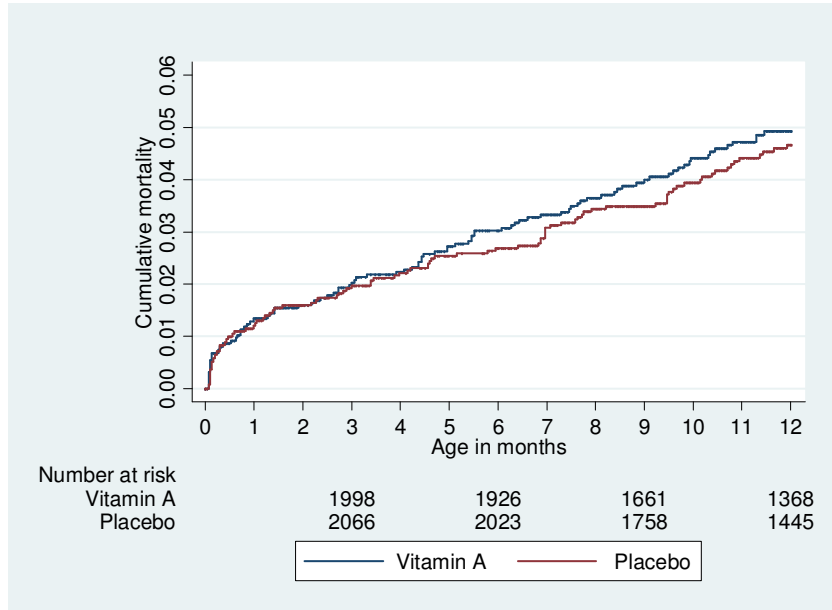


Neonatal vitamin A supplementation trials Guinea-Bissau



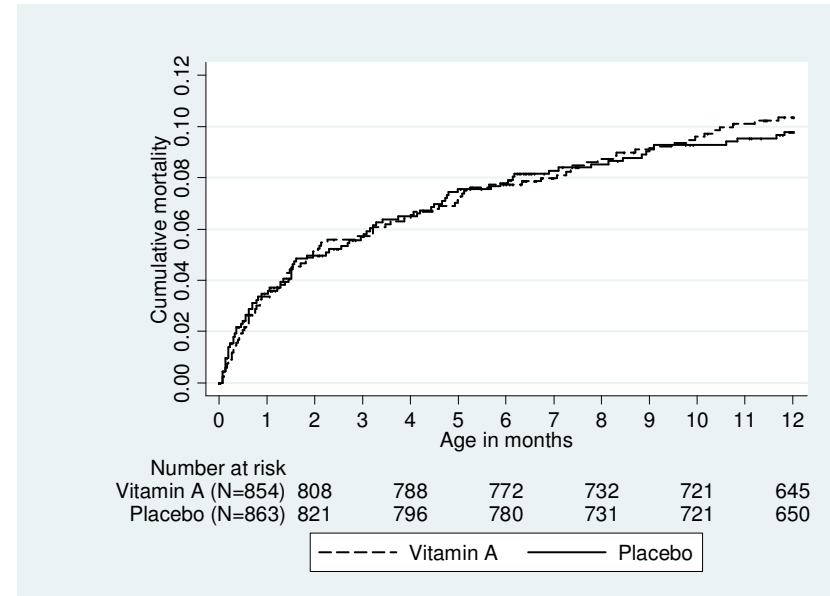
Vitamin A supplementation versus placebo with BCG to neonates in Guinea-Bissau

Hypothesis: BCG=😊



Normal-birth-weight: **1.07 (0.79-1.44)**

Benn et al. BMJ 2008



Low-birth-weight: **1.08 (0.79-1.47)**

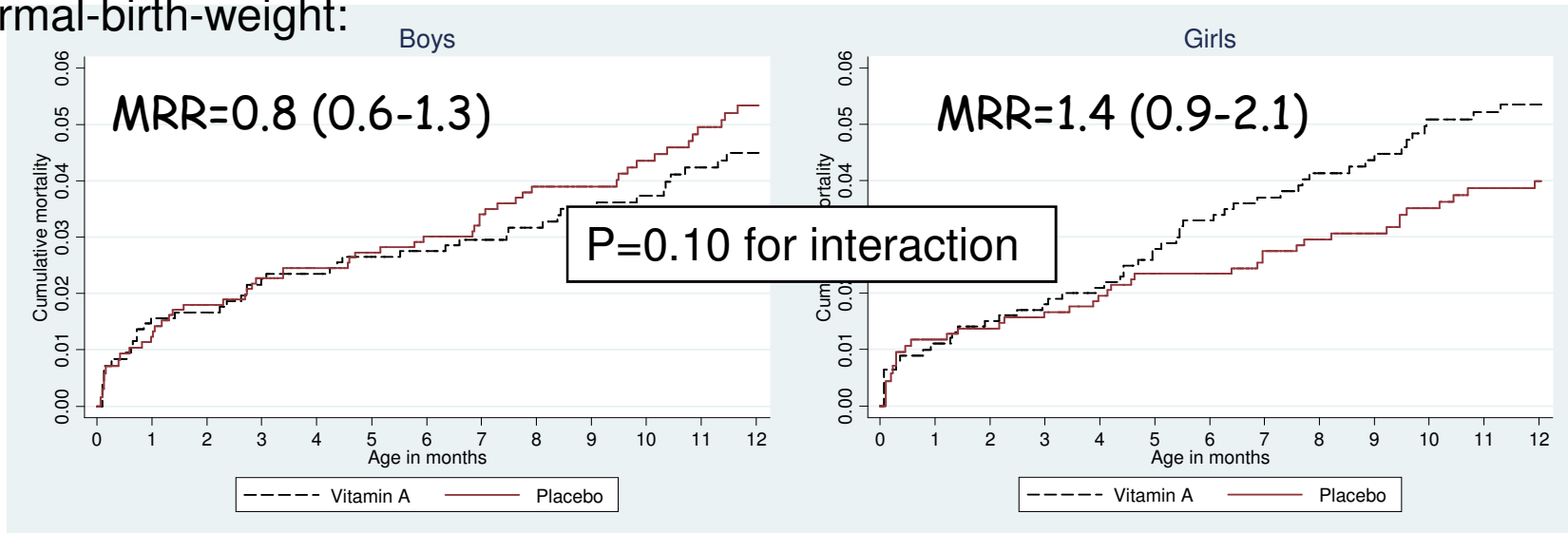
Benn et al. BMJ 2010

Meta-estimate of the two trials in Guinea-Bissau:
MRR=1.08 (0.87-1.33)

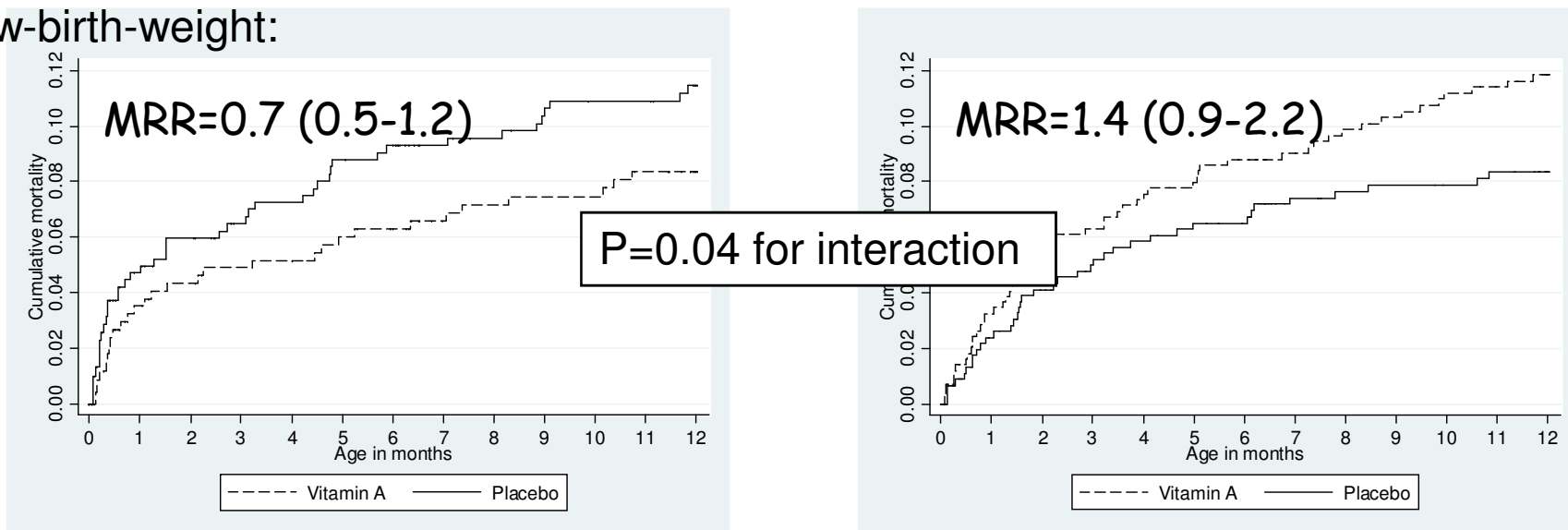


Vitamin A supplementation at birth and mortality by sex

Normal-birth-weight:

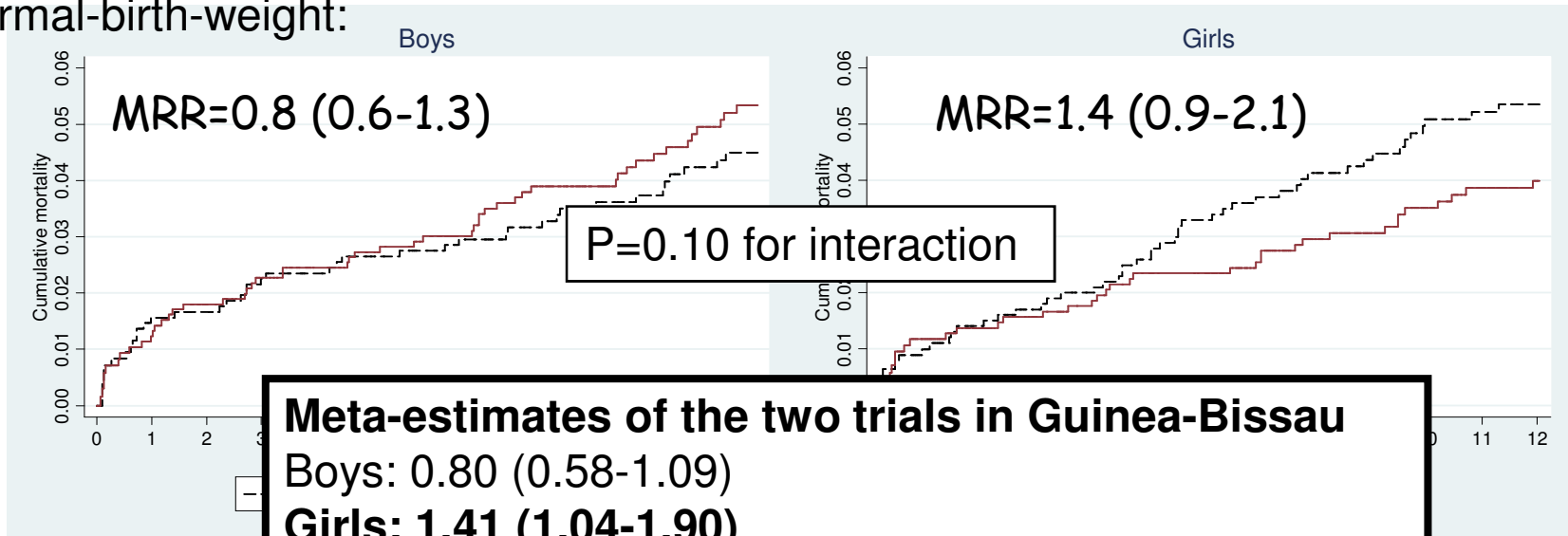


Low-birth-weight:



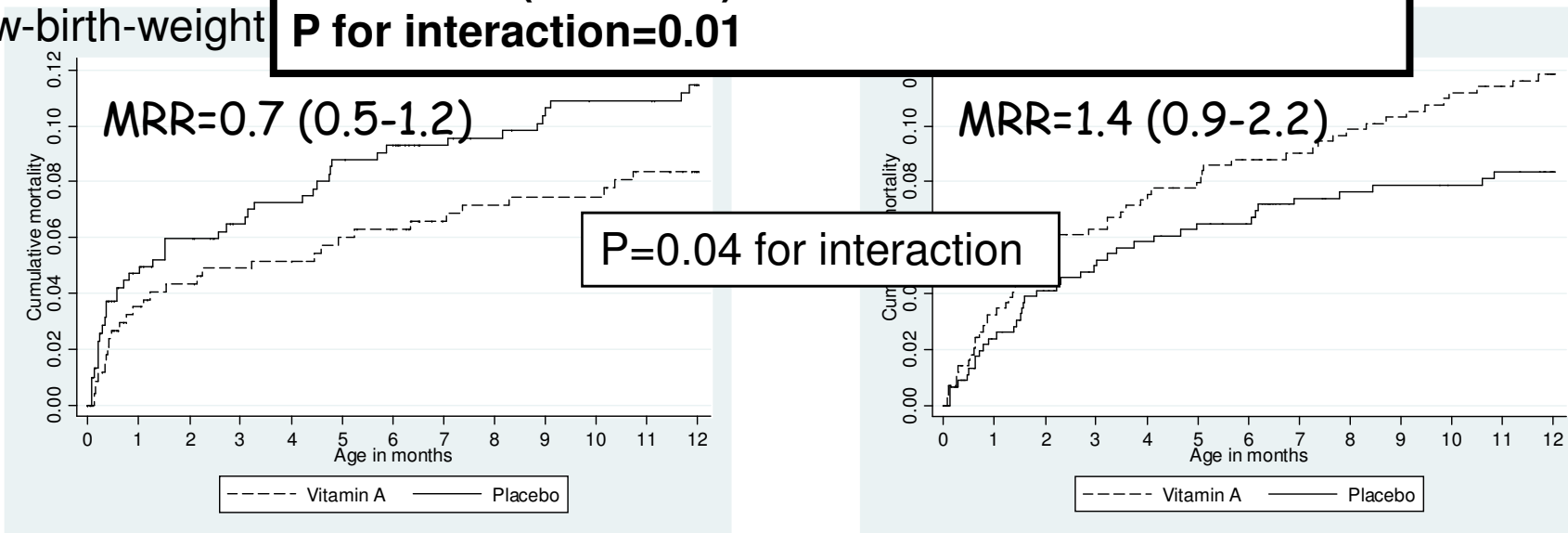
Vitamin A supplementation at birth and mortality by sex

Normal-birth-weight:

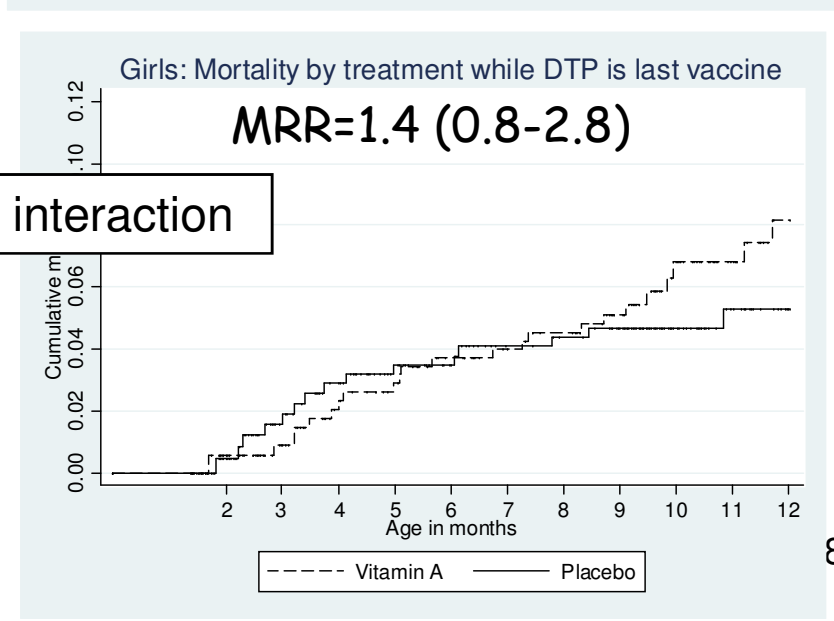
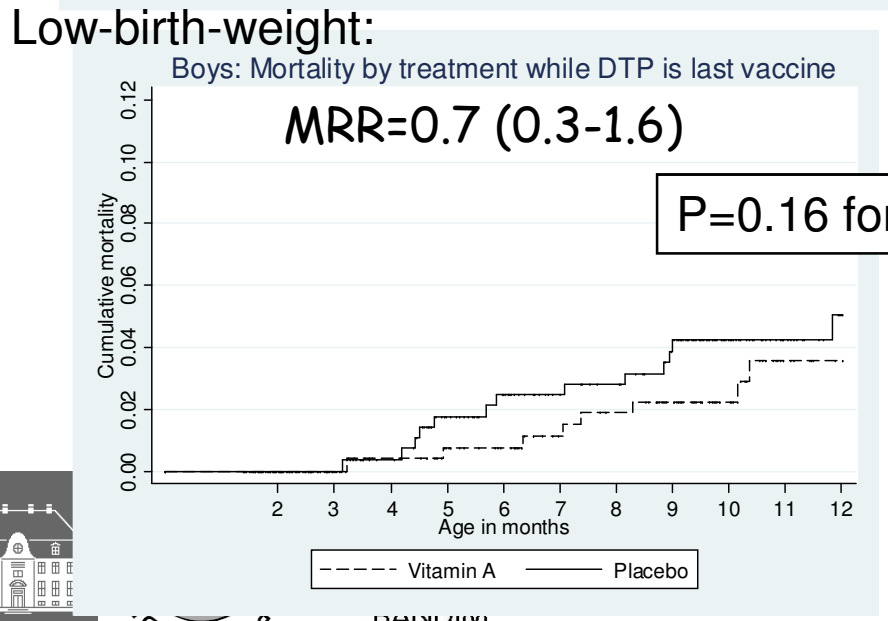
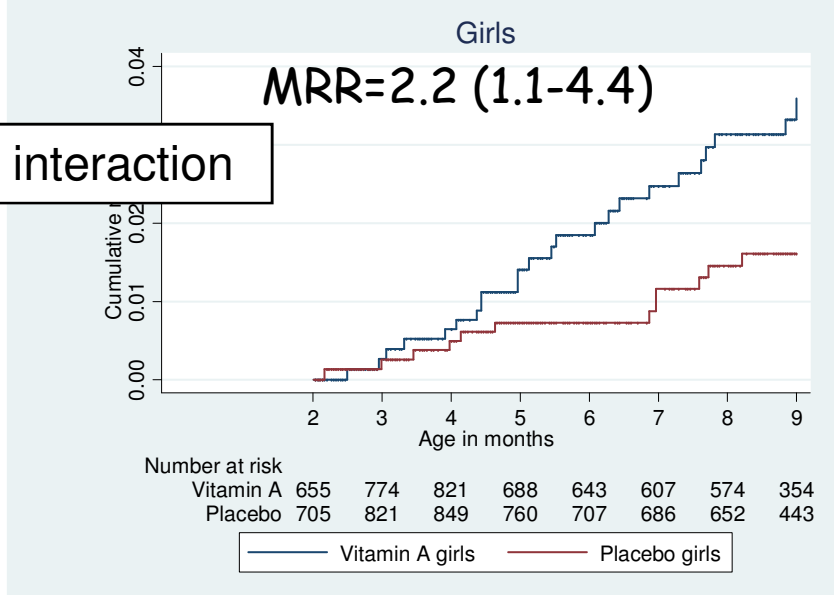
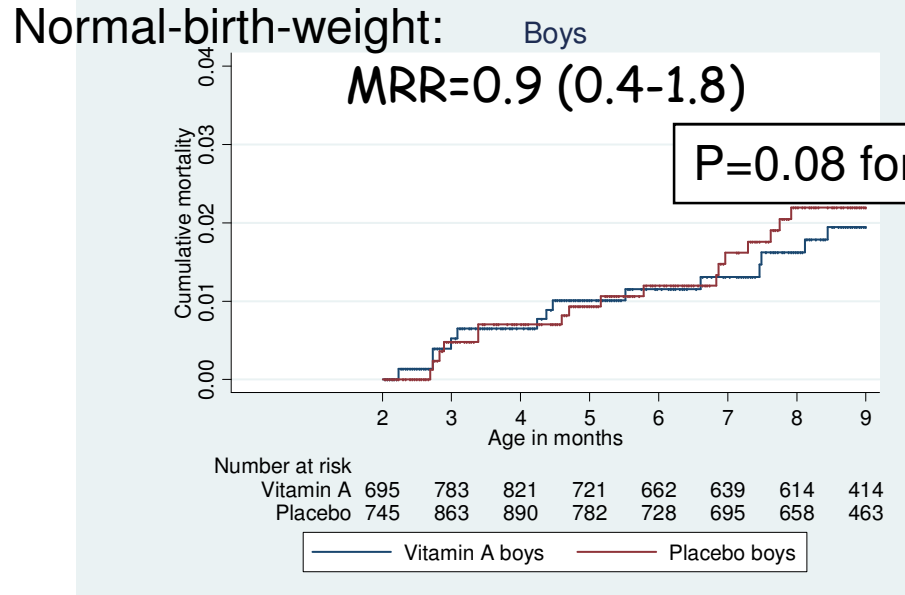


Meta-estimates of the two trials in Guinea-Bissau
Boys: 0.80 (0.58-1.09)
Girls: 1.41 (1.04-1.90)
P for interaction=0.01

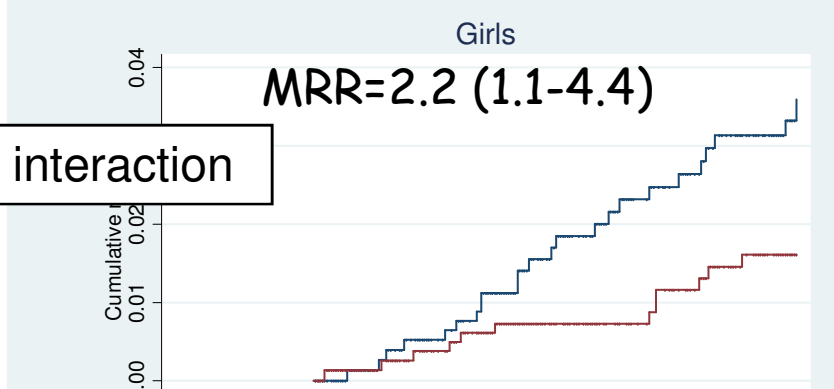
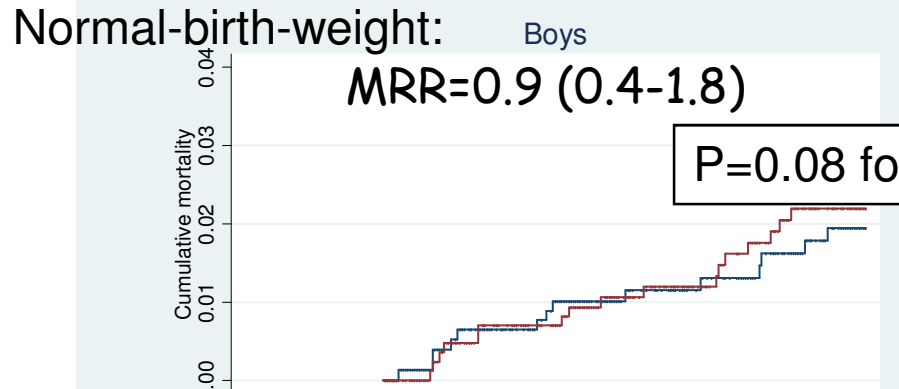
Low-birth-weight:



Vitamin A at birth associated with higher mortality than placebo in girls when they receive DTP vaccine

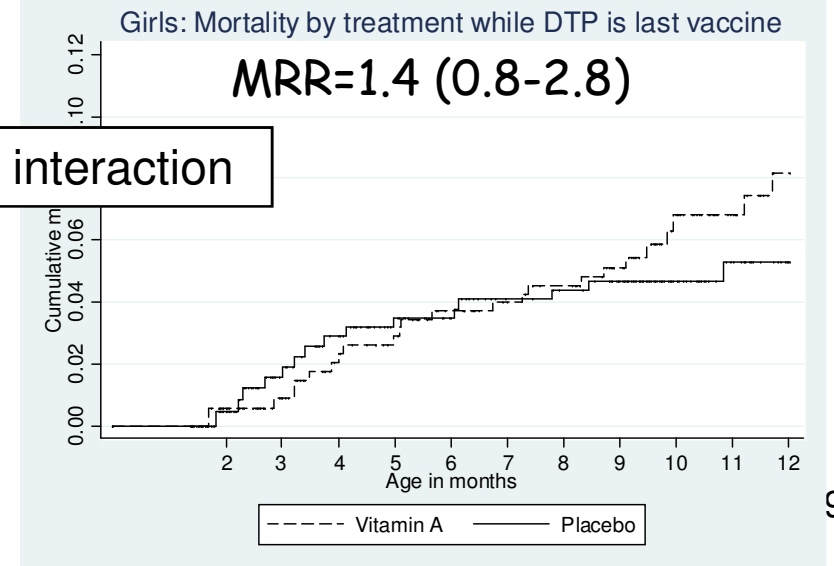
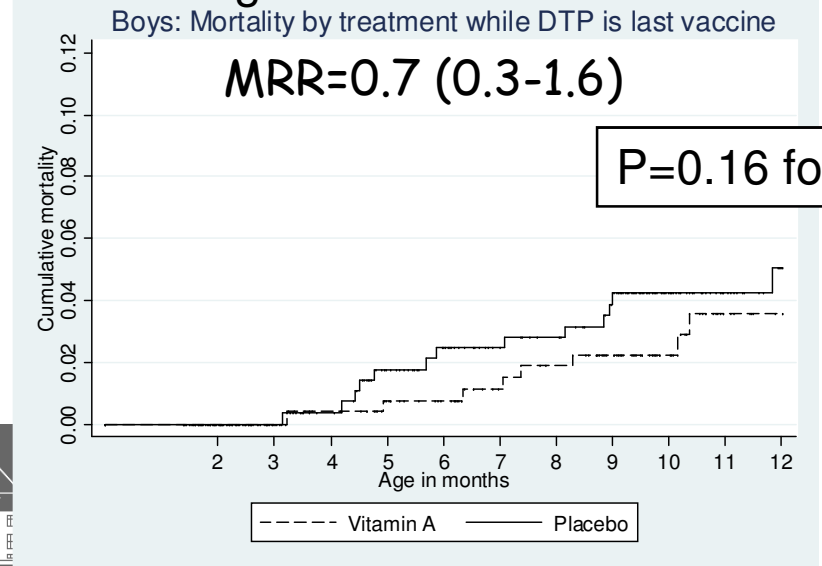


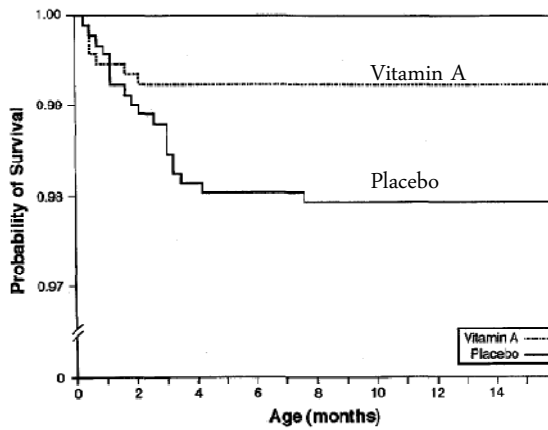
Vitamin A at birth associated with higher mortality than placebo in girls when they receive DTP vaccine



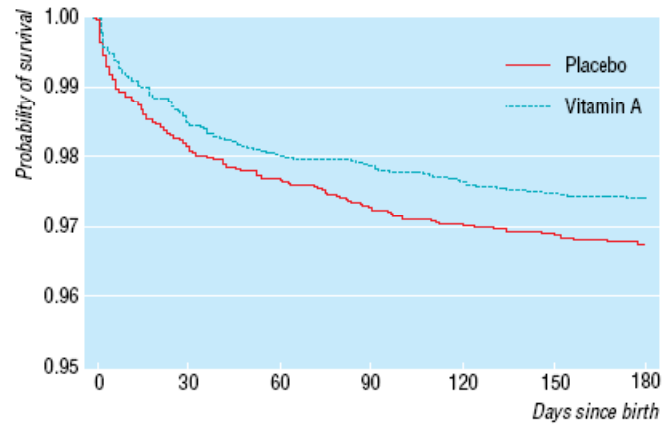
Vitamin A supplementation at birth negative effect on survival after DTP vaccination in girls

Meta-estimate all girls after DTP: **MRR=1.8 (1.1-2.8) p=0.02**

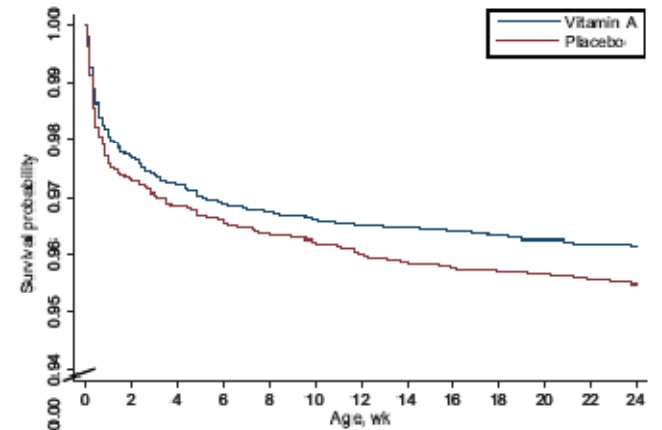




Indonesia 1992-4



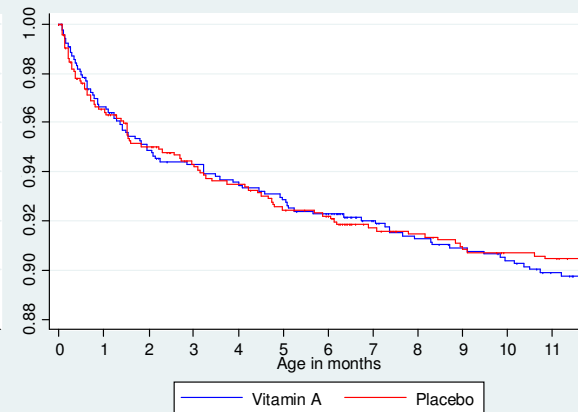
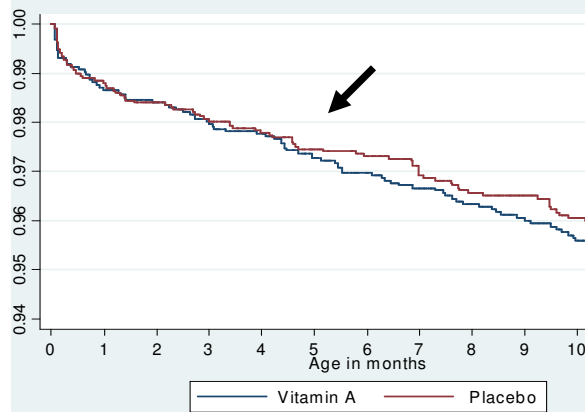
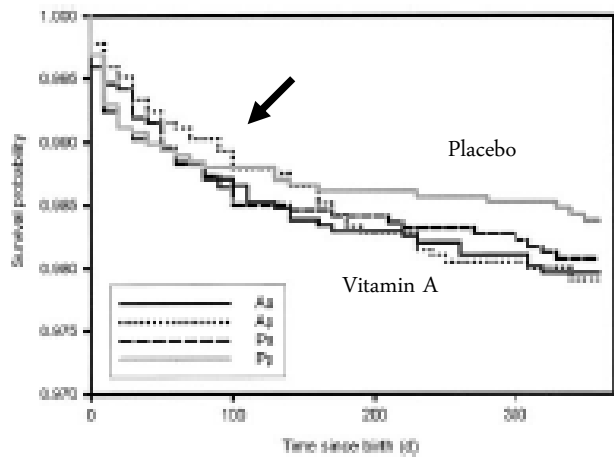
India 1998-2001



Bangladesh 2004-7

Zimbabwe 1997-2001

Guinea-Bissau 2002-8



Our interpretation of current evidence

- Neonatal VAS beneficial during the first months of life
- The effect may shift when the children receive DTP
 - areas with high mortality throughout infancy
 - areas with high DTP coverage
 - areas which follow the WHO recommended vaccination schedule of first BCG and then DTP
- Of utmost importance that the three new WHO/Gates sponsored trials in Kintambo, Ifakara and India follow children to 12 months of age and analyse data by sex and vaccination status



Neonatal vitamin A supplementation and early measles vaccine (MV) trial Guinea-Bissau



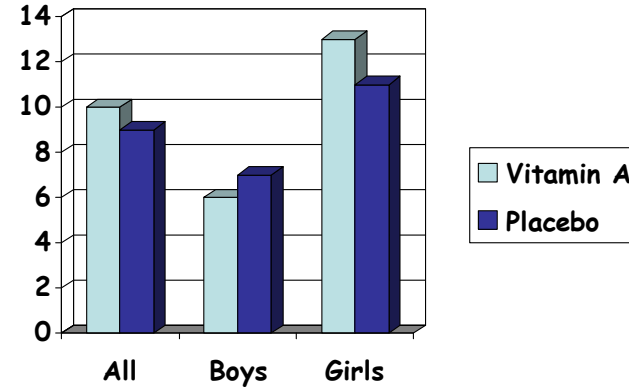
VAS versus Placebo at birth

Children who had DTP3 at 4 mo and MV at 9 mo

From 4-8 months: DTP

RR VAS/placebo=1.1 (0.5-2.2)

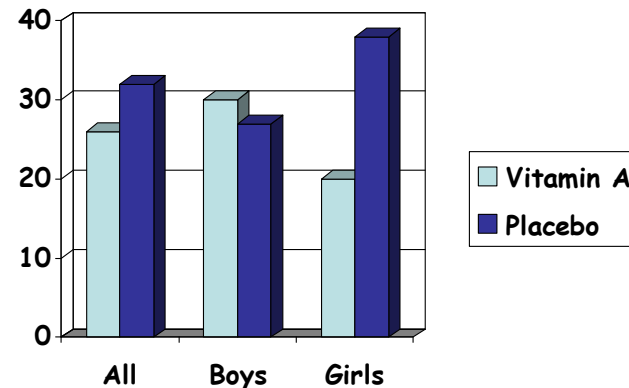
Girls: VAS/Placebo=1.7 (0.7-4.3)



From 9-36 months: MV

RR VAS/placebo=0.8 (0.5-1.2)

Girls: VAS/Placebo=0.5 (0.3-1.0)



Significant inversion of VAS effect in girls from DTP to MV, $p=0.04$

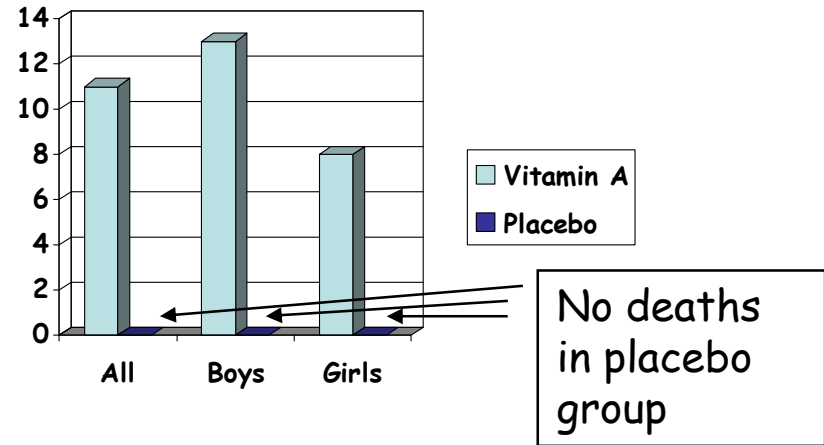


VAS versus Placebo at birth

Children who had MV at 4 mo and MV at 9 mo

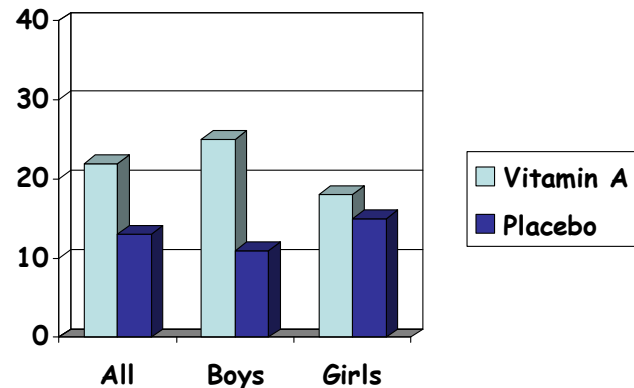
From 4-8 months: 1st MV

RR VAS/placebo negative effect,
P=0.004



From 9-36 months: 2nd MV

RR VAS/placebo=1.6 (0.8-3.5)



Overall VAS effect from 4-36 months: MRR=2.5 (1.2-5.3)



Summary:

Neonatal vitamin A and vaccines

- Negative interaction between neonatal vitamin A and DTP, even given months apart, in girls (RR=1.8 (1.1-2.8))
- Negative interaction between vitamin A and early MV at 4 mo of age (4 weeks after DTP) (RR=2.5 (1.2-5.3))
- Potentially positive interaction between VAS and MV at 9 months of age (5 months after DTP) in girls (RR=0.5 (0.3-1.0))



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, +DTP vaccine in girls, +early measles vaccine
- Vitamin A may have sex-differential effects
- We can optimise the use of vitamin A supplementation if we take the immuno-modulatory sex-differential effects into account



Further information or questions?

- Please contact Christine Stabell Benn at

E-mail: cb@ssi.dk

Tel: +45 3268 8354

Thank you for your attention!

