Is routine Vitamin A supplementation still justified for children in Nepal? Trial synthesis findings applied to Nepal national mortality estimates

Samjhana Shrestha, Saki Thapa, Paul Garner, Maxine Caws, Suman Chandra Gurung, Tilly Fox, Richard Kirubakaran, Khem Narayan Pokhrel

1 Birat Nepal Medical Trust (BNMT), READ-It Project, Kathmandu, Nepal, 2 Centre for Evidence Synthesis in Global Health, Liverpool School of Tropical Medicine, Liverpool, United Kingdom, 3 Department of Clinical Sciences, Center for Drugs and Diagnostics, Liverpool School of Tropical Medicine, Liverpool, United Kingdom, 4 Prof BV Moses Centre for Evidence-Informed Healthcare and Health Policy, Vellore, India

These authors contributed equally to this work.

Abstract

Background
The World Health Organization has recommended Vitamin A supplementation for children in low- and middle-income countries for many years to reduce child mortality. Nepal still practices routine Vitamin A supplementation. We examined the potential current impact of these programs using national data in Nepal combined with an update of the mortality effect estimate from a meta-analysis of randomized controlled trials.

Methods
We used the 2017 Cochrane review as a template for an updated meta-analysis. We conducted fresh searches, re-applied the inclusion criteria, re-extracted the data for mortality and constructed a summary of findings table using GRADE. We applied the best estimate of the effect obtained from the trials to the national statistics of the country to estimate the impact of supplementation on under-five mortality in Nepal.

Results
The effect estimates from well-concealed trials gave a 9% reduction in mortality (Risk Ratio: 0.91, 95% CI 0.85 to 0.97, 6 trials; 1,046,829 participants; low certainty evidence). The funnel plot suggested publication bias, and a meta-analysis of trials published since 2000 gave a smaller effect estimate (Risk Ratio: 0.96, 95% CI 0.89 to 1.03, 2 trials, 1,007,587 participants), with the DEVTA trial contributing 55.1 per cent to this estimate. Applying the estimate from well-concealed trials to Nepal’s under-five mortality rate, there may be a reduction in mortality, and this is small from 28 to 25 per 1000 live births; 3 fewer deaths (95% CI 1 to 4 fewer) for every 1000 children supplemented.
Conclusions
Vitamin A supplementation may only result in a quantitatively unimportant reduction in child mortality. Stopping blanket supplementation seems reasonable given these data.

Background
For over 20 years, the World Health Organization (WHO) have recommended Vitamin A supplements to all children under five years (6–59 months) in low- and middle-income countries (LMICs) [1]. Although recommendations have changed with Vitamin A supplementation (VAS) now only being recommended when more than 1% of children have night blindness, or when one-fifth of the children have low retinol levels, in practice, most governments continue with giving supplements routinely [2]. Nepal, for instance, has been distributing large amounts of supplements to children since its start in 1993 [3] despite substantial progress in the health of under-five children [4].

The global evidence that the country refers to for child survival benefits of VAS has come from the Cochrane review by Imdad et al. who conclude, “Vitamin A supplementation is associated with a clinically meaningful reduction in morbidity and mortality in children.” However, the trials in the review are a decade-old trials [5,6], and were conducted against a backdrop of high childhood infections rates, greater malnutrition, and higher child mortality. On top of this, the Cochrane review has considerable unexplained heterogeneity ($I^2 = 61\%$) [6] which may indeed mean that the intervention works in some circumstances, but not in others. We know that the health status in Nepal has been improved (See Table 1 for details). In this analysis, we assess whether the mortality reduction with VAS in randomized controlled trials (RCTs) translates into important health benefits today in Nepal.

Aim and objectives
Our research question was whether routine vitamin A supplementation was still justified in Nepal? We sought to estimate the effects of routine vitamin A supplementation by a) generating an up-to-date reliable estimate of the effect of Vitamin A on mortality by updating the 2017 Cochrane meta-analysis of mortality, and then b) estimating the effects of supplementation on absolute mortality using contemporary health status measures of children.

Methods
Update of Cochrane review
We used the same methods from the 2017 Cochrane systematic review to update it [6]. We considered RCTs and cluster RCTs conducted among children for assessing the effect of VAS in reducing child mortality. We restricted the outcomes to all-cause child mortality. Full details of the methods are included in the supporting information (“S1 Appendix”) which details our prespecified effect modifiers and sub-group analysis and intended analysis of absolute effects against current measures of child health status in Nepal.

Search methods for identification of studies
We searched databases and trials registers from 2016 to March 2021 using the same search strategies as used in the Cochrane review [6] to identify any new relevant studies besides those included in the review.
Table 1. Secular changes in child health and health care delivery in Nepal.

| Secular changes                              | Earlier estimate | Contemporary estimate |
|----------------------------------------------|------------------|----------------------|
| Under Five Mortality Rate (U5MR)             | 1996             | 2019                 |
|                                              | 118 deaths per 1,000 live births¹ | 28 deaths per 1,000 live births² |
| Measles burden                              | 2003             | 2019                 |
|                                              | 5419 cases³      | 424 cases³           |
| Prevalence of diarrhoea                      | 1996             | 2016                 |
|                                              | 28% ¹            | 8% ¹                 |
| Diarrhoea Case Fatality Rate                 | -                | 2019                 |
|                                              |                  | Less than 1 per 1000 ³ under-five children |
| Measles immunization coverage                | 1996             | 2016                 |
|                                              | 57% ¹            | 90% ⁴               |
| Vitamin A coverage                           | 32% ¹            | 86% ⁴               |
| Vitamin A Deficiency (Serum retinol<0.7micromol/L) | 1998         | 2016                 |
|                                              | 32.3% ³           | 12.5% ⁶             |
| Vitamin A Deficiency (Modified Relative Dose-Response (MRDR) >0.060) | -               | 2016                 |
|                                              |                  | 4.2% ⁶              |
| Night blindness (12–59 months)               | -                | 1998                 |
|                                              |                  | 0.27% ⁵             |
| Stunting prevalence                          | 1996             | 2019                 |
|                                              | 57% ¹            | 31.5% ²             |
| Wasting prevalence                           | -                | 15% ¹               |
|                                              |                  | 12% ²               |
| Under-weight prevalence                      | 42% ¹            | 24% ²               |

¹ Nepal Family Health Survey 1996 [7].
² Multi-Indicator Cluster Survey 2019 [8].
³ Annual Report, Department of Health Services, 2018/19 [3].
⁴ Nepal Demographic Health Survey 2016 [9].
⁵ Nepal Micronutrient Survey 1998 [10].
⁶ Nepal National Micronutrient Status Survey 2016 [11].

Data collection and analysis

Using the inclusion criteria noted in our systematic review protocol (CRD42021249941), we screened the trials included in the 2017 Cochrane review and the trials that resulted from a new search. We extracted data on the effect modifiers from each trial. For trials where such data are not reported, we considered estimates of such modifiers from different sources such as the Global Health Observatory data repository [12] and other potential data sources like demographic health surveys, multi-indicator cluster surveys, and the World Bank data repository [13].

Assessment of risk of bias

We assessed the risk of bias using the Cochrane Risk of Bias Tool [14]. We improved on the risk of bias in the 2017 Cochrane review by assessing the cluster RCTs by recording baseline imbalance, loss of clusters, and the possibility of bias arising due to recruitment of participants into clusters, incorrect analysis and comparability with individually randomized trials.

Unit of analysis issues

For studies that did report cluster adjustments process or intra-cluster correlation coefficient (ICC), we used the design effects in the previous review [15] to adjust for clustering in those trials which did not control for clustering.
Data synthesis
We conducted a meta-analysis using a fixed-effect model in RevMan version 5.4 software [16]. When the heterogeneity observed in the analysis was substantial (p-value < 0.10 and I² > 50%), we also considered a random-effect model.

Subgroup analysis
We considered current measures of child health status in Nepal for performing subgroup analyses. For instance, we performed subgroup analysis by background U5MR and used the cut-off criteria that reflected the current U5MR in Nepal (categorized as U5MR between 30 and 60 per 1000 live births).

GRADE assessment
We assessed the quality of the evidence generated from the review using the approach, Grading of Recommendations Assessment, Development and Evaluation (GRADE) [17].

Results
Description of studies
Results of the search. We considered 19 studies from the 2017 Cochrane review [6] that were included in the meta-analysis of all-cause mortality. The new electronic searches conducted for the period 2016 to March 2021 only identified one article to be assessed for full-text (See Fig 1). Altogether, 20 full-text articles (19 from the previous review and 1 from the new search) were assessed for eligibility, of which, 4 studies [18–21] were excluded (See “S2 Appendix” for reasons for exclusion). We, thus, identified 16 studies (See “S3 Appendix”) as eligible for inclusion in the review. However, of those 16 studies considered for inclusion, one study [22] did not report the methods well and details were insufficient to be sure this was a genuine RCT. We tried to obtain additional information but were unsuccessful, so excluded this from the analysis.

Included studies
Types of studies. Of the included studies, five trials [23–27] were individual-RCT designs and the remaining ten trials [28–37] were cluster-RCT. Further information about individual studies is available in “S3 Appendix”.
Location/Setting. Studies took place in 6 countries; five trials in India [26,28,32,35,36], three trials in Nepal [29,31,37], one trial in Indonesia [34], two trials in Ghana [25,33], two trials in Guinea-Bissau [23,24] and one trial each in Sudan [30] and Congo [27].
Participants. Trials in this review incorporated approximately around 1,200,679 participants, with a sample size varying from 462 [23] to up to around 1 million participants [35].
Interventions. All trials examined the effects of Vitamin A supplementation given to children. Vitamin A doses used in the trials ranged from 8333 IU to 200,000 IU. In general, younger age groups (<12 months) received lower doses and older age groups (>12 months) received the higher dose.
Comparisons. Five trials compared VAS against usual care [27,29,31,34,35] and the remainder of the ten trials used a placebo as a comparator.
Multiple-arm trials. Two trials had multiple arms, one combining the measles vaccine with Vitamin A and the other combining Vitamin A with deworming tablets [23,35].
Outcomes. All trials reported child death as the outcome and used home visits to collect such mortality data. Only one trial [24] reported side effects associated with Vitamin A supplementation.
Other study characteristics. The background parameters of the trials included in the review featured high child mortality, greater malnutrition—indicated by wasting levels, high xerophthalmia (Night blindness, Bitot’s spot) among children under five years, and no vitamin
A supplementation program (See Table 2). The trials’ background contrasts with the current measures of child health status in Nepal (See Table 2).

### Risk of bias in included studies

We assessed the risk of bias in the 15 studies included in the analysis and assigned them as having high, low or unclear risk. We presented the results of the risk of bias assessment across all trials in Fig 2. Sixty per cent of the included studies (9 studies) did not have sufficient information on the sequence generation and allocation concealment process and thus had an unclear risk of bias. We assessed cluster RCTs for other potential sources of bias. Among the cluster RCTs, six were considered at unclear risk of recruitment bias as there was no explicit...
information on whether the individuals were recruited to the trial after the clusters have been randomized [28–31,34,36]. One trial was at high risk of baseline imbalance, as the baseline mortality in children was slightly different between the intervention and control arm [28]. Regarding incorrect analysis in cluster RCTs, i.e. not taking the clustering into account, most studies have considered the effect of clustering except for a few studies where we could not find any information about cluster adjustment [28, 36]. See “S3 Appendix” for details.

Effects of intervention

**All-cause mortality at longest follow-up.** We incorporated 15 trials with a total of around 1,200,679 children in the meta-analysis for the outcome of all-cause mortality at the longest follow-up. The results showed a considerable qualitative and quantitative heterogeneity, with an overall small protective effect (RR 0.89, 95% CI 0.84 to 0.94; Chi² = 48.87, degrees of freedom (df) = 14; P < 0.00001; I² = 71% Fig 3) of VAS resulting in 11% reduction in mortality, with half the weight attributed to the large DEVTA study.

This effect estimate is almost the same as the estimate reported in a previous review (RR 0.88, 95% CI 0.83 to 0.93) [6]. Due to the heterogeneity, we also conducted the analysis using a random-effects model, producing a differing effect estimate (RR 0.78, 95% CI 0.68 to 0.91, heterogeneity: Tau² = 0.04; Chi² = 48.87, df = 14; P < 0.00001; I² = 71% See “S1 Fig”). Given the heterogeneity, we first investigated if this could be explained by the risk of bias, and then explored the pre-specified effect modifiers.

Sensitivity analyses

**Bias.** Of the included studies, one study had a high risk of bias for sequence generation [30] but only accounted for 4.8% of the weight and did not influence the effect. More than half (60%) of the included studies had an unclear risk of bias for allocation concealment. Stratified analysis of the studies by inadequate allocation concealment (RR 0.84, 95% CI 0.76 to 0.93; I²:70%) and adequate allocation concealment (RR 0.91, 95% CI 0.85 to 0.97; I²: 75%; 6 trials, 1,046,829 participants See Fig 4) suggested that at least some of the effect estimate was the result of bias. We, therefore, used the effect estimate of the higher-quality studies for the primary analysis.
Fig 3. Forest plot of comparison: 1 Vitamin A versus Control, outcome: All-cause mortality at longest follow-up.

https://doi.org/10.1371/journal.pone.0268507.g003

Fig 4. Forest plot of comparison: 1 Vitamin A versus control, outcome: 1.2 All-cause mortality (sensitivity analysis by allocation concealment).

https://doi.org/10.1371/journal.pone.0268507.g004
We generated a funnel plot (Fig 5) for the outcome of mortality based on the number of participants in each study. We categorized the included studies as small studies having less than 1000 participants and between 1000–2000 participants and large studies having greater than 2000 participants. We can see an asymmetrical funnel plot in Fig 5 with no small studies favouring control. While some studies are showing a protective effect in the bottom-left corner, small studies in the bottom-right corner remained unaccounted for. Also, the large protective effects of Vitamin A are mainly demonstrated by smaller studies. It points to the likely presence of small-study effects or publication bias which might have played a role in the overestimation of the mortality reduction effect estimate.

Sub-group analyses. Given the substantial heterogeneity (P-value < 0.10 and I² > 50%) we conducted different sub-group analysis. For details of the sub-group analysis conducted, See “S2–S5 Figs”.

Sub-group analysis by decade. 13 studies conducted before 2000 reported about 20% reduction (RR 0.80, 95% CI 0.74 to 0.87; Chi² = 39.26, degrees of freedom (df) = 12; P < 0.00001; I² = 69%; Fig 6) in mortality associated with VAS [23,25–34,36,37]. In the two studies conducted after 2000, the effect estimate (RR 0.96, 95% CI 0.89 to 1.03; Chi² = 0.03, degrees of freedom (df) = 1; P = 0.87; I² = 0%; 1,007,587 participants) suggested 4% reduction in overall child mortality [24,35]. This 4% reduction, however, included the possibility of both a reduction and an increase in the risk of mortality with Vitamin A. This suggests that the effects from trials conducted over 20 years ago showed some substantive effects and other smaller effects. The 20% reduction is in the presence of substantive heterogeneity, which might
be expected given deficiency is likely to vary. There is no contemporary (last ten years) evidence of an effect, but only two studies are being conducted during this period of ten years.

Sub-group analysis by background/baseline Under-Five Mortality Rate (U5MR). Sub-group analysis stratified by U5MR in the primary studies showed smaller effects (RR 0.96, 95% CI 0.90 to 1.03) when the background U5MR ranged between 90-120/1000 live births compared to when U5MR was greater than 120/1000 live births (RR 0.75, 95% CI 0.68 to 0.83) (See Fig 7). Mortality estimates were not possible to estimate across the sub-groups (U5MR: 30-60/1000 live births and U5MR: 60-90/1000 live births) as none of the included studies had baseline U5MR between 30-90/1000 live births. The background U5MR in all the included trials in the meta-analysis was greater than 90 per 1000 live births and none of the trials had U5MR close to the current U5MR (28/1000 live births) in Nepal. The present mortality in Nepal is almost three times less than the levels reported in those trials. So, there are no trials that could represent the current under-five mortality context of Nepal.

Potential Impact of Vitamin A supplementation in Nepal. We estimated the potential effects of supplementation in Nepal by applying the effect estimates from the review to the current U5MR in Nepal. For this, we used the best estimate of effect obtained from high quality adequately concealed studies to current values of U5MR in Nepal. We also appraised the quality of the evidence using GRADE methods. The certainty of the evidence is of low quality suggesting that VAS may reduce mortality in children. As indicated in Table 3, when the relative

![Fig 6. Forest plot of comparison: Vitamin A versus control, Outcome: All-cause mortality at longest follow-up (sub-group analysis by decade).](https://doi.org/10.1371/journal.pone.0268507.g006)
risk reduction estimate was applied to the national U5MR in Nepal, it resulted in a reduction in mortality from 28 per 1000 live births to 25 per 1000 live births (Low-quality evidence). The absolute benefit of supplementation is small (0.3%) as Vitamin A may only reduce 3 deaths per 1000 children supplemented with Vitamin A (See Table 3). Even in the province where U5MR is as high as 40 per 1000 live births, there would only be a small reduction in mortality to 36 per 1000 live births (low-quality evidence) (See "S1 Table" for details).

**Discussion**

**Summary of main results**

In summary, VAS resulted in a small protective effect against child mortality with most recent trials conducted after 2000 showing small VAS benefits. Evidence from stratified analysis by allocation concealment and U5MR indicated little to no difference in mortality reduction with VAS.
The decrease in the effect of VAS can be linked to the background parameters in the trials and secular changes that occurred over the period of time. If we look into the background parameters for the trials, trials conducted before 2000 featured high U5MR, greater levels of wasting and xerophthalmia and low coverage of measles immunization, while the trials after 2000 reported slightly improved status for these indicators. This might explain the beneficial effect of VAS that was seen in the trials conducted before 2000 when the prevalence of xerophthalmia was much higher. Results from this review corroborate the findings from the previous review [6]. However, the absolute benefits from VAS are small in reducing mortality and the latest effect estimate from the DEVTA trial, which occupies the largest weight in the analysis, did not show any VAS benefits in recent times [35]. Thus the conclusion of the Cochrane review that “Vitamin A supplementation is associated with a clinically meaningful reduction in morbidity and mortality in children” is probably not correct: we recommend national policy makers use the estimates from the review applied to their national data to determine themselves the potential public health benefits of continuing routine supplementation.

Certainty of the evidence (GRADE analysis) and its impact in Nepal

The overall certainty of the best estimate of effect obtained from the well-concealed studies is of low quality. We downgraded the certainty rating of the evidence from high to low due to concerns related to the consistency of the estimate (qualitative and quantitative heterogeneity) and precision (95% CI includes the possibility of both negligible reduction and appreciable important reduction in mortality with VAS).

The potential impact of VAS is found to be low as VAS may result in a little reduction in mortality in absolute terms with only three deaths prevented for every 1000 children supplemented with VAS.
Given the lower absolute benefit of VAS, the relevance of routine VAS for reducing child mortality in the present context in Nepal raises doubts. As evidenced from the analysis, no trials included in the review reflected the current status of mortality rates and other indicators of population health in Nepal. Also, the presence of heterogeneity with small studies reporting larger effects and recent large studies [35] occupying major weight in the analysis reporting no effect limited our confidence in the certainty regarding the potential impact that VAS may have in Nepal in reducing child mortality.

Conclusions
The overall benefit of VAS in reducing child mortality in Nepal is small in absolute terms. There is probably sufficient evidence to cease current routine supplementation programs.

Supporting information
S1 Checklist. PRISMA 2020 checklist.
(DOCX)

S1 Fig. Forest plot of comparison: 1 Vitamin A versus Control, outcome: 1.2 All-cause mortality at longest follow-up (random-effect model).
(TIFF)

S2 Fig. Sub-group analysis by wasting.
(TIFF)

S3 Fig. Sub-group analysis by xerophthalmia.
(TIFF)

S4 Fig. Sub-group analysis by measles immunization coverage.
(TIFF)

S5 Fig. Sub-group analysis by vitamin A coverage.
(TIFF)

S1 Table. Using the GRADE methods for estimating effects of Vitamin A supplementation in Nepal at the sub-national level.
(DOCX)

S1 Appendix. Methods.
(DOCX)

S2 Appendix. Characteristics of excluded studies.
(DOCX)

S3 Appendix Characteristics of included studies.
(DOCX)

Acknowledgments
We would like to acknowledge the national and international nutrition experts and researchers who helped in the conceptualization of this study. The authors would like to thank Professor Peter Heywood, Honorary Research Associate, the University of Sydney, and Dr. Marianne Visser, University of Stellenbosch, South Africa for their invaluable input on the review protocol.
Author Contributions

Conceptualization: Samjhana Shrestha, Saki Thapa, Paul Garner, Maxine Caws, Suman Chandra Gurung, Khem Narayan Pokhrel.

Data curation: Samjhana Shrestha, Richard Kirubakaran, Khem Narayan Pokhrel.

Formal analysis: Samjhana Shrestha, Paul Garner, Khem Narayan Pokhrel.

Funding acquisition: Saki Thapa, Paul Garner, Maxine Caws, Suman Chandra Gurung.

Investigation: Samjhana Shrestha, Saki Thapa, Paul Garner, Maxine Caws, Suman Chandra Gurung, Khem Narayan Pokhrel.

Methodology: Samjhana Shrestha, Saki Thapa, Paul Garner, Maxine Caws, Suman Chandra Gurung, Richard Kirubakaran, Khem Narayan Pokhrel.

Project administration: Samjhana Shrestha, Saki Thapa, Paul Garner, Maxine Caws, Suman Chandra Gurung, Tilly Fox, Khem Narayan Pokhrel.

Resources: Samjhana Shrestha, Saki Thapa, Paul Garner, Maxine Caws, Khem Narayan Pokhrel.

Software: Samjhana Shrestha, Paul Garner, Tilly Fox, Richard Kirubakaran, Khem Narayan Pokhrel.

Supervision: Saki Thapa, Paul Garner, Maxine Caws, Suman Chandra Gurung, Khem Narayan Pokhrel.

Validation: Samjhana Shrestha, Saki Thapa, Paul Garner, Maxine Caws, Tilly Fox, Khem Narayan Pokhrel.

Visualization: Samjhana Shrestha, Paul Garner, Tilly Fox, Richard Kirubakaran, Khem Narayan Pokhrel.

Writing – original draft: Samjhana Shrestha.

Writing – review & editing: Samjhana Shrestha, Saki Thapa, Paul Garner, Maxine Caws, Suman Chandra Gurung, Tilly Fox, Richard Kirubakaran, Khem Narayan Pokhrel.

References

1. WHO. Guideline: Vitamin A supplementation in infants and children 6–59 months of age. Geneva: World Health Organization; 2011 [cited 2020 30 September]. Available from: https://apps.who.int/iris/bitstream/handle/10665/44664/9789241501767_eng.pdf?sequence=1.

2. UNICEF. United Nations International Children’s Fund Data: Monitoring the Situation of Children and Women 2018 [cited 2021 19 August]. Available from: https://data.unicef.org/topic/nutrition/vitamin-a-deficiency/.

3. DoHS. Annual Report 2075/76 (2018/19) Kathmandu: Government of Nepal, Ministry of Health and Population, Department of Health Services; 2019 [cited 2020 17 October]. Available from: https://dohs.gov.np/wp-content/uploads/2019/07/DoHS-Annual-Report-FY-2074-75-date-22-Ashad-2076-for-web-1.pdf.

4. MoHP, Partnership for Maternal NCH, WHO, World Bank, Alliance for Health Policy and Systems Research. Success factors for women’s and children’s health: Nepal Geneva: World Health Organisation; 2014 [cited 2021 5 January]. Available from: https://www.who.int/pmnch/knowledge/publications/nepal_country_report.pdf?ua=1.

5. Imdad A, Herzer K, Mayo-Wilson E, Yakoob MY, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age. Cochrane Database of Systematic Reviews. 2010;(12). https://doi.org/10.1002/14651858.CD008524.pub2 CD008524. PMID: 21154399

6. Imdad A, Mayo-Wilson E, Herzer K, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age. The Cochrane database of systematic reviews.
Vitamin A supplementation: Shall we stop now

2017; 3(3):Cd008524. Epub 2017/03/11. https://doi.org/10.1002/14651858.CD008524.pub3 PMID: 28282701; PubMed Central PMCID: PMC6464706 responsible for the opinions and views expressed in this publication. Aamer Imdad was paid for writing this review by the WHO. Evan Mayo-Wilson - none known. Zulfiquar A Bhutta’s (ZB) institution received a grant from the WHO for this review and two additional vitamin A related Cochrane reviews (Imdad 2016; Haider 2017). ZB is an Editor for Cochrane Developmental, Pyschosocial and Learning Problems.

7. Pradhan A, Aryal RH, Regmi G, Ban B, Govindasamy P. Nepal Family Health Survey 1996. Kathmandu, Nepal: Ministry of Health/Nepal, New ERA/Nepal, and Macro International, 1997.
8. CBS. Multiple Indicator Cluster Survey 2019, Survey Findings Report. Kathmandu, Nepal: Central Bureau of Statistics (CBS) and UNICEF Nepal, 2020.
9. Ministry of Health—MOH/Nepal, New ERA/Nepal, ICF. Nepal Demographic and Health Survey 2016. Kathmandu, Nepal: MOH/Nepal, New ERA, and ICF, 2017.
10. NMSS. Nepal Micronutrient Status Survey 1998. Kathmandu, Nepal: 1998.
11. NNMS. Nepal National Micronutrient Status Survey, 2016. Kathmandu, Nepal2018 [cited 2020 18 October]. Available from: https://www.unicef.org/nepal/sites/unicef.org/nepal/files/2018-08/NNS% 20Report%202016.pdf.
12. WHO. Global Health Observatory data repository Geneva, Switzerland: World Health Organization; 2021 [cited 2021 20 January]. Available from: https://apps.who.int/gho/data/view.main.1600.
13. World Bank. World Bank Open Data: World Bank; 2021 [cited 2021 20 January]. Available from: https://data.worldbank.org/.
14. Higgins JP, Altman DG, Getzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011; 343:d5928. https://doi.org/10.1136/bmj.d5928 PMID: 22008217
15. Beaton G, Martorell R, Aronson K, Edmonston B, McCabe G, Ross A. Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries—Nutrition policy discussion paper No. 13. Geneva: United Nations, Administrative Committee on Coordination/ Subcommittee on Nutrition (ACC/SCN); 1993;1993;20.
16. Review Manager. Review Manager (RevMan) [Computer program]. Version 5.4. Review Manager 5 (RevMan 5). 5.4 ed: The Cochrane Collaboration; 2020.
17. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011; 64 (4):383–94. https://doi.org/10.1016/j.jclinepi.2010.04.026 PMID: 21195583
18. Andersen A, Fisker AB, Rodrigues A, Martins C, Ravn H, Lund N, et al. National immunization campaigns with oral polio vaccine reduce all-cause mortality: a natural experiment within seven randomized trials. Frontiers in public health. 2018; 6:13. https://doi.org/10.3389/fpubh.2018.00013 PMID: 29456992
19. Barreto ML, Farenzena G, Fiaccone R, Santos L, Assis AMdO, Araújo M, et al. Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. The Lancet. 1994; 344(8917):228–31. https://doi.org/10.1016/s0140-6736(94)92998-x PMID: 7913157
20. Dibley MJ, Sadjinim T, Kjolhede CL, Moulton LH. Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. The Journal of nutrition. 1996; 126(12):434–42. https://doi.org/10.1093/jn/126.2.434 PMID: 8632216
21. Lin J, Song F, Yao P, Yang X, Li N, Sun S, et al. Effect of vitamin A supplementation on immune function of well-nourished children suffering from vitamin A deficiency in China. European journal of clinical nutrition. 2008; 62(12):1412–8. https://doi.org/10.1038/sj.ejcn.1602881 PMID: 17684522
22. Chowdhury S, Kumar R, Ganguly N, Kumar L, Wallia B. Effect of vitamin A supplementation on childhood morbidity and mortality. Indian journal of medical sciences. 2002; 56(6):259–64. PMID: 12649946
23. Benn CS, Aaby P, Balé C, Olsen J, Michaelsen KF, George E, et al. Randomised trial of effect of vitamin A supplementation on antibody response to measles vaccine in Guinea-Bissau, West Africa. The Lancet. 1997; 350(9071):101–5. https://doi.org/10.1016/S0140-6736(96)12019-5 PMID: 9228862
24. Fisker AB, Bale C, Rodrigues A, Balde I, Fernandes M, Jørgensen MJ, et al. High-dose vitamin A with vaccination after 6 months of age: a randomized trial. Pediatrics. 2014; 134(3):e739–e48. https://doi. org/10.1542/peds.2014-0550 PMID: 25136048
25. Ross DA, Dollimore N, Smith P, Kirkwood B, Arthur P, Morris S, et al. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child morbidity. The Lancet. 1993 HEALTH; 342(8682):7–12.
26. Venkatarao T, Ramakrishnan R, Nair N, Radhakrishnan S, Sundaramoorthy L, Mohammad Koya P, et al. Effect of vitamin A supplementation to mother and infant on morbidity in infancy. Indian pediatrics. 1996; 33:279–86. PMID: 8772901
27. Donnen P, Brasseur D, Dramaix M, Vertongen F, Zhindula M, Muhamariza M, et al. Vitamin A supplementation but not deworming improves growth of malnourished preschool children in eastern Zaire. J Nutr. 1998; 128(8):1320–7. Epub 1998/08/04. https://doi.org/10.1093/jn/128.8.1320 PMID: 9687551.

28. Agarwal DK, Pandey CM, Agarwal KN. Vitamin A administration and preschool child mortality. Nutrition Research. 1995; 15(5):669–80.

29. Daulaire N, Starbuck ES, Houston RM, Church MS, Stukel TA, Pandey MR. Childhood mortality after a high dose of vitamin A in a high risk population. British Medical Journal. 1992; 304(6821):207–10. https://doi.org/10.1136/bmj.304.6821.207 PMID: 1739794

30. Herrera MG, Nestel P, Weld L, El Amin A, Mohamed KA, Fawzi W. Vitamin A supplementation and child survival. The Lancet. 1992; 340(8814):267–71. https://doi.org/10.1016/s0140-6736(92)92357-1 PMID: 1353192

31. Pant C, Pokharel G, Curtale F, Pokhrel R, Grosse R, Lepkowski J. Impact of nutrition education and mega-dose vitamin A supplementation on the health of children in Nepal. Bulletin of the World Health Organization. 1996; 74(5):533. PMID: 9002334

32. Rahmathullah L, Underwood BA, Thulasiraj RD, Milton RC, Rameswamy K, Rahmathullah R, et al. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. New England journal of medicine. 1990; 323(14):929–35. https://doi.org/10.1056/NEJM199010043231401 PMID: 2205798

33. Ross DA, Kirkwood BR, Binka FN, Arthur P, Dollimore N, Morris SS, et al. Child morbidity and mortality following vitamin A supplementation in Ghana: time since dosing, number of doses, and time of year. American Journal of Public Health. 1993 SURVIVAL; 85(9):1246–51.

34. Sommer A, Djunaedi E, Loeden A, Tarwotjo I, West JR K, Tilden R, et al. Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. The Lancet. 1986; 327(8491):1169–73. https://doi.org/10.1016/s0140-6736(86)91157-8 PMID: 2871418

35. Awasthi S, Peto R, Read S, Clark S, Pande V, Bundy D, et al. Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. The Lancet. 2013; 381(9876):1469–77. https://doi.org/10.1016/S0140-6736(12)62125-4 PMID: 23498849

36. Vijayaraghavan K, Radhaiah G, Prakasam BS, Sarma KR, Reddy V. Effect of massive dose vitamin A on morbidity and mortality in Indian children. The Lancet. 1990; 336(8727):1342–5. https://doi.org/10.1016/0140-6736(90)92895-o PMID: 1978164

37. West KP Jr, Katz J, Leclerq SC, Pradhan EK, Tielsch JM, Sommer A, et al. Efficacy of vitamin A in reducing preschool child mortality in Nepal. The Lancet. 1991; 338(8759):67–71. https://doi.org/10.1016/0140-6736(91)90070-6 PMID: 1676467

38. International Institute for Population Sciences—IIPS/India. India National Family Health Survey 1992–93. Mumbai, India: IIPS/India, 1995.

39. MICS. Multiple Indicator Cluster Survey 2000 Guinea-Bissau: UNICEF Guinea-Bissau; 2000. Available from: https://www.rhsupplies.org/uploads/bx_rhscpublications/Guinea-Bissau_2000_MICS_Report.pdf.

40. West K, Rice A, Sugimoto JD. Tables on the Global Burden of Vitamin A Deficiency and Xerophthalmia Among Preschool Aged Children and Low Vitamin A Status, Vitamin A Deficiency, and Night Blindness Among Pregnant Women By WHO Region Baltimore, MD: Center for Human Nutrition, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University 2005 [20 January 2021]. Available from: https://silos.tips/download/keith-p-west-jr-drph-amy-rice-phd-jonathan-d-sugimoto-mhs#.