Received: 4 October 2023 | Revised: 11 December 2023 | Accepted: 16 December 2023

DOI: 10.1111/all.15997

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

TASK FORCE REPORT

A systematic review and meta-analysis on nutritional and dietary interventions for the treatment of acute respiratory infection in pediatric patients: An EAACI taskforce

Gregorio P. Milani[1,2] | Ilaria Alberti[1] | Martina Abodi[2] | John Lakoumentas[3] | George N. Konstantinou[4] | Nikolaos G. Papadopoulos[5] | Raluca M. Pop[6] | Ioana C. Bocsan[6] | Dimitrios Cassimos[7] | Inger Kull[8,9] | Silvia Bettocchi[1] | Antonio Corsello[2] | Marco Cugliari[2] | Letizia Ciliberti[2] | Giulia C. I. Spolidoro[2] | Carlo Agostoni[1,2] | Berber Vlieg Broerstra[10,11] | Carina Venter[12] | Liam O'Mahony[13] | Emilia Vassilopoulou[1,3]

[1]Pediatric Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[2]Department of Clinical Science and Community Health, University of Milan, Milan, Italy

[3]Department of Nutritional Sciences and Dietetics, International Hellenic University, Thessaloniki, Greece

[4]Department of Allergy and Clinical Immunology, 424 General Military Training Hospital, Thessaloniki, Greece

[5]Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece

[6]Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj Napoca, Romania

[7]Department of Medicine, Democritus University of Thrace, Alexandroupolis, Greece

[8]Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

[9]Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm, Sweden

[10]Department of Pediatrics, OLVG Hospital, Amsterdam, The Netherlands

[11]Rijnstate Allergy Centre, Rijnstate Hospital, Arnhem, The Netherlands

[12]Section of Allergy and Immunology, Department of Pediatrics, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado, USA

[13]Department of Medicine and School of Microbiology, APC Microbiome Ireland, University College Cork, Cork, Ireland

Correspondence
Gregorio P. Milani and Ilaria Alberti, Pediatric Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, via della Commenda 9, Milan, Italy.
Email: milani.gregoriop@gmail.com and albertilaria@gmail.com

Funding information
European Academy of Allergy and Clinical Immunology

Abstract

Acute respiratory infections are a major cause of morbidity and mortality in children worldwide. Dietary and nutritional interventions, including minerals and vitamin supplementation, have been explored as potential treatments for these infections. However, the evidence on their efficacy is limited and inconclusive. This systematic review and meta-analysis aim to provide a comprehensive summary of the available evidence on the effectiveness of dietary and nutritional interventions for treating acute respiratory tract infections in children. A systematic review was conducted according to the PRISMA 2020 guidelines in April 2022 and updated in April 2023. Clinical trials focusing on dietary or nutritional interventions, including supplementations, in

Abbreviations: CI, confidence intervals; RCT, randomized controlled trial.

children with acute respiratory tract infections were included. The selection of interventions and outcomes was based on biological plausibility. Data were extracted using a standardized form, and the risk of bias was assessed using the Cochrane Risk of Bias Tool. Meta-analysis was performed using random-effect models. A total of 50 studies were included in the review. Four trials were conducted in low, 32 in lower-middle, 12 in upper-middle, and only two in high-income countries. The studies evaluated various dietary interventions, including zinc, vitamin A, vitamin E, vitamin D, and probiotics. The results of individual studies on the efficacy of these interventions were mixed, with some showing positive effects on clinical outcomes such as duration of symptoms, while others showed no significant impact. Meta-analysis was conducted for zinc supplementation in children with pneumonia, and the pooled results suggested a potential limited benefit in terms of reduced hospital length of stay but not time to recovery. Meta-analyses on vitamin D did not show any effect in children with pneumonia. This systematic review fills a critical gap in the literature by synthesizing the available evidence on the efficacy and safety of nutritional or dietary interventions for acute respiratory tract infections in children. The findings indicate no dietary or nutritional intervention can currently be recommended for the routine treatment of respiratory tract infections in children based on single supplement studies. The meta-analysis suggests that zinc supplementation might have a beneficial effect on length of hospitalization in children with pneumonia. New studies are needed to establish more conclusive evidence for pediatric acute respiratory diseases especially for children living in a context of high-income countries.

KEYWORDS
acute respiratory tract infections, childhood, diet, nutrients, supplementation, treatment

1 | INTRODUCTION

Acute respiratory infections are one of the leading causes of morbidity and mortality in children, particularly in low- and middle-income countries.[1,2] Despite the availability of antibiotics and vaccines to prevent and treat acute respiratory infections, the disease burden remains high in both resource-limited and high-income countries.[3,4]

Diet plays a significant role in the pathophysiology of infections in children.[5] Dietary interventions can boost the immune system, prevent malnutrition, and reduce the risk of infection.[6] Conversely, poor dietary habits, such as consuming inadequate amounts of protein, essential vitamins, and minerals, can lead to increased susceptibility to infections and worsen the severity of acute respiratory tract infections.[7]

Interventions such as vitamin A supplementation, micronutrient fortification, probiotics, and zinc supplementation have been proposed as an additional approach to treat respiratory infections.[8] However, the evidence base for the efficacy of these interventions is limited and inconclusive.[9–11]

To address this gap, we conducted a systematic review and meta-analysis on the use of nutritional and dietary interventions for treating children with acute upper or lower respiratory infections. The primary aim of this study was to identify and summarize available literature on this topic. The secondary aims were to provide evidence-based recommendations for healthcare providers and to suggest future research areas on this topic.

2 | METHODS

We performed a systematic review according to PRISMA 2020 guidelines.[12] The study protocol was pre-registered (CRD42022328700). To ensure the highest level of evidence, we specifically focused on clinical trials (including randomized controlled trials, quasi-randomized controlled trials, and controlled clinical trials) on nutritional intervention conducted in subjects below 18 years of age with symptoms suggestive of an acute respiratory infection. The selection of nutrients (micronutrients, macronutrients, prebiotics, and probiotics) and of the dietary regimens was based on their biological plausibility.[13] Furthermore, only trials written in English evaluating clinical outcomes as primary or secondary endpoints were considered. There was no restriction regarding the date of publication and the geographical area where the study was conducted. Trials

employing herbal medicines or exclusively focusing on a symptom instead of a disease (e.g., cough) or trials providing dietary intervention to prevent or before the onset of acute respiratory tract infections were excluded. Studies reported as letters or abstracts or not conducted in human subjects were also ruled out.

After the systematic review, we planned to perform a meta-analysis when at least three studies assessed the same intervention (independently from the dose or duration of the intervention) in children on strong outcomes (time to recovery, length of hospital stay, or mortality). To reduce heterogeneity, studies without a well-defined diagnosis (e.g., studies just reporting "lower respiratory tract infection" instead of bronchitis, bronchiolitis, or pneumonia) were not included in the meta-analysis.

2.1 | Literature search

The literature search was conducted on April 15, 2022, and updated on April 30, 2023, through the following databases: PubMed, Excerpta Medica, and Web of Science. The detailed search strategy for each database is reported in the Appendix S1. Pairs of reviewers conducted the study selection and controversies were solved involving a third researcher. Rayyan was used to manage articles to be included or excluded.[14] Explanations for the exclusion of studies during the full-text screening phase were recorded.

2.2 | Data extraction

An Excel-based data extraction form was used, which allowed pairs of reviewers to extract pertinent data from the selected studies independently. To ensure its effectiveness, the data extraction form was evaluated and improved prior to being employed for the complete data extraction process. In cases of disagreement in data extraction between reviewers, this was resolved via discussion or involving a third reviewer. The following data were extracted: first author's name, year of publication, country of the study, number of arms of the trial, type (if any) of blindness, the period when the study was performed, study population (including demographics, presence of comorbidities, nutritional status, and the respiratory condition), recruitment procedures, number of recruited subjects and of those who completed the study, nutritional intervention (including type, dose, and duration), adverse reactions, clinical outcomes (and methods for its assessment), and duration of follow-up. The income of the country where the study was conducted was defined according to the 2022–2023 World Bank classification.[15]

2.3 | Assessment of risk of bias

The Cochrane Risk of Bias Tool was utilized to evaluate the Risk of Bias (ROB) of the included studies. Two reviewers worked independently in pairs to conduct the assessment process, while any discrepancies were resolved through discussion. Revman 5.3 was used to generate figures for the summary risk of bias.

2.4 | Data analysis

Characteristics of the included studies were reported using descriptive tables. Furthermore, in cases where a meta-analysis was not feasible, we conducted a narrative synthesis of the pertinent evidence. For interventions and outcomes where a meta-analysis was feasible, random-effect models were used. Standardized mean difference and 95% confidence interval were pooled and summarized as proposed by Harrer et al.[16] In the case of studies not reporting outcomes as mean and standard deviation (e.g., studies providing results as non-parametric summary statistics), data were imputed according to the strategies proposed by Luo et al.[17] and by Shi et al.[18] Statistical heterogeneity was measured by τ^2 (tau squared) and the "SJ" algorithm, I^2 (I squared) and Cochrane's Q test. Individual standardized mean difference (SMDs), pooled SMD, and heterogeneity results were visualized with the forest plot presenting the calculated effect size along with a 95% confidence interval of each included paper. Additionally, the method's heterogeneity statistics are provided. Funnel plots were used to check for publication bias. The corresponding *p*-Curve plots were also generated. In the case of Cochrane's Q test, a statistical significance was indicated if $p < .05$. R-lang with the assistance of the RStudio IDE (R version 4.1.22021-11-01, RStudio version 2021-09-1 + 372) were used.

2.5 | Grading of evidence

The certainty of evidence (high, moderate, low, and very low) obtained through the meta-analysis was rated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

3 | RESULTS

3.1 | Systematic review

A total of 4471 articles were screened (Figure 1). After literature screening, 50 articles published between 1996 and 2022 were retained for the systematic review.[19–68] The studies were conducted in the following continents: 33 in Asia,[22,26,27,29,31–33,35–41,43,45,47–54,57–62,65–67] eight in Africa,[23,25,34,42,44,55,63,68] five in South America,[20,21,24,28,46] two in North America,[56,64] one in Central America,[19] and one in Oceania.[30] Four trials were conducted in low income,[25,33,42,55] 32 in lower middle income,[22,23,26,27,29,31,32,35–41,43–45,47–50,52–54,57,60–63,65,66,68] 12 in upper middle income,[19,21,24,28,34,46,51,56,58,59,64,67] and two in high-income[20,30] countries (Table S1). The trials enrolled a total of 16,342 patients. The studies were mostly double-blinded except for two single-blinded,[30,37] two triple-blinded[36,56] and three

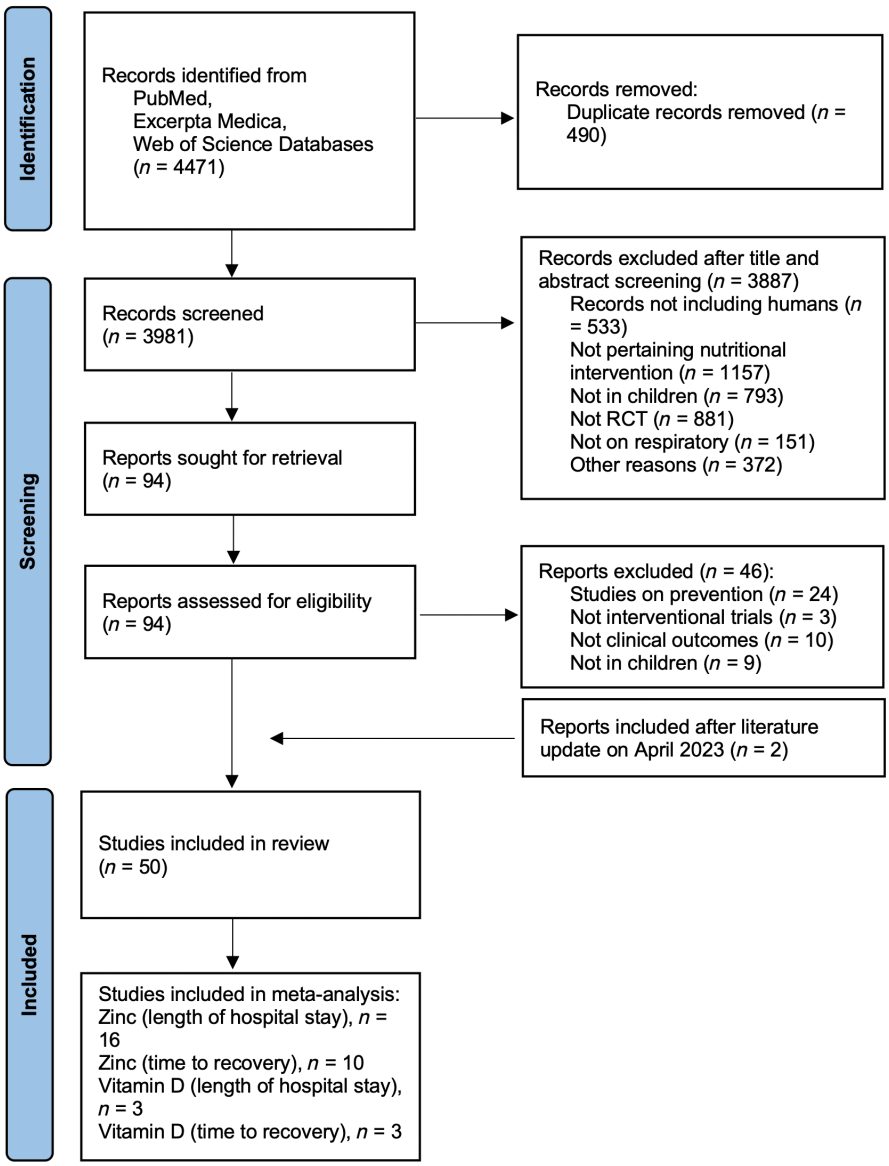


FIGURE 1 Flow chart of study selection.

that were not blinded[51,52,68] In four studies, blindness was not specified.[47,49,57,65] All trials included two arms, except for four, which included more than two arms.[27,30,60,66] A total of 44 studies dealt with children affected by infections of the lower respiratory tract,[19,21–33,35–50,52–63,66,68] 39 were specifically focused on children with pneumonia,[21–24,26,28,29,32–35,37–51,53–57,59–63,65,68] one on bronchiolitis and pneumonia[19] and one on bronchiolitis alone.[66] One study focused on children affected by pharyngitis, tonsillitis, and pharyngotonsillitis,[64] one study included children with upper or lower respiratory tract infections,[67] and one trial included children with respiratory diseases associated to respiratory syncytial virus.[20] One trial included only HIV children with pneumonia[34] and one only children with low levels of zinc at baseline and affected by pneumonia.[51]

The intervention group received zinc in 26 trials,[26,29,32,35–39,41–49,51,53–59,62,65] vitamin A in six,[19,20,22–24,28] vitamin C and E in one,[31] vitamin D in six,[33,40,50,52,61,63] and probiotics or prebiotics in two.[64,67] Zinc and vitamin A were concurrently evaluated in three trials,[27,30,68] zinc or probiotics in one trial,[60] vitamin A and E in two trials,[21,25] and zinc and vitamin D in one trial.[66] A multimicronutrients supplementation was used in one study.[34]

The majority of trials on zinc tested a daily dose of 20 mg.[26,27,29,32,35,36,41,43,46,48,49,53,57,66] Nine trials tested different daily doses (between 10 and 20 mg) of zinc according to age (<6 months vs. older subjects[54] or <12 months vs. older subjects[37,39,42,47,56,62,68]). Two trials tested a daily dose of 10 mg,[32,55] two of 15 mg,[58,59] one of 2 mg/kg,[38] and one of 5 mL (dose in mg not specified).[45] In one trial, it was reported that the zinc dose was in accordance with the WHO recommendations.[65] Three trials tested vitamin A doses of 100,000 IU (for subjects aged < 12 months) and 200,000 IU (for older subjects).[19–21] One trial tested vitamin A dose of 200,000 IU (for subjects aged < 12 months) and 400,000 IU (for older subjects).[22] One trial provided vitamin A 100,000 IU for infants aged <1 year on the first day and 50,000 IU on the second day, whereas 200,000 IU for older children on the first day and 100,000 IU on the second day.[24] One trial tested uniquely a dosage of 100,000 IU of vitamin A.[25]

One trial tested a daily dose of 200 mg of vitamin E plus 100 mg of vitamin C.[31] Four trials tested a vitamin D dose 100,000 IU.[33,50,52,63] One trial tested a daily vitamin D dose of 1000 IU (for subjects aged <12 months) and 2000 IU (for older subjects).[40] One trial tested vitamin D 20,000 IU in children < 6 months, 50,000 IU in children 6–12 months, and 100,000 in children 13–59 months on first day followed by 10,000 IU daily for all participants.[61] One trial tested 100 IU/kg daily of vitamin D.[66] Dosages of multi-micronutrient, probiotics, or prebiotics are reported in Table S1. All studies provided a placebo in the control group except for six studies which did not provide any supplementation.[47,51,52,60,66,68] In one trial, patients in the control group received either placebo or no supplementation.[57]

No information on the nutritional status at baseline was reported in eight trials on zinc.[45,47–49,51,54,57,62] However, data on nutritional studies and definition of malnutrition largely varied in the remaining studies on zinc (Table 1). No information on the nutritional status at baseline was reported in three trials on vitamins.[20,33,63] However, similarly to studies on zinc, data on nutritional studies and definition of malnutrition in trials testing the effects of vitamins largely varied in the remaining studies. Baseline data about the nutritional status of participants and of circulating values of the micronutrients supplemented in the trials are provided in detail, when available, in Table 1. Although the adverse reactions investigated in the original studies largely varied among trials and sometimes were not addressed at all, most studies did not detect any relevant safety issue (Table S2).

3.1.1 | Synthesis of the results

Trials on zinc

Results from trials gauging the effects of zinc supplementation were not consistent.

A few trials including patients with pneumonia found some beneficial clinical effects from zinc supplementation on signs, symptoms, or time to recovery ($n = 17$),[26,38,45,47–49,54–56,59,62,65,68] length of hospitalization ($n = 8$),[32,38,45,48,49,54,57,68] and fatality rate ($n = 1$).[42] One trial found some beneficial clinical effects from zinc supplementation on time to recovery and length of hospitalization in patients affected with lower respiratory tract infections.[58] On the contrary, 10 studies in patients with pneumonia[29,35,37,39,41,43,44,46,51,53] and one study in patients with lower respiratory tract infections[36] found no clinical effects of zinc supplementation. Similarly, one study supplementing zinc in combination with vitamin A in patients with lower respiratory tract infections did not find any beneficial clinical effect.[30]

The geographical origin of the studies finding beneficial clinical effects from zinc supplementation ($n = 14$, 78%, from Asia,[26,27,32,38,45,47–49,54,57–59,62,65] $n = 3$, 17%, from Africa,[42,55,68] and $n = 1$, 5.5%, in North America[56]) was similar to that of studies which did not find any beneficial effect ($n = 10$, 77%, from Asia,[29,35–37,39,41,43,51,53,66] $n = 1$, 7.7%, from Africa,[44] $n = 1$, 7.7%, from South America[46] and $n = 1$, 7.7%, from Oceania[30]). The income country where studies were conducted was also similar. Among studies finding beneficial clinical effects from zinc supplementation, 13 (72%) were conducted in lower-middle income countries,[26,27,32,38,45,47–49,54,57,62,65,68] three (17%) in upper middle-income[56,58,59] and two (11%) in low income countries.[42,55] Among studies that did not find any beneficial clinical effect, 10 (77%) were conducted in lower-middle income countries,[29,35–37,39,41,43,44,53,66] two (15%) from upper middle countries[46,51] and one (7.7%) in a high-income country.[30]

Trials on vitamins

One study found a positive effect of vitamin A on time to recovery from pneumonic effusion and duration of hospitalization in children affected by pneumonia.[68] Only one further trial found positive effects of vitamin A on symptoms and duration of hospitalization in a subgroup analysis including children with respiratory illness associated to respiratory syncytial virus and oxygen saturation level ≤ 90% in room air.[20] Three studies on vitamin A in children affected by lower respiratory tract infections (including also pneumonia and bronchiolitis) did not identify any relevant positive effect[19,27,30] and one on children with pneumonia did not find any positive effect except for the length of hospitalization in moderately malnourished children.[22] One trial found that children with pneumonia supplemented with vitamin A had a negative effect on clinical signs and symptoms.[24] One trial evaluating vitamins A and E in subjects with pneumonia found a positive effect on the occurrence of fever on Day 3 and response to the first-line antibiotic treatment, but no effect on duration of the underlying pneumonia.[21] A further trial on vitamin A and E in children with lower respiratory tract infections found no difference in the duration of hospitalization and of fever.[25] Most studies evaluating vitamin D and E did not identify any clear clinical effects in children with lower respiratory tract infections (including pneumonia).[31,33,40,50,52,61,66] In one trial, children affected with pneumonia and receiving vitamin D experienced a longer length of hospitalization compared to those receiving a placebo.[63]

Trials on probiotics and prebiotics

One trial evaluating the effect of Limosilactobacillus reuteri found a positive effect on clinical signs and symptoms of children with pharyngitis, tonsillitis, or pharyngotonsillitis.[64] On the contrary, another trial evaluating a mixture of prebiotics and probiotics found no clinical effect on clinical signs and symptoms and length of hospitalization of children with pneumonia.[60]

Trial on multi-micronutrient

In a trial evaluating the effect of a multi-micronutrient supplementation in children with pneumonia, no effect on the duration of hospitalization was observed.[34]

3.1.2 | Quality assessment

A total of 12 (24%) studies presented a low risk of bias,[36,38,43,50,52,53,55,58,59,61–63,66] 28 (56%) some concerns[19–21,23–29,31,32,34,35,37,39–42,44–46,48,49,54,57,60,67] and 10 (20%) a

TABLE 1 Nutritional information reported in the 50 papers.

Name	Definition of nutritional status	Nutritional status at baseline	Intervention	Normal reference values reported in the paper	Pre-supplementation circulating levels	Post-supplementation circulating levels	Sub-analysis
Kjolhede CL et al.[19]	Severely malnutrition: <70% of the median of the normal weight/height ratio. Normal ratio defined according to national Center for Health Statistics reference	Weight/length z score—median Intervention group: −0.69 Control group: −0.63	Vitamin A	Serum retinol level ≥0.70 μmol/L	Median Intervention group: 0.92 μmol/L Control group: 0.87 μmol/L	Only for subjects whom the initial retinol value was low (<0.70 μmol/L)—mean change in levels Intervention group: 0.67 μmol/L Control group: 0.73 μmol/L	/
Dowel SF et al.[20]	Not reported	Not reported	Vitamin A	Not reported	Mean (IQR) Intervention group: 24.1 (13–53) μg/dl Control group: 23.5 (10–45) μg/dl $p = .6$	Intervention group: 29.6 μg/dL Control group: 29.5 μg/dL	Lower serum retinol concentrations at the time of enrollment were associated with more severe disease
Nacul LC et al.[21]	Not reported	Weight-for-height z score—mean ± SD Intervention group: −0.76 ± 1.23 Control group: −0.72 ± 1.15	Vitamin A	Serum retinol level ≥0.70 μmol/L	Mean ± SD Intervention group: 0.45 ± 0.34 μmol/L Control group: 0.38 ± 0.28 μmol/L	Mean (day 11) Intervention group: 1.04 μmol/L Control group: 0.91 μmol/L $p = .009$	/
Si NV et al.[22]	Without malnutrition: weight-for-age > 80% of the US Nation Centre for Health Statistics reference median	Intervention group: Without malnutrition: 52.9% Moderate malnutrition: 47.1% Control group: Without malnutrition: 57.7% Moderate malnutrition: 42.3%	Vitamin A	Not reported	Not reported	Not reported	Malnourished children had a shorter time of hospitalization, especially females
Fawzi WW et al.[23]	Wasted children: <−2 z scores in weight-for-height but at or > −2 z scores in height-for-age. Stunted children: < −2 z scores in height-for-age but at or > −2 z scores in weight-for-height. Z scores were defined according to WHO (World Health Organization) criteria	Intervention group: Stunted: 26.6% Wasted: 13.6% Wasted and stunted: 2.3% Normal: 49.4% Unknown: 8.1% Control group: Stunted: 21.7% Wasted: 13.8% Wasted and stunted: 2.9% Normal: 51.3% Unknown: 10.3%	Vitamin A	Not reported	Not reported	Not reported	/

TABLE 1 (Continued)

Name	Definition of nutritional status	Nutritional status at baseline	Intervention	Normal reference values reported in the paper	Pre-supplementation circulating levels	Post-supplementation circulating levels	Sub-analysis
Stephensen CB et al.[24]	Weight-for-height < 70th percentile of the National Center for Health Statistics Reference standards was considered an exclusion criteria	Z score mean ± SD Intervention group: Height-for-age: −0.56 ± 1.43 Weight-for-age: −0.64 ± 1.08 Weight-for-height: −0.33 ± 1.04 Control group: Height-for-age: −0.60 ± 2.24 Weight-for-age: −0.35 ± 1.37 Weight-for-height: 0.22 ± 1.35	Vitamin A	Not reported	Mean ± SD Intervention group: 0.24 ± 0.17 μmol/L Control group: 0.31 ± 0.24 μmol/L	Not reported	/
Julien MR et al.[25]	Not reported	Weight—mean ± SD Intervention group: 10.2 ± 2.6 Control group: 10.0 ± 2.6	Vitamin A	Serum retinol level < 10/20 μg/dL was considered to divide patients	Not reported	Mean ± SD Intervention group: 8.9 ± 6.9 μg/dL Control group: 7.9 ± 6.2 μg/dL $p = .450$	/
Brooks WA et al.[26]	Severe malnutrition: weight-for-age < 60% based on the National Center for Health Statistics reference data	% weight for age—mean ± SD Intervention group: 82.6 ± 11.7 Control group: 82.1 ± 11.6	Zinc	Serum zinc concentration > 14 μmol/L	Mean ± SD Intervention group: 10.1 ± 1.1 μmol/L Control group: 10.1 ± 1.0 μmol/L	Mean ± SD Intervention group: 14.8 ± 2.8 μmol/L Control group: 11.3 ± 2.1 μmol/L	/
Mahalanabis D et al.[27]	Not reported	Weight for age z score—median (IQR) Group 1: −1.83 (1.01) Group 2: 1.43 (1.07) Group 3: −1.72 (1.00) Group 4: −1.64 [1.06]	Vitamin A and zinc	Not reported	Mean ± SD Retinol (μmol/L): Group 1: 0.70 ± 0.73 Group 2: 0.705 ± 0.532 Group 3: 0.812 ± 0.503 Group 4: 0.712 ± 0.616 Zinc (μmol/L): Group 1: 9.912 ± 2.503 Group 2: 9.639 ± 3.365 Group 3: 9.459 ± 2.329 Group 4: 9.270 ± 2.077	Mean ± SD Retinol (μmol/L): Group 1: 1.564 ± 0.658 Group 2: 1.564 ± 0.658 Group 3: 1.723 ± 0.651 Group 4: 1.260 ± 0.549 Zinc (μmol/L): Group 1: 16.79 ± 5.35 Group 2: 10.900 ± 4.990 Group 3: 17.400 ± 5.802 Group 4: 11.278 ± 3.822	/
Rodriguez A et al.[28]	Underweight: weight-for-age ≤ −2 SD Normal weight: weight-for-age ≥ −2 SD Nutritional status was defined according to US National Center Health of Statistics growth curve	Weight for age z score—mean ± SD Intervention group: −1.56 ± 1.16 Control group: −1.27 ± 1.33	Vitamin A	Plasma retinol concentration > 200 μg/L	Mean ± SD Intervention group: 152 ± 64.5 μg/L Control group: 162 ± 70.2 μg/L	Mean ± SD Intervention group: 273 ± 107 μg/L Control group: 285 ± 112 μg/L	Time to remission of respiratory signs in children with basal serum retinol concentration > 200 μg/L was significantly lower than all the subjects analyzed: Intervention group: 69.9 ± 49.9 h Placebo group: 131.3 ± 143.9 h $p = .049$

(Continues)

TABLE 1 (Continued)

Name	Definition of nutritional status	Nutritional status at baseline	Intervention	Normal reference values reported in the paper	Pre-supplementation circulating levels	Post-supplementation circulating levels	Sub-analysis
Bose A et al.[29]	Severe malnutrition: weight-for-age < 60% of the reference for Indian Children	Weight-for-age z score ≤ −2.0% Intervention group: 41.3% Control group: 37.6%	Zinc	Normal value for plasma zinc obtained using the method reported in the paper: 70–125 μg/100 mL (10.7–19.1)	Mean ± SD Intervention group: 11.0 ± 2.2 μmol/L Control group: 10.9 ± 2.4 μmol/L	Mean ± SD Intervention group: 13.0 ± 2.5 μmol/L Control group: 12.0 ± 4.1 μmol/L $p = .013$	/
Chang AB et al.[30]	Z scores were calculated using Epi Info—Centers for Disease Control and Prevention Stunted: height-for-age z scores ≤ −2 Wasted: weight-for-height z scores ≤ −2 Underweight: weight-for-age z scores ≤ −2	Underweight—% Group 1: 7% Group 2: 11% Group 3: 6% Group 4: 12% Wasted—% Group 1: 8% Group 2: 2% Group 3: 5% Group 4: 19% Stunted—% Group 1: 10% Group 2: 11% Group 3: 5% Group 4: 3%	Vitamin A and zinc	Serum zinc level reference range: 10–18 μmol/L	Mean Zinc: Intervention group: 16.5 μmol/L Control group: 14.0 μmol/L $p = .31$ Vitamin A: Intervention group: 0.5 μmol/L Control group: 0.8 μmol/L $p = .26$	Not reported	/
Mahalanabis D et al.[31]	Not reported	Weight-for-age z score—mean ± SD Intervention group: −1.92 ± 1.18 Control group: −1.78 ± 1.18	Vitamin E and C	α-tocopherol low levels <8.8 μmol/L	Mean ± SD α-tocopherol levels: Intervention group: 10.18 ± 4.60 μmol/L Control group: 10.25 ± 5.03 μmol/L $p = .15$	Mean ± SD α-tocopherol levels: Intervention group: 18.68 ± 12.25 μmol/L Control group: 12.21 ± 6.44 μmol/L $p = .002$	/
Coles CL et al.[32]	Underweight: weight-for-age z scores ≤ −2	Underweight—% Suspected nonbacterial pneumonia: Intervention group: 42.5% Control group: 39.3% Suspected bacterial pneumonia: Intervention group: 39.5% Control group: 31.0%	Zinc	Not reported	Median (CI) Suspected nonbacterial pneumonia: Intervention group: 10.7 (10.3–11.5) μmol/L Control group: 10.6 (10.1–11.17) μmol/L Suspected bacterial pneumonia: Intervention group: 10.6 (9.6–11.5) μmol/L Control group: 10.2 (9.6–12.2) μmol/L	Not reported	/
Manaseki-Holland S et al.[33]	Not reported	Not reported	Vitamin D	Not reported	Not reported	Not reported	/

TABLE 1 (Continued)

Name	Definition of nutritional status	Nutritional status at baseline	Intervention	Normal reference values reported in the paper	Pre-supplementation circulating levels	Post-supplementation circulating levels	Sub-analysis
Mda S et al.[34]	Z scores were calculated according to the National Centre for Health Statistics reference values	Weight-for-age—mean ± SD Intervention group: −2.57 ± 1.43 Control group: −2.83 ± 1.24 Length-for-age—mean ± SD Intervention group: −2.22 ± 1.55 Control group: −2.31 ± 1.62 Weight-for-length—mean ± SD Intervention group: −1.52 ± 1.34 Control group: −1.45 ± 1.21	Micronutrient	Not reported	Not reported	Mean ± SD Retinol: Intervention group: 0.76 ± 0.36 μmol/L Control group: 0.78 ± 0.39 μmol/L Zinc: Intervention group: 8.6 ± 3.3 μmol/L Control group: 7.7 ± 2.7 μmol/L	/
Valentiner-Branth P et al.[35]	Stunted: length-for-age z scores ≤ −2 Wasted: weight-for-length z scores ≤ −2. Reference values were defined according to WHO Child Growth Standards	Stunted—% Nonsevere pneumonia 2–11 months of age Intervention group: 10% Control group: 9.1% ≥ 12 months of age Intervention group: 35% Control group: 38% Severe pneumonia 2–11 months of age Intervention group: 16% Control group: 7.1% ≥ 12 months of age Intervention group: 37% Control group: 63% Wasted—% Nonsevere pneumonia 2–11 months of age Intervention group: 2.6% Control group: 3.8% ≥ 12 months of age Intervention group: 6.1% Control group: 4.6% Severe pneumonia 2–11 months of age Intervention group: 3.6% Control group: 7.1% ≥12 months of age Intervention group: 11% Control group: 11%	Zinc	Not reported	Mean ± SD Nonsevere pneumonia 2–11 months of age Intervention group: 8.8 ± 2.1 μmol/L Control group: 8.9 ± 2.4 μmol/L ≥12 months of age Intervention group: 9.0 ± 2.4 μmol/L Control group: 8.8 ± 2.4 μmol/L Severe pneumonia 2–11 months of age Intervention group: 8.1 ± 2.9 μmol/L Control group: 8.9 ± 2.2 μmol/L *≥ 12 months of age* Intervention group: 13 ± 13 μmol/L Control group: 7.9 ± 1.5 μmol/L	Change in plasma zinc concentration from enrollment to after 14 days of supplementation—mean ± SD Intervention group: 5.9 ± 6.7 μmol/L Control group: 0.5 ± 3.1 μmol/L	/

(Continues)

TABLE 1 (Continued)

Name	Definition of nutritional status	Nutritional status at baseline	Intervention	Normal reference values reported in the paper	Pre-supplementation circulating levels	Post-supplementation circulating levels	Sub-analysis
Bansal A et al.[36]	Malnutrition: weight-for-age < 50% of reference value	Signs of nutritional deficiency—% Intervention group: Nil: 50% Anemia: 44.2% Rickets: 0.9% Control group: Nil: 56.6% Anemia: 43.3% Rickets: 5.7%	Zinc	Normal value for serum zinc obtained using calorimetric method: 9.8–16.8 μmol/L	Yes but missing data	Increase in blood zinc levels in the zinc group Mean difference: 7.5 (CI 2.7–12.3) μmol/L	/
Ganguly C et al.[37]	Not reported	Weight—median (IQR) Intervention group: 8.5 ± 5.3 Control group: 8.5 ± 8.5 $p = .593$ Height—median (IQR) Intervention group: 74.2 ± 15.24 Control group: 74.4 ± 15.31 $p = .963$	Zinc	Not reported	Not reported	Not reported	/
Valavi E et al.[38]	Not reported	Weight—mean Intervention group: 10.13 Control group: 10.19 kg Height—mean Intervention group: 77.4 cm Control group: 10.19 kg	Zinc	Not reported	Not reported	Not reported	/
Basnet S et al.[39]	Stunting: length-for-age z scores ≤ 2 Wasting: weight-for-length z score ≤ 2 Nutritional status was defined according to 2006 WHO Child Growth Standards	Wasting—% Intervention group: 29.1% Control group: 23.8% Stunting—% Intervention group: 9.4% Control group: 7.4%	Zinc	Not reported	Not reported	Not reported	/
Choudhary N et al.[40]	Not reported	Wight—mean ± SD Intervention group: 7.5 ± 2.5 kg Control group: 7.3 ± 2.7 kg Length—mean ± SD Intervention group: 70.0 ± 10.6 cm Control group: 70.1 ± 11.9 cm	Vitamin D	Not reported	Not reported	Not reported	/
Shah GS et al.[41]	Definition of malnutrition was based on WHO criteria	Weight-for-height z score—median (IQR) Intervention group: −0.510 (−1.41–0.830) Control group: −0.770 (−1.77–0.275) $p = .241$	Zinc	Not reported	Not reported	Not reported	/

TABLE 1 (Continued)

Name	Definition of nutritional status	Nutritional status at baseline	Intervention	Normal reference values reported in the paper	Pre-supplementation circulating levels	Post-supplementation circulating levels	Sub-analysis
Srinivasan MG et al.[42]	Not reported	Weight-for-age z score <2 Intervention group: 17.1% Control group: 22.9% Height-for-age z score <2 Intervention group: 26.1% Control group: 25.1%	Zinc	Not reported	Median (IQR) Intervention group: 4.4 (1.3–8.0) μmol/L Control group: 4.8 (2.3–10.4) μmol/L	Not reported	/
Wadhwa N et al.[43]	Severely underweight z score < −3	Severely underweight—% Intervention group: 21.2% Control group: 24.6%	Zinc	Serum zinc concentration >9.2 μmol/L was considered to divide patients.	Mean ± SD Intervention group: 9.3 ± 3.9 μmol/L Control group: 9.2 ± 3.6 μmol/L	Not reported	/
Fataki MR et al.[44]	Length-for-age and weight-for-length z scores calculated using the 2006 WHO Child Growth Standards	Weight-for-height z score ≤2% Intervention group: 20.8% Control group: 17.4% Height-for-age z score ≤2% Intervention group: 25.0% Control group: 30.4%	Zinc	Serum zinc concentration > 70 μg/dL was considered to divide patients	Mean ± SD Intervention group: 72.1 ± 16.1 μg/dL Control group: 68.0 ± 31.1 μg/dL	Not reported	No significant effect of zinc supplementation on hospitalization duration among individuals with baseline plasma zinc <70 μg/dL (IRR for discharge: 0.70; 95% CI: 0.44–1.14; $p = .15$) or after adjustment of baseline variables (IRR for discharge: 0.70; 95% CI: 0.44–1.14; $p = .15$)
Qasemzadeh MJ et al.[45]	Not reported	Not reported	Zinc	Not reported	Not reported	Not reported	/
Sempértegui F et al.[46]	Wasted: weight-for-length or weight-for-height z scores < −2	Weight-for-age z scores—mean ± SD Intervention group: −1.05 ± 1.30 Control group: −1.01 ± 1.21 Height-for-age z scores—mean ± SD Intervention group: −0.93 ± 1.39 Control group: −1.05 ± 1.36 Weight-for-height/length z scores—mean ± SD Intervention group: −0.08 ± 1.99 Control group: −0.19 ± 1.90 Underweight: 18% Stunted: 19% Wasted: 14%	Zinc	Plasma zinc concentration > 70 μg/dL (after adjustment by C-reactive protein concentration)	Mean ± SD Zinc adjusted Intervention group: 76.40 ± 27.23 μg/dL Control group: 74.2 ± 24.9 μg/dL	Only zinc adjusted was reported	Higher baseline zinc concentration was associated with a reduction in time to remission of chest indrawing ($p = .011$). There was no significant interaction between basal plasma zinc and height-for-age z score on time to resolution of chest indrawing. Better weight-for-height/length and height-for-age z scores were associated with a reduction in time to remission to tachypnea
Ayub MR et al.[47]	Not reported	Not reported	Zinc	Not reported	Not reported	Not reported	/
Manohar B et al.[48]	Not reported	Not reported	Zinc	Normal zinc levels: 65–150 mg%	Not reported	Not reported	/
Shehzad N et al.[49]	Not reported	Not reported	Zinc	Not reported	Not reported	Not reported	/

(Continues)

TABLE 1 (Continued)

Name	Definition of nutritional status	Nutritional status at baseline	Intervention	Normal reference values reported in the paper	Pre-supplementation circulating levels	Post-supplementation circulating levels	Sub-analysis
Gupta P et al.[50]	Z scores were compared to WHO reference standards for growth < 5 children	Weight-for-age z scores—mean ± SD Intervention group: −1.7 ± 0.95 Control group: −1.6 ± 1.01 Height-for-age z scores—mean ± SD Intervention group: −1.4 ± 1.19 Control group: −1.5 ± 1.14 Weight-for-height z scores—mean ± SD Intervention group: −1.2 ± 1.11 Control group: −1.1 ± 1.07 Body mass index—mean ± SD Intervention group: 15.2 ± 1.39 Control group: 15.3 ± 1.54	Vitamin D	Serum 25(OH)D > 12 ng/mL	Median (IQR) Intervention group: 14.4 (7.9–23.5) ng/ml Control group: 15.3 (7.9–23.2) ng/mL	Change in serum level of 25(OH) vitamin D from baseline to 2 weeks—mean ± SD Intervention group: 30.1 ± 27.1 ng/mL Control group: 1.9 ± 14.7 ng/mL	Data on secondary outcomes are not reported
Yuan X et al.[51]	Not reported	Not reported	Zinc	Normal reference range of serum zinc: 58.00–100.00 μmol/L	Mean ± SD 1–3 months: 40.75 ± 17.02 μmol/L 4–12 months: 58.00 ± 19.22 μmol/L	Mean ± SD Within 24 h: Normal serum zinc group: 63.80 ± 21.00 μmol/L Intervention group: 40.77 ± 8.54 μmol/L Control group: 42.55 ± 9.34 μmol/L D7 of Admission: Normal serum zinc group: 59.23 ± 14.25 μmol/L Intervention group: 50.18 ± 11.30 μmol/L Control group: 46.84 ± 10.74 μmol/L D12 ± 2 of Admission: Normal serum zinc group: 59.20 ± 12.70 μmol/L Intervention group: 53.20 ± 10.75 μmol/L Control group: 43.76 ± 4.66 μmol/L	Only subjects with low levels of zinc were supplemented
Somnath SH et al.[52]	Not reported	Malnutrition—% Intervention group: 32.1% Control group: 25%	Vitamin D	Sufficiency 25(OH)D level ≥ 30 ng/mL	Mean ± SD Intervention group: 17.97 ± 11 35 ng/mL Control group: 18.75 ± 14.35	Mean ± SD Intervention group: 64.96 ± 32.22 ng/mL *p*-value before and after admission <.01 Control group: NA	/

TABLE 1 (Continued)

Name	Definition of nutritional status	Nutritional status at baseline	Intervention	Normal reference values reported in the paper	Pre-supplementation circulating levels	Post-supplementation circulating levels	Sub-analysis
Bagri NK et al.[53]	Severely underweight: weight-for-age z score < −3. Severely underweight was defined according to WHO growth charts	Severely underweight—% Intervention group: 22.3% Control group: 28.6%	Zinc	Serum zinc level >9.2 μmol/L was considered to divide patients	Mean ± SD Intervention group: 8.66 ± 3.4 μmol/L Control group: 8.99 ± 2.98 μmol/L	Not reported	/
Baruah A et al.[54]	Not reported	Not reported	Zinc	Not reported	Mean ± SD Intervention group: 139.5 ± 47.9 μg/dL Control group: 139.3 ± 66.2 μg/dL $p = .98$	No increase in serum zinc levels between zinc group (137.6 ± 76.4 μg/dL) and placebo group (137.3 ± 41.9 μg/dL) at 3 months after admission ($p = .97$)	/
Howie S et al.[55]	Severe wasted: weight-for-height z score < −3 Severe stunted: height-for-age z score < −2 wasted and stunted were defined according to WHO growth charts	Severe wasted—% Intervention group: 6.6% Control group: 8.4% Weight-for-height z score—median (IQR) Intervention group: −1.3 (−2.0, −0.6) Control group: −1.4 (−2.3, -0.8) Severe stunted—% Intervention group: 4.0% Control group: 7.0% Height-for-age z score—median (IQR) Intervention group: −1.3 (−2.0, −0.6) Control group: −1.4 (−2.3, −0.8)	Zinc	Serum zinc concentration >9.9 μmol/L	Median (IQR) Intervention group: 11.3 (7.6–19.4) μmol/L Control group: 14.0 (7.5–23.7) μmol/L	Mean from 6 months Intervention group: 19.92 Control group: 22.04 Difference = 2.53 CI = -0.75–5.81 $p = .131$	/
Acevedo-Murillo JA et al.[56]	Not reported	Weight—mean ± SE Intervention group: 11.15 ± 0.5 kg Control group: 9.4 ± 0.5 kg $p = .01$ Height—mean ± SE Intervention group: 81.4 ± 2.3 cm Control group: 74.9 ± 2.2 cm $p = .05$ Body mass Index—mean ± SE Intervention group: 16.5 ± 0.4 Control group: 15.9 ± 0.3 $p = .35$ Malnutrition—% Intervention group: 23% Control group: 28% $p = .41$	Zinc	Normal serum zinc: 63.8–110 μg/dL (9.8–16.8 μmol/L)	Mean ± SE Intervention group: 23 ± 1.8 μg/dL Control group: 21 ± 1.9 μg/dL	Mean ± SE Intervention group: 33 ± 4 μg/dL p-value pre- vs. post-zinc levels = .003 Control group: 29 ± 2.8 μg/dL p-value pre- vs. post-zinc levels = .08	/

(Continues)

TABLE 1 (Continued)

Name	Definition of nutritional status	Nutritional status at baseline	Intervention	Normal reference values reported in the paper	Pre-supplementation circulating levels	Post-supplementation circulating levels	Sub-analysis
Laghari GS et al.[57]	Not reported	Not reported	Zinc	Not reported	Not reported	Not reported	/
Rerksuppaphol S et al.[58]	Not reported	Weight—mean ± SD Intervention group: 11.4 ± 4.3 kg Control group: 10.5 ± 2.4 kg Height—mean ± SD Intervention group: 82.2 ± 14.7 cm Control group: 80.1 ± 11.4 cm	Zinc	Cutoff of serum zinc level in children <10 years old: Morning non-fasting: 65 mg/dL Afternoon: 57 mg/dL	Mean ± SD Intervention group: 75.0 (21.1) μg/dl Control group: 76.6 (22.6) μg/dl $p = .767$	Mean ± SD Intervention group: 113.5 ± 29.9 μg/dL Control group: 89.4 ± 21.5 $p < .0011$	34.4% of Thai children with ALRI had low-serum zinc levels. Lower serum zinc levels were observed in Nigerian children that were hospitalized with ALRI compared to controls
Rerksuppaphol L et al.[59]	Not reported	Weight—mean ± SD Intervention group: 12.1 ± 4.1 kg Control group: 10.6 ± 2.9 kg Height—mean ± SD Intervention group: 84.6 ± 14.7 cm Control group: 80.7 ± 15.2 cm	Zinc	Serum zinc concentration > 65 μg/dL	Mean ± SD Intervention group: 74.2 (19.9) μg/dl Control group: 77.2 (21.8) μg/dl $p = .481$	Not reported	/
Binesh S et al.[60]	Not reported	Not reported	N/A	N/A	N/A	N/A	/
Chowdhury F et al.[61]	Severe malnutrition: z score < −3 SD from the median for weight-for-height or weight-for-age or height-for-age Severe underweight: z score < −3 Severe wasting: z score < −3	Severe underweight—% Intervention group: 56.7% Control group: 59.0% Severe wasting—% Intervention group: 24.7% Control group: 34.0%	Vitamin D	Vitamin D ≥ 50 nmol/L	Mean ± SD Intervention group: 53.7 ± 30.8 nmol/L Control group: 54.1 ± 29.0 nmol/L	Mean ± SD Intervention group: 93.22 ± 42.1 nmol/L Control group: 63.1 ± 29.1 nmol/L	Outcome duration based on vitamin D status (deficient/sufficient): no significant interaction observed for any of the endpoints
Hashemian H et al.[62]	Not reported	Not reported	Zinc	Not reported	Not reported	Not reported	/
Labib JR et al.[63]	Not reported	Not reported	Vitamin D	Vitamin D level ≥ 30 ng/mL	Median (IQR) intervention group: 15.8 (7–18.2) control group: 16.7 (8.9–21.7) $p = .119$	Median (IQR) intervention group: 67.7 (58.8–84.5) control group: 14.3 (8.9–20.6) $p = .000$	/
Maya-Barrios A et al.[64]	Not reported	Not reported	N/A	N/A	N/A	N/A	/

TABLE 1 (Continued)

Name	Definition of nutritional status	Nutritional status at baseline	Intervention	Normal reference values reported in the paper	Pre-supplementation circulating levels	Post-supplementation circulating levels	Sub-analysis
Ahmad K. et al.[65]	Not reported	Weight—mean ± SE Intervention group: 11.19 ± 0.7 kg Control group: 9.6 ± 2.6 kg $p = .01$ Height—mean ± SE Intervention group: 80.4 ± 2.4 cm Control group: 70.5 ± 2.2 cm $p = .04$ Body mass Index—mean ± SE Intervention group: 16.4 ± 0.5 Control group: 14.6 ± 0.5 $p = .45$	Zinc	Not reported	Mean ± SE Intervention group: 23 ± 1.8 μg/dL Control group: 21 ± 1.9 μg/dL $p = .34$	Median ± SE intervention group: 33 ± 4 μg/dL control group: 29 ± 2.8 μg/dL $p = .45$	/
Khoshnevisasl P et al.[66]	Not reported	Weight—mean ± SD Group 1: 8.5 ± 3.4 kg Group 2: 8.1 ± 2.1 kg Group 3: 8.4 ± 2.4 kg $p = .881$	Vitamin D	Not reported	Not reported	Not reported	/
Mageswary MU et al.[67]	Not reported	Weight—mean ± SD Intervention group: 8.79 ± 0.26 kg Control group: 10.70 ± 1.40 kg $p = .781$ Height—mean ± SD Intervention group: 73.02 ± 1.68 cm Control group: 72.18 ± 1.55 cm $p = .384$	N/A	N/A	N/A	N/A	/
Saied A et al.[68]	Subjects were categorized using CDC (Center of Disease Control and Prevention) and WHO growth charts	Underweight—% Group 1: 8.0% Group 2: 12.0% Group 3: 8.0% Overweight—% Group 1: 20.0% Group 2: 12.0% Group 3: 8.0% Obese—% Group 1:28.0% Group 2:32.0% Group 3: 44.0%	Zinc and vitamin A	Not reported	Not reported	Not reported	/

high risk of bias.[22,30,33,47,51,53,56,64,65,68] Figure 2 presents the summary of quality assessment for studies employing an intention to treat and per protocol approach. The details of the quality assessment of each study are provided in the Appendix S1 (Figure S1).

3.2 | Meta-analysis

Two meta-analyses testing the effect of zinc (on length of hospitalization of children with pneumonia, respectively, on time to recovery of children with pneumonia) and two meta-analyses testing the effect of vitamin D (on length of hospitalization of children with pneumonia, respectively, on time to recovery of children with pneumonia) were performed.

Zinc

The first meta-analysis (Figure 3) included 16 studies[26,29,32,38,41,44,47,49,51,56–58,60,62,65] and was focused on the length of hospitalization of children with pneumonia. A difference in favor of zinc versus placebo (SMD -0.44 (−0.87; −0.01) days) was found. The second meta-analysis (Figure 4) included 10 studies[29,32,38,41,43,48,49,53,56,58,65] and was focused on the time to recovery of children with pneumonia. No relevant difference between zinc and placebo was observed (−0.24 [−0.63; 0.14]). A heterogeneity >90% was observed in both meta-analyses. The *p*-curve plots of the two meta-analyses are shown in Figures S2 and S3 (Appendix S1) and showed that *p*-curve plots are right-skewed as expected when the studies measure a true effect. Sub-analyses limited to studies with low risk of bias showed no significant effect of zinc on length of hospitalization (Figure S4) and time to recovery (Figure S5) in children with pneumonia and a marginally reduced heterogeneity. The funnel plots of risk of publication bias are reported in the Appendix S1 (Figures S6 and S7) and showed no evident risk for such bias.

Vitamins

The first meta-analysis (Figure 5) included three studies[40,50,63] and was focused on length of hospitalization of children with pneumonia. A heterogeneity >70% was found. No difference between vitamin D and placebo was observed on length of hospitalization (0.17 (−0.50; 0.83) days). Similarly, a second meta-analysis (Figure 6) including four studies[33,40,50,61] and focusing on time to recovery of children with pneumonia did not find any significant difference between vitamin D and placebo on time to recovery (−0.07 (−0.30: 0.17) days). A low heterogeneity was observed (<20%). Funnel plots of risk of publication bias are reported in the Appendix S1 (Figures S8 and S9) and showed no evident risk for such bias.

The GRADE results for each of the meta-analyses pointed out a certainty between low and moderate (Tables S3–S6).

FIGURE 2 Domain and overall risk of bias score (green: "low risk," yellow: "some concern" and red: "high risk of bias") of intention to treat (upper panel) and per protocol (lower panel) studies included within the systematic review. Results are reported as percentage of the total number of papers of both the groups ("Intention to treat" and "Per protocol").

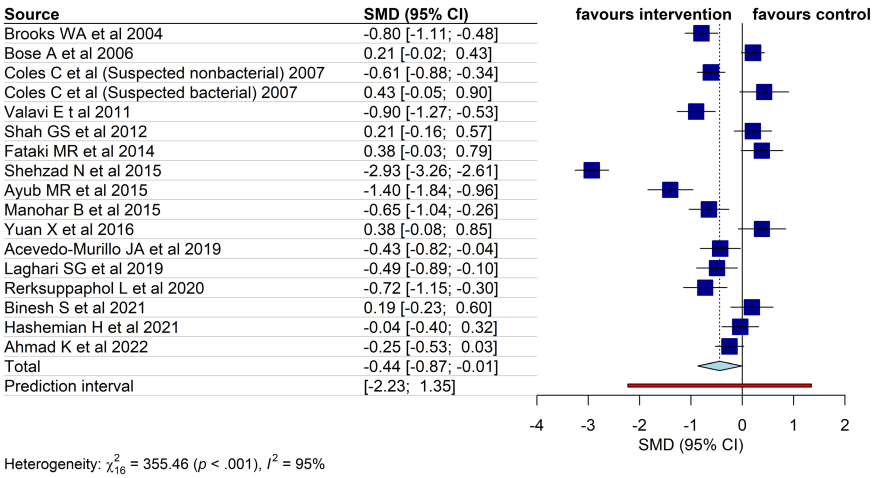


FIGURE 3 Meta-analysis and forest plot about pooled standardized mean difference of length of hospitalization in children with pneumonia treated with zinc or placebo. The area of the squares indicates the weight of each study in the analysis.

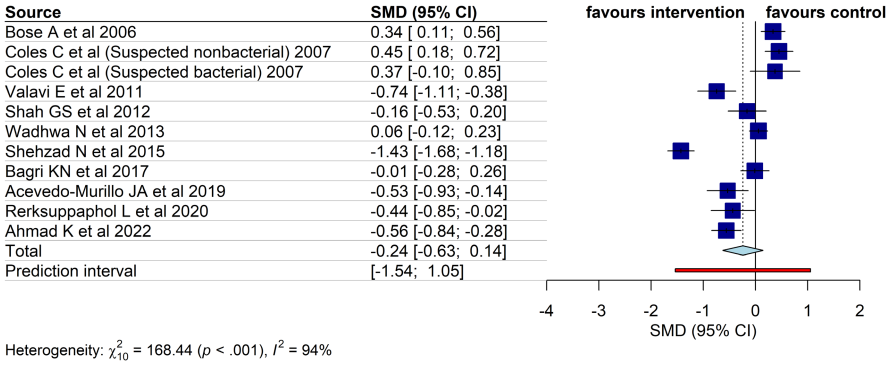
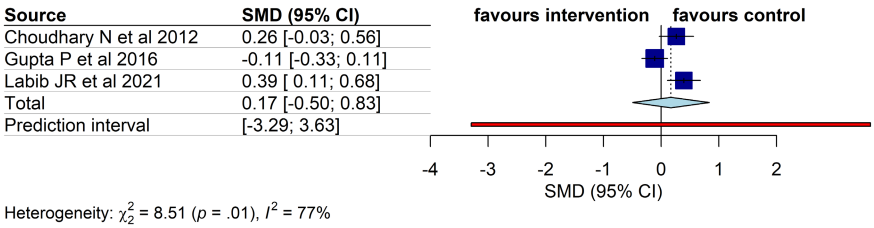


FIGURE 4 Meta-analysis and forest plot about pooled standardized mean difference of time to recovery in children with pneumonia treated with zinc or placebo. The area of the squares indicates the weight of each study in the analysis.



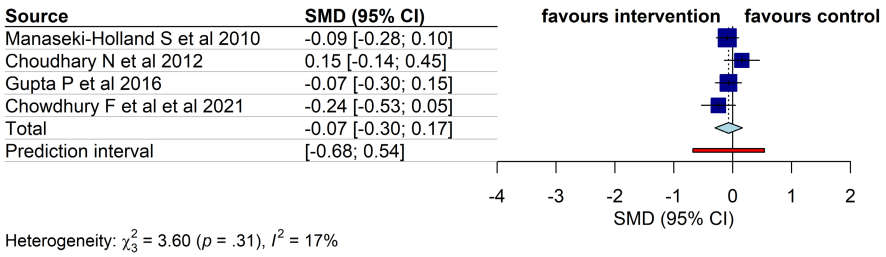


FIGURE 5 Meta-analysis and forest plot about pooled standardized mean difference of length of hospitalization in children with pneumonia treated with vitamin D or placebo. The area of the squares indicates the weight of each study in the analysis.

FIGURE 6 Meta-analysis and forest plot about pooled standardized mean difference of time to recovery in children with pneumonia treated with vitamin D or placebo. The area of the squares indicates the weight of each study in the analysis. The red bar in a forest plot stands for the 95% prediction interval.

4 | DISCUSSION

This is the first systematic review comprehensively investigating the potential effect of nutritional and dietary interventions in children affected by a respiratory tract infection. This review provides at least four relevant findings: (1) no supplementation was found to be consistently effective; (2) most trials evaluated zinc supplementation; (3) no trial on the effect of dietary habits modification on the

course of acute respiratory infections clinical course was found; (4) almost all studies were conducted in low, lower middle, and upper middle-income countries.

A recent meta-analysis evaluating the potential of zinc supplementation to prevent infectious diseases in childhood did not identify any consistent positive effect.[13] The data from our systematic review showed mixed results. Some studies reported beneficial effects on signs, symptoms, duration, and length of hospitalization for lower respiratory tract infections, while others found no significant effects. The two meta-analyses indicated a marginal effect of zinc supplementation on the length of hospitalization (Level of evidence low) but no effect on time to recovery in children with pneumonia (Level of evidence moderate). However, when limiting the meta-analyses to low risk of bias trials, no significant effect was observed for both outcomes. These data are consistent with the results of previous literature analyses that did not identify any relevant effect of zinc.[69,70] All together these data do not support the routine use of zinc to treat children with pneumonia worldwide. Similarly, the few available trials evaluating vitamins A, D, and E did not consistently demonstrate positive clinical effects on acute respiratory tract infections.

The potential of probiotics in the management of infections has received increasing attention,[71,72] due to the interplay between the intestinal microbiome and the immune system.[73] However, our results point out that data on the treatment of pediatric acute respiratory infection are very limited. The trial on probiotics (Limosilactobacillus reuteri) showed some positive effects on clinical signs and symptoms of children with respiratory conditions,[64] while the trial on a mixture of prebiotics and probiotics did not show any clinical benefits for children with pneumonia, suggesting that bacterial strain-specific properties may be important for in vivo effects.[60]

The current analysis highlights some gaps in the literature. Recent data point out that ketogenesis might reduce the burden of viral infections such as SARS-CoV-2[74,75] and intermittent fasting might be effective to treat affected patients.[76] However, we were not able to identify any trial investigating the role of dietary regimens during childhood respiratory infections. Similarly, although some data suggest that polyunsaturated fatty acids might be effective in preventing respiratory infections, no trial evaluated these compounds on children with respiratory infections.[77] A further gap in the literature is that most available studies deal with pneumonia or, more in general, lower respiratory tract infection. Although bronchiolitis is the main cause of hospitalization in Western countries during the first 2 years of life, only one study evaluated the potential of dietary supplementation in this condition.[19] These findings are in line with the fact that no specific dietary recommendation is available for weaned infants affected with bronchiolitis managed in the outpatient setting or in a regular ward.[78,79] Furthermore, only one trial was focused on upper respiratory tract infections. Only few studies adjusted their results in view of the baseline nutritional status of the participants. The majority of studies were conducted in low or limited-resource countries. It is possible that the relevant frequency of malnourishment in these countries might have played a role in the trials.[80] Therefore, the findings of this study cannot be extrapolated to the whole pediatric population. The occurrence of adverse reactions was not homogenously and systematically addressed. Finally, investigating the potential of adhering to an immune-supportive diet—rich in fiber intake and low in ultra-processed foods—to induce positive effects on the interaction between microbiota and immune health is both challenging and promising.[81,82]

This systematic review has limitations. The available evidence was limited and heterogeneous, and the quality of the included studies varied. We were able to pool data only for two types of interventions in children with pneumonia. Although homogenous outcomes were considered, their definitions might partially vary among studies. It was not possible to conduct separate analyses according to the nutritional status of children. The small number of studies out of those on zinc or vitamin D supplementation prevented us from conducting meta-analyses for other dietary interventions. The heterogeneity observed in the meta-analyses was relevant for most of the analyses. The variations in dosage regimens and outcome measures may contribute to the differences in results and hinder the ability to draw definitive conclusions. Additionally, the small number of studies included in the meta-analyses on vitamin D limited the statistical power and precision of the pooled estimates.

In conclusion, this review points out that no nutritional or dietary intervention can be currently recommended for the routine treatment of respiratory tract infections in children. On the other hand, zinc supplementation might have a beneficial effect on length of hospitalization in children with pneumonia. Further research is needed to establish more conclusive evidence especially for well-nourished children living in a context of high-income countries.

AUTHOR CONTRIBUTIONS

GPM conceptualized and supervised the study, interpreted the data, and wrote the first draft of the manuscript. IA, MA, GNK, RMP, ICB, DC, IK, SB, AC, MC, LC, and GCIS performed literature search, extracted data, and performed the quality assessment and gave a significant contribution to data interpretation. JL performed statistical analysis and gave a significant contribution to data interpretation. NGP, CA, BVB, CV, and LOM gave a significant contribution in data interpretation and discussion in their field of expertise. EV conceptualized and supervised the study, interpreted the data, and gave a significant contribution in her field of expertise. All authors critically reviewed the manuscript.

ACKNOWLEDGMENTS

EAACI funding acknowledgment: This systematic review and meta-analysis was supported by the European Academy of Allergy and Clinical Immunology (EAACI) under the EAACI "Systematic review on the dietary interventions in children after acute respiratory or skin infections" (Year-2022).

CONFLICT OF INTEREST STATEMENT

GPM received unrestricted grant from Angelini Pharma S.P.A and Reckitt Benckiser Healthcare S.P.A. GNK has received personal fees and/or honoraria from Pfizer Inc., AstraZeneca, Chiesi, GSK, Menarini, Novartis, Nutricia, Sanofi-Aventis, and Vianex. NGP has served advisory board for Abbott, Abbvie, Astra Zeneca, GSK, HAL, Medscape, Menarini/Faes Farma, Mylan, Novartis, Nutricia, OM Pharma, and Regeneron/Sanofi. Also, he has received research support from Capricare, Nestle, Numil, REG, Vianex. BVB received research funding from Nutricia, consulting or speaker's fees from Vinimini, Nestlé, and Nutricia.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Gregorio P. Milani https://orcid.org/0000-0003-3829-4254
George N. Konstantinou https://orcid.org/0000-0003-1371-6764
Nikolaos G. Papadopoulos https://orcid.org/0000-0002-4448-3468
Inger Kull https://orcid.org/0000-0001-6096-3771
Giulia C. I. Spolidoro https://orcid.org/0000-0002-3365-1171
Berber Vlieg Broerstra https://orcid.org/0000-0001-7962-5406
Carina Venter https://orcid.org/0000-0002-7473-5355
Liam O'Mahony https://orcid.org/0000-0003-4705-3583

REFERENCES

1. Um S, Vang D, Pin P, Chau D. Trends and determinants of acute respiratory infection symptoms among under-five children in Cambodia: analysis of 2000 to 2014 Cambodia demographic and health surveys. *PLOS Glob Public Health*. 2023;3(5):e0001440.
2. WHO. Child mortality (under 5 years). 2022. https://www.who.int/news-room/fact-sheets/detail/levels-and-trends-in-child-under-5-mortality-in-2020
3. Schot MJC, Dekker ARJ, van Werkhoven CH, et al. Burden of disease in children with respiratory tract infections in primary care: diary-based cohort study. *Fam Pract*. 2019;36(6):723-729.
4. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet*. 2022;399(10340):2047-2064.
5. Millward DJ. Nutrition, infection and stunting: the roles of deficiencies of individual nutrients and foods, and of inflammation, as determinants of reduced linear growth of children. *Nutr Res Rev*. 2017;30(1):50-72.
6. Childs CE, Calder PC, Miles EA. Diet and immune function. *Nutrients*. 2019;11(8):1933.
7. Morais AHA, Aquino JS, da Silva-Maia JK, Vale SHL, Maciel BLL, Passos TS. Nutritional status, diet and viral respiratory infections: perspectives for severe acute respiratory syndrome coronavirus 2. *Br J Nutr*. 2021;125(8):851-862.
8. Pecora F, Persico F, Argentiero A, Neglia C, Esposito S. The role of micronutrients in support of the immune response against viral infections. *Nutrients*. 2020;12(10):3198.
9. Guarino A, Bruzzese E, Lo Vecchio A, Dagan R, Tsolia M. Definitions and outcomes of nutritional interventions in children with respiratory infections: the approach of the COMMENT initiative. *Ann Nutr Metab*. 2013;63(3):248-255.
10. van der Gaag EJ, Hummel TZ. Food or medication? The therapeutic effects of food on the duration and incidence of upper respiratory tract infections: a review of the literature. *Crit Rev Food Sci Nutr*. 2021;61(16):2691-2704.
11. Milani GP, Macchi M, Guz-Mark A. Vitamin C in the treatment of COVID-19. *Nutrients*. 2021;13(4):1172.
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *PLoS Med*. 2021;18(3):e1003583.
13. Vlieg-Boerstra B, de Jong N, Meyer R, et al. Nutrient supplementation for prevention of viral respiratory tract infections in healthy subjects: a systematic review and meta-analysis. *Allergy*. 2021;77:1373-1388.
14. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210.
15. World Bank. New World Bank country classifications by income level: 2022–2023. 2022-2023.
16. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. *Doing Meta-Analysis with R: A Hands-on Guide*. 1st ed. Chapman & Hall/CRC Press; 2021.
17. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27(6):1785-1805.
18. Shi J, Luo D, Weng H, et al. Optimally estimating the sample standard deviation from the five-number summary. *Res Synth Methods*. 2020;11(5):641-654.
19. Kjolhede CL, Chew FJ, Gadomski AM, Marroquin DP. Clinical trial of vitamin a as adjuvant treatment for lower respiratory tract infections. *J Pediatr*. 1995;126(5 Pt 1):807-812.
20. Dowell SF, Papic Z, Bresee JS, et al. Treatment of respiratory syncytial virus infection with vitamin A: a randomized, placebo-controlled trial in Santiago, Chile. *Pediatr Infect Dis J*. 1996;15(9):782-786.
21. Nacul LC, Kirkwood BR, Arthur P, Morris SS, Magalhães M, Fink MC. Randomised, double blind, placebo controlled clinical trial of efficacy of vitamin a treatment in non-measles childhood pneumonia. *BMJ*. 1997;315(7107):505-510.
22. Si NV, Grytter C, Vy NN, Hue NB, Pedersen FK. High dose vitamin a supplementation in the course of pneumonia in Vietnamese children. *Acta Paediatr*. 1997;86(10):1052-1055.
23. Fawzi WW, Mbise RL, Fataki MR, et al. Vitamin a supplementation and severity of pneumonia in children admitted to the hospital in Dar es Salaam, Tanzania. *Am J Clin Nutr*. 1998;68(1):187-192.
24. Stephensen CB, Franchi LM, Hernandez H, Campos M, Gilman RH, Alvarez JO. Adverse effects of high-dose vitamin a supplements in children hospitalized with pneumonia. *Pediatrics*. 1998;101(5):E3.
25. Julien MR, Gomes A, Varandas L, et al. A randomized, double-blind, placebo-controlled clinical trial of vitamin a in Mozambican children hospitalized with nonmeasles acute lower respiratory tract infections. *Trop Med Int Health*. 1999;4(12):794-800.
26. Brooks WA, Yunus M, Santosham M, et al. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. *Lancet*. 2004;363(9422):1683-1688.
27. Mahalanabis D, Lahiri M, Paul D, et al. Randomized, double-blind, placebo-controlled clinical trial of the efficacy of treatment with zinc or vitamin a in infants and young children with severe acute lower respiratory infection. *Am J Clin Nutr*. 2004;79(3):430-436.
28. Rodríguez A, Hamer DH, Rivera J, et al. Effects of moderate doses of vitamin a as an adjunct to the treatment of pneumonia in underweight and normal-weight children: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2005;82(5):1090-1096.
29. Bose A, Coles CL, Gunavathi, et al. Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2 y old. *Am J Clin Nutr*. 2006;83(5):1089-1096. quiz 1207.
30. Chang AB, Torzillo PJ, Boyce NC, et al. Zinc and vitamin a supplementation in indigenous Australian children hospitalised with lower

respiratory tract infection: a randomised controlled trial. *Med J Aust*. 2006;184(3):107-112.
31. Mahalanabis D, Basak M, Paul D, et al. Antioxidant vitamins E and C as adjunct therapy of severe acute lower-respiratory infection in infants and young children: a randomized controlled trial. *Eur J Clin Nutr*. 2006;60(5):673-680.
32. Coles CL, Bose A, Moses PD, et al. Infectious etiology modifies the treatment effect of zinc in severe pneumonia. *Am J Clin Nutr*. 2007;86(2):397-403.
33. Manaseki-Holland S, Qader G, Isaq Masher M, et al. Effects of vitamin D supplementation to children diagnosed with pneumonia in Kabul: a randomised controlled trial. *Trop Med Int Health*. 2010;15(10):1148-1155.
34. Mda S, van Raaij JM, de Villiers FP, MacIntyre UE, Kok FJ. Short-term micronutrient supplementation reduces the duration of pneumonia and diarrheal episodes in HIV-infected children. *J Nutr*. 2010;140(5):969-974.
35. Valentiner-Branth P, Shrestha PS, Chandyo RK, et al. A randomized controlled trial of the effect of zinc as adjuvant therapy in children 2-35 mo of age with severe or nonsevere pneumonia in Bhaktapur, Nepal. *Am J Clin Nutr*. 2010;91(6):1667-1674.
36. Bansal A, Parmar VR, Basu S, et al. Zinc supplementation in severe acute lower respiratory tract infection in children: a triple-blind randomized placebo controlled trial. *Indian J Pediatr*. 2011;78(1):33-37.
37. Ganguly A, Chakraborty S, Datta K, Hazra A, Datta S, Chakraborty J. A randomized controlled trial of oral zinc in acute pneumonia in children aged between 2 months to 5 years. *Indian J Pediatr*. 2011;78(9):1085-1090.
38. Valavi E, Hakimzadeh M, Shamsizadeh A, Aminzadeh M, Alghasi A. The efficacy of zinc supplementation on outcome of children with severe pneumonia. A randomized double-blind placebo-controlled clinical trial. *Indian J Pediatr*. 2011;78(9):1079-1084.
39. Basnet S, Shrestha PS, Sharma A, et al. A randomized controlled trial of zinc as adjuvant therapy for severe pneumonia in young children. *Pediatrics*. 2012;129(4):701-708.
40. Choudhary N, Gupta P. Vitamin D supplementation for severe pneumonia—a randomized controlled trial. *Indian Pediatr*. 2012;49(6):449-454.
41. Shah GS, Dutta AK, Shah D, Mishra OP. Role of zinc in severe pneumonia: a randomized double bind placebo controlled study. *Ital J Pediatr*. 2012;38:36.
42. Srinivasan MG, Ndeezi G, Mboijana CK, et al. Zinc adjunct therapy reduces case fatality in severe childhood pneumonia: a randomized double blind placebo-controlled trial. *BMC Med*. 2012;10:14.
43. Wadhwa N, Chandran A, Aneja S, et al. Efficacy of zinc given as an adjunct in the treatment of severe and very severe pneumonia in hospitalized children 2-24 mo of age: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2013;97(6):1387-1394.
44. Fataki MR, Kisenge RR, Sudfeld CR, et al. Effect of zinc supplementation on duration of hospitalization in Tanzanian children presenting with acute pneumonia. *J Trop Pediatr*. 2014;60(2):104-111.
45. Qasemzadeh MJ, Fathi M, Tashvighi M, et al. The effect of adjuvant zinc therapy on recovery from pneumonia in hospitalized children: a double-blind randomized controlled trial. *Scientifica (Cairo)*. 2014;2014:694193.
46. Sempértegui F, Estrella B, Rodríguez O, et al. Zinc as an adjunct to the treatment of severe pneumonia in Ecuadorian children: a randomized controlled trial. *Am J Clin Nutr*. 2014;99(3):497-505.
47. Ayub MR, Rashid N, Akbar N. Role of zinc supplementation in treatment of pneumonia. *Pakistan J Medical Health Sci*. 2015;9(3):1110-1112.
48. Manohar B, Sasi Kumar B, Krishna B, et al. Role of zinc in severe pneumonia. *Res J Pharm Biol Chem Sci*. 2015;6(3):612-617.
49. Shehzad N, Anwar MI, Muqaddas T. Zinc supplementation for the treatment of severe pneumonia in hospitalized children: a randomized controlled trial. *Sudan J Paediatr*. 2015;15(1):37-41.
50. Gupta P, Dewan P, Shah D, et al. Vitamin D supplementation for treatment and prevention of pneumonia in under-five children: a randomized double-blind placebo controlled trial. *Indian Pediatr*. 2016;53(11):967-976.
51. Yuan X, Qian SY, Li Z, Zhang ZZ. Effect of zinc supplementation on infants with severe pneumonia. *World J Pediatr*. 2016;12(2):166-169.
52. Somnath SH, Biswal N, Chandrasekaran V, Jagadisan B, Bobby Z. Therapeutic effect of vitamin D in acute lower respiratory infection: a randomized controlled trial. *Clin Nutr ESPEN*. 2017;20:24-28.
53. Bagri NK, Bagri N, Jana M, et al. Efficacy of Oral zinc supplementation in radiologically confirmed pneumonia: secondary analysis of a randomized controlled trial. *J Trop Pediatr*. 2018;64(2):110-117.
54. Baruah A, Saikia H. Effect of zinc supplementation in children with severe pneumonia: a randomised controlled study. *J Clin Diagn Res*. 2018;12(11):SC08-SC11.
55. Howie S, Bottomley C, Chimah O, et al. Zinc as an adjunct therapy in the management of severe pneumonia among Gambian children: randomized controlled trial. *J Glob Health*. 2018;8(1):10418.
56. Acevedo-Murillo JA, García León ML, Firo-Reyes V, Santiago-Cordova JL, Gonzalez-Rodriguez AP, Wong-Chew RM. Zinc supplementation promotes a Th1 response and improves clinical symptoms in fewer hours in children with pneumonia younger than 5 years old. A randomized controlled clinical trial. *Front Pediatr*. 2019;7:431.
57. Laghari GS, Hussain Z, Taimur M, Jamil N. Therapeutic role of zinc supplementation in children hospitalized with pneumonia. *Cureus*. 2019;11(4):e4475.
58. Rerksuppaphol S, Rerksuppaphol L. A randomized controlled trial of zinc supplementation in the treatment of acute respiratory tract infection in Thai children. *Pediatr Rep*. 2019;11(2):7954.
59. Rerksuppaphol L, Rerksuppaphol S. Efficacy of adjunctive zinc in improving the treatment outcomes in hospitalized children with pneumonia: a randomized controlled trial. *J Trop Pediatr*. 2020;66(4):419-427.
60. Binesh S, Keykhosravi A, Nematshahi M, Akbarian MJ, Sani SMR. Synbiotic or zinc supplementation in the treatment of children with bacterial pneumonia, a double-blinded randomized clinical trial. *Int J Pediatr*. 2021;9(12):15029-15046.
61. Chowdhury F, Shahid A, Tabassum M, et al. Vitamin D supplementation among Bangladeshi children under-five years of age hospitalised for severe pneumonia: a randomised placebo controlled trial. *PLoS One*. 2021;16(2):e0246460.
62. Hashemian H, Heidarzadeh A. Role of vitamin D 25(OH)D deficiency in development of pneumonia in children. *Arch Pediatr Infect Dis*. 2017;5(3):e57276.
63. Labib JR, Ibrahem SK, Ismail MM, et al. Vitamin D supplementation and improvement of pneumonic children at a tertiary pediatric hospital in Egypt: a randomized controlled trial. *Medicine (Baltimore)*. 2021;100(13):e25011.
64. Maya-Barrios A, Lira-Hernandez K, Jiménez-Escobar I, et al. Limosilactobacillus reuteri ATCC PTA 5289 and DSM 17938 as adjuvants to improve evolution of pharyngitis/tonsillitis in children: randomised controlled trial. *Benef Microbes*. 2021;12(2):137-145.
65. Ahmad MK, Murari K, Ranjan R. Randomized clinical assessment of Synbiotic or zinc supplementation in the treatment of children with bacterial pneumonia. *Int J Pharm Clin*. 2022;14(10):321-328.
66. Khoshnevisasl P, Sadeghzadeh M, Kamali K, Ardalani A. A randomized clinical trial to assess the effect of zinc and vitamin D supplementation in addition to hypertonic saline on treatment of acute bronchiolitis. *BMC Infect Dis*. 2022;22(1):538.
67. Mageswary MU, Ang XY, Lee BK, et al. Probiotic Bifidobacterium lactis Probio-M8 treated and prevented acute RTI, reduced antibiotic use and hospital stay in hospitalized young children: a randomized, double-blind, placebo-controlled study. *Eur J Nutr*. 2022;61(3):1679-1691.

68. Saied A, El Borolossy RM, Ramzy MA, Sabri NA. Effect of zinc versus vitamin a supplementation on pediatric patients with community-acquired pneumonia. *Front Pharmacol*. 2022;13:933998.
69. Brown N, Kukka AJ, Mårtensson A. Efficacy of zinc as adjunctive pneumonia treatment in children aged 2 to 60 months in low-income and middle-income countries: a systematic review and meta-analysis. *BMJ Paediatr Open*. 2020;4(1):e000662.
70. Tie HT, Tan Q, Luo MZ, Li Q, Yu JL, Wu QC. Zinc as an adjunct to antibiotics for the treatment of severe pneumonia in children <5 years: a meta-analysis of randomised-controlled trials. *Br J Nutr*. 2016;115(5):807-816.
71. Wahab S, Almaghaslah D, Mahmood SE, et al. Pharmacological efficacy of probiotics in respiratory viral infections: a comprehensive review. *J Pers Med*. 2022;12(8):1292.
72. Rueda-Robles A, Rodríguez-Lara A, Meyers MS, Sáez-Lara MJ, Álvarez-Mercado AI. Effect of probiotics on host-microbiota in bacterial infections. *Pathogens*. 2022;11(9):986.
73. Wiertsema SP, van Bergenhenegouwen J, Garssen J, Knippels LMJ. The interplay between the gut microbiome and the immune system in the context of infectious diseases throughout life and the role of nutrition in optimizing treatment strategies. *Nutrients*. 2021;13(3):886.
74. Karagiannis F, Peukert K, Surace L, et al. Impaired ketogenesis ties metabolism to T cell dysfunction in COVID-19. *Nature*. 2022;609(7928):801-807.
75. Wang Y, Chi H. Fasting as key tone for COVID immunity. *Nat Metab*. 2022;4(10):1229-1231.
76. Horne BD, Bunker T. Pathogenic mechanisms of the severe acute respiratory syndrome coronavirus 2 and potential direct and indirect counteractions by intermittent fasting. *Nutrients*. 2022;15(1):20.
77. de Cosmi V, Mazzocchi A, Turolo S, Syren ML, Milani GP, Agostoni C. Long-chain polyunsaturated fatty acids supplementation and respiratory infections. *Ann Nutr Metab*. 2022;1-8:8-15.
78. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5):e1474-e1502.
79. Manti S, Staiano A, Orfeo L, et al. UPDATE – 2022 Italian guidelines on the management of bronchiolitis in infants. *Ital J Pediatr*. 2023;49(1):19.
80. Saengnipanthkul S, Chongviriyaphan N, Densupsoontorn N, et al. Hospital-acquired malnutrition in paediatric patients: a multicentre trial focusing on prevalence, risk factors, and impact on clinical outcomes. *Eur J Pediatr*. 2021;180(6):1761-1767.
81. Vlieg-Boerstra B, Groetch M, Vassilopoulou E, et al. The immune-supportive diet in allergy management: a narrative review and proposal. *Allergy*. 2023;78(6):1441-1458.
82. Venter C, Meyer RW, Greenhawt M, et al. Role of dietary fiber in promoting immune health-an EAACI position paper. *Allergy*. 2022;77(11):3185-3198.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Milani GP, Alberti I, Abodi M, et al. A systematic review and meta-analysis on nutritional and dietary interventions for the treatment of acute respiratory infection in pediatric patients: An EAACI taskforce. *Allergy*. 2024;00:1-21. doi:10.1111/all.15997