

# Newborn Vitamin A Dosing and Neonatal Mortality

## Why do the Results Differ?

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The primary purpose of this article is to provide a description of the studies that examined early infant survival following vitamin A supplementation of newborn infants. These descriptions will provide a background for the accompanying papers by Drs Benn and Klemm on the wider issues surrounding the vitamin A dosing of newborns. In addition, I will describe the effects of the high dose of vitamin A on retinol reserves in the neonate, compare it with the amount of vitamin A obtained from human colostrum, and examine breast feeding practices in or near to the countries where the vitamin A dosing studies were done. Two recent studies have highlighted some of the consequences of delayed initiation of breast feeding on mortality of the neonate, and their results may be of relevance in the interpretation of the newborn vitamin A dosing trials.

### The neonatal vitamin A supplementation trials

Three randomized, placebo-controlled trials, in Indonesia<sup>1</sup>, Bangladesh<sup>2</sup> and South India<sup>3</sup> all demonstrated a significant reduction in infant mortality among newborn infants who were supplemented with 50,000 IU (52  $\mu\text{mol}$  retinol equivalents (RE)) vitamin A within 48 hr of birth compared to control groups. In contrast, no reduction in mortality was detected in two similar studies in sub-Saharan Africa; in Guinea Bissau<sup>4</sup> and in Zimbabwe.<sup>5</sup>

The first of the trials was done in a hospital in Bandung, Indonesia. Mothers delivering in this hospital were enrolled and if their infants were more than 1,500 g and without any life-threatening illness, they

were given either the vitamin A (n=1,034) or control (n=1,033) treatments and followed up to 12 mo.<sup>1</sup> There was a surprisingly large difference in infant mortality, with a relative risk ratio of 0.36 – that is, 64% fewer deaths in the vitamin A group (n=19) compared with the controls (n=7) at 12 mo (**Table 1**). The



Vitamin A dosing of newborn infant

impact was greater in boys, infants of normal compared with low birth weight, and those of greater ponderal index ( $\text{kg}/\text{m}^3$ ). Safety studies carried out at the same time examined infants for potentially acute side-effects over the first 48 hr. The groups were comparable at baseline, but a bulging fontanel was observed at 24 hr and 48 hr in the vitamin A (4.6%, 4.5%) and control (2.7%, 2.4%) groups respectively. The authors concluded that neonatal vitamin A supplementation of 50,000 IU had minimal side effects and appeared to reduce infant mortality rate and the prevalence of severe respiratory infection among young infants.

The next study was done by Rahmathullah and colleagues in Tamil Nadu, Southern India.<sup>3</sup> This was a community-based study in which 11,619 infants were allocated to doses of 24,000 IU (25 µmol) oral vitamin A (n=5,786) or placebo (n=5,733) on days 1 and 2 after delivery. After the first dose, the supervisor revisited the household to give the second dose and record any adverse events. Adverse events were limited to vomiting (placebo, 6; vitamin A, 3), and there were no reports of bulging fontanel. Project staff visited the households every two weeks to assess vital status and collect morbidity data for up to six months. There were 188 deaths in the placebo group and 146 in the vitamin A group. Supplementing newborn infants with vitamin A was associated with 22% less mortality and analysis of infant survival curves indicated that the placebo group did progressively worse from

2 weeks to 3 months. Interestingly the protective effects of vitamin A were stronger in boys (30%) and not significant in girls (13%) and only significant in those with birth weights <2,500 g (**Table 1**).

The third study to report lower mortality in neonates supplemented with vitamin A was carried out in Bangladesh. Infants were dosed with oral vitamin A (50,000 IU, n=7953) or placebo (n=7984), and 99.8% received their supplement at a median age of seven hours.<sup>2</sup> The study piggy-backed on a maternal vitamin A and β-carotene supplementation trial, but this did not appear to influence the results. The main outcome measure was mortality during the first 24 weeks, which was assessed at weekly visits for the first 12 weeks and then again at 24 weeks of age. There were few adverse effects. Mothers reported bulging fontanel in 154 (vitamin A,

1.9%) and 178 (control 2.2%), but of these only 11 and 21 cases respectively were clinically confirmed ~1 day later. The trial was halted when there had been 306 (vitamin A) and 360 (control) deaths, representing a relative risk of 0.85 or 15% reduction attributable to the vitamin A (**Table 1**).

There were other similarities between the studies in Bangladesh and Southern India,<sup>3</sup> where mortality rates were far greater than those in Indonesia. The studies in Bangladesh and Southern India were both done in rural communities, and infant survival in the control group was progressively worse from one up to ~16 weeks. However, in contrast to Southern India, there was stronger evidence of protection among girls, term infants, infants born to mothers with parity one or higher, and a relationship between survival and

**Table 1:** Mortality statistics in the newborn vitamin A supplementation trials

Study	Sample size	Total deaths	Mortality rate/1000 person/years	Relative risk ratio (95% CI)	Period of measurement (months)	Survival difference between groups	Sub-groups benefiting from vitamin A
Indonesia <sup>1</sup>	VA 1,034	7	7.2	0.36 (0.16, 0.87)	12	Better in VA group between 2 wk and 4 mo	Boys; normal birth weight; greater ponderal index
	C 1,033	19	19.8				
Southern India <sup>3</sup>	VA 5,786	146	53.8	0.78 (0.63, 0.96)	6	Better in VA group between 2 wk and 3–4 mo	Boys; birth weights >2,500 g
	C 5,833	188	69.1				
Bangladesh <sup>2</sup>	VA 7,953	306	38.5	0.85 (0.73, 1.00)	6	Better in VA group between 2 wk and 4 mo	Girls; term infants; mothers' parity >1
	C 7,984	360	45.1				
Zimbabwe <sup>5</sup>	VA 4,592	88	21.0	1.08 (0.80, 1.46)	12	No period advantage	None reported of survival
	C 4,601	82	19.3				
Guinea Bissau <sup>4</sup>	VA 2,145	88	49.0	1.07 (0.79, 1.44)	12	No period of survival advantage	Boys; infants born in dry season
	C 2,200	86	45.6				
				1.00 (0.65, 1.56)	First 4 mo		

VA: Vitamin A; C: Control

birth weight was not detected (**Table 1**).

Malaba and colleagues<sup>5</sup> working in Zimbabwe reported the first study to find no benefit of vitamin A given to neonates. The study was a 2x2 factorial designed trial of infants from HIV-negative mothers where mothers and infants were randomized to receive vitamin A (mothers 400,000 and infants 50,000 IU) or placebo. There were approximately 2,300 mother-infant pairs per group and 42–46 deaths in any group receiving vitamin A compared with 36 deaths in the group where neither mothers nor infants received vitamin A. Mortality rates were similar with those in Indonesia. Survival curves tended to be poorer in the three groups receiving vitamin A, but none of the differences from the group receiving no vitamin A were significant. Thus the authors concluded that vitamin A supplementation of neonates and post-partum women was unlikely to reduce infant mortality, and, the authors added, “in relatively well-nourished populations even when infectious diseases are the commonest cause of death” (**Table 1**).

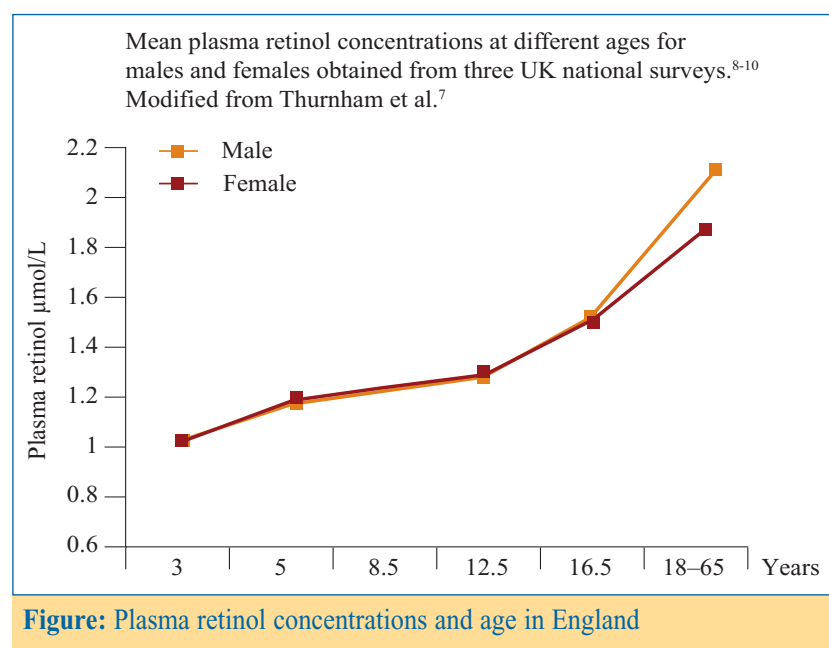
Lastly Benn and colleagues<sup>4</sup> reported no effects of 50,000 IU vitamin A on infant mortality when they randomized 4,345 infants who were due to receive BCG vaccine at birth, with vitamin A or placebo. Their study was done in Guinea Bissau, West Africa and excluded infants below 2,500 g at birth. Infants were followed through the routine registration system every 3 mo and were visited by a special team at 12 mo. 174 children died during follow-up, and overall mortality rates were high and comparable with Bangladesh and Southern India. However, the 12 mo mortality risk ratio was 1.07. There was also no evidence of any survival

advantage for the vitamin A group during the first 4 mo when the ratio was 1.0 and it was 1.13 between mo 4 to 8 (**Table 1**). So the group failed to find any important effect of vitamin A on overall mortality, but when the genders were examined separately, the effect tended to be beneficial for boys but harmful for girls i.e. a commonality with the studies in Indonesian and Bangladesh.<sup>1,3</sup>

### Vitamin A status

In a previous article in SIGHT AND LIFE Magazine,<sup>6</sup> Tielsch and colleagues argue that a principle factor explaining the different outcomes between the intervention studies was the vitamin A status,

of, the health care system in choosing to give birth in the hospital<sup>1</sup>, and the retinol concentrations in the trial women were comparable with those obtained from women in industrialized countries like the UK<sup>7–10</sup> and the USA.<sup>11</sup> Please compare the mean retinol concentration of the Indonesian mothers (**Table 2**) with that of adult UK women in the **Figure**. However, there was certainly evidence of vitamin A deficiency in the other two Asian studies, since in Southern India 5–6% of the women reported a history of night blindness,<sup>3</sup> and in Bangladesh approximately 10% of women reported night blindness in a previous pregnancy.<sup>2</sup>



for it was reasonable to assume that there was unlikely to be a mortality benefit if the vitamin A status was good, as was found in the two African studies.<sup>4,5</sup> However, a major difficulty in this hypothesis was the lack of evidence of vitamin A deficiency in the Indonesian study (**Table 2**). The Indonesia women recruited were relatively privileged in that they had access to, and made use

The vitamin A status reported in the two African studies was different to that in the Indian sub-continent. In Zimbabwe, no woman reported night blindness, and the authors suggest that the maternal plasma concentrations were similar to those of a reference American population of reproductive age. However, comparison with NHANES 3 data<sup>11</sup> which is essentially the same as that shown in the

**Table 2:** Vitamin A status and other socio-economic factors in the five neonatal vitamin A supplementation trials

Study	Blood levels	Night blindness	Socio-economic factors
Indonesia <sup>1</sup>	Mean maternal retinol in a subsample (n=150) ~1.77 µmol/L	None reported	Women had access to and chose to give birth in hospital. Most infants (>80%) in Indonesia are born at home
Southern India <sup>3</sup>	No measurements	5–6% reported in current pregnancy	Study done in 2 rural districts in Tamil Nadu. Most infants born either at home (~37%) or at hospital (54%)
Bangladesh <sup>2</sup>	Mean (SD) maternal serum retinol (first trimester) ~1.15 (0.32) µmol/L	10% reported history in previous pregnancy	Study done in 19 unions of rural NW Bangladesh, typical lower socio-economic community; 94% infants delivered at home
Zimbabwe <sup>5</sup>	Mean maternal retinol of sub-groups 1.09–1.25 µmol/L	None reported	Study done in Harare; Mothers HIV negative at delivery. National Survey found 36% of pre-school children had serum retinol <0.7 µmol/L in 1999
Guinea Bissau <sup>4</sup>	Mean RBP measurements equivalent to – maternal retinol 1.75, infants 0.82 (6 wk) and 0.98 µmol/L (4 mo)	None reported	Bandim health project in 6 suburban districts of G-B, malaria endemic, birth weight >2,500 g. Infants born at home and in hospitals

RBP: Retinol binding protein

**Figure** suggests the mean Zimbabwean plasma retinol concentrations are ~30% lower than American data. Nevertheless such data are unlikely to indicate deficient liver stores of vitamin A, as relative dose response tests carried out on Thai women with slightly lower mean retinol concentrations found no evidence of deficient liver reserves.<sup>12</sup> However, the relatively low plasma retinol concentrations of the Zimbabwean women could well impair milk retinol concentrations.<sup>13</sup>

In the case of the study in Guinea Bissau, the authors took blood from sub-samples of mothers and infants at 6 weeks and 4 mo of age. In general they measured vitamin A status using retinol binding protein (RBP). To convert their data to plasma retinol concentrations, they analysed a few samples

by HPLC and calculated a regression equation. Using the authors' equation, the mean maternal retinol concentrations they obtained were 1.82 µmol/L (95% CI 1.77, 1.87), which, as they suggest, were equivalent to those of American women. Furthermore the mean retinol concentrations of the infants at 6 weeks and 4 mo of age were ~0.96 and 1.14 µmol/L respectively and were equivalent to those of preschool age children in England (**Figure**). Thus there was very little evidence to suggest any vitamin A deficiency in Guinea Bissau apart from a relatively high proportion of infants with low retinol concentrations. However the latter may be due to inflammation. The authors measured CRP as a marker of inflammation in the infant blood because of the high exposure to infection in the community. There were ~23% with a CRP concentration >5 mg/L,

but the authors failed to measure the marker of chronic inflammation α<sub>1</sub>-acid glycoprotein (AGP). Children with chronic inflammation usually outnumber those with acute inflammation, as seen in the recent study in The Gambia where at 6 mo there were 20% of infants with a raised CRP but 50% with a raised AGP concentration.<sup>14</sup> Thus the high proportion of low retinol results in the infants may have been a consequence of chronic inflammation and not vitamin A deficiency, further emphasising the fact that vitamin A status of this population was probably reasonably good.

In summary, in the two studies where night blindness was reported, vitamin A supplements were associated with lower neonatal mortality. However, vitamin A has the same effect in Indonesia, where vitamin A status of the mothers was

good, but had no effect in the two African studies, where vitamin A status also appeared to be good. Thus the presence of vitamin A deficiency in the community does not appear to be the main determinant for a successful reduction in mortality following neonatal dosing with vitamin A.

### Time of initiation of breast feeding and neonatal mortality

Two studies have recently shown that failure to provide human milk to the neonate in the first hour after delivery will increase the risk of neonatal mortality.<sup>15,16</sup> It has been recognized for a long time that all infants, irrespective of maternal vitamin A status, are born with little or no reserves of vitamin A, and infants are dependent on the vitamin A in breast milk to supply their needs for growth and storage.<sup>17</sup> In addition, breast milk, and especially the colostrum, is an important source of protein and immunoglobulins. The concentration of these is highest on day one, halves by day two and then progressively decreases at a slow rate thereafter. Such factors may accelerate intestinal maturation, resistance to infection and epithelial recovery after infection.<sup>15</sup>

### Two studies have recently shown that failure to provide human milk to the neonate in the first hour after delivery will increase the risk of neonatal mortality

In Ghana, West Africa, 70% of infants were exclusively fed breast milk, and for another 27%, breast milk was the predominant feed. Breast feeding was initiated by 71% of infants within the first day, and all but 1.3% had started by day 3. However, it was breast feeding within the first hour that reportedly saved 22%

of neonatal deaths, and 16% if all infants were breast fed from day 1. Late initiation (after day 1) was associated with a 2.4-fold higher risk of mortality and a four-fold higher risk in children given milk-based fluids or solids in addition to breast milk (Table 3).<sup>15</sup>

A similar pattern of the neonatal mortality risk was associated with breast feeding initiation in southern Nepal.<sup>16</sup> The authors suggested that 7.7 and 19.1% of neonatal deaths may be avoided by universal initiation of breast feeding within the first day and hour respectively. However, when the confounders of birth weight and prematurity were taken into account, the effects of early initiation were no longer significant, but the trend for a higher risk with longer initiation times was still significant ( $p < 0.03$ ). As also noted in Ghana, partial as opposed to exclusive breast feeding was associated with ~2-fold higher mortality (1.77 95% CI 1.32, 2.39).

### Does neonatal vitamin A supplementation substitute for the vitamin A in colostrum?

Many studies have shown that the vitamin A content of human milk is high in the colostrum at birth and then decreases by half to two thirds in mature milk. A review of the literature by Ross & Harvey<sup>18</sup> suggested that the potential amount of vitamin A from colostrum over the six days from a mother living in a poor environment is ~3.6 mg (12.5  $\mu\text{mol RE}$ ). If the mother receives vitamin A supplements during pregnancy, the potential amount increases to 4.6 mg (16  $\mu\text{mol RE}$ ). These amounts are lower than the vitamin A obtained by an infant from a vitamin A supplement (52  $\mu\text{mol RE}$ , 50,000 IU), where estimates suggest infant liver reserves increase by ~28  $\mu\text{mol RE}$ .<sup>19</sup> However, the stimulus of early breast feeding is believed to increase rates of exclusive<sup>16</sup> and sustained breast feeding through infancy<sup>15</sup> to maintain the supply of vitamin A. Thus early initiation of breast feeding may provide equivalent health benefits to the neonatal vitamin A supplement.

**Table 3:** Influence of time of breast feed initiation and risk of neonatal mortality

	Time of initiation (hours)	Percent of sample	Potential deaths saved (%)	Total neonatal deaths (48 hr to 28 d)	Mortality rate
Nepal <sup>16</sup>	<1	3.4	19.1	297	12.6/1000
	<24	56.6	7.7		
Ghana <sup>15</sup>	<1	43.5	22	145	13.3/1000
	<24	72	16		

Thus it is possible that where the neonatal vitamin A supplement appeared to lower mortality compared to the placebo treatment, the supplement may have been making good a deficit in those advantages obtained from colostrum. These circumstances may have applied in Southern India and Bangladesh and hence the vitamin A supplement lowered the mortality in the vitamin A group. In contrast, the rapid

good, but the early introduction of non-human milks may have influenced the mortality statistics, giving the appearance of benefit from the vitamin A supplement. Lastly, there is no direct information on initiation of breast feeding or of complementary feeding in the Guinea Bissau study, so it is difficult to know whether or not these factors may have influenced the outcome. The high vitamin A status and

suggest that prevalence of inflammation was lower in the dry than in the wet season.<sup>20</sup>

**Breast feeding practices in the neonatal mortality trials**

The benefits of earlier initiation of breast feeding, and especially of receiving colostrum, on neonatal mortality have only recently been demonstrated<sup>15,16</sup> and, unfortunately, information on the breast feeding habits of the infants in the neonatal vitamin A supplementation trials is incomplete (Table 4).

**The benefits of earlier initiation of breast feeding, and especially of receiving colostrum, on neonatal mortality have only recently been demonstrated**

In Indonesia, although most mothers gave breast milk to their infants, there is no information on feeding habits in the first 12 hours, but up to 2% (n=41) of infants may never have received breast milk, and at 4 mo 82% received complementary foods. The authors report ~98% of infants in both the vitamin A and placebo groups were breast fed at baseline, but baseline was the time of administering the supplement and

initiation of breast feeding in Zimbabwe lowered the efficacy of the vitamin A supplement, so no benefit was seen even though mothers' vitamin A status may have slightly lowered the breast milk vitamin A content. In Indonesia, mothers' vitamin A status was

potentially high prevalence of inflammation may have precluded any benefit from the vitamin A treatment, and this is to some extent supported by the suggestion that the vitamin A supplement was of benefit to infants born in the dry season. Experience in The Gambia would

**Table 4:** Breast feeding habits reported in the vitamin A supplementation trials

Study	Not breast fed in first 12 hours	Not breast fed at all	Use of complementary foods	Other information
Indonesia <sup>1</sup>	No information	1–2% not BF or fed <1 mo (2%, n=41)	At 4 mo 82% receiving complementary foods	Early introduction of non-breast-milk foods customary in Indonesia
Southern India <sup>3</sup>	20% (n=1,157) in VA group 18% (n=1,050) in placebo group	11% (n=636) in VA group 15% (n=875) in placebo group	No information	Median time to 1 <sup>st</sup> dose VA was 26 h and mothers encouraged to BF immediately after dose
Bangladesh <sup>2</sup>	52.8% (n=4,199) in VA group 52.6% (n=4,200) in placebo group	No information	No information	Approximately 5% (n=797) in both groups did not get any colostrum
Zimbabwe <sup>5</sup>	2.4–3.0% (n~280)	None	No information	
Guinea Bissau <sup>4</sup>	No information	No information	No information	Almost all children in study area BF to at least 18 mo

BF: Breast feeding

~12% (n=248) had not received their supplement at 24 hr. The mortality rate in the Indonesian cohort was relatively low (total 26 deaths) and delayed initiation of breast feeding, and early introduction of complementary feeding may both have influenced mortality and not been accounted for in assessing the effects of the vitamin A trial on mortality.

In the Southern India study<sup>3</sup>, approximately 19% of infants did not receive breast milk in the first 12 hours and 11–15% were not fed breast milk at all (**Table 4**). Mothers were encouraged to breast feed immediately following the treatment to reduce losses of the supplements, but median first-treatment time was 26 hours. There were a total of 334 deaths (146 VA; 188 placebo) in those infants treated within the first 48 hours, when it appeared vitamin A had its greatest benefit (risk ratio 0.77; 95% CI 0.61, 0.97), but this group will have included a large number of infants not given colostrum in the first 12 hours. Infant feeding habits do not appear to have been included in the data analysis, thus delayed initiation of breast feeding may also have contributed to the neonatal mortality and any differences between the two groups may have not been entirely due to vitamin A.

In the Bangladesh study, 79% of live born infants were administered the supplement within 24 hours (median age 7, inter-quartile range 2, 18 h) and new-born care practices (breast feed initiation, colostrum consumption etc.) were comparable between the two treatment groups. However, more than half of all infants did not receive breast milk in the first 12 hours and there were 32 more mothers in the vitamin A than the placebo group who reported giving no colostrum. No relationship between time of initiation of breast

feeding or colostrum consumption and neonatal mortality was reported by the authors. There were 54 fewer deaths in the group who received vitamin A than the placebo treatment, and a more detailed analysis of breast feeding initiation and infant mortality within the first 24 h might be justified. This is particularly relevant if one considers the data from Zimbabwe, where ~40% of mothers initiated breast feeding within 1 hr of delivery and 97% within 12 hr.<sup>5</sup> These habits are in sharp contrast to those in the Southern India and Bangladesh studies (**Table 4**).

In Guinea Bissau no information is given on the time of breast feeding initiation; only that mothers breast fed children to at least 18 mo.<sup>4</sup> Guinea Bissau is in West Africa, and concern has been expressed over breast feeding practices in West and Central Africa, which has some of

the highest malnutrition and mortality rates in the world.<sup>21</sup> In The Gambia, which is geographically close to Guinea Bissau, initiation of breast feeding is reported to be usually delayed until more than 24 hr after delivery. In addition, pre-lacteal feeds are common, and exclusive breast feeding is rare.<sup>22</sup> If breast feeding initiation in Guinea Bissau is similar to that reported from The Gambia, then the high mortality rates reported in Guinea Bissau (in spite of an apparently well-controlled vaccination schedule for the infants) may share a similar etiology to mortality rates in Bangladesh and Southern India. However, in Guinea Bissau there was no overall effect on neonatal mortality of the vitamin A treatment, and this difference may have arisen because vitamin A status appeared to be satisfactory in both mothers and infants.

#### Key findings at a glance

- There was less infant mortality in Indonesia, Southern India and Bangladesh after neonatal vitamin A supplementation with 50,000 IU compared with placebo
- Similar trials in Zimbabwe and Guinea Bissau in Africa had no effects on infant mortality
- Night blindness was evidence of poor vitamin A status in Southern India and Bangladesh
- Vitamin A status was moderate to good in Zimbabwe, Indonesia and Guinea Bissau
- Delayed initiation of breast feeding was common in Southern India and Bangladesh
- Delayed initiation of breast feeding was associated with higher mortality in two studies (Ghana, Nepal)
- There was no delay in breast feeding in Zimbabwe, with ~40% starting within 1 hr of delivery, but no information for Indonesia and Guinea Bissau
- The cumulative effect on vitamin A status of feeding colostrum in the first hour after birth may be similar to that of oral vitamin A dosing with 50,000 IU vitamin A
- Good vitamin A status, early initiation of breast feeding and vitamin A supplements are associated with lower infant mortality
- Late initiation of breast feeding, poor vitamin A status, early introduction of complementary feeds are associated with higher infant mortality

## Conclusions

Late initiation of breast feeding may be a major factor in the high neonatal mortality rates in Bangladesh, Southern India and Guinea Bissau, and in these circumstances vitamin A status is particularly important and, where it is poor, neonatal dosing with vitamin A reduced infant mortality. In the Zimbabwean and Indonesian studies, infant vitamin A status was relatively good due to early initiation of breast feeding in Zimbabwe and the higher socio-economic status in Indonesia. In these circumstances, neonatal vitamin A supplement provided no further benefit in Zimbabwe but did provide benefit in Indonesia, where there was early introduction of non-breast-milk foods.



Newborn supplements

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