Six-monthly vitamin A from 1 to 6 years of age

DEVTA: cluster-randomised trial in 1 million children in North India

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Support: **USAID, CTSU, UP ICDS; vit A from Sight & Life**

Pre-school rural North India

- Vit A deficiency common
- IMR ~ 87/1000 live births
- 2-3% die at ages 1-6 (mainly acute infection)
- DEVTA: can 6-monthly vit A reduce this mortality?

DEVTA: cluster-randomised trial
8000+ villages in 72 clusters

36 blocks	36 blocks
6-monthly	allocated open
VITAMIN A	CONTROL

Also, visit all villages 6 monthly to get <u>mortality</u> (25,000 child deaths recorded)

DEVTA vit A schedule, 1999-2004

Dosage: 200,000 IU vit A on the 6-monthly mass treatment days to all then aged 6-72 months.

Mean compliance: miss 1 of 11 doses.

Controls: get mean of 1 non-trial dose.

DEVTA: biomedical monitoring

Annually, 1 village per block randomly chosen & children examined

Comparing 36 vit A vs 36 control clusters

- Bitot's spots 2.2% vs 4.3%, 2p=0.003

- Plasma retinol < 0.35 μM/L (10 μg/dL), ie, severe deficiency: 11% vs 22%, 2p<0.00001

DEVTA: biomedical monitoring

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(comparing 36 vit A vs 36 control clusters)

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Measles (past 3 weeks) 1.4% vs 0.8%, 2p=0.20

Pneumonia (ditto) 2.6% vs 4.1%, 2p=0.03

DEVTA: mean plasma retinol (μM/L) in 5166 children in the randomly selected villages in 36 vit A vs 36 control blocks

Age (yrs)	Mean retinol, vit A vs control	Increase (% ± se)	2p (36 vs 36)
1-2	0.59 vs 0.53	12% ± 3	0.0003
3-4	0.61 vs 0.51	18% ± 3	<0.00001
5-6	0.62 vs 0.51	21% ± 3	<0.00001
All	**0.603 vs 0.516***	**17% ± 2**	**<0.00001**

*For comparison, mean serum retinol in 1097 of the children in the Ghana vit A trials 0.68 vs 0.60 μM/L (13% increase, vit A vs control); Am J Clin Nutr 1995; 61: 853

DEVTA: mortality results (ages 1-6)

Mean probability that a 1.0-year-old would die by age 6.0 years,

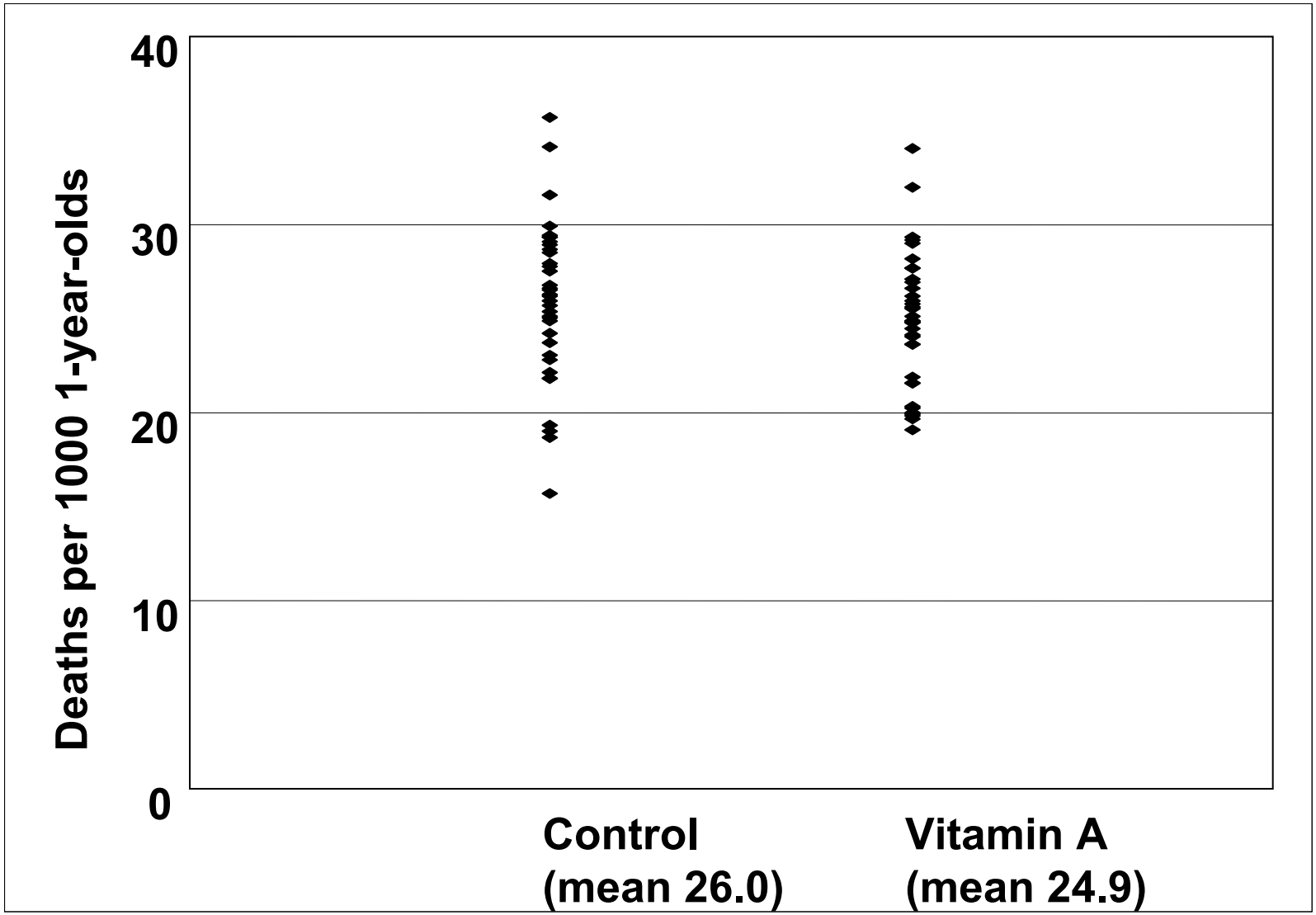
36 vit A vs 36 control blocks:

24.9 vs 26.0 per 1000

2p = 0.24, not significant

(comparing 36 vs 36 blocks)

DEVTA: 72 cluster-specific death risks at ages 1-6
36 control blocks vs 36 vitamin A blocks



DEVTA: Cause-specific mortality (per 1000 aged 1.0), vit A vs control

Cause of death (at ages 1-6)	36 vitamin A vs 36 control blocks	Difference ± se *
Diarrhoea	6.9 vs 7.3	0.4 ± 0.4
Pneumonia	3.7 vs 3.6	-0.1 ± 0.3
Measles	1.6 vs 1.7	0.1 ± 0.2
Other infection**	8.2 vs 8.8	0.6 ± 0.6
Malnutrition	2.0 vs 2.0	0.0 ± 0.2
Other ***	2.5 vs 2.6	0.1 ± 0.2
All causes	**24.9 vs 26.0**	**1.1 ± 0.9**

* 36 vit A vs 36 control cluster-specific values

** Mostly fever; also includes the few wholly unspecified causes

*** 60% accident or homicide, 40% non-infective disease

DEVTA: subgroup analyses

No significant heterogeneity between proportional mortality reductions produced by vit A among:

- **Male and female**
- **De-wormed regularly and not de-wormed**
- **Younger and older (ages 1-2 and 3-6)**

DEVTA: Mortality by age (per 1000 aged 1.0), vit A vs control

Age range*	36 vitamin A vs 36 control blocks	Difference ± se**
1.0 – 2.9	15.2 vs 15.7	0.5 ± 0.6
3.0 – 6.0	9.6 vs 10.2	0.6 ± 0.5
Total, 1-6	24.9 vs 26.0	1.1 ± 0.9

* Many ages were given as whole numbers of years

** Calculated only from the 72 block-specific rates

DEVTA: vit A vs control mortality ratio, R, = 0.96 (99% CI 0.88-1.05)

DEVTA on its own is consistent both with little effect on mortality and with prevention of >10% of all mortality

So, DEVTA must be considered not on its own but with the other relevant trials (which collectively show definite benefit)

8 other major randomised &/or placebo-controlled community-based vit A trials in children, 1986-93

Indonesia, India (2), Nepal (2),

Sudan, Ghana (small and large)

Meta-analysis of 8 community trials

$R \approx 0.77$ (99% CI ≈ 0.67-0.88)

$2p < 0.00001$

DEVTA and the 8 other trials

DEVTA: R = 0.96, 2p = 0.24

(99% CI 0.88-1.05)

8 others: R ≈ 0.77, 2p <0.00001

(99% CI ≈ 0.67-0.88)

Total: R ≈ 0.89, 2p <0.0001

(95% CI ≈ 0.84-0.94)

Difference between R in DEVTA & in the 8 other trials: 2p = 0.001. Extreme play of chance????

Community vit A supplementation: change produced by DEVTA in the totality of the trial evidence

Mortality reduction still highly significant (2p <0.0001) in DEVTA + the 8 other trials

But, much more likely to be about 10-15% than, as previously estimated, about 20-30%

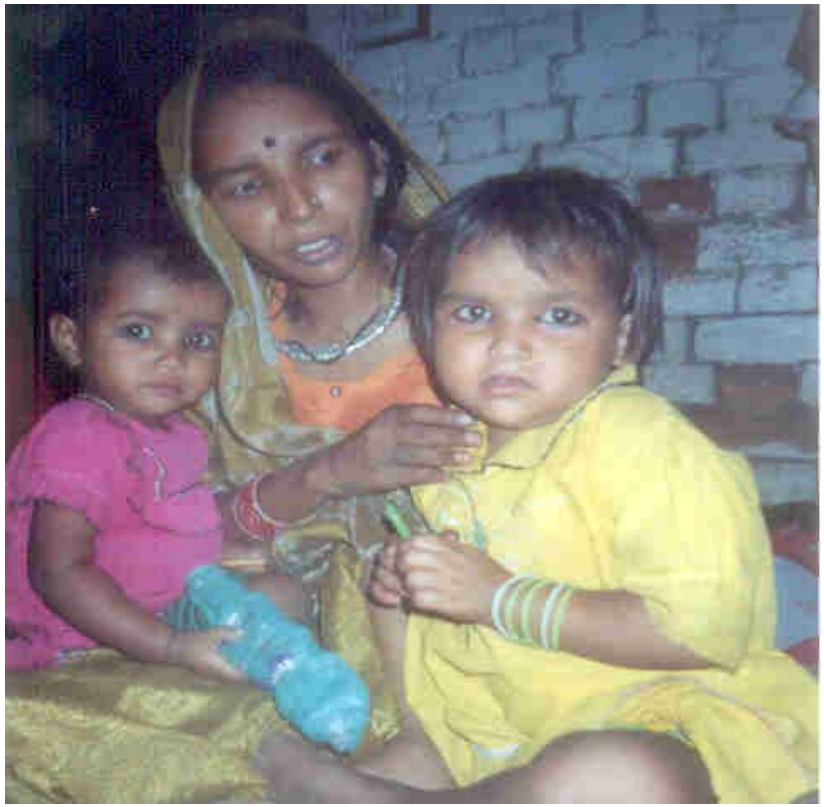
Next Steps: DEVTA now needs to be properly published, (with full details of all potentially important aspects of its methods and findings) and fully subjected to various types of very intensive scientific scrutiny.

If DEVTA is **eventually** accepted as an appropriately conducted cluster-randomised trial in a relevant population, **then** DEVTA should be taken together with the other relevant vit A trial results (1986-93), and they with it.

In aggregate, DEVTA and the other studies would show that vit A supplementation of deficient populations yields a very **definite** ($2p<0.0001$), but only **moderate** (CI 6-16%), gain.

NB: Cost-effective even with a 10% mortality reduction.

Village to Village Riders



DEVTA: correspondence between cluster and individual randomisation

Correspondence between 95% CI for the mortality ratio, R, in a **cluster**-randomised trial & equivalent numbers of deaths (treated vs control) in a large, evenly balanced, **individually** randomised trial:

95% CI of (0.89-1.03) for R=0.96 in DEVTA
would be equivalent to 1411 vs 1470 deaths*

*95% CI corresponds to (1+R)k vs (1+1/R)k deaths, where k is the square of 3.92/log (upper/lower limit)

Ghana trial: correspondence between cluster and individual randomisation

95% CI of (0.68-0.98) for R=0.81 in Ghana **would be equivalent to** 208 vs 257 deaths*

*95% CI corresponds to (1+R)k vs (1+1/R)k deaths, where k is the square of 3.92/log (upper/lower limit).

Conversely, x vs y deaths yields R = x/y with lower and upper confidence limits $R*\exp(\pm 1.96\sqrt{(1/x+1/y)})$.

DEVTA (2007) and 8 other community-based randomised and/or placebo-controlled trials of vit A (1986-93): deaths

Year, 1st author, country	R	& 95% CI	Equivalent deaths, vit A vs control*
1986, Somer, Indonesia	0.66	0.44-0.97	41 vs 62
1990, Vijayaragavan, India	1.0	0.65-1.55	40 vs 40
1990, Ramathulla, India	0.46	0.30-0.71	30 vs 66
1990, West, Nepal	0.70	0.56-0.88	128 vs 183
1992, Daulaire, Nepal	0.74	0.55-0.99	77 vs 105
1992, Herrera, Sudan	1.06	0.82-1.37	120 vs 113
1992, Arthur, Ghana	0.30	0.12-0.75	6 vs 20
1993, VAST, Ghana	0.81	0.68-0.98	208 vs 257
1986-93 subtotal (8 trials)	0.77	0.70-0.85	650 vs 846
2007, DEVTA, India	0.96	0.89-1.03	1411 vs 1470
Total (DEVTA + 8 others)	**0.89**	**0.84-0.94**	**2061 vs 2316**

*No. of deaths in a large, evenly balanced, individually randomised trial to get the same RR & CI. (For subtotal & total, RR & CI come from nos.)