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Impact of vitamin A supplementation on infant and childhood mortality

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Introduction: [illegible]

Past reviews have evaluated the impact of vitamin A supplementation on infant and childhood mortality. A meta-analysis combining 6 community-based RCTs showed a reduction of 30% [Relative risk (RR) 0.70 95% confidence interval (CI): 0.62-0.79] in all-cause mortality and a reduction of 39% [RR 0.61 95% CI: 0.50-0.76] in deaths from diarrheal disease in pre-school children [4]. There was no effect on deaths related to respiratory diseases. Another systematic review including 10 RCTs with 8 included in a meta-analysis, showed a significant reduction of 23% [RR 0.77; 95% CI 0.68-0.88) in all-cause mortality among vitamin A supplemented children compared to controls in children 6-60 months of age [5]. The review reported a significant reduction in mortality due to diarrheal disease [RR 0.71; 95% CI: 0.57-0.88) and measles [RR = 0.46; 95% CI: 0.22-0.98] and a non-significant effect on deaths attributed to respiratory disease [RR = 0.94; 95% CI: 0.63-1.42]. A review of vitamin A supplementation in childhood and pregnancy published in Lancet Under-nutrition Series by Gogia et al. [6] also showed a significant reduction in all-cause mortality in pre-school children [RR = 0.77, 95% CI: 0.63-0.95].

Reviews have also been conducted for neonatal vitamin A supplementation. An analysis for neonatal vitamin A supplementation by Haider et al. showed a reduction of 20% [RR 0.80; 95 % CI: 0.66-0.96] in infant mortality at 6 months of age; the results for mortality at 12 months of age were, however, not statistically significant [RR 0.90; 95% CI: 0.61 to 1.32] [7]. Another meta-analysis published in British Medical Journal evaluating

Data abstraction

We abstracted the data of included studies onto a standardized abstraction form [9] for each outcome of interest. We abstracted key variables with regard to the study identifiers and context, study design and limitations, intervention specifics, and outcome effects. The data were entered by two authors and discrepancies were removed if found.

Validity assessment

Each study was assessed and graded according to the CHERG adaptation of the GRADE technique [9,10]. This method of assessment is based on scores allocated to individual studies on the basis of study design, quality of methods, relevance to the objectives of the review and consistency across studies. Studies received an initial score of high if a randomized or cluster randomized trial and then the grade was decreased for each study design limitation, if applicable. In addition, studies reporting an intent-to-treat analysis or with statistically significant strong levels of association (>80% reduction) receive 1-2 grade increases. Each study was assigned a quality grade of “high” “moderate” “low”

pooled relative risk and the strength of the statistical evidence for an association between the intervention and the health outcome as reflected in the p-value. In this way, we generated estimated efficacy of vitamin A supplementation in reducing disease specific mortality for the developing countries in community settings and gave our recommendations for input to Lives Saved Tool (LiST) model [9].

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Trial flow

We identified 1251 titles from searches conducted in all databases (Figure 1). After screening the titles and abstracts, 40 studies were initially considered eligible and finally, 21 studies were selected for final data abstraction. We evaluated the impact of preventive vitamin A supplementation on the following outcomes: all-cause mortality, disease specific mortality of diarrhea, pneumonia, measles, meningitis and sepsis.

Study characteristics

Additional File 1 presents characteristic of included studies. There were 21 randomized controlled trials that addressed preventive vitamin A supplementation in infants or children and reported all-cause mortality [20-40]. Of these, 10 were individual RCTs [28,31-37,39,40], while 10 were cluster randomized trials [20-25,27,29,30,38]. The paper by WHO VAST (Vitamin A Supplementation Treatment) group [26] in Ghana was divided into two studies: VAST survival study (mainly looked at mortality outcomes) and VAST health study (mainly looked at morbidity outcomes). VAST health study was an individual randomized controlled trial while VAST survival study was cluster randomized. Participants in five studies

were all neonates [31,35-38], while in nine they were aged 1-59 months [21,22,24,28,30,32,33,39,40]. Seven studies also included children more than five years of age [20,23,25-27,29,34]. Disaggregated data for children < 5 years of age was available from two of these studies and was thus used accordingly [20,23]. For rest of the studies we used the data according to the inclusion criteria. Vitamin A was supplemented in synthetic form in a dose of 50,000 IU to neonates (0-28 days of life), 100,000 IU to infants (1-12 months of age) and 200,000 IU to children older than infants according to WHO guidelines [41] except in three studies [21,33,39]. In one of these studies [21], participants received a weekly dose of 8333 IU for 52 weeks, while in other two studies [33,39] it was a dose of 25 000 IU with immunization schedule. In three studies comparison group did not receive a placebo but children were simply observed as controls [20,24,39]. The coverage of intervention was high and it reached > 90 % in fifteen of the included studies [20-23,25-27,31-33,35-38,40]. All the included studies were from developing countries. Additional File 2 presents risk of bias table according to the Cochrane handbook.

Quantitative data synthesis

All-cause mortality

Pooled results from all the 21 included studies showed that prophylactic vitamin A supplementation reduced all-cause mortality by 15% [RR 0.85, 95% CI: 0.76-0.94, random model] in children 0-59 months of age (data not shown). We did separate analyses for vitamin A supplementation in neonates, infants 1-6 months and children 6-59 months of age. Data for preventive effect of neonatal vitamin A supplementation was analyzed in two stages: one when infant mortality was measured at 6 months and then that at 12 months of age. Combined results from six studies in neonatal period showed that vitamin A supplementation reduced all-cause mortality by 12% at six months of age [RR 0.88, 95% CI: 0.79-0.98, fixed model]. The sub-group analysis with respect to geographical region for this outcome is also shown which showed that neonatal vitamin A supplementation has a protective effect in Asia but not in Africa (Figure 2). The overall result was, however, not statistically significant at 12 months of age [RR 0.90, 95% CI: 0.56-1.46, random model] (data not shown). In children 1-6 months of age, vitamin A supplementation had no effect on all-cause mortality [RR 1.05; 95 % CI 0.88-1.26, fixed model] (Figure 3). Preventive vitamin A supplementation in children 6-59 months of age reduced all-cause mortality by 25% [RR 0.75, 95% CI: 0.64-0.88, random model], with geographical sub-group analysis shown (Figure 4). This subgroup analysis indicated that preventive vitamin A supplementation had a prominent effect in reducing all-cause mortality in Asia but the results

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Daulaire 1992* -0.01 0.4538

Mahalanabis 1997 0.0582 0.3632

West 1995b 0.1133 0.1352

(5 %)

Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%

Test for overall effect: Z = 0.80 (P = 0.42)

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Newton 2008 1.536 1.086

(5 %)

Heterogeneity: Not applicable

Test for overall effect: Z = 1.41 (P = 0.16)

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WHO 1998¶ -0.0408 0.1397

(5 %)

Heterogeneity: Not applicable

Test for overall effect: Z = 0.29 (P = 0.77)

(5 %)

Heterogeneity: Chi² = 2.53, df = 4 (P = 0.64); I² = 0%

Test for overall effect: Z = 0.53 (P = 0.60)

Test for subgroup differences: Chi² = 2.45, df = 2 (P = 0.29), I² = 18.4%

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for Africa and Latin America were not statistically significant. Applying a test for subgroup difference, showed no statistically significant difference among the groups (p=0.16). In infants 1-6 months there was no effect in any of the geographical regions. In group 6-59 months of age, five studies included children > 5 years of age and disaggregated data were not available. Excluding these studies from the analysis gives an estimate of 0.72 (95 % CI 0.62-0.83) which is not statistically different form the overall estimate (p=0.36).

Disease specific mortality

Twelve studies reported disease specific mortality of diarrhea and pneumonia [21,23-26,29,31,34-37,40]. Four of these studies included neonates only [31,35-37] and seven included children 6-59 of age [21,23-26,29,34]. Only one study in age group 1-6 months reported cause specific mortality [40]. Pooled results from these studies showed that prophylactic vitamin A supplementation reduces diarrhea specific mortality by 26% [RR 0.74, 95% CI: 0.58-0.93, random model] in children 0-59 months of age. This effect was also significant for supplementation in children 6-59 months of age [RR 0.70, 95% CI: 0.58-0.86, fixed model] (Figure 5), but not on mortality at 12 months for neonatal supplementation [RR 0.97, 95% CI: 0.43-2.19, random model] (Figure 6). One study from group 1-6 months reported a non-

study from group 1-6 months also showed no significant effect [RR 0.35; 95 % CI 0.01-8.53] on meningitis specific mortality[40]. Four neonatal studies reported sepsis specific mortality at 12 months [31,35-37] and the pooled results showed that vitamin A supplementation had no significant effect on sepsis specific mortality [RR 0.81, 95% CI: 0.52-1.26, fixed model] (Figure 12).

Recommendations for LiST model

We followed standardized guidelines to get estimates of efficacy of vitamin A supplementation in reducing diar-

'moderate" level. We recommended the above mentioned estimate for LiST model based on CHERG 'rule 2' which states that "***If*** there is high- or moderate-quality evidence of effect on cause-specific mortality…***Then*** use the mortality effect". The p-value for this estimate was <0.0001, which shows the strength of statistical association.

Pooled estimates for effect of vitamin A supplementation showed a non-significant reduction in pneumonia [RR 0.94 95% CI: 0.67-1.30, p=0.70], measles [RR 0.71, 95% CI: 0.43-1.16, p=0.17] and meningitis [RR 0.73, 95% CI: 0.22-2.48, p=0.62] specific mortality in children 6-59 months of age. The quality grade for all these estimates was that of 'low' level. These estimates are not being recommended for LiST model as results were not statistically significant and p value for all the above estimates was more than 0.10. According to CHERG method's paper a p value of < 0.10 is required for pooled estimate to be considered for inclusion in the LiST tool [9].

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The impact of vitamin A supplementation on infant and childhood mortality had been reviewed previously and it has been established that vitamin A has a definite role in reducing all-cause mortality in children older than six months of age [351(s5211096<ai18,42].t)-346An reeant tital coeducre thhat isoatllishe,e showed thattamin A

studies does not change the results significantly for all-cause mortality in children 6-59 months of age [RR 0.78, 95 % CI: 0.68-0.91, random model].

Preventive vitamin A supplementation in children 6-59 months of age showed a highly significant reduction of 30% (95% CI: 14%-42%) in diarrhea specific mortality. There was no heterogeneity in the pooled data (I^2=0%). The qualitative assessment of the available evidence according to GRADE criteria was that of 'moderate' level. The estimated reduction also corresponds to reduction in all-cause mortality in the same age group (Figure 4) and diarrhea specific mortality reported in other reviews [4,5]. This concludes that reduction of 30 % (95% CI: 14%-42%) is the best estimate of efficacy of vitamin A supplementation in reducing diarrhea specific mortality in children 6-59 months of age.

Despite the non-significant findings in our meta-analysis, an effect of vitamin A supplementation on measles-specific mortality is biologically plausible given the strong beneficial effect of vitamin A for treatment of measles at 200,000 IU for 2 days [RR: 0.40 95% CI 0.19-0.87] [13]. Preventive effect of vitamin A supplementation for measles related mortality may not be as apparent as administration at the onset of disease; as the incidence of disease has decreased at the first place due to large scale measles vaccination and extremely large trials are required to detect a statistically significant difference in measles related mortality. Nevertheless, in the absence of statistically significant data to support an effect, preventive vitamin A supplementation cannot be linked with measles mortality in this edition of the LiST model [9]. Impacts of preventive vitamin A supplementation on

other disease specific morta

has no protective effect on all-cause mortality at 12

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