“Role of oral zinc in treatment of acute diarrhea in children under 5 year of age in South-Asia and specifically India: A systematic review of Randomized Controlled Trials”

A dissertation submitted in partial fulfillment of the requirements for the award of

Post-Graduate Diploma in Health and Hospital Management

By

Prashant Pathak

PG/10/090

International Institute of Health Management Research

New Delhi -110075

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Provisional Certificate of Internship

Date: _____

TO WHOM IT MAY CONCERN

This is to certify that **Mr. Prashant Pathak** has successfully completed a two and half month period of internship with the National Health Systems Resource Centre (NHSRC) from February 22, 2012 to May 9, 2012. He will be completing his three months May 22, 2012. During this period he has worked on the **Role of Oral Zinc in the treatment of acute diarrhea in children under 5 year of age in South-Asia and specifically India: A systematic review of Randomized Controlled Trials** under the guidance of the Child Health Team at **NHSRC**.

His sincerity and commitment in obtaining and analyzing the required material is commendable. The output he has produced will be an important contribution to child health discussions.

Dr. Rajani R. Ved
Advisor, Community Processes, NHSRC

Certificate of Approval

The following dissertation titled **"Role of oral zinc in treatment of acute diarrhea in children under 5 year of age in South-Asia and specifically India: A systematic review of Randomized Controlled Trials"** is hereby approved as a certified study in management carried out and presented in a manner satisfactory to warrant its acceptance as a prerequisite for the award of **Post- Graduate Diploma in Health and Hospital Management** for which it has been submitted. It is understood that by this approval the undersigned do not necessarily endorse or approve any statement made, opinion expressed or conclusion drawn therein but approve the dissertation only for the purpose it is submitted.

Dissertation Examination Committee for evaluation of dissertation

Name	Signature
_____	_____
_____	_____
_____	_____

Certificate from Dissertation Advisory Committee

This is to certify that **Mr./Ms. Prashant Pathak** , a graduate student of the **Post- Graduate Diploma in Health and Hospital Management**, has worked under our guidance and supervision. He/She is submitting this dissertation titled " **Role of oral zinc in treatment of acute diarrhea in children under 5 year of age in South-Asia and specifically India: A systematic review of Randomized Controlled Trials** " in partial fulfillment of the requirements for the award of the **Post- Graduate Diploma in Health and Hospital Management**.

This dissertation has the requisite standard and to the best of our knowledge no part of it has been reproduced from any other dissertation, monograph, report or book.

Faculty Mentor	**Organizational Advisor**
Dr. Nitish Dogra	Dr. Anuradha Jain
Assistant Professor,	Senior Consultant,
IIHMR, New Delhi	Public Health planning, NHSRC
Date: _____	Date: _____

ABSTRACT

Role of oral zinc in treatment of acute diarrhea in children under 5 year of age in South-Asia and specifically India: A systematic review of Randomized Controlled Trials

By
Prashant Pathak

Background
In India, diarrhea causes around 650 deaths every day in children under 5 year of age. World Health Organization and UNICEF recommended zinc as an adjunct with ORS for the treatment of diarrhea.

Objectives
To study, the role of oral zinc in the treatment of acute diarrhea, in children under 5 year of age, in Indian context.

Search methods
In March 2012, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2010, Issue 11), MEDLINE and reference lists.

Selection criteria
Randomized controlled trials comparing oral zinc supplementation with placebo in children aged zero to five years with acute diarrhea.

Data collection and analysis
Trial eligibility and risk of bias was assessed, extracted and analyzed data, and drafted the review. Diarrhea duration and severity were the primary outcomes. Dichotomous outcomes were summarized using risk ratios (RR) and continuous outcomes using mean differences (MD) with 95% confidence intervals (CI).

Main results
There is not any significant role of zinc in the treatment of acute diarrhea, in non-malnourished children under 5 year of age in South- Asian countries and in Indian context.

Acknowledgement

I owe my deep sense of gratitude to **Dr. T. Sundararaman,** Executive Director, NHSRC and **Dr. Rajni Ved**, Advisor, Community Processes, NHSRC, for giving me an opportunity to learn systematic review.

My special thanks to **Dr. Rajesh Khanna,** Coordinator, NCHRC, NIHFW **and Dr. Anuradha Jain**, Senior Consultant, Public Health Planning, NHSRC, for their guidance, support, interest, involvement and encouragement. They left no stone unturned in updating me about the subject.

I also thank **Dr. Nitish Dogra,** Assistant Professor, IIHMR, New Delhi, for his guidance throughout the training period.

My sincere gratitude to **Dr. L.P. Singh, Director, and Dr. Rajesh Bhalla, Dean** International Institute of Health Management Research, New Delhi, who always have been a source of motivation and inspiration.

Mr. Prashant Pathak

(Post Graduate Diploma in Health and Hospital Management)

International Institute of Health Management Research, New Delhi

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PART-I

INTERNSHIP REPORT

Internship Report

Internship Organization: NHSRC

Department: Public Health Planning

Introduction to Organization and its Profile:

The National Health Systems Resource Centre (NHSRC) was set up under the National Rural Health Mission (NRHM) and it started functioning from May 2007. The NHSRC was registered as a society in January 2007. A Governing Board was constituted with 21 members, 11 of whom were ex-officio government officials and 10 non-government public health experts (from academics and civil society). The Chairperson of the Governing Board is the Secretary, MoHFW (Ministry of Health and Family Welfare) and the Vice Chairperson was the Additional Secretary of the Ministry, and Mission Director of NRHM. The officials on the board were six senior officials from the central ministry and two secretaries and two mission directors from the High Focus states. The non-officials were selected from a list of public health experts forwarded by leading academic institutions which are active in public health systems development.

Its mandate is to assist in policy and strategy development, and in the provision and mobilization of technical assistance to the states and in capacity building in the Ministry of Health and Family Welfare and in the states.

Its annual governing board meet sanctions its work agenda and its budget, against which these work reports are submitted. The NHSRC has a regional office in the north-east region. The North East Regional Resource Centre (NERRC) has a considerable functional autonomy and a similar range of activities.

The Management of NHSRC

The Governing Board lays down the policies, frames the rules, and approves the annual plan and budget. In between Governing Board meetings, the Executive Committee which is chaired by the Mission Director NRHM and made up of 10 of the 21 Board members guides the organization. The Executive Director reports to this committee and in between meetings of the executive committee to the Mission Director, NRHM. For the purposes of management, NHSRC has opted for a flat management structure. The 30 consultants at Delhi and another 20 fellows and facilitators spread over the states report to their division heads who may be advisors or senior consultants. These division heads in turn report to the Executive Director. All the administrative staff report to the Principal Administrative Officer who also reports to the Executive Director. To make the process of decision making more consultative and transparent, two management committees are functional. The first is the eight member secretariat which is part of the decision making process on all administrative issues and the second is 11 member program committee which discusses, reviews and advises on all program content and strategy areas. In addition the consultants' fortnightly meeting provides a platform for sharing the conceptual issues and work in progress of each division. This platform acts as a medium of internal capacity building and sharing of the work across divisions. The NHSRC is an ISO 9001:2008 certified organization.

Location

National Health Systems Resource Centre,
NIHFW Campus,
Baba Gangnath Marg
Munirka, New Delhi 110067
Ph: 011-26108982, 83, 84, 92, 93
Fax: 011-26108994
Website: www.nhsrcindia.org

Departments

The NHSRC currently consists of seven divisions:

1. Community processes
2. Public health planning
3. Human resources for health
4. Quality improvement in healthcare
5. Financing of healthcare
6. Health informatics
7. Public health administration

Functions of each department of NHSRC for supporting NRHM

1. Community Process:
   - Policy and strategy development support
   - Capacity building in states–skill development and developing institutional capacity
   - Conducting appraisals and evaluation studies
   - Development of training modules and kits
   - Ongoing monitoring of the ASHA program
   - Assistance to states in identifying constraints and seeking joint solutions
   - Building partnerships with civil society

2. Public health planning
   - Policy and strategy development
   - Capacity building for district health planning
   - Support to state and district plan implementation
   - Evaluations, studies, program reviews for evidence based decision making
   - Support to MoHFW for state plan appraisals and monitoring
   - Building up of State Health Systems Resource Centers (SHSRC) or equivalent bodies

3. Human resource for health
    - Studies and policy dialogues for assisting states and MoHFW in designing human resource (HR) strategies.
    - Studies and policy dialogues on attraction and retention of skilled human resources for health in remote and rural areas.
    - Support to development of curriculum/material/training strategies for HR development.

4. Quality improvement in healthcare
    - Developing parameters, techniques and guidebooks for improving quality in public health facilities.
    - Contributing towards policy and strategy development for quality in public health services, and for improving hospital management and Rogi Kalyan Samiti function
    - Support to states for quality improvements/certification of public hospitals and health facilities

5. Financing of healthcare
    - Policy and strategy Development.
    - Expenditure Studies- budget tracking at national, state and district levels.
    - Procurement and infrastructure audits.
    - Studies of PPPs and alternative financing – including insurance schemes.
    - Capacity building at the state and district levels on health financing, financial management, PPP, contracts management etc.

6. Health informatics
    - Rationalization and choice of data elements and indicators.
    - Building and maintaining systems of data collection, flow, management, processing and analysis to improve data quality.
    - Use of information for planning and program management.
    - Assessing state preparedness and data quality and assisting states in improving data quality
    - Building state capacity for HMIS management.
    - Development of other areas of use of health information-GIS, Hospital Management Information
    - Systems, Human Resources Information Systems, M-Health, and Name-based Tracking Systems.
    - Website development to facilitate decentralized health planning.

7. Public health administration
    - Support to states of Bihar and Uttar Pradesh for implementing NRHM.
    - Improving quality of monitoring and supervision.

- Assisting in the development of guidelines and orders for support to public health administration for appropriate orders, and orientation for implementation of key programs.

Engagement and task involvement:

I was appointed in Public health planning department. My reporting was to senior consultant.
My main task was to complete my dissertation and learning systematic review.

Simultaneously I was involved in other works also. For the dissertation purpose I have visited National Child Health Resource Center (NCHRC) to meet Dr. Rajesh Khanna Coordinator, NCHRC and to learn systematic review from him.

I have also visited National Medical Library (NML) for retrieving full papers from various journals.

I was asked to collect data regarding cause specific morbidity and mortality in India and to convert that in to interpretable form. I was asked to search studies on global burden of diseases and to identify and note the methodology they have used to estimating disease burden.

Other than this I was also involved in working with Health informatics department to manage data of family planning (Effectiveness of Strategies that address unmet needs for contraception in the high focus states) and to convert that in interpretable form.

I was also involved in completing the report on 7 years of National rural Health Mission (NRHM).

Reflective Learning

1. I have learnt how NHSRC works with MoHFW and how it is strengthening NRHM by giving technical support.
2. I learnt about basics of Program Implementation and Planning (PIP).
3. MS-Office is really important and we should know its each function so we can work with efficiency.
4. How an organization work for its day to day working, how the in-house finance system works for various expenditures.
5. How to search relevant research studies, learnt about importance of key words and medical sub headings.
6. Learned working on soft-wares (Reference manager and Review manager).
7. Learned a lot about interpreting data from various aspects (this was somewhat intellectual learning rather than academic or practical learning).

PART-II

DISSERTATION REPORT

Role of oral zinc in treatment of acute diarrhea in children under 5 year of age in South-Asia and specifically India: A systematic review of Randomized Controlled Trials

Background

Problem

About 1.4 million children under the age of 5 years die annually from diarrhea, accounting for 19% of all under-5 mortality [1]. In India it causes around 650 deaths every day of this age group [2]. Diarrhea is considered as one of the main cause of malnutrition among survivors. Oral rehydration solution (ORS) is very well known treatment option for treating diarrhea. It has been shown to reduce mortality level in dehydrating diarrhea; however it does not decrease the duration of episodes nor the consequences, such as malnutrition.

Dietary zinc deficiency is wide spread in growing world because of inadequate food intake, low intake of foods from animal sources. High phytate content in diet decreases the zinc absorption in vegetarian population. It is frequently provoked by intermittent acute and chronic infections like diarrhea. The World Health organization (WHO) estimates the burden of global annual mortality attributable to zinc deficiency to be 750,000 deaths per year [6]. Zinc has been recommended as an adjunct treatment option with ORS for the treatment of diarrhea by World Health Organization (WHO) and United Nations Children's Fund (UNICEF), as it was shown to decrease duration of diarrhea. Indian Government made the combination therapy (low osmolarity oral rehydration solution and zinc) available through public health system under the National Rural Health Mission (NRHM).

Physiological Importance of Zinc:

Zinc is a primal micronutrient that is present in all organs, tissue and body fluid. After iron zinc is the second most ample trace element in the human body and arbitrates a wide range of physiological functions. Adequate (7-12 mg/day) zinc nutrition is necessary as zinc's vital structural and functional roles in multiple enzyme systems that are involved in gene expression, cell division and growth and reproductive functions. Zinc is also considered as an immunomodulator agent for the treatment of particularly 3 childhood infections (diarrhea, pneumonia and septicemia) [3]. In case of diarrhea zinc supplementation exhibits therapeutic action by facilitating the transport of water and electrolytes across the intestinal mucosa, preventing villous atrophy and improving overall immunity [9].

In the case of zinc deficiency there is reduction in the number of B and T lymphocytes (CD4+ lymphocytes in particular) through increased apoptosis, and reduction in their functional capacity [10]. Zinc deficiency disrupts the intestinal mucosa, reduces brush border enzymes and increases mucosal permeability and the intestinal secretion of water [11, 12]. Zinc also acts as a potassium channel blocker, inhibiting cyclic adenosine monophosphate-mediated chlorine secretion [13]. Despite of the importance of zinc, body does not lay in zinc and demands a constant dietary intake. In case of zinc deficiency, as consequence, children's physical growth gets affected and the risk and severity of variety of infections increases.

Resources and Types of zinc salt:

The richest dietary sources of zinc are the organs and flesh of mammals, fowls, fish and crustaceans, and zinc-fortified foods. Eggs and dairy products are also rich in zinc and free of phytates, but they have slightly lower zinc content in comparison of organ and flesh foods. Absorption of zinc takes place in the small intestine and among the several factors that interfere with digestion and absorption of dietary zinc, the phytate content of the diet is most important. The higher order phytates, like inositol hexaphosphate and pentaphosphates found in most cereal and legumes limits the absorption of zinc from the intestines. Although most cereals and legumes have relatively high amounts of zinc, they contain high concentrations of phytates, which reduce the amount of absorbable zinc from these foods, and therefore they are relatively poor sources of zinc [14]. Starchy roots and tubers have much lower zinc content than legumes and cereals. Fruits and vegetables are not considered as rich sources of zinc, although some green leafy vegetables like spinach have moderate amounts of zinc but with uncertain bioavailability.

Zinc is given as a supplement in the form of salt, usually zinc sulfate, zinc acetate, or zinc gluconate, as these are water soluble compounds. In terms of adverse effects, zinc can cause vomiting because of its metallic taste. High doses of zinc can also cause epigastric pain, lethargy and fatigue.

Geographical Basis:

According to Fig. 1 South Asian and African Countries have high prevalence of stunting in children under 5 year of age, and it is seen that chances of zinc deficiency are higher in stunted children. There is not any large scale survey has been conducted which provides evidence regarding sub-clinical zinc deficiency. The only evidence available is from IZiNCG is accepted worldwide, and it shows prevalence of nutritional stunting in children under 5 year of age, and not exactly zinc deficiency. According to this other than Sri Lanka all rest South Asian Countries have prevalence of stunting in children under 5 year of age ≥ 30%.

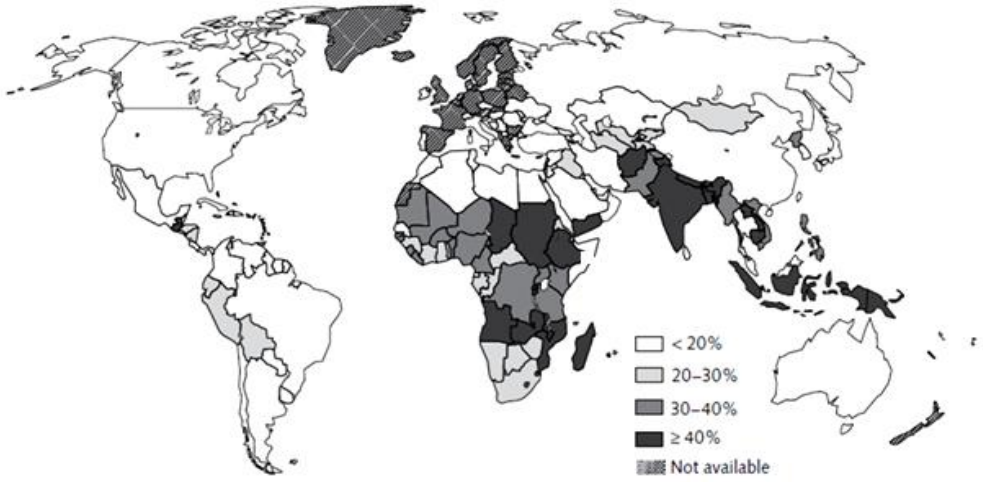

Figure 1: Prevalence of nutritional stunting in children under 5 year of age. Source (IZiNCG)

Age based variations:

In May 2004, WHO (World Health Organization) and UNICEF (United Nations Children's Fund) recommended the zinc supplementation for the treatment of diarrhea: 20 mg per day, for 10 – 14 days in children over 6 months and 10 mg per day if under 6 months of age [6]. In this recommendation dose for infant below six month is lower than the children above six months. Infants up to 6 months are dependent on the mother's milk because of Exclusive Breast Feeding (EBF), so chances of zinc deficiency are less and infants may be able to mobilize hepatic stores accumulated during gestation if required. If they are born with normal birth weight, probability of zinc deficiency is less in them. In this age group, role of zinc supplement limited to children with zinc deficiency.

Rationale for this Review:

According to India health profile diarrhea is responsible for 13% of deaths among children under 5 year of age (India: Health Profile by WHO, 2008). India's under 5 mortality rate (U5MR) is 61 per thousand live births (SRS 2010) and IMR contributes 47 deaths in this which is around 80%.

According to "Report on causes of death in India 2001-2003" diarrhea is responsible for 10% of all the deaths below age of 1 year and 24% of all the deaths among age of 1-4 years. This is the only cause specific mortality data available for India, no recent data is available. There is also lack of data in terms of age specific morbidity of diarrhea in India.

There are various systematic reviews available regarding the role of zinc in treatment of diarrhea, but they are either giving results for global scenario or for developing world. Previous reviews also included the trials in which all participants are malnourished. Outcomes of previous reviews have heterogeneity regarding the effect of zinc in diarrhea over the infants below 6 months of age. In some trials results were not statistically significant for this age group.

India has been categorized under 'moderate to severe zinc deficient' based on the 40% prevalence of nutritional stunting and dietary habits (IZiNCG).

There have been no specific large-scale studies yet on prevalence of sub-clinical zinc deficiency in India and any other South Asian Country, so lack of adequate evidence.

A recent updated Cochrane review concluded 'zinc supplementation is beneficial for children aged six months or more, in areas where diarrhea is an important cause of child mortality and the risk of zinc deficiency is moderate to high'. This review was global and included trends with malnourished children.

So we want to look about the Indian condition. We want to see effectiveness of oral zinc supplementation in treatment of diarrhea in South Asian Countries (Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Sri Lanka), particular focus on India.

Objectives

To study, the role of oral zinc in treatment of acute diarrhea, in children under 5 years of age, in Indian context.

Methodology:

Criteria for considering studies for this review

Types of studies

Randomized Control Trial, either in hospital setting or community setting will be included.

Types of participants

Children with acute diarrhea, aged 0-5 years. Acute diarrhea defined as three or more loose stools in a 24-hour period.

Trials including participants above the age of 5 years and those require special attention, like low birth weight, pre-term children or children having HIV infection, if all the participants are malnourished at the time of recruitment, trials done over children with persistent diarrhea, studies recruiting participants with co-infections like pneumonia, malaria etc. will be excluded.

Types of interventions

Trials including oral zinc supplementation, in tablet or syrup or any other oral form will be included.

Studies where ORS-zinc was used will be excluded, since the amount of zinc introduced through ORS-zinc depends on the total amount of ORS consumed and thus may differ from child to child. Trials would also be excluded where additional research variables (such as optimal delivery system and frequency of administration), and fortification interventions (such as milk fortification).

Control:

Control group should have Placebo.

Concurrent supplementation of other minerals and vitamins are eligible only if administered to both intervention and control group.

Types of outcome measures

Primary outcomes

1. Diarrhea duration.
2. Diarrhea at three, five, and seven days after starting intervention.
3. Stool frequency
4. Stool output

Secondary outcomes

1. Hospitalization (from any cause and diarrhea specific).
2. Death (from any cause and diarrhea specific).

Adverse events

1. Serious adverse events (life-threatening or requiring hospitalization).
2. Any adverse event that results in the discontinuation of treatment.
3. Other adverse events, such as vomiting and reduced copper levels.

Search methods for identification of studies

Databases of published trials:

We have used the following published trials databases.

- MEDLINE (1966 to December 2011).
- Cochrane Infectious Disease Group Specialized Register (December 2011).
- Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 11, 2011).

Note: Non English articles or articles in other languages are not included.

Reference List:

We have also checked for the reference list of all studies identified by our method.

Search Strategy: We have searched using following keywords: “zinc” and “diarrhea” and “supplement” limited to “humans” and “trials” and “Children < 5 yrs of age.

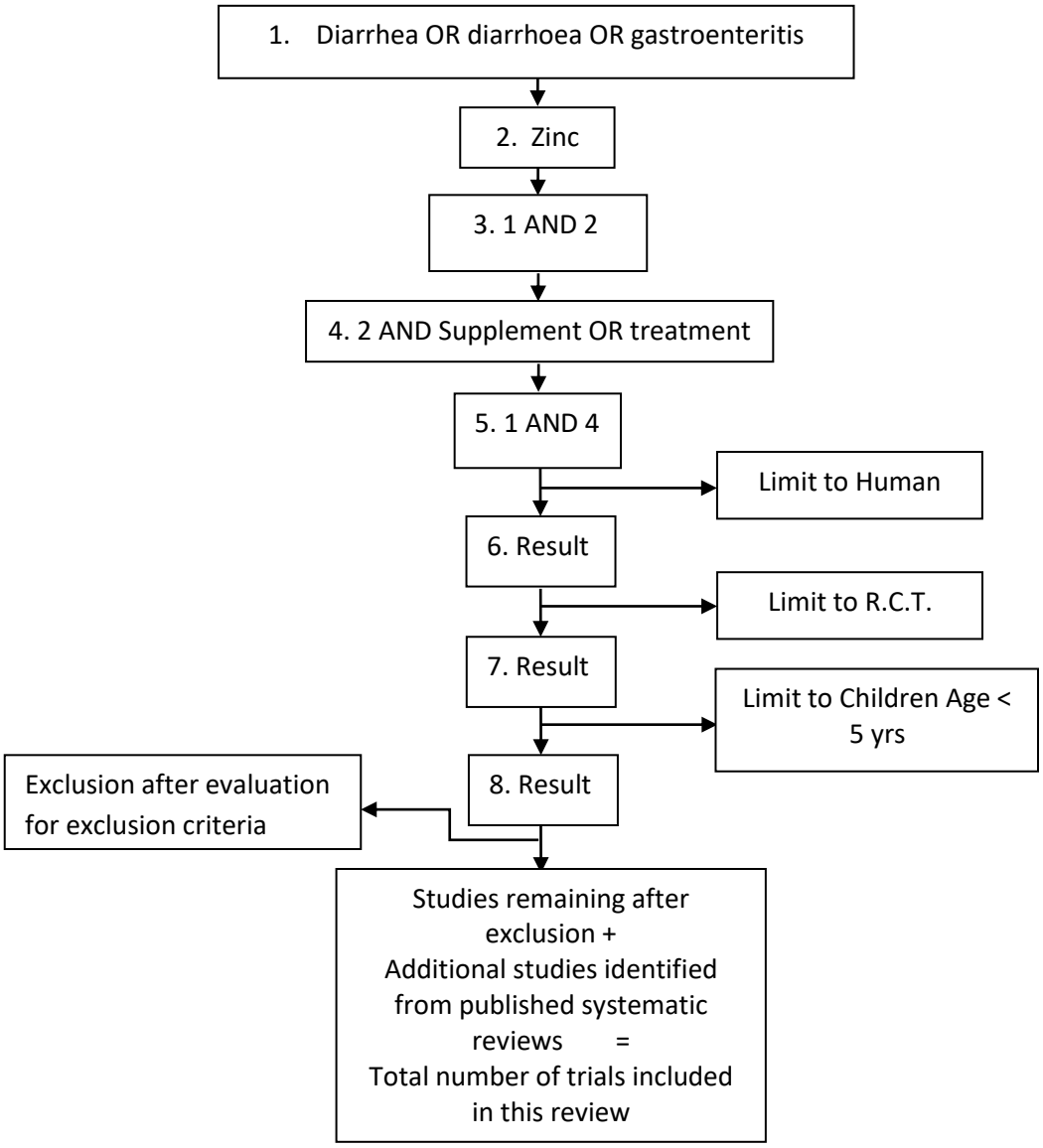

Figure 2: Search Strategy

Data collection and analysis

As we searched according to our search strategy we found total of 194 studies.

Selection of studies

All trials identified during search were screened. After initial screening all potential relevant trials were retrieved and got checked for eligibility. An 'In-Out Sheet' was used for decision

of inclusion of the trial (Appendix-1). In case of doubts, mentor was consulted regarding inclusion / exclusion.

Data extraction and management

Data was extracted in a pilot tested 'data extraction form' (Appendix-2). To avoid any sort of mistakes due to manipulation, we have first extracted data as that was reported and transformed subsequently. Extracted data was entered into Review Manager- 5.1. For binary / dichotomous outcomes we have recorded the number of participants' experiencing specific event in 'case' and 'control' group. For continuous outcomes we have recorded arithmetic mean, standard deviation and number of participants assessed in each group.

Assessment of risk of bias in included studies

Review author independently assessed the risk of bias of included studies using a form with the standard criteria described by the Cochrane group. For bias identification, we rated the quality of the body of evidence for each key outcome as 'High', 'Low', or 'Unclear' risk of bias, by using Cochrane bias scale. No study was excluded on the basis of their risk of bias but sources of bias were reported explicitly while reporting the results of the studies.

Data Synthesis

Data were analyzed using Review Manager 5.1. All results are presented with 95% Confidence Interval (CI). If outcomes were in the form of dichotomous data, they were reported using risk ratio (RR). If the outcomes were in the continuous form and they are summarized using arithmetic mean and standard deviation (SD), they are reported using mean difference (MD). If the means were given as geometric mean, they were transformed in arithmetic mean with their transformation on log scale.

Sub group analysis and heterogeneity

We assessed heterogeneity among trials by visually inspecting the forest plot, using the chi2 test for heterogeneity with a 5% level of statistical significance, and the I2 statistic with a value of 50% representing a moderate level of heterogeneity.

We stratified the analyses for acute diarrhea results by age (children aged less than and greater than six months) because we observed clear a difference in zinc effect according to the age of children enrolled and significant heterogeneity if all the trials were pooled together. As in the rationale of the study we said that we want to look specifically for India so we analyzed the data only for India for all outcomes.

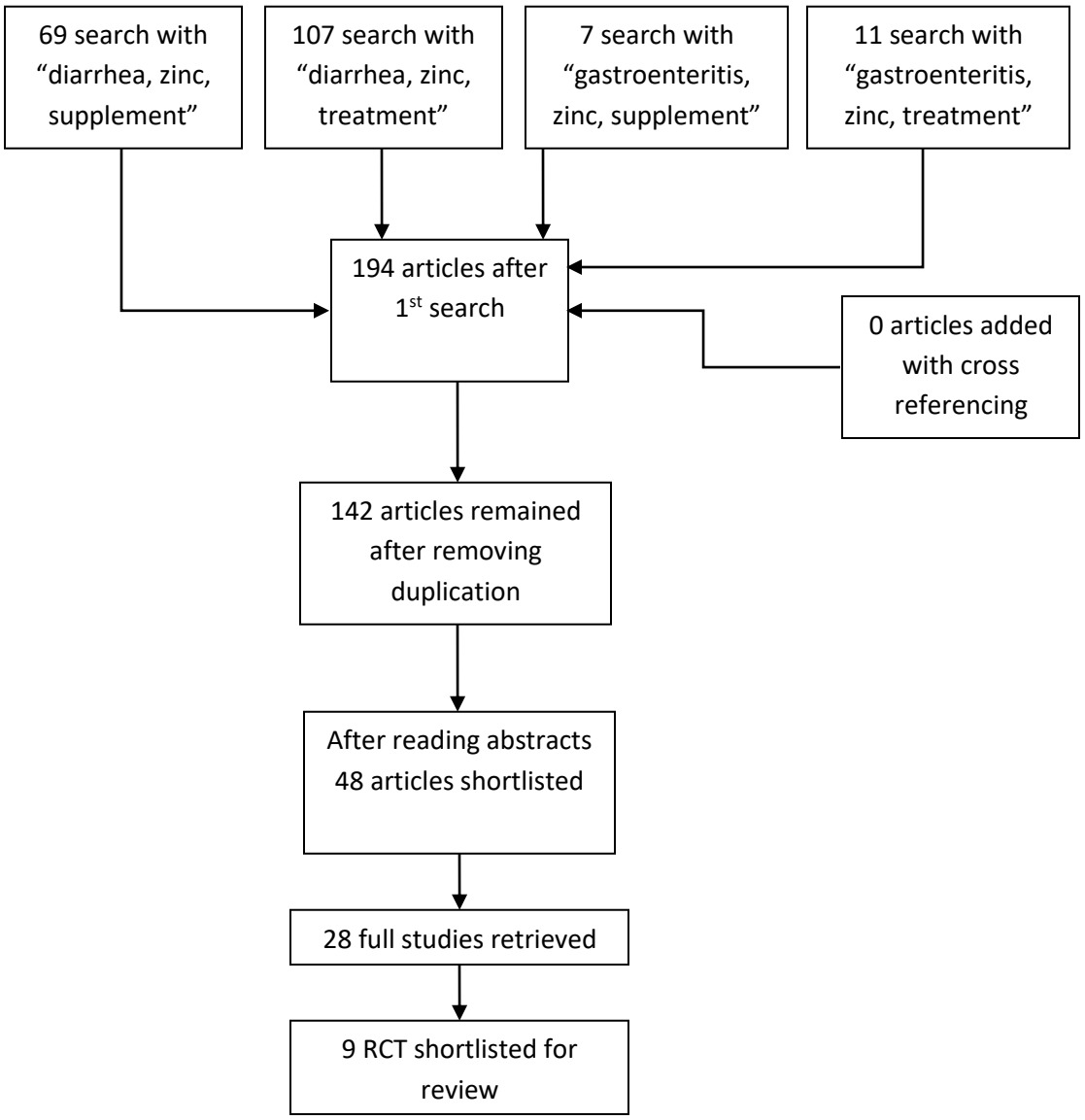

Figure 3: Studies short listing procedure

Results:

194 articles were identified after search, 0 articles added from cross referencing. After removal of duplication 142 articles remained. After reading abstracts 48 articles were shortlisted first. Then again consulted with mentor and 28 full studies were retrieved. These

28 studies were checked on “In-Out Sheet”. After reading all 9 RCTs were finalized for the review.

Descriptions of studies: 9 trials enrolling 6399 children met our inclusion criteria. Reasons for excluded studies are given in the “Characteristics of excluded studies”.

2 of the included trials presented results divided in 2 or more sub-group:- One trial presented two intervention groups on the basis of dose of zinc given (20 mg and 5 mg, Brooks 2005); and one trial presented data for three different study sites (Ethiopia, India and Pakistan, Fischer Walker 2006), out of which data from India and Pakistan is included in our study as they are relevant to our study; so their results entered separately.

- Age: 2 Trials enrolled only children less than 6 months (Brooks 2005, Fischer Walker 2006). 5 Trials only enrolled children above 6 months (Bahl 2002, Faruque 1999, Patel 2009, Sachdev 1988, Strand 2002). 2 Trials enrolled children of different ages greater than 2 months (Bhatnagar 2004, Larson 2005).

- Nutritional Status: One trial enrolled children regardless of nutritional status (Larson 2005). Rest of 8 trials enrolled children who were well nourished or with moderate malnutrition. There was variability with in trials in terms of definition of malnutrition, like few used weight/ age and few weight/ height.

- Sex: 2 trials enrolled only male children (Bhatnagar 2004, Brooks 2005). Rest of 7 trials enrolled children of both sexes.

- Geographic Region and zinc deficiency in countries: We have considered trials held only in South Asian countries in our inclusion criteria. There was not any trial from Afghanistan, Bhutan, Maldives and Sri Lanka out of South Asian Countries. 3 Trials were from Bangladesh (Brooks 2005, Faruque 1999 and Larson 2005), 4 trials were from India (Bahl 2002, Bhatnagar 2004, Patel 2009, Sachdev 1988), 1 trial from Nepal (Strand 2002) and 1 trial was conducted in both India and Pakistan (Fischer Walker 2006).
  Out of 9 trials only one trial (Strand 2002) was conducted in Nepal which is not a high zinc deficiency country according to IZiNCG 2004.

- Zinc dose given: Only 2 trials (Larson 2005, Sachdev 1988) gave zinc in dose of 20 mg/ day. One trial (Fischer Walker 2006) gave 10 mg of zinc per day. Brooks 2005 used zinc 5 mg and 20 mg, but there were only children less than of 6 months age. 4 trials used different dose depending on age (Zinc < 20 mg in infants and ≥mg in older children), but results were not reported separately for each treatment group (Bahl

2002, Bhatnagar 2004, Faruque 1999 and Strand 2002). One trial reported a per kilo dose (2 mg/ kg/ day) (Patel 2009).

- Type of zinc salt: 5 Trials considered zinc sulphate (Bhatnagar 2004, Fischer Walker 2006, Larson 2005, Patel 2009, Sachdev 1988), 2 considered zinc acetate (Brooks 2005, Faruque 1999) and 2 considered zinc gluconate (Bahl 2002, Strand 2002) as their supplement/ treatment option.

- Comparator: All trials used placebo for comparison, only one trial (Patel 2009) compared zinc alone versus copper versus placebo as concomitant copper supplementation.

- Setting: Out of 9, 5 trials were conducted in hospital. 3 Trials conducted in community (Bahl 2002, Fischer Walker 2006, and Strand 2002) and one trial (Larson 2005) was held in both hospital and community.

- Treatment regimen:
  - Duration of treatment: 2 Trials gave zinc for 7 days after recovery (Bahl 2002, Strand 2002). One trial (Brooks 2005) gave zinc until recovery; Sachdev 1988 was unclear about the duration of treatment. Larson 2005, on adverse events administered only one dose of zinc. Rest all trials administered zinc for 14 days.

  - Formulation: 6 trials administered zinc as syrup, one trial gave in the form of powder (Sachdev 1988) and two trials gave zinc in the form of dispersible tablet (Fischer Walker 2006 and Larson 2005).

  - Dose Frequency: Sachdev 1988 gave twice a day, Bhatnagar 2004 thrice a day, Patel 2009 has not specified and rest gave once a day.

  - Additional Treatments: 6 trials administered zinc alone, one used zinc and multi vitamin (Bhatnagar 2004), Faruque 1999 used zinc and vitamin A and Patel 2009 used concomitant copper.

- Outcomes:
  - Duration of diarrhea: Out of 9, 7 trials reported data on diarrhea duration (Bahl 2002. Bhatnagar 2004, Brooks 2005, Faruque 1999, Fischer Walker 2006, Patel 2009 and Sachdev 1988), data were presented as means and standard deviation (SD) or means, and 95% CI.

- Diarrhea at 3rd, 5th and 7th day: 3 Trials (Bahl 2002, Patel 2009 and Strand 2002) repoted diarrhea on 3rd day. 3 Trials (Bahl 2002, Bhatnagar 2004 and Patel 2009) repoted diarrhea on 5th day. 6 Trials (Bahl 2002, Bhatnagar 2004, Faruque 1999, Fischer Walker 2006, Patel 2009 and Strand 2002) reported diarrhea on 7th day. This data was presented in the dichotomous form.

- Stool frequency and output: Stool frequency was reported in 4 trials (Bahl 2002, Brooks 2005, Fischer Walker 2006 and Sachdev 1988) in continuous form as mean and SD, while Stool Output data were in 3 trials (Bhatnagar 2004, Brooks 2005 and Patel 2009) and these data could not be combined together as measuring methods and units were different in them.
- Hospitalization and death: 2 Trials (Fischer Walker 2006 and Strand 2002) reported information regarding hospitalization and declared follow-up period for these 2 trials was "until recovery from diarrhea". Death was reported in 3 trials (Brooks 2005, Fischer walker 2006 and Patel 2009).
- Vomiting: Data of vomiting was reported in 6 (Bahl 2002, Brooks 2005, Bhatnagar 2004, Larson 2005, Sachdev 1988 and Strand 2002) out of 9 trials.

Risk of Bias:

There were 9 studies included in this review and risk of bias of included studies identified using a form with the standard criteria described by the Cochrane EPOC group. Identified risk of biases is reported in this systematic review for each study.

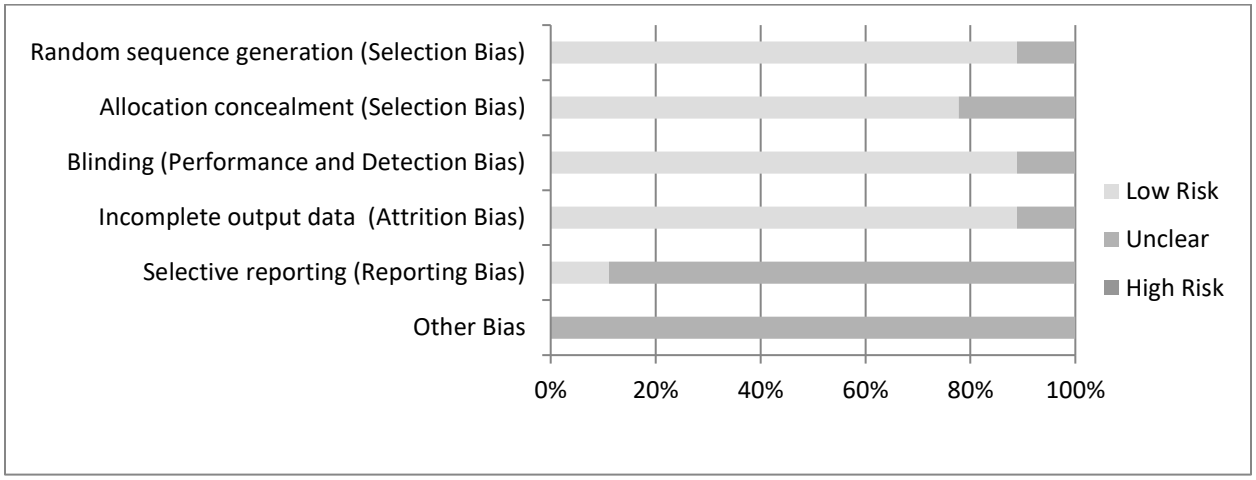

Figure 4: Methodological quality

- Random sequence generation: Eight trials used adequate methods to generate the allocation sequence, methods used in the Sachdev 1988 trial was unclear.
- Allocation concealment: Seven trials reported methods that assured adequate allocation concealment. The remaining two were unclear (Brooks 2005 and Sachdev 1988).
- Blinding: Eight trials were double blinded. The use of blinding was unclear in the remaining one (Sachdev 1988).
- Inclusion of all randomized participants: Eight trials included more than 90% of the randomized participants in the analysis and the number included was unclear in the remaining trial (Sachdev 1988).

Effects of intervention:

1.1. Diarrhea Duration: Not significant effect was seen on diarrhea duration in the findings for South Asian countries -1.81 hour (mean difference, 95% CI -5.70 to 2.70 hour) in a comparison involving nine trials (9 comparisons) and 3468 children, there was significant heterogeneity between trials (I^2 53%). Stratification by age reduced statistical heterogeneity and shown that no benefit was evident in children under six months (1171 children, two trials) without significant heterogeneity; pooled point estimate shown a benefit for zinc in children > 6 months although this was not statistically significant and there was moderate heterogeneity (MD-2.97 hour, 95% CI -7.67 to 1.73 hour; 2031 children, four trials); a significant benefit was observed in studies enrolling both age groups (MD-8.80 hour, 95%CI -18.77 to -1.17 hour; 266 children, one trial) with heterogeneity not applicable as only single trial was available.

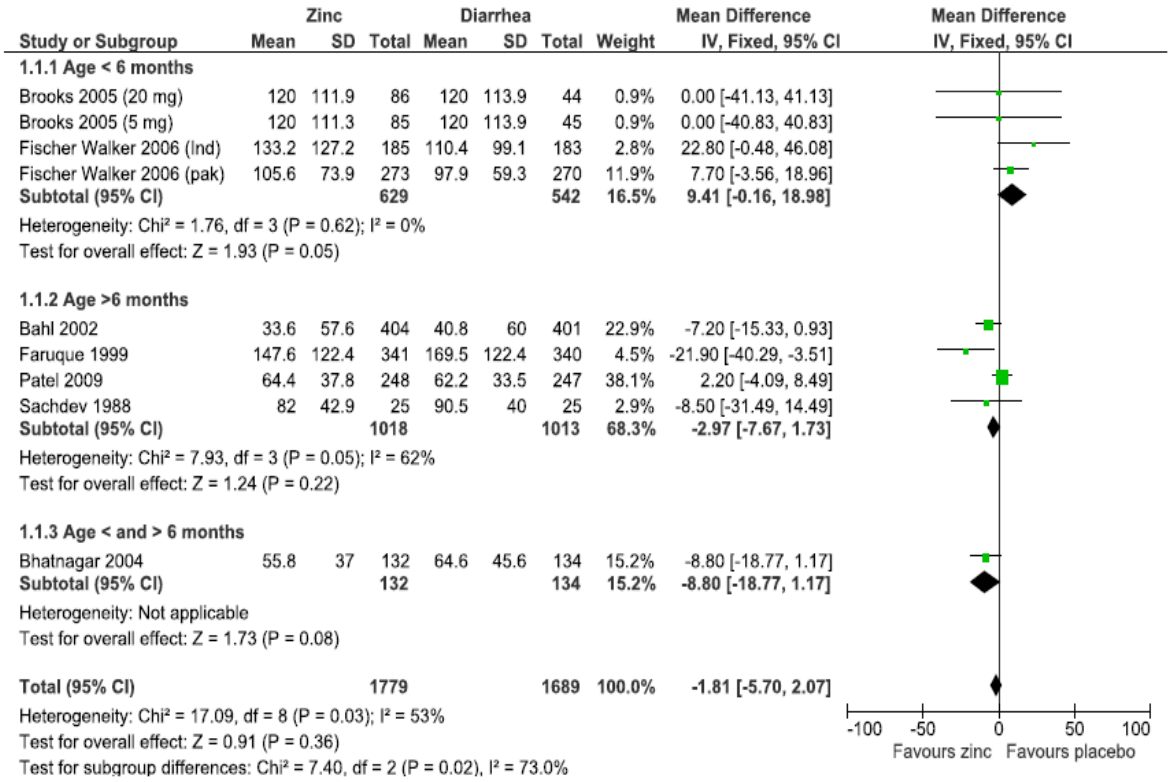

Figure 5: Forest plot of comparison: Zinc versus placebo, outcome: Average Diarrhea Duration (hour) (South –Asian Countries).

There was no significant effect of zinc on diarrhea duration in the findings of India, -2.14 hour (mean difference, 95% CI -6.44 to 1.17 hour), in a comparison involving five trials with 1984 children, there was significant heterogeneity between trials with I^2 value 67.5%. Stratification by age reduced statistical heterogeneity in group of children with age > 6 months, while in other 2 groups it was not applicable. In all 3 sub groups zinc has shown no benefit. Results in children under six months (265 children, one comparison), pooled point estimate shown no benefit of zinc, in children > 6 months (1350 children, 3 trials) zinc has not shown benefit with pooled point benefit -1.64 hour (mean difference, 95% CI -6.51 to3.22 hour and there 44% heterogeneity. Only one trial was there in the subgroup of children with both age groups (MD-8.80 hour, 95%CI -18.77 to -1.17 hour; 266 children, one trial) with heterogeneity not applicable.

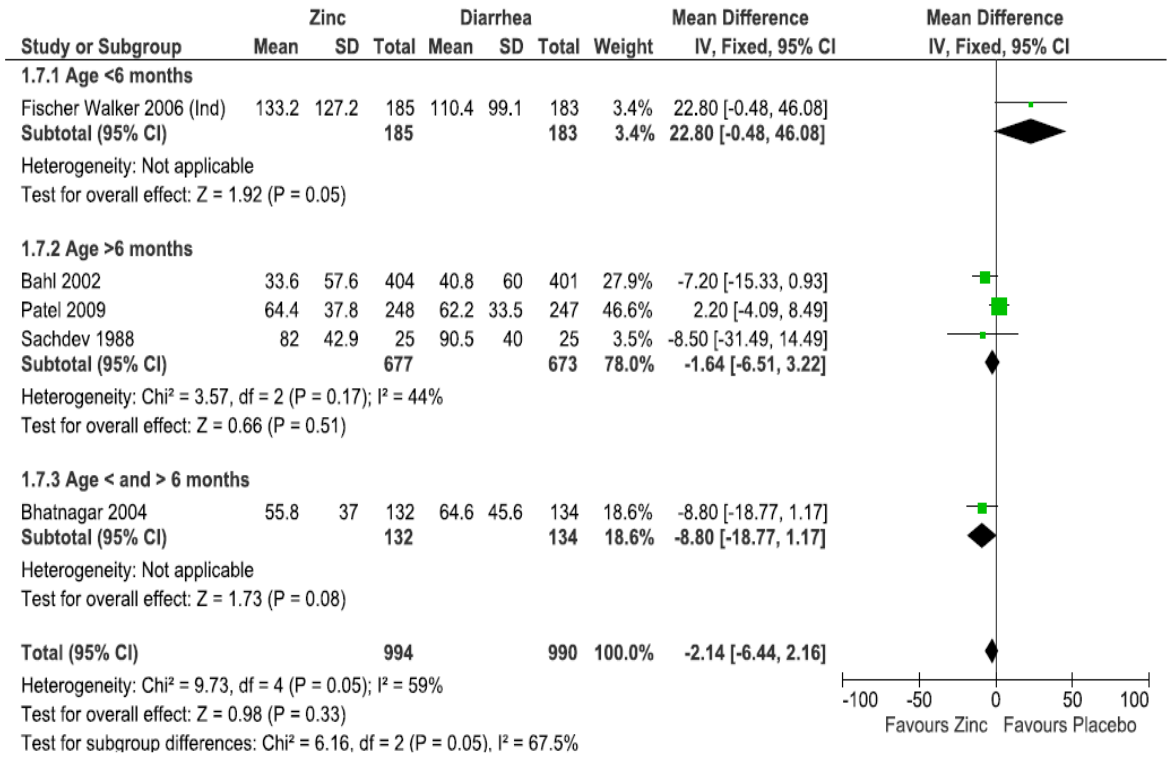

Figure 6: Forest plot of comparison: Zinc versus placebo, outcome: Average Diarrhea Duration (hour) (India).

1.2.Diarrhea on Day 3: Treatment with zinc resulted in significantly less diarrhea at day three (RR 0.84, 95% CI 0.73 to 0.96; 2191 children, three trials). Although it has shown benefit but the upper limit of CI was very close to null value. There were not any subgroups on the basis of ages. Heterogeneity level was moderately less with I^2 value 36%.

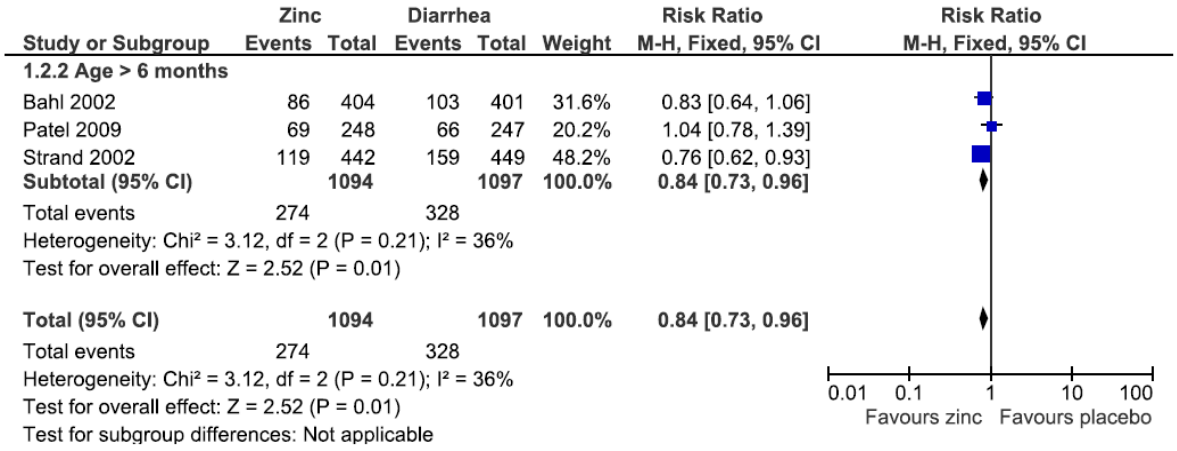

Figure 7: Diarrhea on day 3 (South-Asian Countries)

In Indian context zinc treatment in diarrhea has not shown any significant results at day three (RR 0.91, 95% CI 0.77 to 1.10; 1300 children, two trials). Limits of CI was covers the null value. There were not any subgroups on the basis of ages. Heterogeneity level was quite less with I^2 value 27%.

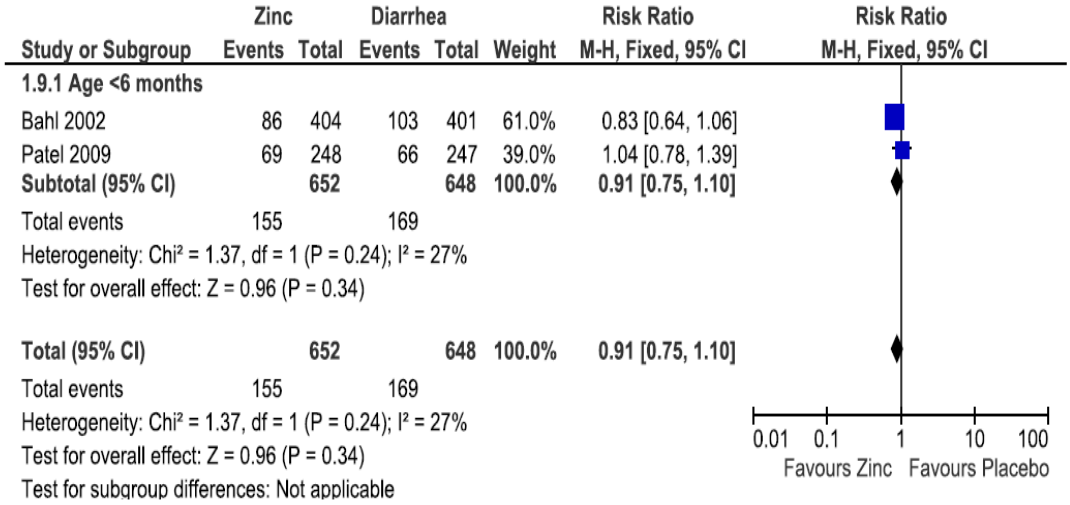

Figure 8: Diarrhea on day 3 (India)

1.3.Diarrhea on Day 5: Analysis for diarrhea at day five (RR 0.77, 95%CI 0.58 to 1.04; 1566 children, 3 trials) was having all the studies from India only so there is not any different analysis has been done. It has shown no benefit in results and CI limits covers the null value and at the same time heterogeneity was moderately high with 52% I^2 value.

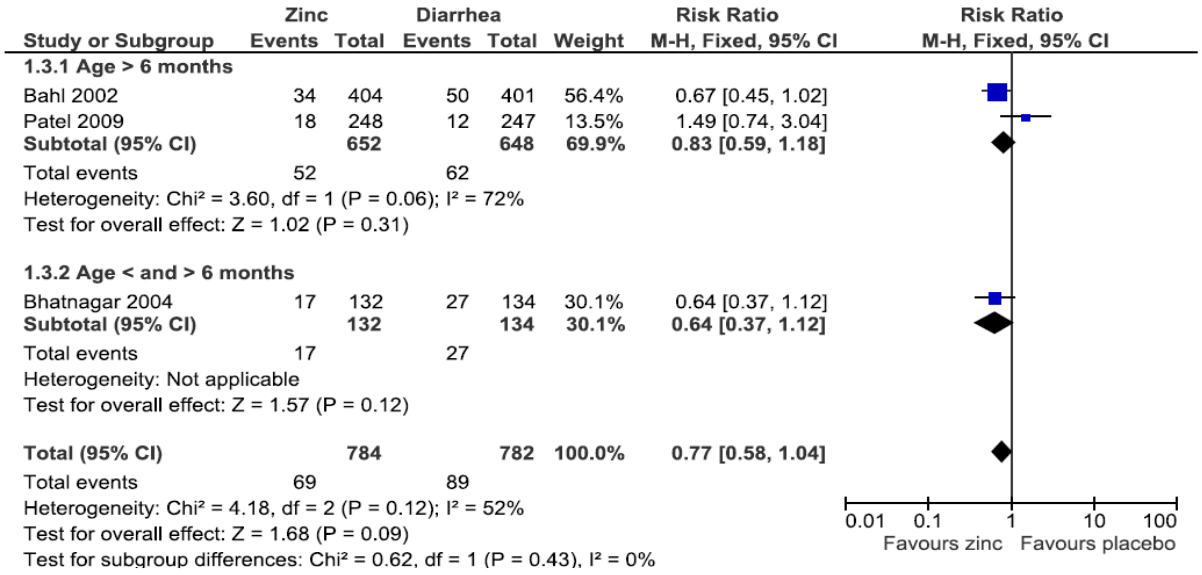

Figure 9: Diarrhea on day 5

1.4.Diarrhea on Day 7: At day seven (RR 0.90, 95% CI 0.76 to 1.07; 4049 children, 6 trials, 7 comparisons) and very high heterogeneity. Heterogeneity was reduced if results were stratified by age. No benefit of zinc was detected in children under six months (911 children, two comparisons, heterogeneity 0% as both comparisons were from same trial), while zinc had a benefit in children older than six months (RR 0.70, 95% CI 0.55 to 0.89; 2872 children, four trials) with upper limit of CI close to null value and in children of both ages (RR 0.90, 95%CI 0.76 to 1.07; 266 children, one trials) results does not shows any benefit and.

In Indian situation, zinc has at day seven (RR 1.04, 95% CI 0.80 to 1.34; 4049 children, 6 trials, 7 comparisons) and high heterogeneity. Heterogeneity was reduced if results were stratified by age. No benefit of zinc was detected in children under six months (911 children, two comparisons, heterogeneity 0% as both comparisons were from same trial) and in children older than six months (RR 0.95, 95% CI 0.62 to 1.45; 1300 children, two trials). In children of both ages (RR 0.11, 95%CI 0.01 to 0.88; 266 children, one trial) zinc was beneficial but heterogeneity was not applicable and CI limits are close to null value.

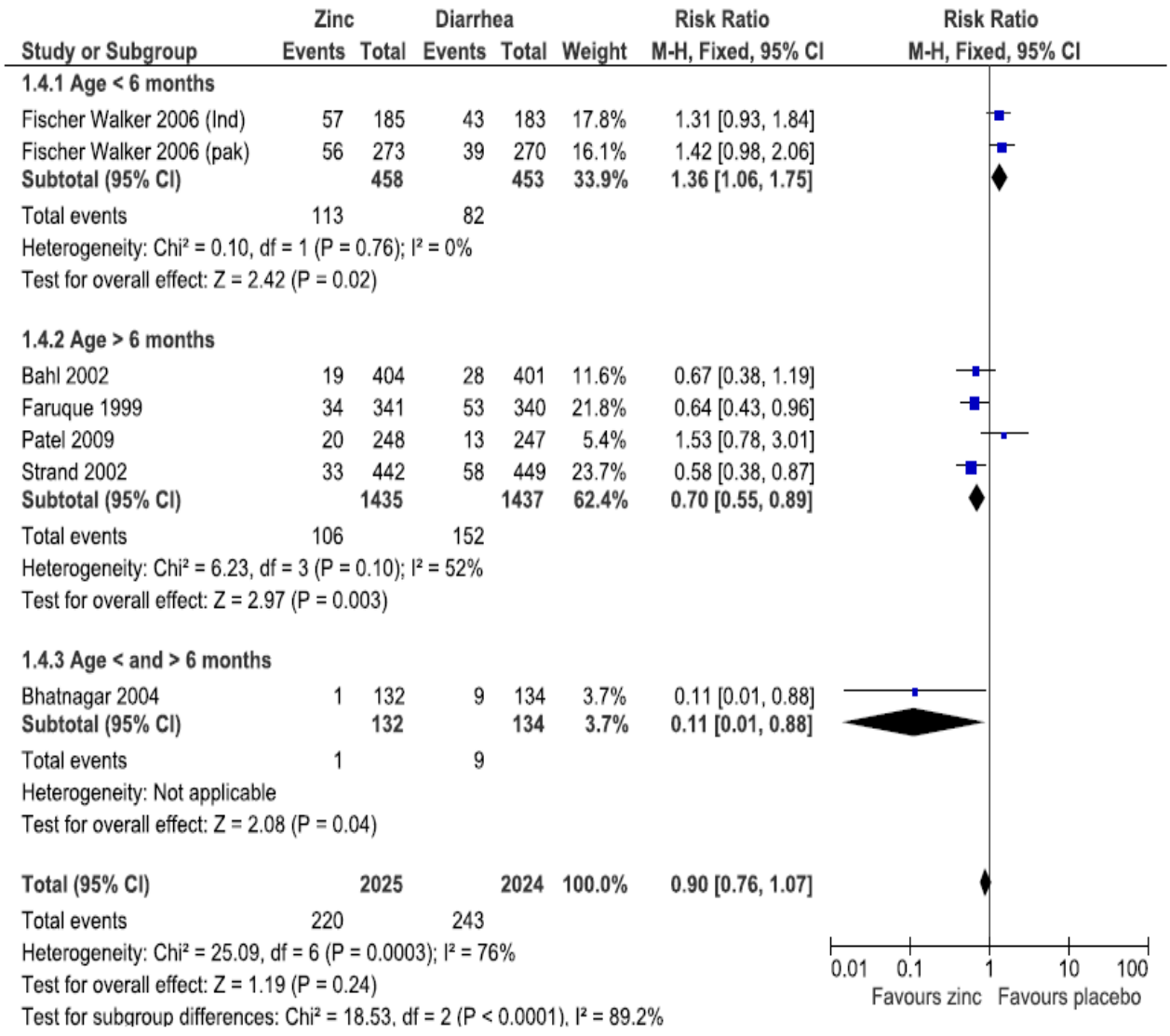

Figure 10: Diarrhea on day 7 (South-Asian Countries)

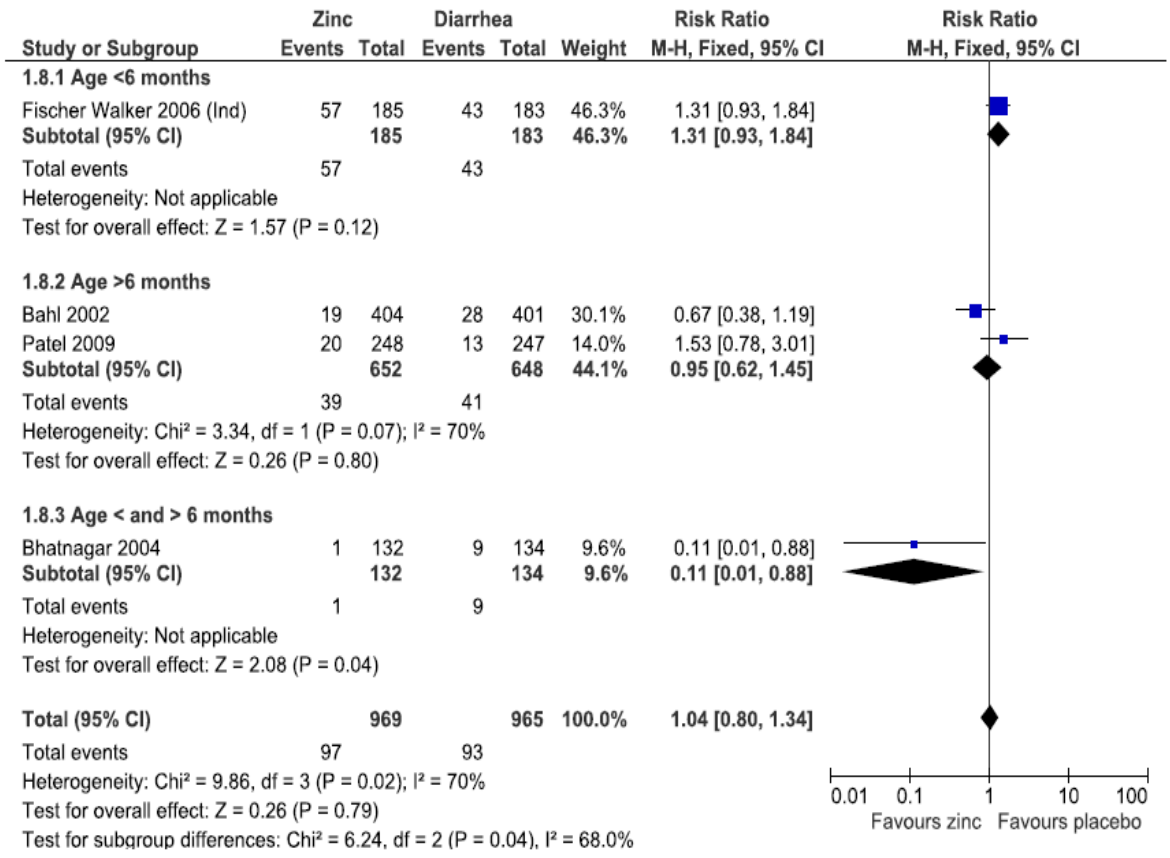

Figure 11: Diarrhea on Day 7 (India)

1.5.Stool Frequency: There was no evidence of a benefit of zinc on stool frequency overall (2026 children, four trials, 6 comparisons) in South-Asian Countries.

In terms of India Also there is not any benefit of zinc with 855 children and 3 comparisons.

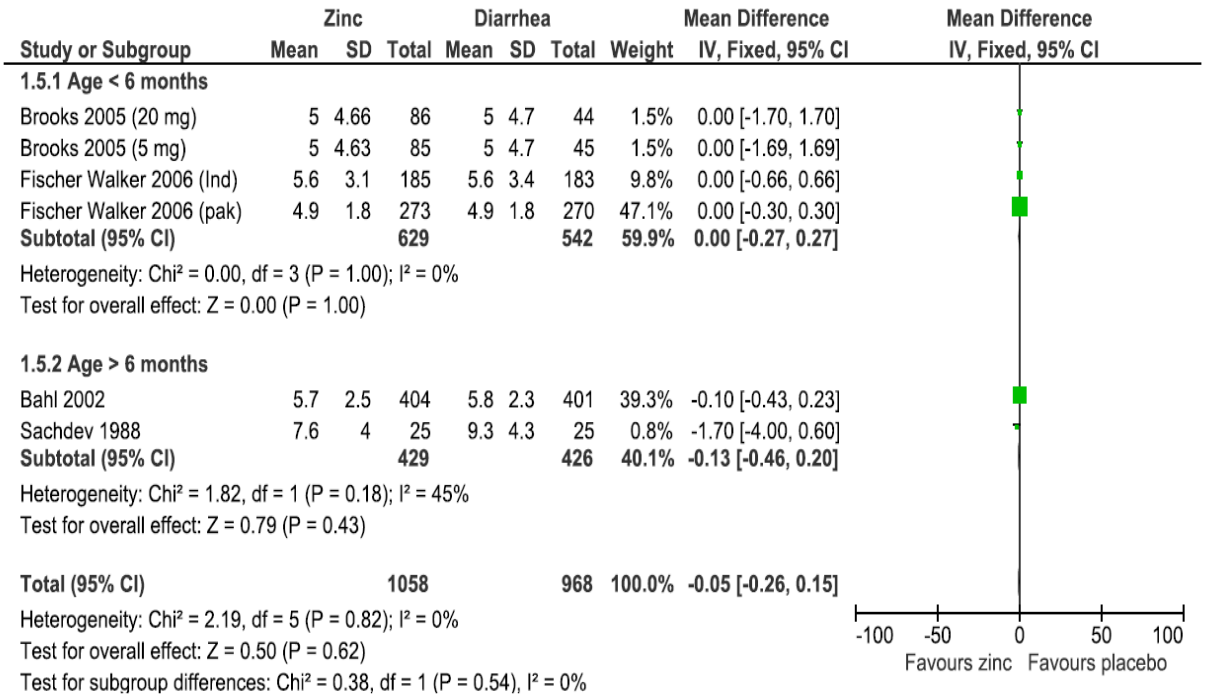

Figure 12: Stool Frequency (South-Asian Countries)

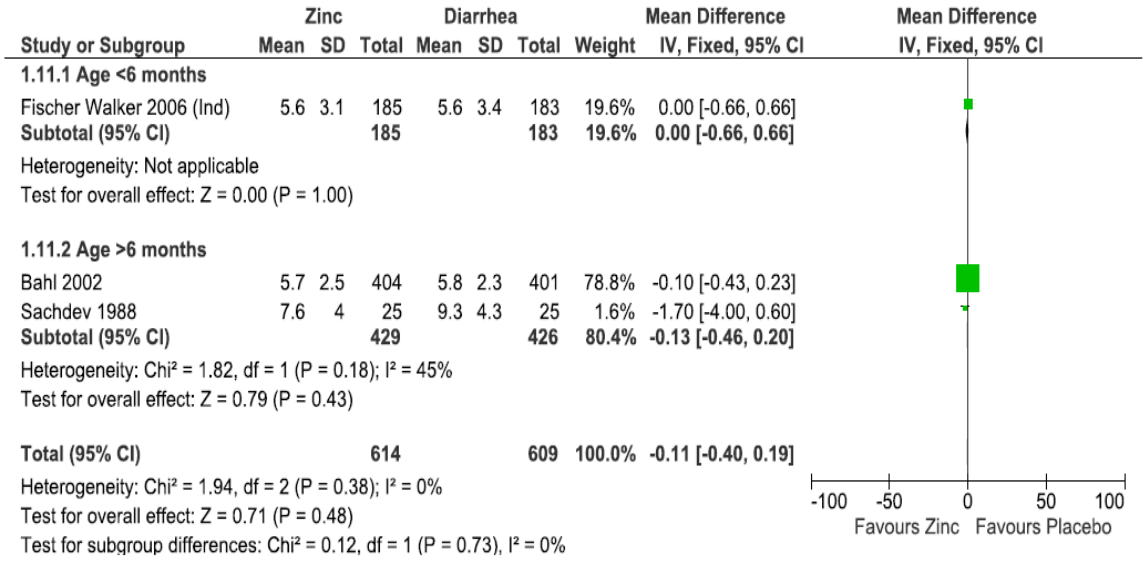

Figure 13: Stool Frequency (India)

1.6. Stool Output: Stool output was measured using different units at different units at different time points, so results could not be pooled together. Brooks 2005 reported results on children <6 months with no evidence of a difference, Patel 2009 reported on children >6 months with no evidence of a difference. Bhatnagar 2004 reported on children < and > 6 months, showed reduction in stool output with zinc.

1.7. Hospitalization: Strand 2002 with 891 participants (community trial) showed no difference, Fischer Walker 2006 with 1074 participants reported 1 hospitalization in placebo group but country was not specified.

1.8. Death: Brooks 2005 did not observe any death, Fischer Walker 2006 reported one death in each treatment group but country was not specified. Patel 2009 reported one death in zinc group, 0 deaths in zinc plus copper group and 2 deaths in placebo group.

1.9. Adverse Events: Six trials reported vomiting, which was significantly more common in the zinc group (RR 1.57, 95% CI 1.36 to 1.81 REM; 2976 children, 6 trials, 7 comparisons, Figure 7), and across all age groups. There was significant heterogeneity among trials (P = 0.001, I^2 75%), and differences in control event rates.

Three trials reported on copper levels, with no significant differences between the zinc and placebo groups. Two studies reported the mean change in serum copper on the last day of supplementation (seven and 14 days after recovery): -1.1± 5.5 μmol/dL in the zinc group versus -1.5 ± 4.2 μmol/dL in the placebo group in one trial (Strand 2002), and -41.2 ± 418.8 μgr/dL in the zinc group versus -79.4 ± 429.2 μgr/dL in the placebo group in the second trial (Patel 2009). Mean serum copper after 14 days was 121 mg/L in zinc group versus 127 mg/L in the control in one trial (Bhatnagar 2004).

There were 3 trials conducted in India, and the overall analysis shows that zinc causes vomiting with pooled point estimate 0.79 (95% CI 0.66 to 0.94, 898 children).

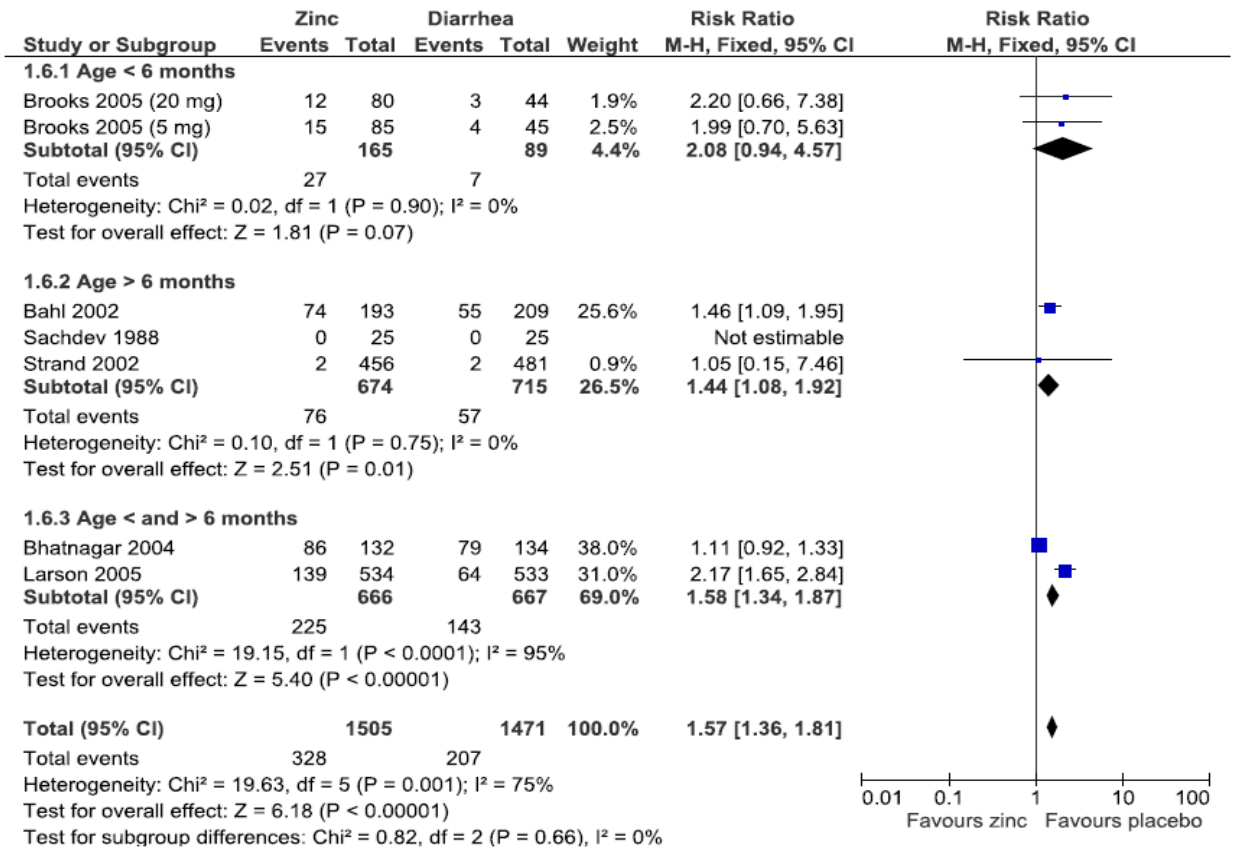

Figure 14: Adverse Event – Vomiting (South-Asian Countries)

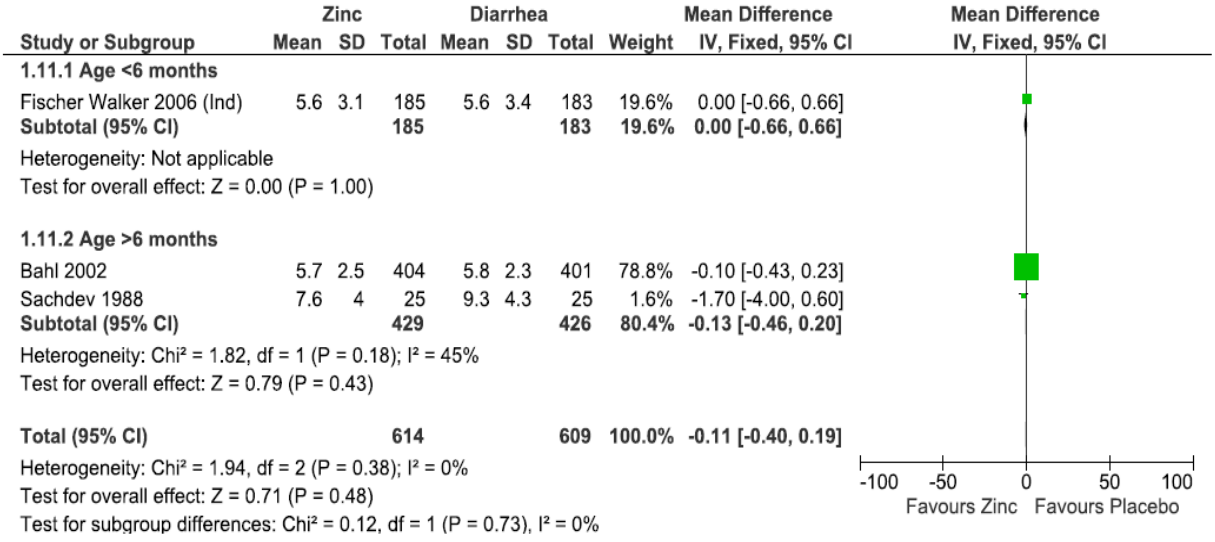

Figure 15: Adverse Event – Vomiting (India)

Outcome Table: Effects of Zinc (South-Asian Countries)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Average Diarrhea Duration (hour)	9	3468	Mean Difference (IV, Fixed, 95% CI)	-1.81 [-5.70, 2.07]
1.1.1 Age < 6 months	4	1171	Mean Difference (IV, Fixed, 95% CI)	9.41 [-0.16, 18.98]
1.1.2 Age < and > 6 months	4	2031	Mean Difference (IV, Fixed, 95% CI)	-2.97 [-7.67, 1.73]
1.1.3 Age > 6 months	1	266	Mean Difference (IV, Fixed, 95% CI)	-8.80 [-18.77, 1.17]
1.2 Diarrhea at 3rd day	3	2191	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.96]
1.2.2 Age > 6 months	3	2191	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.96]
1.3 Diarrhrea at 5th day	3	1566	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.58, 1.04]
1.3.1 Age > 6 months	2	1300	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.59, 1.18]
1.3.2 Age < and > 6 months	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.37, 1.12]
1.4 Diarrhea at 7th day	7	4049	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.76, 1.07]
1.4.1 Age < 6 months	2	911	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.06, 1.75]
1.4.2 Age > 6 months	4	2872	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.55, 0.89]
1.4.3 Age < and > 6 months	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.88]
1.5 Stool frequency (stools / day)	6	2026	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.26, 0.15]
1.5.1 Age < 6 months	4	1171	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.27, 0.27]
1.5.2 Age > 6 months	2	855	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.46, 0.20]
1.6 Adverse event (vomiting)	7	2976	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.36, 1.81]
1.6.1 Age < 6 months	2	254	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [0.94, 4.57]
1.6.2 Age > 6 months	3	1389	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.08, 1.92]
1.6.3 Age < and > 6 months	2	1333	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.34, 1.87]

Outcome Table: Effects of Zinc (India)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1Average diarrhea duration in India	5	1984	Mean Difference (IV, Fixed, 95% CI)	-2.14 [-6.44, 2.16]
1.1.1 Age <6 months	1	368	Mean Difference (IV, Fixed, 95% CI)	22.80 [-0.48, 46.08]
1.1.2 Age >6 months	3	1350	Mean Difference (IV, Fixed, 95% CI)	-1.64 [-6.51, 3.22]
1.1.3 Age < and > 6 months	1	266	Mean Difference (IV, Fixed, 95% CI)	-8.80 [-18.77, 1.17]
1.2 Diarrhe on 3 day India	2	1300	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.10]
1.2.1 Age <6 months	2	1300	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.10]
1.3 Diarrhea on 5 Day India	3	1566	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.58, 1.04]
1.3.1 Age >6 months	2	1300	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.62, 1.45]
1.3.2 Age < and > 6 months	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.88]
1.4 Diarrhea on 7th day India	4	1934	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.80, 1.34]
1.4.1 Age <6 months	1	368	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.93, 1.84]
1.4.2 Age >6 months	2	1300	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.59, 1.18]
1.4.3 Age < and > 6 months	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.37, 1.12]
1.5 Stool Frequency (Stools/ day)	3	1223	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.40, 0.19]
1.5.1 Age <6 months	1	368	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.66, 0.66]
1.5.2 Age >6 months	2	855	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.46, 0.20]
1.6 Vomiting India	3	898	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.66, 0.94]
1.6.1 Age >6 months	2	452	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.09, 1.95]
1.6.2 Age < and > 6 months	1	446	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.37, 0.59]

Discussion:

We identified 9 randomized controlled trials that compared zinc with placebo in young children with acute diarrhea. Overall, zinc was not found effective for acute diarrhea in children aged less than six months. Effect of zinc was not significant in reducing the duration of acute diarrhea in South- Asian countries, specifically in India.

Analysis showed that zinc was found only beneficial in diarrhea at day 3 in South-Asian countries but the upper limit (0.96) of the CI was very close to the null point (1.00) which requires further research for role of zinc in acute diarrhea. In all other situations zinc was not found effective.

This systematic review shows results different than the previous reviews and specially updated Cochrane review. Probable reasons behind this can be that Cochrane review has included trials from across the countries including Africa where problem of malnutrition is higher. And Cochrane review has also included trials which have enrolled participants suffering from persistent diarrhea and malnourished children. While for this systematic review trials enrolling malnourished children and children with persistent diarrhea were excluded and this review has included trials conducted only in South-Asia.

Treatment with zinc was causing an increase in episodes of vomiting; this increase was consistent across trials in all age groups. Larson et al. 2005 reported that vomiting was limited to one episode in most children and mainly occurred within 10minutes of administration, this may be because of metallic taste of zinc. Development of a more palatable formulation may minimize this adverse effect of zinc. None of the trial has shown evidence of copper deficiency resulting from zinc supplementation.

In general, the methodological quality of the trials included in this review was good. Our results are similar with the previous Cochrane review in children age less than 6 months that zinc does not play a significant role in the treatment of diarrhea for this age group. Our analysis does not show effectiveness of zinc for the treatment of acute diarrhea in children aged 6 months to 5 year, which is different from the Cochrane, it may be because of above stated reasons.

Limitation of the study:

- This study has searched only one electronic data-base that is ‘Medline’.
- There were trials only from four South-Asian countries (Bangladesh, India. Nepal and Pakistan).

Conclusion:

Hence we can conclude that zinc is not effective in treatment of acute diarrhea in non mal-nourished children, in South-Asian countries as well as in India.

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Annexure I

List of Figures

Annexure II

APPENDIX I: IN / OUT SHEET

1. IDENTIFICATION OF STUDY / PAPER

Study ID: _____ Date of review: _____

Title: _____

Journal details: _____

Author/s: _____

Country of research: _____

2. INCLUSION CRITERION (Put √ where appropriate)

a) Study design:	Yes	No	Unclear
Randomized control trial	☐	☐	☐

If not yes, reason for it _____

b) Participants:	Yes	No	Unclear
0-5 yrs. of age	☐	☐	☐

Not any co-infection with diarrhoea
If not yes, reason for it _____

c) Intervention:	Yes	No	Unclear
Oral Zinc supplement/ treatment	☐	☐	☐

If not yes, reason for it _____

d) Comparator group:	Yes	No	Unclear
Placebo	☐	☐	☐

If any other should be given to both groups

If not yes, reason for it _____

3. DECISION ABOUT INCLUSION OF STUDIES	**4. IS THIS STUDY INCLUDED?**	
If all answers in 2 are' Yes' - ***Include***		
If any answer 'No' - ***Exclude***	Yes	No
If any answer unclear, to discuss with other reviewer and decide	☐	☐
If any specific case, not fit in criterion but have important results, inclusion after consulting mentors		

APPENDIX II: BIAS ASSESSMENT FORM

Bias	Authors' judgement			Support for judgement
	High	Low	Unclear	
Random sequence generation (selection bias)				
Allocation concealment (selection bias)				
Blinding of participants and personnel (performance bias)				
Blinding of outcome assessment (detection bias)				
Incomplete outcome data (attrition bias)				
Selective reporting (reporting bias)				
Other bias				

APPENDIX III: DATA EXTRACTION SHEET

1. Study ID: _____ **2. Date of data extraction:** _____

3. Study design:_____

4. Quality assessment: _____

(as in Quality Assessment Form)

5. Country of research:

a) Name of country: _____

6. Participants:

a) Age group: _____

b) Sex: _____

c) Sample size: _____

d) Malnourished children (n): _____

e) Characteristics: _____

f) Exclusion criteria: _____

_____

g) Comment (if any): _____

7. Intervention:

a) Form of zinc given: _____

b) Compound of zinc given: _____

c) Dose of zinc given: _____

d) Duration of zinc

Supplement/Treatment: _____

e) Comment (if any): _____

8. Comparator group:

a) Sample size (n): _____

b) Malnourished

children (n): _____

c) Placebo description: _____

d) Comment (if any): _____

9. Enrolment period: _____

10. Duration of treatment _____

11. Length of follow-up: _____

(Specify)

12. Outcome/s and Results:

A. *Primary outcome*	*Measure of effect*	*Value*	*95% CI*
a) Measures of diarrhea duration:			
a1. Diarrhea Duration:	_____	_____	_____
a2. Diarrhea at 3rd day, after starting intervention:	_____	_____	_____
a3. Diarrhea at 5th day, after starting intervention:	_____	_____	_____
a4. Diarrhea at 7th day, after starting intervention:	_____	_____	_____

b) Measures of diarrhea severity:

b1. Stool frequency: _____ _____ _____

b2. Stool output: _____ _____ _____

c) Any other outcome: _____

_____

_____

_____

d) Comment (if any): _____

B. Specify Secondary outcome/s and fill the details as below

Secondary outcome	*Measure of effect*	*Value*	*95% CI*
a) Hospitalization: (Referral)	_____	_____	_____
b) Death:	_____	_____	_____

C. Adverse effects, if reported fill the details below

Adverse effect	*Measure of effect*	*Value*	*95% CI*
a) _____	_____	_____	_____
b) _____	_____	_____	_____
c) _____	_____	_____	_____

d) Comment (if any): _____

_____

Annexure III

Characteristics of included studies

Bahl 2002

Methods	RCT, Community setting
Participants	Participant Number: 1219 Inclusion criteria: age 6 to 35 months; acute diarrhoea (less than 4 days duration) Exclusion criteria: visible blood in stools; likely to emigrate in the next 4 weeks; required hospitalization; previously enrolled; sibling concurrently enrolled; refusal of consent
Interventions	1. Zinc gluconate 30 mg (>12 months) or 15 mg (<12 months) 2. Placebo
Outcomes	1. Average duration of diarrhoea 2. Diarrhoea at day 3 3. Diarrhoea at day 5 4. Diarrhoea at day 7 5. Stool frequency 6. Adverse events (vomiting)
Notes	India

Bias	**Author's Judgement**	**Support of judgement**
Random sequence generation (selection bias)	Low Risk	Computer generated randomization lists
Allocation concealment (selection bias)	Low Risk	The glass bottles containing the products were labeled with the patient's number corresponding to the randomization list by an independent individual. There was no difference between zinc and the placebo in appearance; a minor metallic aftertaste of zinc was hardly detectable
Blinding of participants and personnel (performance bias)	Low Risk	Four-blinded
Blinding of outcome assessment (detection bias)	Low Risk	Four-blinded
Incomplete outcome data (attrition bias)	Low Risk	2% lost to follow up
Incomplete outcome data (attrition bias)	Unclear Risk	Protocol not available

Other bias	Unclear Risk	Information not available

Bhatnagar 2004

Methods	RCT, Community setting
Participants	Participants Number: 287 Inclusion criteria: male; 3 to 36 months; acute diarrhoea (< 72 h) with mild dehydration Exclusion criteria: severe malnutrition (weight/height < 65% of NCHS median); visible blood in stool; severe systemic illness
Interventions	1. Zinc sulphate: 15 mg (< 12 months) or 30 mg (> 12 months) syrup 2. Placebo Both groups: multivitamin
Outcomes	1. Average duration of diarrhoea 2. Diarrhoea at day 5 3. Diarrhoea at day 7 4. Stool output 5. Adverse events (vomiting)
Notes	India

Bias	**Author's Judgement**	**Support of judgement**
Random sequence generation (selection bias)	Low Risk	Table of random numbers
Allocation concealment (selection bias)	Low Risk	Central randomization performed at a site remote from trial location (World Health Organization, Geneva)
Blinding of participants and personnel (performance bias)	Low Risk	Double blind
Blinding of outcome assessment (detection bias)	Low Risk	Double blinded
Incomplete outcome data (attrition bias)	Low Risk	7% lost at follow up
Incomplete outcome data (attrition bias)	Unclear Risk	Protocol not available
Other bias	Unclear Risk	Information not available

Brooks 2005

Methods	RCT, Hospital setting
Participants	Participants Number: 275 Inclusion criteria: male, 1 to 6 months; onset < 72 h; some dehydration or > 100 mL of watery stool within a 4-observation period Exclusion criteria: clinical signs of zinc deficiency; kwashiorkor, weight/age < 60% NCHS; grossly bloody stool comorbidity; cholera
Interventions	1. Zinc acetate: 20 mg 2. Zinc acetate: 5 mg 3. Placebo
Outcomes	1. Death 2. Average duration of diarrhoea 3. Stool output 4. Stool frequency 5. Adverse events (vomiting)
Notes	Bangladesh

Bias	**Author's Judgement**	**Support of judgement**
Random sequence generation (selection bias)	Low Risk	Random numbers
Allocation concealment (selection bias)	Low Risk	Bottles labelled with randomization numbers; no other details
Blinding of participants and personnel (performance bias)	Low Risk	Double blind
Blinding of outcome assessment (detection bias)	Low Risk	Double blinded
Incomplete outcome data (attrition bias)	Low Risk	5% lost at follow up
Incomplete outcome data (attrition bias)	Unclear Risk	Protocol not available
Other bias	Unclear Risk	Information not available

Brooks 2005 (20 mg)

Methods	See Brooks 2005
Participants	Participants Number: 91 (5% lost at follow up)
Interventions	1. Zinc acetate: 20 mg 2. Placebo

Outcomes	See Brooks 2005
Notes	See Brooks 2005

Bias	Author's Judgement	Support of judgement
Random sequence generation (selection bias)	Low Risk	See Brooks 2005
Allocation concealment (selection bias)	Unclear Risk	See Brooks 2005
Blinding of participants and personnel (performance bias)	Low Risk	Blinding (performance bias)
Blinding of outcome assessment (detection bias)	Low Risk	Blinding (detection bias)
Incomplete outcome data (attrition bias)	Low Risk	5% lost at follow up
Incomplete outcome data (attrition bias)	Unclear Risk	See Brooks 2005
Other bias	Unclear Risk	See Brooks 2005

Brooks 2005 (5 mg)

Methods	See Brooks 2005
Participants	Participants Number: 91 (7% lost at follow up)
Interventions	1. Zinc acetate: 5 mg 2. Placebo
Outcomes	See Brooks 2005
Notes	See Brooks 2005

Bias	Author's Judgement	Support of judgement
Random sequence generation (selection bias)	Low Risk	See Brooks 2005
Allocation concealment (selection bias)	Unclear Risk	See Brooks 2005
Blinding of participants and personnel (performance bias)	Low Risk	Blinding (performance bias)
Blinding of outcome assessment (detection bias)	Low Risk	Blinding (detection bias)
Incomplete outcome data (attrition bias)	Low Risk	7% lost at follow up
Incomplete outcome data	Unclear Risk	See Brooks 2005

(attrition bias)		
Other bias	Unclear Risk	See Brooks 2005

Faruque1999

Methods	RCT, Hospital Setting
Participants	Participants Number: 684 Inclusion criteria: children 6 to 24 months with acute diarrhoea, some dehydration and no severe dehydration; underweight or stunted children were not excluded Exclusion criteria: marasmus; kwashiorkor; systemic illnesses
Interventions	1. Zinc acetate: 14.2 mg (first 417 children) or 40 mg (other 273 children randomized) 2. Placebo Both groups: vitamin A
Outcomes	1. Average duration of diarrhoea 2. Diarrhoea at day 7
Notes	Bangladesh

Bias	**Author's Judgement**	**Support of judgement**
Random sequence generation (selection bias)	Low Risk	Random numbers
Allocation concealment (selection bias)	Low Risk	Bottles serially numbered according to the randomization schedule to correspond to the serial number of the participant; supplements prepared by pharmaceutical company and provided in dark-colored bottles
Blinding of participants and personnel (performance bias)	Low Risk	Double blind
Blinding of outcome assessment (detection bias)	Low Risk	Double blind
Incomplete outcome data (attrition bias)	Low Risk	4% lost at follow up
Incomplete outcome data (attrition bias)	Unclear Risk	Protocol not available
Other bias	Unclear Risk	Information not available

Fisher Walker 2006

Methods	RCT, community Setting
Participants	Participants Number: 1110 Inclusion criteria: infants 1 to 5 months of age with acute diarrhea (< 72 h) Exclusion criteria: severe malnutrition (< -3 z score weight for age); signs of pneumonia if < 2 months (cough and difficult or fast breathing with a respiratory rate of > 60 breaths/min); signs severe pneumonia if 2 to 5 months of age (cough or difficult fast breathing and chest in-drawing, nasal flaring, or grunting); required hospitalization (overnight stay at a healthcare facility) for any reason; known major congenital malformation; any other serious pre-existing medical condition; lived out of or planned to move out of study area within following 3 months; previously enrolled in the study
Interventions	1. Zinc sulphate: 10 mg 2. Placebo
Outcomes	1. Death 2. Average duration of diarrhea 3. Diarrhea at day 7 4. Stool frequency 5. Hospitalization 6. Adverse events (vomiting)
Notes	Ethiopia, India, and Pakistan

Bias	**Author's Judgement**	**Support of judgement**
Random sequence generation (selection bias)	Low Risk	Random numbers
Allocation concealment (selection bias)	Low Risk	Randomization scheme assigned in Geneva and kept secure until completion of data collection and initial analysis; upon enrolment, infants assigned chronological study identifiers corresponding to a pre-labeled blister pack of either zinc or placebo tablets
Blinding of participants and personnel (performance bias)	Low Risk	Double blind
Blinding of outcome assessment (detection bias)	Low Risk	Double blind
Incomplete outcome data (attrition bias)	Low Risk	India -1% lost at follow up, Pakistan - 3% lost at follow up

Incomplete outcome data (attrition bias)	Unclear Risk	Protocol not available
Other bias	Unclear Risk	Information not available

Fisher Walker 2006 (Ind)

Methods	See Fischer Walker 2006
Participants	Participants Number: 373 (1% lost at follow up)
Interventions	See Fischer Walker 2006
Outcomes	See Fischer Walker 2006
Notes	India

Bias	Author's Judgement	Support of judgement
Random sequence generation (selection bias)	Low Risk	See Fischer Walker 2006
Allocation concealment (selection bias)	Low Risk	See Fischer Walker 2006
Blinding of participants and personnel (performance bias)	Low Risk	See Fischer Walker 2006
Blinding of outcome assessment (detection bias)	Low Risk	See Fischer Walker 2006
Incomplete outcome data (attrition bias)	Low Risk	1% lost at follow up
Incomplete outcome data (attrition bias)	Unclear Risk	See Fischer Walker 2006
Other bias	Unclear Risk	See Fischer Walker 2006

Fisher Walker 2006 (Pak)

Methods	See Fischer Walker 2006
Participants	Participants Number: 560 (3% lost at follow up)
Interventions	See Fischer Walker 2006
Outcomes	See Fischer Walker 2006
Notes	Pakistan

Bias	Author's Judgement	Support of judgement
Random sequence generation (selection bias)	Low Risk	See Fischer Walker 2006
Allocation concealment (selection bias)	Low Risk	See Fischer Walker 2006
Blinding of participants and personnel (performance bias)	Low Risk	See Fischer Walker 2006
Blinding of outcome assessment (detection bias)	Low Risk	See Fischer Walker 2006
Incomplete outcome data (attrition bias)	Low Risk	3% lost at follow up
Incomplete outcome data (attrition bias)	Unclear Risk	See Fischer Walker 2006
Other bias	Unclear Risk	See Fischer Walker 2006

Larson 2005

Methods	RCT, Hospital Setting
Participants	Participants Number: 1067 Inclusion criteria: child aged 3 to 59 months; acute diarrhea; having taken oral rehydration solution as instructed; no vomiting in the past 2 h for the short-stay ward or 30 minutes in the outpatient clinic, and no longer dehydrated Exclusion criteria: returning to the hospital with diarrhea; receiving zinc
Interventions	1. Zinc sulphate: 20 mg 2. Placebo
Outcomes	1. Adverse events (vomiting)
Notes	Bangladesh

Bias	Author's Judgement	Support of judgement
Random sequence generation (selection bias)	Low Risk	Random numbers
Allocation concealment (selection bias)	Low Risk	Opaque envelopes numbered in which the assigned zinc tablet, placebo tablet, or a similar-sized button was placed;randomization schedule kept in a locked cabinet
Blinding of participants and personnel	Low Risk	Double blind

(performance bias)		
Blinding of outcome assessment (detection bias)	Low Risk	Double blind
Incomplete outcome data (attrition bias)	Low Risk	None lost at follow up
Incomplete outcome data (attrition bias)	Unclear Risk	Protocol not available
Other bias	Unclear Risk	Information not available

Patel 2009

Methods	RCT, Hospital Setting and follow up in the community
Participants	Participants Number: 808 Inclusion criteria: age 6 to 59 months; acute diarrhea (duration up to 72 h); ability to accept oral fluids or feeds Exclusion criteria: severe dehydration and unable to drink, chronic or severe complicating illness, known positive HIV status, kwashiorkor, residing outside a radius of 30 km around the hospital, participating in another study or already enrolled in this study
Interventions	1. Zinc sulphate 2 mg/kg/die 2. Zinc sulphate 2 mg/kg/die + copper 0.2 mg/kg/die 3. Placebo
Outcomes	1. Death 2. Average duration of diarrhea 3. Diarrhea at day 3 4. Diarrhea at day 5 5. Diarrhea at day 7
Notes	India

Bias	**Author's Judgement**	**Support of judgement**
Random sequence generation (selection bias)	Low Risk	Single-site, blocked randomization procedure with blocks of sizes three, six and nine in equal proportions
Allocation concealment (selection bias)	Low Risk	Randomization list generated off site by an investigator not directly involved in the data collection. The code list of the placebo and the treatment groups was secured and held only by the

		pharmacist at the Universal Medicaments Pvt. Ltd, Nagpur, until initial data analysis was completed
Blinding of participants and personnel (performance bias)	Low Risk	Double blind
Blinding of outcome assessment (detection bias)	Low Risk	Double blind
Incomplete outcome data (attrition bias)	Low Risk	7% lost at follow up
Incomplete outcome data (attrition bias)	Low Risk	Protocol available. Trial registered in Meta Register of Controlled Trials (ISRCTN85071383)
Other bias	Unclear Risk	Information not available

Sachdev 1988

Methods	RCT, Hospital Setting
Participants	Participants Number: 50 Inclusion criteria: children 6 to 18 months; dehydration secondary to acute diarrhea of < 4 days' duration Exclusion criteria: antibiotics; severe malnutrition (grades III and IV); concomitant features (meningitis, pneumonia, liver disease, otitis media, fever > 39 °C)
Interventions	1. Zinc sulphate: 20 mg 2. Placebo
Outcomes	1. Average duration of diarrhea 2. Stool frequency 3. Adverse events (vomiting)
Notes	India

Bias	**Author's Judgement**	**Support of judgement**
Random sequence generation (selection bias)	Unclear Risk	No detail
Allocation concealment (selection bias)	Unclear Risk	No detail
Blinding of participants and personnel (performance bias)	Unclear Risk	No detail
Blinding of outcome assessment (detection	Unclear Risk	No detail

bias)		
Incomplete outcome data (attrition bias)	Unclear Risk	No detail
Incomplete outcome data (attrition bias)	Unclear Risk	Protocol not available
Other bias	Unclear Risk	Information not available