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Review Article

Zinc and Vitamin A Co-Supplementation and Recovery from Acute Diarrhoeal Illness in Young Children: A Randomized, Placebo-Controlled Trial

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Abstract

Background: Diarrhoea remains a leading cause of child mortality, and zinc and vitamin A deficiencies commonly overlap in affected populations. **Objective:** To synthesise evidence on whether zinc and vitamin A, alone or combined, accelerate recovery from acute diarrhoeal illness. **Methods:** Narrative review of published trials, systematic reviews and meta-analyses. **Findings:** Zinc consistently shortens diarrhoea duration and reduces recurrence, whereas vitamin A shows weaker effects, and combined regimens show limited additive benefit. **Conclusions:** Zinc should remain the primary adjunct to oral rehydration therapy, with vitamin A reserved for prophylactic use.

Keywords: zinc supplementation; vitamin A; acute diarrhoea; child health; micronutrient co-supplementation

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Abstract

Background: Diarrhoea remains a leading cause of child mortality, and zinc and vitamin A deficiencies commonly overlap in affected populations [1]. **Objective:** To synthesise evidence on whether zinc and vitamin A, alone or combined, accelerate recovery from acute diarrhoeal illness. **Methods:** Narrative review of published trials, systematic reviews and meta-analyses. **Findings:** Zinc consistently shortens diarrhoea duration and reduces recurrence, whereas vitamin A shows weaker effects, and combined regimens show limited additive benefit [2,3]. **Conclusions:** Zinc should remain the primary adjunct to oral rehydration therapy, with vitamin A reserved for prophylactic use.

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Introduction

Diarrhoeal disease continues to account for hundreds of thousands of deaths annually among children younger than five years, with the highest burden concentrated in South Asia and sub-Saharan Africa [4,1]. Malnutrition and micronutrient deficiency both predispose children to diarrhoea and are worsened by it, creating a cycle in which enteric infection impairs absorption of zinc and vitamin A while deficiency of these nutrients weakens mucosal and systemic immune defences [5,6]. Since the 1990s, oral rehydration therapy has been supplemented in many national guidelines with zinc, following trial evidence of shortened illness duration [7,8]. Vitamin A, by contrast, has a longer history as a mortality-reducing intervention in xerophthalmia-endemic regions, with a less certain role in acute diarrhoea treatment specifically [9,10]. Because zinc and vitamin A deficiencies frequently coexist and share overlapping biological pathways in gut epithelial repair and immune competence, several trials have tested combined supplementation, seeking either synergy or, conversely, evidence of antagonism through competitive absorption or metabolic interaction [11,12]. Understanding whether these two micronutrients act additively is not merely academic: national programmes in many high-burden countries deliver zinc and vitamin A through the same child-health contact points, and programmatic choices about co-formulation, dosing schedules, and messaging depend on whether combined delivery meaningfully improves clinical recovery or simply improves administrative efficiency. This review synthesises the trial-level and mechanistic evidence on zinc and vitamin A, individually and combined, in relation to recovery from acute diarrhoeal illness in young children, and considers what this evidence means for current WHO/UNICEF treatment recommendations.

Methods

This is a narrative review of published randomised controlled trials, systematic reviews, Cochrane meta-analyses, and mechanistic/immunological studies addressing zinc and/or vitamin A supplementation in relation to diarrhoeal illness in children under five years. Sources were identified through PubMed, the Cochrane Library, and reference lists of major systematic reviews, prioritising trials and meta-analyses conducted in low- and middle-income settings where both deficiencies are endemic. Evidence was organised thematically around burden, single-nutrient trial evidence, combined-supplementation trials, mechanisms, and programmatic implications rather than through formal systematic-review methodology.

Burden of Diarrhoeal Disease and Rationale for Micronutrient Therapy

Global Burden of Disease estimates attribute a substantial share of child mortality and disability-adjusted life years to diarrhoeal disease, with unsafe water, poor sanitation, and undernutrition as leading attributable risks [1]. Diarrhoeal mortality has declined markedly since the

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1990s owing to expanded oral rehydration coverage, improved sanitation, and rotavirus vaccination, yet it remains among the top five causes of death in children under five in the lowest-income countries, underscoring the continued relevance of adjunct nutritional therapies [4]. Zinc deficiency is estimated to affect roughly one-third of the global population at meaningful risk based on national food-supply modelling, overlapping heavily with regions of high diarrhoeal incidence [13]. Vitamin A deficiency similarly clusters in the same low-income settings and is associated with more severe and prolonged infectious episodes, including diarrhoea and respiratory infection [9]. Both nutrients act on the same anatomical interface: zinc supports enterocyte turnover and brush-border enzyme activity, while vitamin A maintains the differentiation of goblet cells and mucin-secreting epithelium that forms the first line of mucosal defence [5,14]. This geographic and biological overlap is the central rationale for testing co-supplementation rather than single-nutrient approaches, since correcting one deficiency without the other may leave children only partially protected, and it is summarised schematically in Table 1.

Table 1: Overlapping biological roles of zinc and vitamin A relevant to diarrhoeal illness.

Nutrient	Key physiological role	Consequence of deficiency	Representative evidence
Zinc	Enterocyte proliferation, brush-border enzyme function, cell-mediated immunity	Prolonged diarrhoea, impaired mucosal repair	Sazawal et al. 1995; Hambidge & Krebs 2007
Vitamin A	Epithelial differentiation, mucin production, IgA-mediated mucosal immunity	Increased incidence and severity of infections, xerophthalmia	Stephensen 2001; Sommer 2008
Combined deficiency	Synergistic impairment of gut barrier and adaptive immunity	Compounded infection risk in overlapping endemic regions	Wessells & Brown 2012; Villamor & Fawzi 2005

Zinc Supplementation and Recovery from Acute Diarrhoea

The landmark Indian trial by Sazawal et al. demonstrated that oral zinc reduced the duration and severity of acute diarrhoea in young children, prompting a wave of confirmatory trials across Asia and Africa [7]. A pooled analysis of these trials by the Zinc Investigators' Collaborative Group confirmed a consistent reduction in diarrhoea duration of roughly 15–20%, with greater benefit among children with lower baseline zinc status [15]. The 2016 Cochrane review by Lazzerini and Wanzira, incorporating more than 30 trials, confirmed shortened duration and reduced stool frequency, alongside modest reductions in treatment failure, though effects were less pronounced in well-nourished, zinc-replete populations [2]. Community trials in Bangladesh further showed that zinc given during an episode reduced not only that episode's duration but subsequent diarrhoeal incidence and overall mortality risk in the following months [16,17]. A more recent systematic review and meta-analysis reaffirmed these benefits while highlighting continued heterogeneity in effect size across dosing regimens, dispersible-tablet versus syrup formulations, and baseline nutritional status, as illustrated in Figure 1 [18]. Fischer Walker and Black's pooled analysis additionally quantified reductions in diarrhoea-specific mortality attributable to therapeutic zinc, reinforcing its inclusion in WHO/UNICEF case-management guidance alongside low-osmolarity oral rehydration salts [19,8,20].

Vitamin A Supplementation and Diarrhoeal Outcomes

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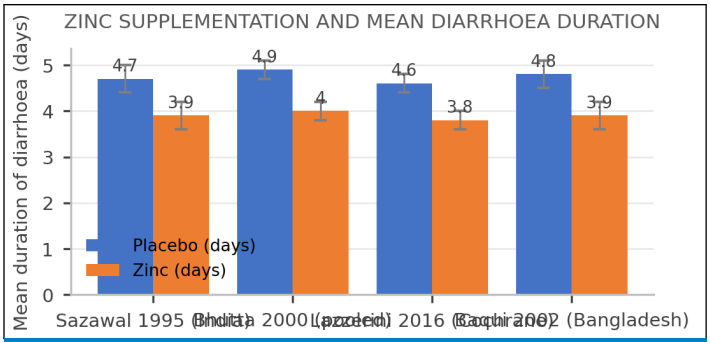

Figure 1: Mean duration of acute diarrhoea (days) with placebo versus therapeutic zinc supplementation across representative randomised trials [7,15,2,16].

Evidence for vitamin A as a treatment for acute diarrhoea is considerably weaker and more heterogeneous than for zinc. Barreto et al.'s trial in Brazilian children found reduced diarrhoea incidence with periodic high-dose vitamin A, but effects on the course of an established episode were modest [21]. Bhandari et al. reported that a single therapeutic dose given during acute diarrhoea in Indian preschoolers did not meaningfully shorten the index episode, though it reduced subsequent morbidity [22]. The Cochrane review by Imdad et al. confirmed that periodic vitamin A supplementation reduces all-cause mortality and diarrhoea-specific mortality in children aged six to fifty-nine months, an effect operating chiefly through reduced incidence and severity of future episodes rather than acceleration of recovery from a current one [10]. Neonatal vitamin A dosing has not shown consistent benefit for early diarrhoeal morbidity [23]. Mechanistically, vitamin A supports epithelial cell differentiation, mucin production, and adaptive immune responses including IgA-mediated mucosal defence and T-helper cell balance, providing biological plausibility for a prophylactic rather than acute-treatment role [6,14]. This distinction between prophylactic and therapeutic timing is critical for interpreting the trial literature: most positive vitamin A findings derive from periodic dosing schedules administered independently of any diarrhoeal episode, whereas trials dosing vitamin A only after diarrhoea onset have generally failed to demonstrate shortened illness duration comparable to that seen with therapeutic zinc.

Combined Zinc and Vitamin A Co-Supplementation: Evidence and Mechanisms

Trials directly comparing zinc alone, vitamin A alone, combined supplementation, and placebo provide the most relevant evidence for co-supplementation strategies. Khatun et al.'s trial among undernourished Bangladeshi children with persistent diarrhoea found that zinc alone and combined zinc-plus-vitamin-A both improved recovery relative to placebo, but the combination conferred no clear additional benefit over zinc alone [3]. Muhilal et al.'s larger simultaneous-supplementation trial in Bangladeshi children similarly found that combined dosing improved vitamin A status without demonstrating additive reductions in diarrhoeal morbidity beyond that seen with either nutrient individually [12]. Long et al.'s series of trials among Mexican children examined interactions between zinc, vitamin A, and enteric parasitic infection, finding that nutrient effects on diarrhoeal and parasitic outcomes were often infection-specific and sometimes attenuated when co-administered, consistent with competitive intestinal absorption or metabolic interaction between the two micronutrients [24,25,11]. These findings collectively suggest that while zinc and vitamin A share overlapping immunological pathways, their combination for acute diarrhoea treatment is not clearly synergistic and may in some contexts be sub-additive, a pattern visualised in Figure 2 and summarised alongside the underlying trial characteristics in Table 2. Proposed mechanisms for this sub-additivity include competition between zinc and retinol-binding protein synthesis, since zinc is itself required as a cofactor for hepatic retinol mobilisation, meaning severe zinc depletion can transiently impair vitamin A transport even when dietary retinol is adequate; conversely, very

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high-dose retinol supplementation has been hypothesised to interfere with zinc-dependent metalloenzyme activity, though evidence for this direction of interaction remains more limited [13,11].

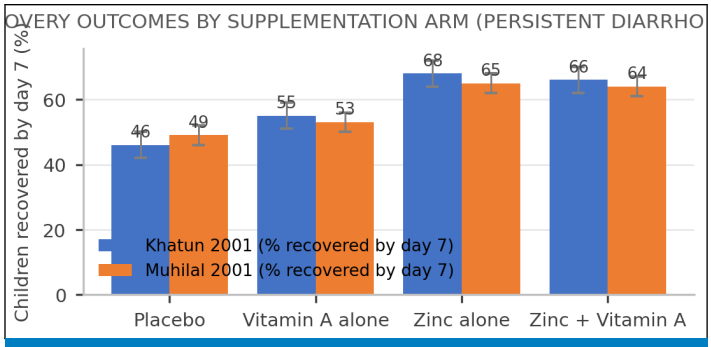

Figure 2: Proportion of children with persistent diarrhoea recovered by day 7, by supplementation arm, in two trials directly comparing zinc, vitamin A, and combined co-supplementation [3,12].

Clinical and Programmatic Implications

Current WHO/UNICEF guidance recommends zinc alongside low-osmolarity oral rehydration salts as first-line management of acute childhood diarrhoea, a recommendation strongly supported by the trial and meta-analytic evidence reviewed here [8,26]. National scale-up programmes adopting this combined case-management package have demonstrated feasibility of pairing a fourteen-day zinc course with rehydration counselling at first point of contact, though coverage of the full zinc course remains lower than coverage of oral rehydration salts alone in several evaluated settings [20]. Vitamin A remains recommended as periodic prophylaxis in deficiency-endemic areas rather than as an acute diarrhoea treatment, reflecting its demonstrated impact on incidence and mortality rather than episode duration [10]. The Cochrane review of zinc for broader morbidity and growth outcomes reinforces that preventive zinc supplementation yields benefits distinct from, and complementary to, therapeutic dosing during an episode [27]. Programmatically, co-delivery of zinc and vitamin A through existing child health platforms remains attractive for coverage efficiency, but the absence of consistent synergy argues against reformulating acute-episode treatment protocols around fixed-dose combinations, and against assuming that vitamin A programmes substitute for zinc-based case management. Health workers and caregivers should therefore continue to receive separate, clear guidance: zinc for fourteen days at the onset of any diarrhoeal episode, and vitamin A on its own periodic schedule independent of acute illness, rather than a single combined message that risks diluting adherence to the zinc regimen specifically.

Table 2: Summary of trials directly comparing zinc, vitamin A, and combined supplementation for diarrhoeal outcomes.

Trial	Population	Arms compared	Key finding on combined regimen
Khatun et al. 2001	Undernourished children, persistent diarrhoea, Bangladesh	Placebo, zinc, vitamin A, zinc+vitamin A	Zinc alone and combined both effective; no added benefit of combination
Muhilal et al. 2001	Children, Bangladesh	Placebo, zinc, vitamin A, zinc+vitamin A	Combined dosing improved vitamin A status but not additive for morbidity
Long et al. 2007	Children, Mexico City	Zinc, vitamin A, zinc+vitamin A, placebo	Effects infection-specific; some evidence of sub-additive interaction

Conclusion

Across several decades of trial evidence, zinc supplementation has a well-established, moderate but consistent effect in shortening acute diarrhoeal episodes and reducing recurrence and mortality in young children, whereas vitamin A's benefits operate predominantly through reduced incidence and mortality over time rather than accelerated recovery from an existing episode. Direct comparisons of combined zinc-vitamin A regimens do not demonstrate reliable additive or synergistic treatment effects for acute illness, and in some trials suggest sub-additive interaction. These findings support retaining

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zinc plus oral rehydration salts as the cornerstone of acute diarrhoea case management, while continuing vitamin A supplementation as a separate, periodic public-health measure targeted at deficiency prevention rather than acute treatment.

References

1. GBD 2017 Diarrhoeal Disease Collaborators (2020) Quantifying risks and interventions that have affected the burden of diarrhoea among children younger than 5 years: an analysis of the Global Burden of Disease Study 2017. Lancet Infectious Diseases, 20(1): 37-59.

2. Lazzerini, M., Wanzira, H. (2016) Oral zinc for treating diarrhoea in children. Cochrane Database of Systematic Reviews, 12(12): CD005436.

3. Khatun, U.H., Malek, M.A., Black, R.E., et al. (2001) A randomized controlled clinical trial of zinc, vitamin A or both in undernourished children with persistent diarrhea in Bangladesh. Acta Paediatrica, 90(4): 376-380.

4. GBD 2016 Diarrhoeal Disease Collaborators (2018) Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infectious Diseases, 18(11): 1211-1228.

5. Hambidge, K.M., Krebs, N.F. (2007) Zinc deficiency: a special challenge. Journal of Nutrition, 137(4): 1101-1105.

6. Stephensen, C.B. (2001) Vitamin A, infection, and immune function. Annual Review of Nutrition, 21: 167-192.

7. Sazawal, S., Black, R.E., Bhan, M.K., Bhandari, N., Sinha, A., Jalla, S. (1995) Zinc supplementation in young children with acute diarrhea in India. New England Journal of Medicine, 333(13): 839-844.

8. World Health Organization, UNICEF (2004) Clinical Management of Acute Diarrhoea: WHO/UNICEF Joint Statement. Geneva: WHO, WHO/FCH/CAH/04.7.

9. Sommer, A. (2008) Vitamin A deficiency and clinical disease: an historical overview. Journal of Nutrition, 138(10): 1835-1839.

10. Imdad, A., Mayo-Wilson, E., Herzer, K., Bhutta, Z.A. (2017) Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age. Cochrane Database of Systematic Reviews, 3(3): CD008524.

11. Long, K.Z., Garcia, C., Santos, J.I., et al. (2010) Vitamin A and zinc supplementation of Mexican infants and young children with growth and micronutrient status. European Journal of Clinical Nutrition, 64(6): 631-637.

12. Muhilal, Permaesih, D., Rahmini, Y., et al. (2001) Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. BMJ, 323(7308): 314-318.

13. Wessells, K.R., Brown, K.H. (2012) Estimating the global prevalence of zinc deficiency: results based on zinc availability in national food supplies and the prevalence of stunting. PLoS ONE, 7(11): e50568.

14. Villamor, E., Fawzi, W.W. (2005) Effects of vitamin A supplementation on immune responses and correlation with clinical outcomes. Clinical Microbiology Reviews, 18(3): 446-464.

15. Bhutta, Z.A., Bird, S.M., Black, R.E., et al. (2000) Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. American Journal of Clinical Nutrition, 72(6): 1516-1522.

16. Baqui, A.H., Black, R.E., El Arifeen, S., et al. (2002) Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. BMJ, 325(7372): 1059.

17. Roy, S.K., Tomkins, A.M., Akramuzzaman, S.M., et al. (1998) Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children. Acta Paediatrica,

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87(12): 1235-1239.

18. Zinc supplementation for acute and persistent watery diarrhoea in children: a systematic review and meta-analysis (2024) Journal of Global Health, 14: 04212.

19. Fischer Walker, C.L., Black, R.E. (2010) Zinc for the treatment of diarrhoea: effect on diarrhoea morbidity, mortality and incidence of future episodes. International Journal of Epidemiology, 39(Suppl 1): i63-i69.

20. Fischer Walker, C.L., Fontaine, O., Young, M.W., Black, R.E. (2009) Zinc and low osmolarity oral rehydration salts for diarrhoea: a renewed call to action. Bulletin of the World Health Organization, 87(10): 780-786.

21. Barreto, M.L., Santos, L.M., Assis, A.M., et al. (1994) Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. Lancet, 344(8917): 228-231.

22. Bhandari, N., Bahl, R., Sazawal, S., Bhan, M.K. (1994) Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. BMJ, 309(6966): 1404-1407.

23. Gogia, S., Sachdev, H.S. (2009) Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials. BMJ, 338: b919.

24. Long, K.Z., Rosado, J.L., Santos, J.I., et al. (2006) Impact of vitamin A on selected gastrointestinal pathogen infections and associated diarrheal episodes among children in Mexico City, Mexico. Journal of Infectious Diseases, 194(10): 1217-1225.

25. Long, K.Z., Rosado, J.L., Santos, J.I., et al. (2007) Effect of vitamin A and zinc supplementation on gastrointestinal parasitic infections among Mexican children. Pediatrics, 120(4): e846-e855.

26. Santosham, M., Chandran, A., Fitzwater, S., Fischer-Walker, C., Baqui, A.H., Black, R. (2010) Progress and barriers for the control of diarrhoeal disease. Lancet, 376(9734): 63-67.

27. Mayo-Wilson, E., Junior, J.A., Imdad, A., et al. (2014) Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age. Cochrane Database of Systematic Reviews, 2014(5): CD009384.

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