Perspective

Neonatal Vitamin A Supplementation for Improving Infant Survival: Hope or hype?

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In 2008, in the first *Lancet* Series on Nutrition, Bhutta *et al.* concluded that neonatal vitamin A supplementation reduced mortality in infants younger than 6 months in Asia, and recommended it as a 'core intervention' for this region.[1] However, this recommendation was contested by one of the co-authors of the same research paper who pointed out that the relevant meta-analysis was flawed as it had excluded an elig2ible but negative trial from South Asia;[2] inclusion of this trial would lead to no convincing evidence that neonatal vitamin A supplementation prevented mortality in young infants. This correspondence led to a fierce debate and fortunately the stakeholders took serious notice of the brittle evidence base to make any global recommendations.

The World Health Organization (WHO) therefore commissioned a systematic review to evaluate the effect of neonatal vitamin A supplementation on infant mortality, morbidity and adverse effects.[3] In an ensuing meeting to discuss the results of this systematic review, WHO recommended initiation of three large, randomized, placebo-controlled trials of neonatal vitamin A supplementation in settings of high infant mortality to generate relevant evidence to inform global policy. Following a rigorous selection process by independent experts, three sites (two in Africa—Ghana and Tanzania, and one in Asia—India) were selected to conduct rigorous randomized controlled trials with funding from the Bill and Melinda Gates Foundation and oversight by the WHO. These efficacy trials, done independently but with a similar design, aimed to establish the effect of 50 000 IU of vitamin A, given to neonates once orally either on the day of birth or in the next 2 days, on mortality in the first 6 months of life in comparison to placebo.

The results of these three large trials have now been published.[4–6] Overall, there was no convincing evidence of mortality benefit with neonatal vitamin A supplementation. There was some evidence of benefit for survival to 6 months of age in India (risk ratio [RR] 0.90, 95% CI 0.81–1.00; p=0.057).[4] However, there was no evidence of a mortality benefit for survival to 6 months in the trials from Tanzania and Ghana; conversely, there was a suggestion of increased risk of mortality (in Tanzania, RR 1.10, 95% CI 0.95–1.26; in Ghana, relative risk 1.12, 95% CI 0.95–1.33).[5,6] Study factors including attrition rate, concurrent maternal vitamin A supplementation, number of vitamin A doses, period of follow-up, and region where the study was conducted did not explain differences in results among studies. There was no evidence of reduction of diarrhoea or pneumonia-specific mortality while the effects on morbidity were inconsistent. Overall, supplementation with 50 000 IU vitamin A within the first 72 hours of life was generally safe and well-tolerated, with the exception of an excess risk of transient bulging fontanelle in India (205 cases in the vitamin A group confirmed by physician *versus* 80 cases in the placebo group, risk ratio 2.56 [95% CI 1.98–3.32]).

In summary, these contemporary data[4–6] confirm the findings of two earlier systematic reviews[7,8] while contradicting the meta-analysis and recommendations made by the first *Lancet* series on nutrition.[1] Thus, there is no convincing evidence in the current era that adopting neonatal vitamin A supplementation as a public health measure will improve infant survival. Although the strategy may be consistent with improved survival in some settings, it can lead to increased mortality in other regions. In the absence of any reliable predictors of a small survival benefit, there is no case for recommending neonatal vitamin A supplementation as a public health intervention. Further, the finding of excess bulging fontanelle, particularly the 2.6-fold higher risk in India, cannot be ignored at the population level as the long-term developmental consequences of this have not been evaluated. In an accompanying editorial, Bhutta *et al.*[9] admitted: 'Perhaps slightly prematurely, a recommendation was made by the series authors for inclusion of this intervention in the repertoire of nutrition actions in south Asia. We concur with the conclusion that there is no overwhelming or consistent evidence of benefit of this intervention among newborn infants, at this point in time, to mark this intervention as crucial or lifesaving, a shift in our position from 2008.'[1]

There are potential learnings from this narrative for formulating public health policy in low- and middle-income countries such as India, which are constantly juggling meagre resources for competing public health interventions. First, policy-makers should not get mesmerized by advocacy articles in reputed journals to blindly follow their recommendations. It is easy to get swayed by visible 'magic bullets' or 'quick fixes' promising millions of lives saved with simple cost-effective interventions. However, as illustrated by the neonatal vitamin A supplementation and infant survival story these projections are extremely brittle. The inclusion[2] of an omitted trial in the meta-analysis dramatically altered the global projections of proportion of under-five deaths attributed to vitamin A deficiency from 6.5% (or 667 771)[10] to 2.3% (or 157 000).[11] There is thus an urgent need to institutionalize health policy research in India to take evidence-based decisions relevant to the local context. Second, 'quick fixes' should not become distractors for the broader goal of improving the nutrition profile of the population through sustainable and equitable development including food security and access to healthcare.

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