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

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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 WVO 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)

![Risk ratio (95% CI) and Weight (%) chart]

**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:

Boys

MRR=0.8 (0.6-1.3)  
P=0.10 for interaction

Girls

MRR=1.4 (0.9-2.1)

P=0.04 for interaction

Low-birth-weight:

MRR=0.7 (0.5-1.2)

MRR=1.4 (0.9-2.2)

P=0.04 for interaction
Vitamin A supplementation at birth and mortality by sex

Normal-birth-weight:

Girls:

- MRR = 1.4 (0.9-2.1)
- P for interaction = 0.01

Boys:

- MRR = 0.8 (0.6-1.3)
- P for interaction = 0.10

Low-birth-weight:

Girls:

- MRR = 1.41 (1.04-1.90)
- P for interaction = 0.01

Boys:

- MRR = 0.7 (0.5-1.2)
- P for interaction = 0.04

Meta-estimates of the two trials in Guinea-Bissau

- Boys: 0.80 (0.58-1.09)
- Girls: 1.41 (1.04-1.90)
Vitamin A at birth associated with higher mortality than placebo in girls when they receive DTP vaccine

Normal-birth-weight:

Boys

MRR=0.9 (0.4-1.8)

P=0.08 for interaction

Girls

MRR=2.2 (1.1-4.4)

Low-birth-weight:

Boys: Mortality by treatment while DTP is last vaccine

MRR=0.7 (0.3-1.6)

P=0.16 for interaction

Girls: Mortality by treatment while DTP is last vaccine

MRR=1.4 (0.8-2.8)
Vitamin A at birth associated with higher mortality than placebo in girls when they receive DTP vaccine

Normal-birth-weight:

Boys

MRR=0.9 (0.4-1.8)

MRR=1.4 (0.8-2.8)

P=0.16 for interaction

Girls

MRR=2.2 (1.1-4.4)

P=0.08 for interaction

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

Boys: Mortality by treatment while DTP is last vaccine

MRR=0.7 (0.3-1.6)

P=0.16 for interaction

Girls: Mortality by treatment while DTP is last vaccine

MRR=1.4 (0.8-2.8)
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?

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Thank you for your attention!