Routine antibiotics for infants less than 6 months of age with growth failure/faltering: a systematic review

Aamer Imdad, Fanny F Chen, Melissa François, Momal Sana, Emily Tanner-Smith, Abigail Smith, Olivia Tsistinas, Jai K Das, Zulfiquar Ahmed Bhutta

ABSTRACT

Objective This systematic review commissioned by WHO aimed to synthesise evidence from current literature on the effects of systemically given, routine use of antibiotics for infants under 6 months of age with growth failure/faltering.

Settings Low-income and middle-income countries.

Participants The study population was infants less than 6 months of age with growth failure/faltering.

Intervention The intervention group was infants who received no antibiotics or antibiotics other than those recommended in 2013 guidelines by WHO to treat childhood severe acute malnutrition. The comparison group was infants who received antibiotics according to the aforementioned guidelines.

Primary and secondary outcomes The primary outcome was all-cause mortality, and secondary outcomes: clinical deterioration, antimicrobial resistance, recovery from comorbidity, adverse events, markers of intestinal inflammation, markers of systemic inflammation, hospital-acquired infections and non-response. The Grading of Recommendations Assessment, Development and Evaluation approach was considered to report the overall evidence quality for an outcome.

Results We screened 5137 titles and abstracts and reviewed the full text of 157 studies. None of the studies from the literature search qualified to answer the question for this systematic review.

Conclusions There is a paucity of evidence on the routine use of antibiotics for the treatment of malnutrition in infants less than 6 months of age. Future studies with adequate sample sizes are needed to assess the potential risks and benefits of antibiotics in malnourished infants under 6 months of age.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This WHO funded systematic review was conducted by following the standard methods of Cochrane Collaboration.

⇒ Even though data were available for the use of antibiotics in severely malnourished children 6–59 months of age, no randomised trials were found in infants less than 6 months of age.

⇒ The work was limited due to a lack of studies in this age group. Future studies with large sample size are needed to assess the efficacy and safety of antibiotics in malnourished infants less than 6 months of age.

INTRODUCTION

The WHO and the UNICEF estimate that nearly 14 million children suffer from severe wasting (low weight for height) worldwide. Infants less than 6 months of age are particularly vulnerable to the effects of inadequate nutrition. Higher mortality rates secondary to growth failure are seen in this age group compared with older infants and children. Despite excess mortality risk and increasing prevalence of wasting in this population, limited studies exist to guide the management of young infants with growth failure and faltering.

Malnutrition in children increases the risk of severe infections and triples the mortality risk from pneumonia, measles or diarrhoea. Therefore, the current practice for children 6 months to 5 years of age with wasting is to prescribe routine antibiotics when they get into a nutrition programme, inpatient or outpatient. However, current recommendations state that the same general medical care should be used for infants with severe acute malnutrition (SAM) who are less than 6 months of age as infants above 6 months of age, even though there is limited evidence to support this recommendation. Furthermore, even though antibiotics are effective in children 6–59 months of age with SAM, this practice in infants has the potential to harm due to recently identified risks of antibiotic use in infancy, including the diminishment of infant gut microbiome, future development of obesity, allergic disorders and autoimmune disorders. The urgency in more targeted management guidelines is further underscored by the physiological differences in renal and gastrointestinal function.
in infants compared with older children.\textsuperscript{8} The WHO recently started the guideline development process for preventing and treating wasting in children, including growth failure/faltering in infants under 6 months. This systematic review aimed to synthesise evidence from current literature on the effect of systematically given, routine use of antibiotics for infants less than 6 months of age with growth failure/faltering.

**OBJECTIVE**

**Primary objective**

In infants <6 months with growth failure/faltering, what are the effects of no routine antibiotics or different approaches (eg, types of antibiotics, doses) compared with routine antibiotics following treatment protocols in 2013 WHO guidelines\textsuperscript{2} on the morbidity and mortality outcomes?

**METHODS AND ANALYSIS**

This systematic review was conducted according to methods described in Cochrane Handbook\textsuperscript{9} and reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines 2020.\textsuperscript{10}

**Types of studies**

We considered both individual and cluster randomised trials. We also considered non-randomised trials and cohort studies with a controlled arm. We excluded case–control studies, case reports, case series and commentaries.

**Population**

The population of interest was infants under 6 months of age with growth failure/faltering. We considered the author’s definitions because this age group has no standard definition of growth failure/faltering. We considered studies irrespective of whether they were done in community or hospital settings. We considered studies that included infants infected with HIV. We considered studies with low birth weight or preterm infants; however, we excluded studies on infants admitted to neonatal intensive care units. We excluded studies that only included infants with congenital anomalies.

**Intervention**

We considered all antibiotic treatments given systematically, such as amoxicillin, Augmentin, cephalosporins and macrolides. We considered studies irrespective of dosage, frequency, duration or route of administration; however, topical application of antibiotics was not considered. We considered studies if antibiotics were given empirically at the time of diagnosis of growth failure or faltering, irrespective of the indication, for example, to treat an infection. We excluded studies where antibiotics were given for other reasons, such as suspected serious bacterial infections in otherwise healthy infants, specifically non-malnourished children or infants with no growth failure/faltering. We excluded studies where antibiotics were given for other reasons, such as suspected serious bacterial infections in otherwise healthy infants, specifically non-malnourished children or infants with no growth failure/faltering.

**Comparison**

The comparison group was routine antibiotics following treatment protocols detailed in the 2013 WHO guideline.\textsuperscript{2}

**Outcomes**

- Mortality (dichotomous outcome).
- Clinical deterioration (dichotomous outcome, defined by the development of any danger signs (obstructed breathing, respiratory distress, cyanosis, shock, severe anaemia, convulsion, severe dehydration, profuse watery diarrhoea, intractable vomiting and/or impaired consciousness)).
- Recovery from comorbidity (dichotomous outcome).
- Markers of intestinal inflammation-faecal calprotectin (continuous outcome).
- Markers of systemic inflammation-serum C reactive protein (continuous outcome).
- Hospital-acquired infections (dichotomous outcome).
- Non-response (eg, not achieving recovery within 4 months of initiating treatment) (dichotomous outcome).

All the primary analyses were considered at the longest follow-up. For the outcome of recovery from morbidity, the recovery could be recovery from diarrhoea, pneumonia, measles, etc.

**LITERATURE SEARCH**

We conducted systematic electronic queries using key terms in multiple databases, including MEDLINE via PubMed, EMBASE, Web of Science, CINAHL, Scopus, LILACS, WHO Global Index Medicus and BIOSIS Previews. There were no search restrictions on outcomes, publication year, publication status or publication language. The search strategies for different databases are available in online supplemental appendix 1. The references of formerly published reviews and recently published studies were examined for potential inclusion. We also used The Cochrane Central Register for Controlled Trials and ISRCTN registry to identify studies currently underway. We also searched the websites of pertinent international agencies such as the WHO (including WHO’s Reproductive Health Library, electronic Library of Evidence of Nutrition Actions and Global database on the Implementation of Nutrition Action), UNICEF, Global Alliance for Improved Nutrition, International Food Policy Research Institute, International Initiative for Impact Evaluation, Nutrition International, World Bank, USAID and affiliates (eg, FANTA, SPRING) and the World Food Programme. We searched the abstracts of major conferences, such as annual paediatric academic society meetings. Finally, we used the citation tracking
function of the included studies in PubMed to look for any other eligible studies.

**DATA EXTRACTION AND SYNTHESIS**

**Selection of studies**

Studies identified during the literature search were collected in an electronic reference manager EndNote\textsuperscript{11} literature, and duplicated studies were removed. At least two authors screened study titles and abstracts to assess potential eligibility. Studies selected during this initial phase underwent a full-text review by two authors. The software Covidence\textsuperscript{12} was used during the screening process. Disagreements were resolved by discussion, and the senior author on the team assisted as needed.

**Data extraction**

We planned to extract the data for study region/country, study year, study type, intervention exposure (dose, duration, frequency), comparison, outcomes, population characteristics detailed in subgroup analysis and risk of bias. We also planned to extract information on the intervention’s feasibility, acceptability, equity, and resource use and reported these data in separate tables. We planned to remove raw values for the number of events in the intervention and control group in case of dichotomous outcomes. To avoid reviewer bias, we decided a priori the order of preference for extracting outcomes when data were available in several formats.

**Studies with missing data**

If a study was only available in an abstract, we contacted the authors for full text. If the full text could not be obtained from any sources, we considered the abstract if sufficient details of the study design and outcomes were available. We attempted to find the protocol of each potentially included study to assess the details of the methods. If the study protocol was not publicly available, we contacted the authors for the same. If the randomised trial results were published in more than one report, we considered all the publications related to that study as one study.

**Assessment of risk of bias in included studies**

We aimed to evaluate the risk of bias from randomised controlled trials with the Cochrane risk of bias (ROB 2.0).\textsuperscript{13} The risk of bias assessment according to ROB-2 is done for each outcome, not for a particular study.\textsuperscript{13}

**Data synthesis**

We planned to report the review findings both qualitatively and quantitatively. A narrative synthesis was considered to report all included studies’ characteristics and results. A random-effects meta-analysis was planned when at least two studies possessed sufficient clinical and methodological uniformity for synthesis. The software RevMan was considered for statistical analysis.\textsuperscript{14} We planned to assess the dichotomous outcomes using relative risk effect sizes and continuous outcomes with a mean difference and report with 95% CIs.

**Assessment of heterogeneity**

We aimed to analyse statistical heterogeneity in the pooled data using $\tau^2$, $\chi^2$, and $I^2$ statistics. We also aimed to assess statistical heterogeneity through visual inspection of forest plots, using the $\chi^2$ test (assessing the p value) and calculating the $\tau^2$ and $I^2$ statistics. We considered it significant statistical heterogeneity when the p value was less than 0.1, the $I^2$ value exceeded 50%, and the inspection of forest plots showed substantial variability in the effect of the intervention. Finally, we considered subgroup analysis to identify reasons for eligible statistical heterogeneity.

**Assessment of reporting bias**

We aimed to assess the publication bias of small studies using funnel plots and regression tests for funnel plot asymmetry when the meta-analysis included at least 10 studies.

**Subgroup analysis and investigation of heterogeneity**

We planned the following subgroup analysis; however, none were possible due to a lack of studies.

- By different types/definitions of growth failure/faltering.
- Age at presentation (newborn (0–28 days), 1–3 months, 4–6 months).
- Gestational age: preterm birth (<37 weeks) versus full-term birth (>37 weeks).
- Birth weight: low birth weight (<2500g) versus normal birth weight (>2500g).
- HIV exposure: studies with participants exposed to HIV versus studies with no HIV exposure.
- Presentation: participants with oedema versus participants with no oedema.
- Comorbidities: with or without comorbidities.
- Nutrition: babies breast feeding or non-breastfed babies.
- Location of the treatment: inpatient or outpatient/community.
- Dose of antibiotics.
- Duration of antibiotics: 7 days versus >7 days.
- Type of antibiotics.

**Sensitivity analysis**

We planned to complete sensitivity analysis by the use of the model for meta-analysis.

**Rating of overall quality of evidence**

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was considered to evaluate the overall certainty of evidence using the software GRADEpro.\textsuperscript{15} The GRADE approach is a comprehensive framework used to assess the overall certainty of the evidence for an outcome using study characteristics such as study design, inconsistency, indirectness of evidence, risk of bias, publication bias and imprecision estimates.
Patient and public involvement
Patients and/or the public were not involved in this research’s design, conduct, reporting or dissemination plans.

RESULTS

Literature search
We screened 5137 titles and abstracts; 157 eligible studies were screened for full-text reviews. None of the available studies qualified for inclusion in this review. Figure 1 shows the results of the literature search. The reasons for exclusions are available in the table of excluded studies (online supplemental document 1). In summary, 85 studies were excluded because of wrong study design, 55 were excluded due to ineligible patient population, 7 were excluded because of the ineligible comparison group, 8 were excluded because of ineligible intervention and 2 studies were excluded because of wrong indication.

DISCUSSION
This systematic review aimed to assess the effect of routine use of antibiotics for the treatment of malnutrition in infants less than 6 months of age. Even though we reviewed more than 4000 titles and about 157 full-text studies, none of the studies qualified for inclusion in this review. The three key reasons to publish this work are to document our study question, to report the methodology transparently in enough detail so that it can be replicated in the future as needed, and to highlight the key gaps in research so that the research investigator can design studies for infants <6 months with malnutrition as the mortality risk is the highest due to malnutrition in this age group.

We followed the methodology of the Cochrane Collaboration to conduct this systematic review. A detailed protocol was prepared before the review process and was externally reviewed and registered publicly on PROSPERO’s international database of prospective systematic reviews. The title and abstracts of the studies were screened independently by two study authors. We planned
to study the risk of bias using the revised Cochrane risk of bias 2.0 tool for each outcome within a study rather than determining the risk of bias based on all outcomes for a particular study. However, no eligible study was found to answer the clinical question in this review.

We noted two studies of great interest to our population of interest.16,17 These studies were excluded because of the lack of a comparison group treated with antibiotics according to the current guideline of the WHO for treating wasting.2 Both the studies included participants that fall in the age range (ie, <6 months) considered for this review; however, they also included participants beyond 6 months of age.16,17 Both studies were randomised, double-blind, placebo-controlled trials. One study was conducted in Kenya16 and another study was a multicounty trial.17 The study from Kenya16 used co-trimoxazole in the community settings to prevent mortality in severely malnourished children 2–59 months of age after being treated according to WHO protocol (both groups received antibiotics according to WHO protocol during the stabilisation period). Daily co-trimoxazole after initial treatment for severe malnutrition did not prevent mortality in children 2–59 months of age (HR 0.90, 95% CI 0.71 to 1.16). The results for infants 2 months to 5 months of age were similar to overall results.16 The other study used biannual azithromycin in children 1–59 months of age irrespective of nutritional status17 and showed a 13.5% reduction in mortality in the azithromycin group compared with placebo. A subgroup analysis for malnourished children showed similar results.16 Two other studies could have been included; however, both included both nourished and malnourished participants, and we could not obtain the randomised data for our population of interest.19,20 We also identified a recently completed trial21 and requested the data for inclusion in this review; however, study investigators were submitting their results to a peer-review journal and are not yet willing to share those data.

Implications for research
Future randomised studies, with adequate sample size of infants under 6 months with malnutrition and/or growth faltering, are needed to confirm the therapeutic effect of antibiotic treatment observed in children 6–59 months of age.2 Additional data are also required to assess the appropriate antibiotic, dose, route, frequency and duration of antibiotic treatment. The safety profile regarding acute reactions, such as allergic reactions, gastrointestinal disturbance, etc, and long-term effects, such as effects on the gut microbiome and antibiotic resistance, also need further investigation.

CONCLUSIONS
There is a paucity of evidence to assess the effect of routine use of antibiotics in infants less than 6 months of age with malnutrition. Future studies with large sample sizes are needed to evaluate the potential risks and benefits of antibiotics in malnourished children under 6 months of age.

Acknowledgements We are very thankful to Allison Daniel, Jaden Bendabanda and Zita Weise Prinzio, Kirrily De Polnay for their input in improving this review.

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Disclaimer We conducted literature searches, screening of titles, selection of studies, data extraction, and analysis according to the plan outlined in the protocol.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. We provide the list of excluded studies and our search strategies. The results of the literature search are available on request.

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Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. We provide the list of excluded studies and our search strategies. The results of the literature search are available on request.

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Appendix 1
Search Strategies for Growth Failure AND Antibiotics

PubMed

"infant*"[Title/Abstract] OR "infancy"[Title/Abstract] OR "baby"[Title/Abstract] OR 
"babies"[Title/Abstract] OR "neonat*"[Title/Abstract] OR "neo nat*"[Title/Abstract] OR 
"newborn*"[Title/Abstract] OR "newly born*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "preterms"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre
terms"[Title/Abstract] OR "low"[Title/Abstract] AND "birthweight*"[Title/Abstract] OR "birth 
weight*"[Title/Abstract]))) AND ("Malnutrition"[MeSH Terms] OR "Failure to Thrive"[MeSH Terms] 
OR "Growth Disorders"[MeSH Terms:noexp] OR "Severe Acute 
Malnutrition"[MeSH Terms] OR "Wasting Syndrome"[MeSH Terms:noexp] OR "Infant Nutrition 
Disorders"[MeSH Terms] OR 
"growth failure*"[Title/Abstract] OR "growth falter*"[Title/Abstract] OR "slow 
growth"[Title/Abstract] OR "slowed growth"[Title/Abstract] OR 
"Malnutrition"[Title/Abstract] OR "malnourish*"[Title/Abstract] OR "Severe Acute 
Malnutrition"[Title/Abstract] OR "SAM"[Title/Abstract] OR "wasting"[Title/Abstract] OR 
"wasted"[Title/Abstract] OR "growth restrict*"[Title/Abstract] OR "growth retard*"[Title/Abstract] 
OR "Failure to Thrive"[Title/Abstract]
OR "FTT" OR growth disorder* OR growth arrest* OR growth deficien* OR growth disturb* AND (Anti-Bacterial Agents OR Anti-Bacterial Agents [Pharmacological Action] OR Antibiotic* OR anti bacterial agent* OR antibacterial* OR bactericid* OR bacteriocid* OR antimycobacterial* OR antimycobacterial*) NOT (Animals [MeSH Terms] NOT (Animals [MeSH Terms] AND Humans [MeSH Terms]))

CINAHL
S1 (MH Infant+)
S2 (MH Child+)
S3 (MH Childbirth, Premature+)
S4 TI (infant* OR infancy OR baby OR babies OR neonat* OR newborn* OR newly born* OR preterm OR preterms OR pre term OR pre terms OR lbw OR vlbw OR elbw OR child* OR youth OR juvenile*)
S5 AB (infant* OR infancy OR baby OR babies OR neonat* OR newborn* OR newly born* OR preterm OR preterms OR pres term OR pre terms OR lbw OR vlbw OR elbw OR child* OR youth OR juvenile*)
S6 TI (premature* N2 (birth* OR born OR deliver*))
S7 AB (premature* N2 (birth* OR born OR deliver*))
S8 TI (low N2 (birthweight* OR birth weight*))
S9 AB (low N2 (birthweight* OR birth weight*))
S10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9

S11 (MH Malnutrition+)
S12 (MH Failure to Thrive+)
S13 (MH "Growth Disorders")
S14 (MH "Wasting Syndrome")
S15 (MH “Infant Nutrition Disorders”)
S16 TI ((grow*) N2 (fail* OR falter* OR slow* OR restrict* OR retard* OR deficien* OR arrest* OR disturb* OR disorder*))
S17 AB ((grow*) N2 (fail* OR falter* OR slow* OR restrict* OR retard* OR deficien* OR arrest* OR disturb* OR disorder*))
S18 TI ((fail*) W2 (thrive))
S19 AB ((fail*) W2 (thrive))
S20 TI (Malnutrition OR malnourish* OR &quot;Severe Acute Malnutrition&quot; OR SAM OR wasting OR wasted OR FTT)
S21 AB (Malnutrition OR malnourish* OR &quot;Severe Acute Malnutrition&quot; OR SAM OR wasting OR wasted OR FTT)
S22 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
S23 (MH &quot;Antibiotics+&quot;)
S24 TI (antibiotic* OR &quot;anti bacterial*" OR "antibacterial*" OR bactericid* OR bacteriocid* OR &quot;anti mycobacterial*" OR "antimycobacterial*"
S25 AB (antibiotic* OR &quot;anti bacterial*" OR "antibacterial*" OR bactericid* OR bacteriocid* OR &quot;anti mycobacterial*" OR "antimycobacterial*)
S26 S23 OR S24 OR S25
S27 (MH &quot;Animals&quot;) NOT ((MH &quot;Animals&quot;) AND (MH &quot;Human&quot;))
S28 S10 AND S22 AND S26
S29 S28 NOT S27
S30 S28 NOT S27 Exclude Medline Records
Embase
#1&#39;infant&#39;/exp OR &#39;newborn&#39;/exp OR
&#39;prematurity&#39;/exp OR &quot;low birth weight&quot;/exp OR &quot;very low birth
weight/exp OR #39; extremely low birth weight/exp OR 
#39; juvenile/#39; de OR #39; child/#39; de
#2 infant*:ti,ab OR infancy:ti,ab OR baby:ti,ab OR babies:ti,ab OR neonatal*:ti,ab OR 
#39; neonatal*:ti,ab OR newborn*:ti,ab OR newborn*:ti,ab OR newly born*:ti,ab OR
#39; new born*:ti,ab OR newly born*:ti,ab OR preterm*:ti,ab OR preterms*:ti,ab OR
#39; preterm*:ti,ab OR pre term*:ti,ab OR pre terms*:ti,ab OR lbw:ti,ab OR
#39; vlbw:ti,ab OR elbw:ti,ab OR child*:ti,ab OR
#39; youth:ti,ab OR juvenile*:ti,ab
#3 (premature* NEAR/2 (birth* OR born OR deliver*)):ti,ab
#4 (low NEAR/2 (birthweight* OR & #39; birth weight* & #39;)):ti,ab
#5 #1 OR #2 OR #3 OR #4

#6 & #39; malnutrition/exp OR #39; failure to thrive/exp OR 
#39; growth disorder/exp OR #39; wasting syndrome/exp
OR #39; growth retardation/exp
#7 (grow* NEAR/2 (fail* OR falter* OR slow* OR restrict* OR retard* OR deficien*
OR arrest* OR disturb* OR disorder*)):ti,ab
#8 (fail* NEXT/2 thrive):ti,ab
#9 malnutrition:ti,ab OR malnourish*:ti,ab OR & #39; severe acute
malnutrition#:ti,ab OR sam:ti,ab OR wasting:ti,ab OR wasted:ti,ab OR ftt:ti,ab
#10 #6 OR #7 OR #8 OR #9
#11 & #39; antibiotic agent/exp OR #39; bactericide/exp
OR #39; antimycobacterial agent/exp
#12 antibiotic*:ti,ab OR #39; antibacterial*:ti,ab OR
#39; antibacterial*:ti,ab OR bactericide*:ti,ab OR bac
teriocid*:ti,ab OR antimycobacterial*:ti,ab OR & #39; anti
tuberculosis*:ti,ab
#13 #11 OR #12
#14 #5 AND #10 AND #13
#15 #14 NOT (& #39; animals & #39;):exp NOT & #39; humans & #39; /exp
#16 #15 NOT [medline]/lim
CENTRAL
#1 MeSH descriptor: [Infant] explode all trees
#2 MeSH descriptor: [Child] this term only
#3 MeSH descriptor: [Premature Birth] explode all trees
#4 infant*:ti,ab OR infancy:ti,ab OR baby:ti,ab OR babies:ti,ab OR neonat*:ti,ab OR newborn*:ti,ab OR preterm:ti,ab OR preterms:ti,ab OR lbw:ti,ab OR vlbw:ti,ab OR elbw:ti,ab OR child*:ti,ab OR youth:ti,ab OR juvenile*:ti,ab
#5 (neo NEXT nat* OR new NEXT born* OR newly NEXT born* OR pre NEXT term OR pre NEXT terms):ti,ab
#6 (premature* NEAR/2 (birth* OR born OR deliver*)):ti,ab
#7 (low NEAR/2 (birthweight* OR birth NEXT weight*)):ti,ab
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9 MeSH descriptor: [Malnutrition] explode all trees
#10 MeSH descriptor: [Failure to Thrive] explode all trees
#11 MeSH descriptor: [Growth Disorders] this term only
#12 MeSH descriptor: [Severe Acute Malnutrition] explode all trees
#13 MeSH descriptor: [Wasting Syndrome] this term only
#14 MeSH descriptor: [Infant Nutrition Disorders] this term only
#15 ((grow*) NEAR/2 (fail* OR falter* OR slow* OR restrict* OR retard* OR deficien* OR arrest* OR disturb* OR disorder*)):ti,ab
#16 ((fail*) NEXT/2 (thrive)):ti,ab
#17 (severe NEXT acute NEXT malnutrition):ti,ab
#18 malnutrition:ti,ab OR malnourish*:ti,ab OR sam:ti,ab OR wasting:ti,ab OR wasted:ti,ab OR ftt:ti,ab
#19 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#21 antibiotic*:ti,ab OR antibacterial*:ti,ab OR bactericid*:ti,ab OR bacteriocid*:ti,ab OR antimycobacterial*:ti,ab
#22 (anti NEXT bacterial*):ti,ab
#23 (anti NEXT mycobacterial*):ti,ab
#24 #20 OR #21 OR #22 OR #23
#25 #8 AND #19 AND #24
#26 MeSH descriptor: [Animals] explode all trees
#27 MeSH descriptor: [Humans] explode all trees
#28 (#26 NOT (#26 AND #27))
#29 #25 NOT #28
#30 "accession number" NEAR pubmed
#31 #29 NOT #30

**Scopus**

( ( TITLE-ABS ( infant* OR infancy OR baby OR babies OR neonat* OR &quot;neonat* OR newborn* OR &quot;new born* OR &quot;newly born* OR preterm OR preterms OR &quot;pre term&quot; OR &quot;pre terms&quot; OR lbw OR vlbw OR elbw OR child* OR youth OR juvenile* ) ) OR ( TITLE-ABS ( low W/2 ( birthweight* OR &quot;birth weight* &quot; ) ) ) OR ( TITLE-ABS ( premature* W/2 ( birth* OR born OR deliver* ) ) ) ) AND ( ( TITLE-ABS ( ( grow* ) W/2 ( fail* OR falter* OR slow* OR restrict* OR retard* OR deficien* OR arrest* OR disturb* OR disorder* ) ) ) OR ( TITLE-ABS ( ( fail* ) PRE/2 ( thrive ) ) ) OR ( TITLE-ABS ( malnutrition OR malnourish* OR &quot;Severe Acute Malnutrition&quot; OR sam OR wasting OR wasted OR ftt ) ) ) AND ( TITLE-ABS ( antibiotic* OR &quot;anti bacterial* OR &quot;antibacterial* &quot; OR bactericid* OR bacteriocid* OR &quot;anti mycobacterial* OR &quot;antimycobacterial* &quot; ) ) ) ) AND NOT INDEX ( med line )

**Web of Science**

#1 TI=(infant* OR infancy OR baby OR babies OR neonat* OR &quot;neonat* OR newborn* OR &quot;new born* OR &quot;newly born* OR preterm OR preterms OR &quot;pre term&quot; OR &quot;pre terms&quot; OR lbw OR vlbw OR elbw OR child* OR youth OR juvenile*)
#2 AB=(infant* OR infancy OR baby OR babies OR neonat* OR &quot;neonat* OR newborn* OR &quot;new born* OR &quot;newly born* OR preterm OR preterms OR &quot;pre term&quot; OR &quot;pre terms&quot; OR lbw OR vlbw OR elbw OR child* OR youth OR juvenile*)
#3 TI=(premature* NEAR/2 (birth* OR born OR deliver*))
#4 AB=(premature* NEAR/2 (birth* OR born OR deliver*))  
#5 TI=(low NEAR/2 (birthweight* OR &quot;birth weight&quot;))  
#6 AB=(low NEAR/2 (birthweight* OR &quot;birth weight&quot;))  
#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1  
#8 TI=((grow*) NEAR/2 (fail* OR falter* OR slow* OR restrict* OR retard* OR deficien* OR arrest* OR disturb* OR disorder*))  
#9 AB=((grow*) NEAR/2 (fail* OR falter* OR slow* OR restrict* OR retard* OR deficien* OR arrest* OR disturb* OR disorder*))  
#10 TI=((fail*) NEAR/2 (thrive))  
#11 AB=((fail*) NEAR/2 (thrive))  
#12 TI = (Malnutrition OR malnourish* OR &quot;Severe Acute Malnutrition&quot; OR SAM OR wasting OR wasted OR FTT)  
#13 AB=(Malnutrition OR malnourish* OR &quot;Severe Acute Malnutrition&quot; OR SAM OR wasting OR wasted OR FTT)  
#14 #13 OR #12 OR #11 OR #10 OR #9 OR #8  
#15 TI=(antibiotic* OR &quot;anti bacterial* OR &quot;antibacterial* OR bactericid* OR bacteriocid* OR &quot;anti mycobacterial* OR &quot;antimycobacterial* OR anti mycobacterial* &quot;anti mycobacterial* OR antimycobacterial*) OR #16 AB=(antibiotic* OR &quot;anti bacterial* OR &quot;antibacterial* OR bactericid* OR bacteriocid* OR &quot;anti mycobacterial* OR &quot;antimycobacterial* OR anti mycobacterial* &quot;anti mycobacterial* OR antimycobacterial*)  
#17 #16 OR #15  
#18 #17 AND #14 AND #7  

LILACS  
(mh:(infant)) OR ((mh:(child))) OR ((mh:(&quot;Premature Birth&quot;))) OR ((ti:((premature* AND (birth* OR born OR deliver*)))) OR ((ab:((premature* AND (birth* OR born OR deliver*)))))) OR ((ti:((low AND (birthweight* OR &quot;birth weight&quot;)))) OR ((ab:((low AND (birthweight* OR &quot;birth weight&quot;))))) OR ((ti:(infant* OR infancy OR baby OR babies OR neonat* OR &quot;neonat* &quot; OR newborn* OR &quot;newborn* &quot;) OR &quot;newborn* &quot;) OR &quot;newborn* &quot;)}
born* OR "newly born*" OR preterm OR preterms OR pre term* OR "new born*" OR lbw OR vlbw OR elbw OR child* OR youth OR juvenile*))) OR ((ab:(infant* OR infancy OR baby OR babies OR neonat* OR "neo nat*" OR newborn* OR "new born*" OR "newly born*" OR preterm OR preterms OR "pre term" OR "pre terms" OR lbw OR vlbw OR elbw OR child* OR youth OR juvenile*)) AND ((mh:(malnutrition)) OR ((mh:(&quot;Failure to Thrive&quot;)))) OR ((mh:(&quot;Growth Disorders&quot;))) OR ((mh:(&quot;Severe Acute Malnutrition&quot;))) OR ((mh:(&quot;Wasting Syndrome&quot;))) OR ((mh:(&quot;Infant Nutrition Disorders&quot;))) OR ((ti:(&quot;growth failure*&quot;) OR &quot;growth falter*" OR slow growth* OR &quot;slowed growth*" OR malnutrition OR malnourish* OR &quot;Severe Acute Malnutrition&quot; OR sam OR wasting OR wasted OR &quot;growth restrict*" OR &quot;growth retard*" OR Failure to Thrive* OR ftt OR &quot;growth disorder*" OR &quot;growth arrest*" OR &quot;growth deficien*" OR &quot;growth disturb*"))) OR ((ab:(&quot;growth failure*" OR &quot;growth falter*" OR &quot;slow growth*" OR &quot;slowed growth*" OR malnutrition OR malnourish* OR &quot;Severe Acute Malnutrition" OR sam OR wasting OR wasted OR &quot;growth restrict*" OR &quot;growth retard*" OR Failure to Thrive* OR ftt OR &quot;growth disorder*" OR &quot;growth arrest*" OR &quot;growth deficien*" OR &quot;growth disturb*"))) AND ((mh:(&quot;Anti-Bacterial Agents&quot;)) OR ((ti:(antibiotic* OR "anti bacterial agent*" OR antibacterial* OR &quot;anti bacterial*" OR bactericid* OR &quot;bactericid*" OR antimycobacterial*)))) AND NOT ((mh:(animals)) AND NOT ((mh:(animals)))
((mh:(humans))))
Global Index Medicus
(mh:(infant)) OR ((mh:(child))) OR ((mh:("Premature Birth"))) OR
((ti:((premature* AND (birth* OR born OR deliver*)))) OR ((ab:((premature* AND (birth* OR born OR deliver*)))))) OR
((ti:((low AND (birthweight* OR "birth weight*")))) OR ((ab:((low AND (birthweight* OR "birth weight*")))))) OR
((ti:((infant* OR infancy OR baby OR babies OR neonat* OR "neonat*" OR newborn* OR "new born*" OR "newly born*" OR preterm OR preterms OR OR newborn* OR &quot;new born* OR "newly born* OR preterm OR preterms OR OR lbw OR vlbw OR elbw OR child* OR youth OR juvenile*)))) OR ((ab:((infant* OR infancy OR baby OR babies OR neonat* OR "neonat*" OR newborn* OR "new born*" OR "newly born*" OR preterm OR preterms OR OR lbw OR vlbw OR elbw OR child* OR youth OR juvenile*)))) AND
((mh:(malnutrition)) OR ((mh:(&quot;Failure to Thrive&quot;)))) OR
((mh:(&quot;Growth Disorders&quot;))) OR ((mh:(&quot;Severe Acute Malnutrition&quot;))) OR ((mh:(&quot;Wasting Syndrome&quot;))) OR ((mh:(&quot;Infant Nutrition Disorders&quot;))) OR ((ti:(&quot;growth failure&quot; OR &quot;growth falter&quot; OR &quot;slow growth&quot; OR &quot;slowed growth&quot; OR &quot;growth restrict&quot; OR &quot;growth retard&quot; OR &quot;Failure to Thrive&quot; OR &quot;ftt&quot; OR &quot;growth disorder&quot; OR &quot;growth arrest&quot; OR &quot;growth deficien&quot; OR &quot;growth disturb&quot;))) OR ((ab:(&quot;growth failure&quot; OR &quot;growth falter&quot; OR &quot;slow growth&quot; OR &quot;slowed growth&quot; OR &quot;growth restrict&quot; OR &quot;growth retard&quot; OR &quot;Failure to Thrive&quot; OR &quot;ftt&quot; OR &quot;growth disorder&quot; OR &quot;growth arrest&quot;)))
deficien" OR "growth disturb") OR ((ti:(antibiotic* OR "anti bacterial agent*" OR antibacterial* OR "anti bacterial*" OR "bactericid*" OR "bacteriocid*" OR "anti mycobacterial*" OR antimycobacterial*)) OR ((ab:(antibiotic* OR "anti bacterial agent*" OR antibacterial* OR "anti bacterial*" OR "bactericid*" OR "bacteriocid*" OR "anti mycobacterial*" OR antimycobacterial*))) OR (collection_gim:("IMSEAR" OR "WPRIM" OR "IMEMR" OR "AIM"))) AND NOT ((mh:(animals)) AND NOT ((mh:(animals)) AND ((mh:(humans)))) AND (collection_gim:("IMSEAR" OR "WPRIM" OR "IMEMR" OR "AIM"))))
Antibiotic as an adjunct to treatment of severe acute malnutrition in infants less than six months of age. A protocol for the systematic review

List of Exclusions and Reasons for Exclusions.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for Exclusion</th>
</tr>
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<tbody>
<tr>
<td>Abate 2020</td>
<td>Inappropriate study design and appropriate control was not available</td>
</tr>
<tr>
<td>Adam 1954</td>
<td>Inappropriate Study Design</td>
</tr>
<tr>
<td>Adem 2020</td>
<td>Inappropriate Patient Population. Study was a cohort study and only included children 6-59 months of age</td>
</tr>
<tr>
<td>Ahmed 1999</td>
<td>Inappropriate Patient Population. Even though all the children were severely malnourished, all of them had diarrhea. Also, the study was not a randomized study.</td>
</tr>
<tr>
<td>Ahmed 2001</td>
<td>Inappropriate Study Design. Authors discuss a protocol for treatment of severe acute malnutrition. The study was a descriptive review</td>
</tr>
<tr>
<td>Akbani 1977</td>
<td>Inappropriate study population. Children with SAM who were infected with tuberculosis.</td>
</tr>
<tr>
<td>AmorelliGonzaga 1989</td>
<td>Inappropriate study population. Study investigated miomycin and included both well-nourished and malnourished children.</td>
</tr>
<tr>
<td>Amza 2013</td>
<td>Inappropriate study population. Study investigated mass azithromycin distribution and included children irrespective of the nutritional status.</td>
</tr>
<tr>
<td>Amza 2014</td>
<td>Inappropriate study population. Study investigated mass azithromycin distribution and included children irrespective of the nutritional status.</td>
</tr>
<tr>
<td>Angelakis 2014</td>
<td>Inappropriate study population. Study included patients with Q fever endocarditis patients treated with doxycycline and hydroxychloroquine</td>
</tr>
<tr>
<td>Ashorn 2018</td>
<td>Inappropriate study population. Study included children with diarrhea, dysentery and malnutrition.</td>
</tr>
<tr>
<td>Ashraf 2012</td>
<td>Inappropriate Comparator. Children aged 2-59 months having severe pneumonia with SAM were randomized to day-care or hospital-care. All the children received antibiotics.</td>
</tr>
<tr>
<td>Autret 1989</td>
<td>Inappropriate study Design. Study to assess the pharmacokinetics of gentamicin.</td>
</tr>
<tr>
<td>Ayiyi 1987</td>
<td>Inappropriate study Design. The study was a systematic review</td>
</tr>
<tr>
<td>Aziz 2015</td>
<td>Inappropriate Intervention. Study investigated vitamin K supplementation.</td>
</tr>
<tr>
<td>Berkley 2009</td>
<td>Wrong comparator</td>
</tr>
<tr>
<td>Berkley 2016</td>
<td>Inappropriate Comparator. Both the intervention and comparison group were treated according to the WHO</td>
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<tbody>
<tr>
<td>Bhatnagar 1992</td>
<td>Inappropriate patient population. All the patients had diarrhea. All of them were given gentamicin</td>
</tr>
<tr>
<td>Bhatnagar 1996</td>
<td>Inappropriate Study Design. Observation study in children with persistent diarrhea</td>
</tr>
<tr>
<td>Birindwa 2020</td>
<td>Inappropriate Study Design. Observational study in children with severe pneumonia</td>
</tr>
<tr>
<td>Bleakly 2014</td>
<td>Inappropriate Study Design. Before and after study to assess the effectiveness of a protocol to treat SAM.</td>
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<td>Boesen 1953</td>
<td>Inappropriate Indication. Antibiotics were given for treatment of gastroesophageal reflux.</td>
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<tr>
<td>Bolme 1980</td>
<td>Inappropriate Study Design: Pharmacokinetic study for Penicillin in children</td>
</tr>
<tr>
<td>Bravo 1982</td>
<td>Inappropriate study design: Study to assess the pharmacokinetics</td>
</tr>
<tr>
<td>Bravo 1984</td>
<td>Inappropriate study design: Study to assess the pharmacokinetics</td>
</tr>
<tr>
<td>Bredow 1994</td>
<td>Inappropriate Study Design. Observational study</td>
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<td>Brodwall 2016</td>
<td>Inappropriate Study Design. Letter to editor</td>
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<td>Bruhn 2016</td>
<td>Inappropriate Study Design. Observational study</td>
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<td>Brunozi 2019</td>
<td>Inappropriate Study Design. Observational study</td>
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<td>Buchanan 1977</td>
<td>Inappropriate Study Design. Letter to editor</td>
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<tr>
<td>Buchanan 1978</td>
<td>Inappropriate Study Design. Observational study</td>
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<tr>
<td>Buchanan 1979</td>
<td>Inappropriate Study Design. Observational study</td>
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<tr>
<td>Bunn 2009</td>
<td>Inappropriate Study Design. Commentary</td>
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<td>Cakir 2012</td>
<td>Inappropriate Patient Population. Children studied leukemia</td>
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<td>Caksen 2000</td>
<td>Inappropriate Study Design. Observational study</td>
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<td>Cedrato 1974</td>
<td>Inappropriate Study Design. Observational study</td>
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<tr>
<td>Chisti 2015</td>
<td>Inappropriate Patient Population. Children with respiratory symptoms only</td>
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<tr>
<td>Church 2015</td>
<td>Inappropriate Study Design. Observational study</td>
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<tr>
<td>Cochlovius 1953</td>
<td>Inappropriate intervention. Observational study</td>
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<tr>
<td>Dicko 2016</td>
<td>Inappropriate study population. Intervention was given to all the children irrespective of nutritional status at the time of chemoprophylaxis for malaria.</td>
</tr>
<tr>
<td>Dieng 2014</td>
<td>Inappropriate Study Design. Observational study</td>
</tr>
<tr>
<td>Dubray 2008</td>
<td>Inappropriate study population. Both the study groups received antibiotics and these were given to children 6-59 months of age</td>
</tr>
<tr>
<td>Duffau 1990</td>
<td>Inappropriate study population. Children with diarrhea</td>
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<th>Author</th>
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<tr>
<td>Dutta 2006</td>
<td>Inappropriate study design: Observational study</td>
</tr>
<tr>
<td>Eriksson 1983</td>
<td>Inappropriate Patient Population. Also, observational study</td>
</tr>
<tr>
<td>Eriksson 1988</td>
<td>Inappropriate Patient Population. Also, observational study</td>
</tr>
<tr>
<td>Ford 1976</td>
<td>Inappropriate Study Design. Observational study</td>
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<tr>
<td>Friedrich 2016</td>
<td>Inappropriate Study Design. Commentary</td>
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<tr>
<td>Garcia 1974</td>
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<tr>
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<td>Gensch 1957</td>
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</tr>
<tr>
<td>Gennant 1998</td>
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</tr>
<tr>
<td>Girma 2018</td>
<td>Inappropriate Study Design. Observational study</td>
</tr>
<tr>
<td>Gore Langton 2020</td>
<td>Inappropriate Patient Population. The antibiotics were given irrespective of nutritional status and study included children beyond six months of age. The comparison group was not appropriate.</td>
</tr>
<tr>
<td>Hecht 2015</td>
<td>Inappropriate Patient Population. The study included children beyond six months of age up to 18 years.</td>
</tr>
<tr>
<td>Heikens 1993</td>
<td>Inappropriate Patient Population, mean age of children at 1.2 years.</td>
</tr>
<tr>
<td>Heikens 1993</td>
<td>Inappropriate Comparator, antibiotics compared with receiving health care from community healthcare aids</td>
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<tr>
<td>Hirschhorn 1971</td>
<td>Inappropriate Study Design, paper is a commentary on the current state of research.</td>
</tr>
<tr>
<td>Howard 1967</td>
<td>Inappropriate Study Design, all infants studied had acute diarrhea</td>
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<tr>
<td>Isaack 1992</td>
<td>Inappropriate Study Design, investigates nosocomial infections.</td>
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<tr>
<td>Isanaka 2020</td>
<td>Inappropriate Patient Population. All patients are above 6 months of age.</td>
</tr>
<tr>
<td>Islam 2021</td>
<td>Inappropriate Outcomes. Antibiotic usage was outcome not treatment group. Also all patients have diarrhea.</td>
</tr>
<tr>
<td>ISRCTN 2017</td>
<td>Wrong patient population. Patient age ranged from 2 months to 13 years, unable to obtain subgroup data for under 6 months.</td>
</tr>
<tr>
<td>Kabalo 2017</td>
<td>Inappropriate Patient Population. Patients aged over 6 months.</td>
</tr>
<tr>
<td>Lares-Asseff 1999</td>
<td>Inappropriate Study Design. Study evaluated blood levels for antibiotic not mortality outcome.</td>
</tr>
<tr>
<td>Lares-Asseff 2016</td>
<td>Inappropriate Comparator. Compared different doses of antibiotics to look for toxicity, not mortality.</td>
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<tr>
<td>Lattes 1954</td>
<td>Inappropriate Study Design and lack of full text.</td>
</tr>
<tr>
<td>Lebl 2001</td>
<td>Inappropriate Patient Population, age range 2 years to 18 years.</td>
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**List of Exclusions and Reasons for Exclusions.**

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<tr>
<th>Reference</th>
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<tbody>
<tr>
<td>Lelijveld 2021</td>
<td>Inappropriate Patient Population, age range 6 months to 59 months.</td>
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<tr>
<td>Lepage 1984</td>
<td>Inappropriate Study Design, patients all have bacterial infection treated with antibiotics.</td>
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<tr>
<td>Lewis 1956</td>
<td>Inappropriate Patient Population, patients all over 1 year old.</td>
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<tr>
<td>Maataoui 2020</td>
<td>Inappropriate Patient Population. Patients all over 6 months of age.</td>
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<tr>
<td>Macdougall 1957</td>
<td>Inappropriate Patient Population. Average age is 2 years.</td>
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<tr>
<td>MacLean 1980</td>
<td>Inappropriate Comparator. Antibiotic usage compared to enteral feeding.</td>
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<tr>
<td>Martischning 1952</td>
<td>Inappropriate Intervention and lack of full text.</td>
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<tr>
<td>Mathew 2016</td>
<td>Wrong Patient Population. Patient all aged over 6 months.</td>
</tr>
<tr>
<td>Mathew 2016</td>
<td>Wrong Patient Population. Patient all aged over 6 months.</td>
</tr>
<tr>
<td>Melaku 1999</td>
<td>Inappropriate Patient Population. Patient median age 5.9 years.</td>
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<tr>
<td>Moschovis 2014</td>
<td>Inappropriate Study Design. Patients treated for pneumonia.</td>
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<tr>
<td>Mtango 1986</td>
<td>Inappropriate Intervention. Patients given antibiotics to treat acute respiratory infections.</td>
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<tr>
<td>Muhammad 2020</td>
<td>Inappropriate Comparator. Compares nutritional treatment with antibiotics usage</td>
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<tr>
<td>Mulholland 1995</td>
<td>Inappropriate Patient Population. All patients have pneumonia to treat.</td>
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<tr>
<td>Muller 1953</td>
<td>Inappropriate Study Design and lack of full text.</td>
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<td>Murce 1955</td>
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<tr>
<td>Muwanguzi 2021</td>
<td>Inappropriate Patient Population. Children aged 1 year and above.</td>
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<tr>
<td>Nalwanga 2020</td>
<td>Inappropriate Patient Population. Mean age 14 months.</td>
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<tr>
<td>Nalwanga 2020</td>
<td>Inappropriate Patient Population. Mean age 14 months.</td>
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<td>Nansumba 2018</td>
<td>Inappropriate Study Design. observational study</td>
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<tr>
<td>Nantanda 2008</td>
<td>Inappropriate patient population. paediatric patients with pneumonia</td>
</tr>
<tr>
<td>NCT 2009</td>
<td>Inappropriate patient population. paediatric patients with pneumonia</td>
</tr>
<tr>
<td>NCT 2009</td>
<td>Inappropriate Patient Population. children age 6 months to 5 years</td>
</tr>
<tr>
<td>NCT 2020</td>
<td>Inappropriate outcome. studied the effect of prophylactic azithromycin has on the microbiome</td>
</tr>
<tr>
<td>NCT 2015</td>
<td>Inappropriate patient population. hospitalized patients (not necessarily patients with diarrheal illness) receiving prophylactic course of azithromycin (not antibiotics to treat diarrheal illness) at the time of discharge, outcomes of malnourished patients not published</td>
</tr>
<tr>
<td>NCT 2012</td>
<td>Inappropriate patient population. age 6 months to 5 years</td>
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<tr>
<td>Nuzhat 2005</td>
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Antibiotic as an adjunct to treatment of severe acute malnutrition in infants less than six months of age. A protocol for the systematic review

List of Exclusions and Reasons for Exclusions.

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<th>Study Reference</th>
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<td>O’Brien 2021</td>
<td>Inappropriate population: children with a skin disease</td>
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<tr>
<td>O’Brien 2020</td>
<td>Inappropriate Patient Population: children age 6 to 59 months</td>
</tr>
<tr>
<td>O’Brien 2020</td>
<td>Inappropriate intervention: studied the effect on biannual prophylactic azithromycin (not antibiotics to treat a diarrheal illness) on the mortality rate of malnourished children</td>
</tr>
<tr>
<td>O’Brien 2020</td>
<td>Inappropriate study design: observational study</td>
</tr>
<tr>
<td>O’Brien 2020</td>
<td>Inappropriate intervention: biannual prophylactic azithromycin (not antibiotics for diarrheal illness)</td>
</tr>
<tr>
<td>Page 2013</td>
<td>Inappropriate Patient Population: children age 6 to 59 months</td>
</tr>
<tr>
<td>Pai 1985</td>
<td>Inappropriate Study Design</td>
</tr>
<tr>
<td>Parpia 2020</td>
<td>Inappropriate Study Design: antibiotics were given prophylactically to the children in the study (not in the treatment of diarrheal illness)</td>
</tr>
<tr>
<td>Parpia 2020</td>
<td>Inappropriate patient population: children did not start receiving the prophylactic antibiotics until after 6 months of age</td>
</tr>
<tr>
<td>Pinto 2012</td>
<td>Inappropriate Setting: PICU</td>
</tr>
<tr>
<td>Pinto 2012</td>
<td>Inappropriate study design: observational study</td>
</tr>
<tr>
<td>Polster 1954</td>
<td>Lack of Full Text</td>
</tr>
<tr>
<td>Pombo 2017</td>
<td>Inappropriate patient population: patients were hospitalized with pneumonia, not diarrheal illness</td>
</tr>
<tr>
<td>Pombo 2017</td>
<td>Inappropriate study design: observational study</td>
</tr>
<tr>
<td>Prentice 2013</td>
<td>Inappropriate Study Design: this paper is a review of various studies on the management of malnutrition in children</td>
</tr>
<tr>
<td>Rasul 2006</td>
<td>Inappropriate Study Design: randomized control trial but no placebo control, controls were admitted to the hospital prior to the study and thus did not receive the WHO protocol</td>
</tr>
<tr>
<td>Rasul 2006</td>
<td>Inappropriate patient population: malnourished children age 1 month to 5 years, included hospitalizations for many reasons not just diarrheal illness</td>
</tr>
<tr>
<td>Rasul 2006</td>
<td>Inappropriate intervention: compared WHO protocol vs no WHO protocol, so patients in both groups may have received antibiotics and the difference between the groups includes many interventions other than antibiotics</td>
</tr>
<tr>
<td>Rawson 2016</td>
<td>Inappropriate Study Design: letter to the editor</td>
</tr>
<tr>
<td>Reed 1996</td>
<td>Inappropriate Intervention: desired outcome was the difference in incidence of bacteremia and the difference in mortality rate among bacteremic patients between malnourished and adequately nourished children</td>
</tr>
<tr>
<td>Reed 1996</td>
<td>Inappropriate study design: observational study</td>
</tr>
<tr>
<td>Reed 1996</td>
<td>Inappropriate patient population: age 0 to 5 years</td>
</tr>
<tr>
<td>Roboz 1955</td>
<td>Lack of Full Text</td>
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<tr>
<td>Rogawski 2015</td>
<td>Inappropriate Study design: observational study</td>
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</tbody>
</table>
**Antibiotic as an adjunct to treatment of severe acute malnutrition in infants less than six months of age. A protocol for the systematic review**

**List of Exclusions and Reasons for Exclusions.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rokstad 2013</td>
<td>Inappropriate Patient Population. This paper is a brief review of a study done by Trehan in 2013, which studied a population of children age 6 to 59 months.</td>
</tr>
<tr>
<td>Rosenberg 1974</td>
<td>Inappropriate Study Design. Review/opinion paper</td>
</tr>
<tr>
<td>Roy 2010</td>
<td>Inappropriate Patient Population. Children age 5 to 12 years. Inappropriate indication. Desired outcome as whether there was a difference in the pharmacokinetics of isoniazid in malnourished children vs adequately nourished children.</td>
</tr>
<tr>
<td>Sala 1955</td>
<td>Inappropriate Intervention and lack of full text</td>
</tr>
<tr>
<td>Samotra 1985</td>
<td>Inappropriate Indication. Desired outcome was whether or not there was a difference in the pharmacokinetics of gentamicin in malnourished children vs adequately nourished children.</td>
</tr>
<tr>
<td>Samotra 1986</td>
<td>Inappropriate Indication. Desired outcome was whether there was a difference in the pharmacokinetics of chloramphenicol in malnourished children vs adequately nourished children.</td>
</tr>
<tr>
<td>Sanogo 2018</td>
<td>Inappropriate Indication. Desired outcome was the level of adherence among healthcare providers to WHO guidelines regarding management (antibiotics, oral rehydration therapy, and zinc) of paediatric diarrhoeal illness in Bamako, Mali.</td>
</tr>
<tr>
<td>Santoro 2002</td>
<td>Inappropriate Study Design. Observational study. Desired outcome was to see how many children admitted to the PICU for lower respiratory tract infections needed ICU level care.</td>
</tr>
<tr>
<td>Schapira 1971</td>
<td>Lack of Full Text</td>
</tr>
<tr>
<td>Sepehr 2009</td>
<td>Inappropriate Patient Population. Age 2 to 94 years. Inappropriate study design. Observational study. Inappropriate indication. Desired outcome was optimal length of post-operative antibiotic prophylaxis as well as risk factors associated with post-operative infection.</td>
</tr>
<tr>
<td>Shahira 2002</td>
<td>Inappropriate Patient Population. Population was all pediatric patients at a teaching hospital. Inappropriate study design. Observational study. Inappropriate indication. Desired outcome was risk factors for nosocomial infections.</td>
</tr>
<tr>
<td>Soheir 1981</td>
<td>Inappropriate Indication. Desired outcome was the appropriate dose of chloramphenicol for malnourished children, not mortality.</td>
</tr>
<tr>
<td>Standing 2018</td>
<td>Inappropriate indication. Studied the proper dose of IV ceftriaxone and PO metronidazole needed to achieve a therapeutic level in malnourished children.</td>
</tr>
<tr>
<td>Tan 2020</td>
<td>Inappropriate Indication. Studied the use of anthropometric measurements as opposed to clinical signs to identify malnourished children.</td>
</tr>
<tr>
<td>Taubenslag 1950</td>
<td>Inappropriate Study Design.</td>
</tr>
<tr>
<td>Thame 2001</td>
<td>Inappropriate Study Design. Observational study.</td>
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<tr>
<td>Thorson 1989 135</td>
<td>Inappropriate Indication</td>
</tr>
<tr>
<td>Tilg 2013 136</td>
<td>Inappropriate Study Design. this paper is a review of a few different studies. Inappropriate patient population. Of interest, it discusses the results from Trehan 2013, which has a patient population of children age 6 months to 59 months</td>
</tr>
<tr>
<td>Tornberg-Belanger 2017 137</td>
<td>Inappropriate Study Design. observational study Inappropriate topic. studied adherence to antibiotic guidelines of various hospitals</td>
</tr>
<tr>
<td>Trehan 2010 138</td>
<td>Inappropriate Patient Population. was children age 6 to 59 months Inappropriate study design. observational study</td>
</tr>
<tr>
<td>Trehan 2013 139</td>
<td>Inappropriate Patient Population. children age 6 to 59 months</td>
</tr>
<tr>
<td>Trehan 2016 140</td>
<td>Inappropriate Study Design. same exact study as trehan 2013 Inappropriate patient population. children age 6 to 59 months</td>
</tr>
<tr>
<td>Trehan 2016 141</td>
<td>Inappropriate Patient Population. letter to editor</td>
</tr>
<tr>
<td>Usman 2019 142</td>
<td>Inappropriate Study Design. observational study</td>
</tr>
<tr>
<td>Uzan-Yulzari 2021 143</td>
<td>Wrong patient population. Age of patients range from birth to 2 years.</td>
</tr>
<tr>
<td>Vather 2018 144</td>
<td>Inappropriate Study Design. observational study</td>
</tr>
<tr>
<td>Verani 2019 145</td>
<td>Inappropriate Study Design. observational study.</td>
</tr>
<tr>
<td>Viso Gurovich 2003 146</td>
<td>Inappropriate study design. observational study. Inappropriate Intervention. studied the outcomes of paediatric patients who received antibiotics to treat various infections, most commonly bronchopneumonia, complicated pneumonia, and conjunctivitis.</td>
</tr>
<tr>
<td>Vygen 2013 147</td>
<td>Inappropriate Study Design. case series (descriptive study design) looking at the outcomes of malnourished infants who received care at a nutritional rehab center</td>
</tr>
<tr>
<td>Walsh 2018 148</td>
<td>Inappropriate Intervention. tested the effectiveness of a lactose free legume based nutritional feed to promote the resolution of diarrhea</td>
</tr>
<tr>
<td>Weingaertner 1961 149</td>
<td>Lack of Full Text</td>
</tr>
<tr>
<td>Wittmann 1967 150</td>
<td>Inappropriate Patient Population. age rage was 2 months to 2 years and not all were malnourished</td>
</tr>
<tr>
<td>Woodd-Walker 1972 151</td>
<td>Inappropriate Study Design, inappropriate patient population. age range was from 1 year to 4 years</td>
</tr>
<tr>
<td>Zecca 1951 152</td>
<td>Lack of Full Text and study is from 1951</td>
</tr>
<tr>
<td>BMJ 2013 153</td>
<td>Wrong study design. Research news article.</td>
</tr>
<tr>
<td>Langdon 2018 154</td>
<td>Wrong patient population. Patient ages ranged from 6 weeks to 60 weeks with no subgroup data available for under 6 months.</td>
</tr>
<tr>
<td>Akush 1951 156</td>
<td>Wrong indication. Patients all treated for pneumonia.</td>
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70. ISRCTN. A study to compare antibiotics used to treat children with severe acute malnutrition.  2017 (https://trialsearch.who.int/?TrialID=ISRCTN18051843).


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89. Muhammad A SY, Nisar MI, Baloch B, Yazdani AT, Yazdani N, Jehan F. . Nutritional support for lactating women with or without azithromycin for infants compared to breastfeeding counseling alone in improving the 6-month growth outcomes among infants of peri-urban slums in Karachi, Pakistan-the protocol for a multiarm assessor-blinded randomized controlled trial Trials 2020;1(21):756.
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