Therapeutic Value of Zinc Supplementation in Acute and Persistent Diarrhea: A Systematic Review

Archana Patel1,2,*, Manju Mamtani1,3,*, Michael J. Dibley4, Neetu Badhoniya1, Hemant Kulkarni1,3

1 Lata Medical Research Foundation, Nagpur, India, 2 Indira Gandhi Government Medical College, Nagpur, India, 3 The University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States of America, 4 The Sydney School of Public Health, The University of Sydney, Sydney, Australia

Abstract

Background: For over a decade, the importance of zinc in the treatment of acute and persistent diarrhea has been recognized. In spite of recently published reviews, there remain several unanswered questions about the role of zinc supplementation in childhood diarrhea in the developing countries. Our study aimed to assess the therapeutic benefits of zinc supplementation in the treatment of acute or persistent diarrhea in children, and to examine the causes of any heterogeneity of response to zinc supplementation.

Methods and Findings: EMBASE®, MEDLINE®, and CINAHL® databases were searched for published reviews and meta-analyses on the use of zinc supplementation for the prevention and treatment of childhood diarrhea. Additional RCTs published following the meta-analyses were also sought. The reviews and published RCTs were qualitatively mapped followed by updated random-effects meta-analyses, subgroup meta-analyses and meta-regression to quantify and characterize the role of zinc supplementation with diarrhea-related outcomes. We found that although there was evidence to support the use of zinc to treat diarrhea in children, there was significant unexplained heterogeneity across the studies for the effect of zinc supplementation in reducing important diarrhea outcomes. Zinc supplementation reduced the mean duration of diarrhea by 19.7% but had no effect on stool frequency or stool output, and increased the risk of vomiting. Our subgroup meta-analyses and meta-regression showed that age, stunting, breast-feeding and baseline zinc levels could not explain the heterogeneity associated with differential reduction in the mean diarrheal duration. However, the baseline zinc levels may not be representative of the existing zinc deficiency state.

Conclusions: Understanding the predictors of zinc efficacy including the role of diarrheal disease etiology on the response to zinc would help to identify the populations most likely to benefit from supplementation. To improve the programmatic use of zinc, further evaluations of the zinc salts used, the dose, the frequency and duration of supplementation, and its acceptability are required. The significant heterogeneity of responses to zinc suggests the need to revisit the strategy of universal zinc supplementation in the treatment of acute diarrhea in developing countries.

Citation: Patel A, Mamtani M, Dibley MJ, Badhoniya N, Kulkarni H (2010) Therapeutic Value of Zinc Supplementation in Acute and Persistent Diarrhea: A Systematic Review. PLoS ONE 5(4): e10386. doi:10.1371/journal.pone.0010386

Editor: Qamaruddin Nizami, Aga Khan University, Pakistan

Received January 6, 2010; Accepted April 8, 2010; Published April 28, 2010

Copyright: © 2010 Patel et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The authors have no support or funding to report.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: hemant_kulkarni@yahoo.com

# These authors contributed equally to this work.

Introduction

Despite significant improvements in the interventions to treat diarrhea in children, it continues to pose a daunting public health challenge, especially in children from developing countries. Recent estimates suggest that nearly 3% of neonatal mortality and 17% of under-five child mortality is attributable to diarrhea. Asia and Africa have an alarmingly high incidence of childhood diarrhea. Recent estimates suggest that nearly 3% of neonatal mortality and 17% of under-five child mortality is attributable to diarrhea. Asia and Africa have an alarmingly high incidence of childhood diarrhea. [1,2,3] Although the burden of the diarrhea-related mortality has significantly decreased since the introduction of oral rehydration therapy in 1980, diarrheal diseases in children remain a substantial global health problem. [4,5,6] In 2004, the World Health Organization (WHO) and the United Nations Children’s Fund (UNICEF) took two significant steps to reduce this burden by recommending the use of low-osmolarity oral rehydration solution (ORS), and supplementation with zinc for up to two weeks as part of the case management of acute diarrhea. [7,8]

The latter recommendation was based on the results of several randomized controlled trials, meta-analyses [9] and reviews [10,11,12,13] reported from around the world that have demonstrated the utility of zinc supplementation to shorten the duration of diarrhea and improve other diarrhea related outcomes. Nearly five years have elapsed and substantial additional evidence [14,15,16,17,18,19] has accumulated since the inception of the practice of zinc supplementation. The existing paradigm strongly supports the notion of zinc supplementation; however, recent scientific reports suggest several interesting cues described below indicate that a more focused approach to zinc supplementation may be required.

First, WHO/UNICEF recommends zinc supplementation for diarrhea in developing countries only. [19] The underlying justification for this is the differential prevalence of zinc deficiency. Extension of this line of thought would suggest that differential levels of zinc deficiency in individuals or populations within...
developing countries might modulate the therapeutic benefits attributable to zinc. Second, five meta-analyses have been published thus far [9,16,17,18,20,21] that have all observed a protective effect of zinc on some diarrhea outcomes, but all of these meta-analyses have also reported a significant degree of heterogeneity in effect sizes across studies. Such heterogeneity raises concerns regarding the reliability of the synthetic estimates of the use of zinc supplementation. Third, evidence is emerging that zinc supplementation is not equally effective against all causative organisms. [22,23] Since the causes of acute diarrhea even within developing countries vary widely, the efficacy of zinc supplementation is likely to be heterogeneous. Lastly, it is not clear at present how zinc supplementation complements, if at all, other possible options like vitamin A supplementation and multivitamin supplementation. [23,24,25]

Together, these issues indicate the need for a closer look at the evidence that underpins the policy of blanket zinc supplementation to children with diarrhea in developing countries. This study aimed to assess the therapeutic benefits of zinc supplementation in the treatment of acute or persistent diarrhea in children, and to examine the causes of any heterogeneity of response to zinc supplementation.

Methods

Data Extraction

Data extraction for this study was conducted in two steps. First, we searched the EMBASE®, CINAHL® and MEDLINE® databases for published trials on zinc supplementation. The full strategy for searching these databases and the results obtained are shown in Figure 1. Second, we collected the published reviews and meta-analyses in this field. For this, we searched the same databases using the query “zinc AND diarrhea” and limiting the citations to reviews, we identified 129 review articles of which 50 dealt with “zinc supplementation”. Further restricting the articles to publication type “meta-analysis” identified 10 articles of which seven had formally conducted synthesis of published trials on the preventive or the therapeutic role of zinc in acute or persistent diarrhea. Five of these seven meta-analyses related to the therapeutic use of zinc in diarrhea. We carefully reviewed these five meta-analyses for any additional studies that we may have missed in the first stage of the search (Figure 1, step 7). In total, we identified 26 trials for acute diarrhea and 6 trials for persistent diarrhea. Attached at the end of the manuscript are the PRISMA statement and flowchart detailing the methods of data extraction and abstraction.

Analytical approach

We constructed a correspondence map of the published studies and meta-analyses to identify which studies were included in the different meta-analyses. We then summarized the findings from these meta-analyses into diarrhea-related clinical end-points. For each outcome, we examined the reported summary effect sizes and the heterogeneity across studies. For quantifying heterogeneity, we used the I² statistic since it is comparable across meta-analyses. [26] If a meta-analysis reported the Q test result for heterogeneity then the I² statistic was estimated from it using the formula I² = (Q-df)/Q with the minimum bound set to zero.

For major outcomes that showed significant summary beneficial effect of zinc on diarrhea, and which showed large heterogeneity across trials, we investigated the potential contributors to the heterogeneity. First, we conducted an updated meta-analysis to include the results from other studies that the previous meta-analyses may have omitted. For these meta-analyses, we used the random effects model of DerSimonian and Laird. [27] Depending on the diarrhea related outcome, we used standardized mean difference or summary odds ratios as the summary measures for effect size. For diarrhea-related outcomes showing substantial heterogeneity across studies, we then estimated the contribution of potential predictors of effect size to between-study heterogeneity. For predictor variables that were categorical in nature (geographic location and setting of the study, zinc salt used, co-intervention used, and adequacy of blinding procedures) we used subgroup meta-analyses. For continuous predictor variables we conducted univariate meta-regression analyses as recommended by Higgins et al [26] and Thomson et al [28]. Continuous variables included in these analyses were: mean age, dose of zinc, duration of diarrhea before admission, proportion wasted defined as weight-for-age z score<-2, proportion stunted defined as height-for-age z score<-2, mid-arm circumference, proportion with fever, mean dehydration score, baseline zinc and proportion breastfed. Statistical analyses were conducted using the Stata 10.2 (Stata Corp, College Station, TX) software package.

Results

Systematic map of published meta-analyses on zinc supplementation in diarrhea

In 1998, Black et al [10] conducted the first focused literature review of zinc supplementation, which provided a significant
impeus for the formulation of the WHO/UNICEF recommendation [7] six years later on the use of zinc in the treatment of childhood diarrhea. Together the published meta-analyses have summarized data from 23 randomized controlled trials (9,958 children receiving zinc and 9,940 subjects receiving placebo) excluding four studies [29,30,31,32] published after the meta-analyses. For ease of identification, these meta-analyses are labeled chronologically as M1–M5 in Table 1.

The RCTs of the therapeutic effects of zinc supplementation during diarrhea have reported a wide variety of diarrhea-related outcomes. For example, these RCTs report the domain of diarrheal duration in various ways as mean duration of diarrhea since initiation of treatment, the percentage reduction in the duration of diarrhea, and the proportion of children with continued diarrhea beyond a predefined number of days (1, 3, 5 or 7). In addition, other outcomes have included stool frequency, stool output, risk of vomiting and risk of watery stools. All the five meta-analyses [9,15,16,17,18] and most of the published randomized controlled trials have however, reported the effect of zinc supplementation on mean diarrheal duration. Two meta-analyses [9,17], report that there is about 15–16% reduction in the mean duration of acute diarrhea while four meta-analyses [15,16,17,18] report that zinc supplementation can reduce the acute diarrheal duration by 0.24 to 0.67 days (Table 2). Again, for this important outcome, the more recent meta-analyses [15,16,17,18] suggested that the published evidence demonstrates a statistically significant degree of heterogeneity with $I^2$ statistic ranging from 73% to 85% (Table 2). Alternatively expressed, zinc supplementation appears to reduce the risk of continued diarrhea beyond 7 days by 29% (Table 2), although the results were heterogeneous across the published literature ($I^2>70\%$). On the other hand, zinc supplementation does not provide a statistically significant reduction in stool frequency or stool output and this evidence was not heterogeneous (Table 2).

Meta-analytical synthesis of the influence of zinc supplementation is available for three more outcomes: persistent diarrhea, vomiting after zinc administration and childhood mortality. A smaller number of trials provide the current evidence for the effects of zinc supplementation on persistent diarrhea compared to acute diarrhea. Nonetheless, zinc supplementation offers a clear benefit for persistent diarrhea and this effect was homogeneous across the published studies (Table 3). Three meta-analyses [16,17,18] have summarized the results from randomized controlled trials with vomiting as an outcome, all of which found that the risk of vomiting significantly increased after zinc supplementation [point estimates for odds ratios (OR) ranging from 1.22 to 1.71, Table 2]. The most recent meta-analysis reported significant heterogeneity across study results ($I^2 69\%$, Table 2).

### Table 1. Published studies therapeutic use of zinc against in acute diarrhea.

| No | Author [Ref]       | Year | Zn | Pl | M1  | M2  | M3  | M4  | M5  |
|----|-------------------|------|----|----|-----|-----|-----|-----|-----|
| 1  | Sachdev et al [57]| 1990 | 20 | 20 | X   | X   | X   |     |     |
| 2  | Sazawal et al [47]| 1995 | 456| 481| X   | X   | X   | X   |     |
| 3  | Roy et al [45]    | 1997 | 37 | 37 | X   | X   | X   |     |     |
| 4  | Hidayat et al [42]| 1998 | 738| 659| X   | X   | X   |     |     |
| 5  | Roy et al [53]    | 1998 | 95 | 95 | X   |     |     |     |     |
| 6  | Faruque et al [39]| 1999 | 341| 340| X   |     |     |     |     |
| 7  | Dutta et al [38]  | 2000 | 44 | 44 | X   |     |     |     |     |
| 8  | Khatun et al [50] | 2001 | 44 | 44 |     |     |     |     |     |
| 9  | Strand et al [48] | 2002 | 442| 449|     |     |     |     |     |
| 10 | Bahl et al [34]   | 2002 | 806| 401|     |     |     |     |     |
| 11 | Baqui et al [66]  | 2002 | 3974| 4096|     |     |     |     |     |
| 12 | Al-Sonboli et al [33]| 2003 | 37 | 37 |     |     |     |     |     |
| 13 | Polat et al [44]  | 2003 | 92 | 92 |     |     |     |     |     |
| 14 | Bhattacharyya et al [35]| 2004 | 132| 134|     |     |     |     |     |
| 15 | Brooks et al [37] | 2005 | 171| 89 |     |     |     |     |     |
| 16 | Larson et al [67] | 2005 | 534| 533|     |     |     |     |     |
| 17 | Patel et al [43]  | 2005 | 102| 98 |     |     |     |     |     |
| 18 | Valely et al [25] | 2005 | 107| 108|     |     |     |     |     |
| 19 | Fischer Walker et al [40]| 2006 | 538| 536|     |     |     |     |     |
| 20 | Awasthi et al [49] | 2006 | 1010| 992|     |     |     |     |     |
| 21 | Boran et al [36]  | 2006 | 150| 130|     |     |     |     |     |
| 22 | Roy et al [52]    | 2007 | 28 | 28 |     |     |     |     |     |
| 23 | Gregorio et al [41]| 2007 | 60 | 57 |     |     |     |     |     |
| 24 | Roy et al [32]    | 2008 | 82 | 82 |     |     |     |     |     |
| 25 | Patel et al [31]  | 2009 | 535| 273|     |     |     |     |     |
| 26 | Fijolu et al [29] | 2009 | 30 | 30 |     |     |     |     |     |

X indicates that the trial was included in the specified meta-analysis.

M1, Bhutta et al 2000 [9]; M2, Lukacik et al 2008 [17]; M3, Patro et al 2008 [18]; M4, Lazzarini et al 2008 [16]; M5, Haider and Bhutta [15].

Zn, Number of subjects in the Zn supplementation Group; Pl, Number of subjects in the placebo Group.

doi:10.1371/journal.pone.0010386.t001

Investigation into the heterogeneity: meta-analyses and meta-regressions

The systematic map shows that accompanying the influence of zinc supplementation on diarrhea was heterogeneity of the results across the published trials. We therefore conducted an investigation into the potential contributors to this heterogeneity. Summarizing results from Tables 1 and 2, we focused our analyses on two outcomes: mean duration of diarrhea in therapeutic trials and the risk of vomiting in therapeutic trials. For each of these outcomes we first implemented a random effects meta-analysis and then undertook subgroup meta-analysis and meta-regression.

### Zinc supplementation and mean diarrheal duration from therapeutic trials.

Our updated meta-analysis for this outcome (Figure 2) showed that the published data come off 26 comparisons from 19 trials [25,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48] representing 8,957 children. We excluded trials that either studied the effects of zinc supplementation on future episodes or did not report the mean duration (and measures of variability) of the current diarrheal episodes [29,49,50,51,52,53]. Our results support a statistically significant effect of zinc supplementation on mean diarrheal duration [standardized mean difference (SMD) $-0.25$, 95% CI $-0.35$ – $-0.15$]. Considering the statistical properties of SMD [54], this translates into a reduction in mean diarrheal duration by 19.7% (95% CI 11.9%–27.4%). The extent of heterogeneity across studies was statistically significant ($I^2 86.5\%$, $p<0.001$). For this outcome our subgroup meta-analyses (Table 4) showed that the country of origin could not explain the heterogeneity, however age <12 months and study setting were associated with a differential reduction in the mean diarrheal duration. We also observed that the beneficial effect of zinc was influenced by studies that recruited all the study subjects before 12 months of age. We observed that in the five study groups from two studies that recruited infants only the SMD was 0.06 whereas when analysis was restricted to the studies that included other age groups also the SMD was $-0.32$ – a difference
### Table 2. Outcomes and summary effects related to acute diarrhea observed in published meta-analyses.

| Outcome                               | Meta-analysis | RCTs | N     | Statistic | ES    | 95% CI   | I² (%) | p      |
|---------------------------------------|---------------|------|-------|-----------|-------|----------|--------|--------|
| Recovery from diarrhea                | M1            | 3    | 2446  | RH        | 0.85* | 0.76–0.95 | 65, 0.04|
| Diarrhea at day 1                     | M2            | 5    | 3100  | RR        | 1.01  | 0.99–1.03 | 63, 0.03|
| Diarrhea at day 3                     | M2            | 6    | 3908  | RR        | 0.97  | 0.91–1.03 | 55, 0.05|
| M3                                    | 3             | 1630 | RR    | 0.62*     | 0.44–0.87 | --- |
| Diarrhea at day 5                     | M2            | 6    | 3908  | RR        | 0.94  | 0.84–1.05 | 74, 0.002|
| M3                                    | 2             | 346  | RR    | 0.68      | 0.11–4.31 | --- |
| M4                                    | 2             | 346  | RR    | 0.55*     | 0.32–0.95 | 43, 0.19|
| Diarrhea for ≥7 days                  | M1            | 3    | 289   | OR        | 0.78  | 0.56–1.09 | 0, 0.71 |
| M3                                    | 8             | 5769 | RR    | 0.71*     | 0.53–0.96 | --- |
| M4                                    | 10            | 4087 | RR    | 0.71*     | 0.52–0.98 | 73, 0.0001|
| Duration of diarrhea                  | M1            | 5    | 3177  | %         | 16.2* | 6.8–25.6 | 0, 0.56 |
| M2                                    | 16            | 15272| %     | 15.0      | ---   | 84, 7.5×10^{-14} |
| M3                                    | 13            | 5643 | WMD, d| 0.24*     | 0.21–0.27 | 84.3, 8.9×10^{-14} |
| M4                                    | 13            | 2741 | WMD, h| –12.27*   | –23.02–1.52 | 85, 1.8×10^{-11} |
| M5                                    | 14            | 5670 | WMD, d| –0.50*    | –0.82–0.08 | 84, 4.1×10^{-12} |
| Stool frequency                       | M2            | 7    | 3117  | %         | 18.0  | ---   | --- |
| M3                                    | 3             | 1384 | WMD   | –0.02     | –0.29–0.25 | --- |
| M4                                    | 7             | 1458 | WMD   | –0.02     | –0.19–0.15 | 53, 0.05 |
| Stool output                          | M2            | 3    | 478   | %         | 30.3  | ---   | --- |
| M3                                    | 3             | 606  | WMD   | –0.38     | –1.04–0.27 | --- |
| Vomiting                              | M2            | 11   | 4438  | RR        | 1.55* | 1.30–1.84 | 60.8, 0.004|
| M3                                    | 5             | 3156 | RR    | 1.22*     | 1.05–1.43 | --- |
| M4                                    | 10            | 4727 | RR    | 1.71*     | 1.27–2.30 | 69.3, 0.001|
| Watery stools                         | M3            | 3    | 3476  | RR        | 0.86* | 0.77–0.97 | --- |

M1, Bhutta et al 2000 [9]; M2, Lukacik et al 2008 [17]; M3, Patro et al 2008 [18]; M4, Lazzerini et al 2008 [16]; M5, Haider and Bhutta [15].

OR, odds ratio; RR, relative risk; RH, relative hazards; WMD, weighted mean difference; RCT, Lumber of randomized control trials used; N, Number of subjects included in meta-analysis; ES, summary effect size; CI, confidence interval; d, days; h, hours; %, %, percentage reduction.

M1 reported Q statistic and degrees of freedom and the I² statistic was derived using the formula I² = (Q-df)/Q. *, statistically significant; ---, not mentioned and not estimable.

doi:10.1371/journal.pone.0010386.t002

### Table 3. Outcomes and summary effects related to persistent diarrhea observed in published meta-analyses.

| Outcome                               | Meta-analysis | RCTs | N     | Statistic | ES    | 95% CI   | I² (%) | p      |
|---------------------------------------|---------------|------|-------|-----------|-------|----------|--------|--------|
| Recovery from persistent diarrhea     | M1            | 4    | 680   | RH        | 0.76* | 0.63–0.91 | --- |
| Occurrence of diarrhea at day 1       | M2            | 2    | 221   | RR        | 1.00  | 0.93–1.08 | 0, 0.93 |
| Occurrence of diarrhea at day 3       | M2            | 2    | 221   | RR        | 0.70* | 0.51–0.94 | 0, 0.56 |
| Continuation of diarrhea ≥7 days      | M1            | 4    | 680   | RR        | 0.61  | 0.26–1.46 | --- |
| Duration of persistent diarrhea       | M1            | 4    | 680   | %         | 29.3* | 6.0–52.5 | 0, 0.559|
| M2                                    | 5             | 489  | %     | 15.5     | ---   | --- |
| Vomiting                              | M2            | 5    | 489   | WMD, d   | 0.299*| 0.120–0.478 | 29.9, 0.544|

M1, Bhutta et al 2000 [9]; M2, Lukacik et al 2008 [17].

OR, odds ratio; RR, relative risk; RH, relative hazards; WMD, weighted mean difference; RCT, Lumber of randomized control trials used; N, Number of subjects included in meta-analysis; ES, summary effect size; CI, confidence interval; d, days; %, %, percentage reduction.

M1 reported Q statistic and degrees of freedom and the I² statistic was derived using the formula I² = (Q-df)/Q. *, statistically significant; ---, not mentioned and not estimable.

doi:10.1371/journal.pone.0010386.t003
that was highly statistically significant (unpaired Student’s t test p-value for difference in SMDs = 0.006). The hospital-based studies [25,31,32,33,35,37,38,39,43,45,46] were more likely to show improvement as compared to studies conducted in community settings [34,40,41,42,47,48] (SMD 20.33 versus 20.13, respectively and unpaired Student’s t test p value = 0.049). Studies using zinc gluconate [34,47,48] and those using vitamin A as a co-intervention [25,39,48] showed a significant reduction in diarrheal duration and were homogeneous (Table 4).

We also explored the effect of causative organisms. Seven trials [31,32,33,35,38,45,46] have reported the array of causative organisms for diarrhea and in the present review we observed that the effect of zinc on mean diarrheal duration was significant in trials not reporting Esherichia coli and rotavirus as the causes (SMD 20.14, 95% CI 20.21–20.07; data not shown). Finally, results of our meta-regression analyses showed (Figure 3a and c) that the dose of zinc was the only variable that was statistically significantly associated with diarrheal duration — trials using higher doses generally reported larger effect of zinc supplementation on mean diarrheal duration (p = 0.02). Interestingly, average baseline zinc levels did not contribute to between-study variations in the effect size (p = 0.70).

**Zinc supplementation and risk of vomiting.** Rates of vomiting after zinc administration have been reported in 14 comparisons from 10 trials [25,34,35,36,37,40,44,46,47,48] representing 6,779 children. In a quantitative synthesis of these results (Figure 4), we observed that the risk of vomiting was significantly increased after zinc administration [19.2% in the zinc supplemented group and 9.2% in the zinc withheld group] summary OR 2.13, 95% CI 1.37–3.31). However, this zinc effect was significantly heterogeneously distributed across the trials (I2 81.2%, p < 0.001).

In the subgroup analyses (Table 4) we found that studies from India [34,35,40,47], studies using zinc acetate [37], those using multivitamins as a co-intervention [35,47], and those in which the efficiency of the blinding procedure was unclear [25,36,44] were homogeneous in terms of the reported associations. Of these subgroups, the studies from India, studies using zinc acetate and those using multivitamins did not show a significant association of zinc supplementation with vomiting. The strongest association with vomiting was found in studies [34,36,37,40,44,48] that used no co-intervention in addition to zinc (OR 2.55, 95% CI 1.40–4.63). In addition, well-blinded studies [34,35,37,40,47,48], those studies conducted in hospital settings [25,35,37] and studies using zinc gluconate [34,47,48] reported a high degree of association between zinc supplementation and the risk of vomiting. In meta-regression analyses (Figure 3b and d), we observed that the
duration of diarrhea before admission (13 comparison groups, p = 0.005), the proportion of the children who were stunted (8 comparison groups, p = 0.027) and the proportion of children who were breastfed (6 comparison groups, p = 0.006) were the variables that were significantly associated with the reported rates of vomiting. Since the inference for the association of pre-admission diarrheal duration with vomiting came from almost all the studies included in this meta-regression, we specifically examined this association. The I² statistic after accounting for pre-admission diarrheal duration shrunk from 81.2% to 48.1% indicating that a large proportion of the variability across trials could be explained by the duration of pre-admission diarrhea.

### Table 4. Results of subgroup meta-analyses for the outcomes of mean diarrheal duration and risk of vomiting.

| Variable/Category | Duration | Vomiting |
|-------------------|----------|----------|
|                   | SG* | SMD | 95% CI | I² | SG* | OR | 95% CI | I² |
| Location          |     |     |       |    |     |    |        |    |
| India             | 10  | −0.23 | −0.42—−0.03 | 89.6 | 5  | 1.19 | 0.87—1.64 | 43.0 |
| Bangladesh        | 5   | −0.44 | −0.89—−0.02 | 92.8 | 2  | 2.18 | 0.91—5.22 | 0.0 |
| Indonesia         | 1   | −0.12 | −0.20—−0.04 | —   | —  |   |        |    |
| Nepal             | 3   | −0.21 | −0.28—−0.13 | 0.0  | 3  | 4.23 | 3.26—5.49 | 0.0 |
| Brazil            | 1   | −0.93 | −1.41—−0.45 | —   | —  |   |        |    |
| Turkey            | 2   | −0.44 | −0.84—−0.04 | 77.5 | 2  | 6.18 | 1.92—19.9 | 0.0 |
| Australia         | 1   | −0.01 | −0.20—−0.18 | —   | 1  | 0.51 | 0.05—5.71 | —   |
| Pakistan          | 1   | 0.07  | −0.09—0.24 | —   | —  |   |        |    |
| Ethiopia          | 1   | −0.10 | −0.39—−0.20 | —   | —  |   |        |    |
| Philippines       | 1   | −0.52 | −0.89—−0.15 | —   | —  |   |        |    |
| Age ≥12m          |     |       |         |    |     |    |        |    |
| Yes               | 21  | 0.06  | −0.04—0.16 | 0.0  | 10 | 2.23 | 1.29—3.85 | 85.2 |
| No                | 5   | −0.32 | −0.44—−0.21 | 87.7 | 3  | 1.59 | 1.37—3.31 | 0.0 |
| Setting           |     |       |         |    |     |    |        |    |
| Hospital          | 13  | −0.42 | −0.67—−0.18 | 91.6 | 4  | 1.19 | 0.65—2.20 | 24.1 |
| Community         | 11  | −0.13 | −0.20—−0.05 | 65.7 | 7  | 2.26 | 1.33—3.84 | 87.0 |
| Unclear           | 2   | −0.44 | −0.84—−0.04 | 77.5 | 2  | 6.18 | 1.92—19.9 | 0.0 |
| Zinc salt         |     |       |         |    |     |    |        |    |
| Acetate           | 6   | −0.35 | −0.64—−0.07 | 91.5 | 2  | 2.18 | 0.91—5.22 | 0.0 |
| Gluconate         | 6   | −0.18 | −0.24—−0.11 | 30.0 | 6  | 2.44 | 1.33—4.47 | 88.0 |
| Sulfate           | 14  | −0.31 | −0.51—−0.11 | 88.8 | 5  | 1.58 | 0.78—3.21 | 61.4 |
| Co-intervention   |     |       |         |    |     |    |        |    |
| None              | 14  | −0.16 | −0.26—−0.07 | 72.5 | 8  | 2.55 | 1.40—4.63 | 82.8 |
| Vitamin A         | 3   | −0.15 | −0.25—−0.05 | 21.1 | 2  | 2.07 | 0.30—14.4 | 64.3 |
| Multivitamins     | 2   | −1.01 | −2.59—0.58 | 97.5 | 2  | 0.87 | 0.52—1.44 | 0.0 |
| Erythromycin      | 1   | −0.33 | −0.64—−0.02 | —   | —  |   |        |    |
| ORS               | 6   | −0.43 | −0.79—−0.08 | 93.5 | 1  | 1.74 | 1.14—2.66 | —   |
| Efficient blinding|     |       |         |    |     |    |        |    |
| Yes               | 17  | −0.24 | −0.36—−0.15 | 89.0 | 9  | 2.01 | 1.26—3.21 | 84.8 |
| Unclear           | 7   | −0.29 | −0.51—−0.07 | 75.2 | 3  | 3.28 | 0.67—16.1 | 42.0 |

*, Number of study groups included in meta-analysis.

doi:10.1371/journal.pone.0010386.t004

### Influence of zinc supplementation on persistent diarrhea

Table 3 demonstrates that zinc supplementation has a clear benefit in reducing the incidence of persistent diarrhea by approximately 25%. It improved the recovery from persistent diarrhea by 24% and reduced the proportion of children with persistent diarrhea extending beyond three days after zinc supplementation by 30%. It also reduced the mean duration of persistent diarrhea by 21.5–29.3%, although it was associated with a significantly high risk of vomiting. For all these outcomes, the existing evidence demonstrates a high degree of homogeneity of effects across the published trials. The most recent meta-analysis [16] reported on five trials in children with persistent diarrhea [50,53,55,56,57]. Three trials reported on diarrhea at day three [44,48,56], three trials on diarrhea at day five [35,38,56] and nine at day seven [35,39,40,44,47,48,50,52,56]. There was a reduction in persistent diarrhea by −15.84% [95% CI −25.43—−6.24%]. As no new trials on influence of zinc on outcomes of persistent diarrhea have been published since the publication of these meta-analyses, we did not conduct a redundant synthetic investigation into this effect of zinc. Also, due to the small number of trials we did not conduct subgroup analyses or meta-regression for the outcome of persistent diarrhea.

---

**Zinc in Therapy of Diarrhea**

*PLoS ONE | www.plosone.org 6 April 2010 | Volume 5 | Issue 4 | e10386*
Discussion

The results of our systematic review suggest that zinc supplementation reduced the mean duration of acute diarrhea by approximately 20%, and persistent diarrhea by 15–30%, but had no significant effect on stool frequency or stool output. Further it was associated with a two- to three-fold higher risk of regurgitation in acute and persistent diarrhea, respectively. There was a high degree of statistically significant heterogeneity across the published studies for the effects of zinc supplementation on mean diarrheal duration and risk of vomiting following the administration of zinc.

Consistent with the existing understanding [15,58], the therapeutic trials showed that zinc would reduce diarrhea by nearly a day for an average episode of five days, but again there was a high degree of heterogeneity of this effect across the published studies. The World Health Organization (WHO) recommends zinc supplementation (10–20mg for 10–14 days) for treatment of acute diarrhea. [7] Although the recommendation does not specify the salt, our subgroup analysis showed a significant homogeneous reduction in diarrheal duration in studies using zinc gluconate [34,48] and those using vitamin A as a co-intervention [25,39,48] (Table 4). Vitamin A supplementation up-regulates the Th2 immune response, while zinc supplementation up-regulates Th1 responses, and perhaps these interventions have synergistic effects, a research question which needs further exploration. [23]

Interestingly, higher doses of zinc in the therapeutic trials were associated with larger reductions in the mean duration of diarrhea. It is difficult to comment on the potential relationship between zinc dose and diarrheal duration in the context of achieving a balance between the reduction of diarrhea and risk of vomiting. If similar benefits of treatment are possible with lower doses and there is a lower risk of vomiting with these doses then lower doses
might be advisable. Specific dose-response trials to examine this question would therefore be more appropriate. Similarly, the fact that subgroup analysis but not meta-regression demonstrated a differential benefit of zinc supplementation indicates that there may be a threshold for age beyond which zinc supplementation may be useful. However, the lack of an association between mean age in a trial and the effect of zinc may also reflect a lack of informative content in mean age as a contributor to heterogeneity and thus trials focused to address these issues would be appropriate.

An important finding from our analyses was that zinc supplementation showed no effect on stool frequency and output. This opens up the possibility that care-givers may not perceive a beneficial impact of treating their children with zinc, which might negatively affect their adherence to the treatment regime. Another potential barrier to treatment adherence with zinc supplements was the significantly increased risk of vomiting. These findings imply that use of zinc supplements is unlikely to improve compliance with the treatment for diarrheal disease. It is noteworthy however, that a recent study of the safety of zinc supplementation in acute diarrhea suggests that most of the patients regurgitate only once – a phenomenon that may not affect the continuation of zinc therapy. [59] Further, in our subgroup analyses, compared to zinc acetate, zinc gluconate was significantly associated with a reduction in the duration of diarrhea but also showed a significantly increased risk of vomiting. These findings highlight the imbroglio facing those designing an intervention program - which salt should be used, at what dose, frequency, and duration, to maximize the acceptance and benefits of zinc supplementation as an adjunct in the treatment of childhood diarrhea. Moreover, the fact that zinc supplementation was beneficial in the absence of E. coli and rotavirus calls for a closer look into the clinical and public health scenarios where this intervention may be most beneficial. Whether such a strategy of zinc supplementation that is tiered on the basis of the causative organism will be efficacious and effective is currently unknown. The WHO recommendations do not fully address these issues and protocols for the use of zinc in diarrhea treatment programs need revisiting. Stunted children are likely to be zinc deficient and therefore should benefit from zinc supplementation [60,61]. Our analysis surprisingly showed that factors such as age, malnutrition (proportion stunted and wasted), breast feeding, dehydration at enrolment and baseline zinc, which have previously been reported to affect the response to zinc for reducing duration of diarrhea, did not show a statistically significant effect. It should be noted, however, that the baseline plasma zinc concentrations reported in trials may not fully capture the state of zinc deficiency in the children. Such values are likely confounded by acute phase response, diurnal variations and time since previous meals [62,63,64]. Therefore, our observed lack of an association between baseline plasma concentration and zinc efficacy should be cautiously interpreted. On the other hand diarrheal duration before admission, stunting, wasting, and being breast fed were factors significantly associated with the reported rates of vomiting following supplementation with zinc. Thus, the population most likely to benefit from zinc supplementation was also the population at an increased risk of vomiting.

Figure 4. Forest plot depicting the studies included in our meta-analysis for the outcome of risk of vomiting. Red squares and lines indicate the point and 95% confidence intervals for the odds ratios (OR) and the red diamond denotes the point and confidence interval for the summary effect size. Suffixes a, b and c indicate specific zinc-treated subgroups within the indicated study. Weights are expressed in percentage.

doi:10.1371/journal.pone.0010386.g004
Meta-analyses and meta-regression, like any study design, have inherent limitations. For example, because only a few studies reported information on most of the predictor variables simultaneously, we could not conduct multivariate meta-regression analyses. Thus, the importance of the factors that we identified is unknown in a multivariate context. In addition, even though meta-regression can provide important clues into the potential contributors to the summary effect size [65], it can only examine those covariates reported in the trials examined. Only eight trials [24,31,32,33,34,38,45,46] have reported as covariates, diarrheal etiology or causative organisms as covariates. In the present review, we observed that the effect of zinc on mean diarrheal duration was significant in trials where Escherichia coli and rotavirus were not causes of the diarrhea (SMD −0.14, 95% CI −0.21—−0.07). The role of other unknown covariates like adherence and acceptability remains unknown. Indeed, we did observe that significant heterogeneity across study results remained even after accounting for the potential predictors of between-study heterogeneity. Lastly, subgroup analyses and meta-regression are, by disposition, exploratory tools to provide pointers towards possible sources of heterogeneity - they cannot be taken as confirmatory tests for definitive conclusions and interpretations about the causes of heterogeneity.

Our findings for the use of zinc in the treatment of diarrhea indicate the need to improve upon the current strategy of zinc supplementation for all children with diarrhea, by selecting the populations most likely to benefit from supplementation and using the most effective zinc salt. There is a need to optimize the use of zinc supplementation in childhood diarrheas and this will require further investigation of the factors leading to the heterogeneity of the effects of zinc as an adjunct in its treatment.

Author Contributions

Conceived and designed the experiments: ABP MM MJD HK. Analyzed the data: ABP MM NB HK. Wrote the paper: ABP MM MJD NB HK.

References

1. Boschi-Pinto C, Velteb L, Shibuya K (2000) Estimating child mortality due to diarrhoea in developing countries. Bull World Health Organ 88: 710–717.
2. O’Ryan M, Prado V, Picking LR (2005) A millennium update on pediatric diarrheal illness in the developing world. Semin Pediatr Infect Dis 16: 125–136.
3. Turner SM, Scott-Tucker A, Cooper LM, Henderson IR (2006) Weapons of mass destruction: factors of the global killer enterotoxigenic Escherichia coli. FEMS Microbiol Lett 263: 10–20.
4. Bhan MK (2000) Current and future management of childhood diarrhhea. Int J Antimicrob Agents 14: 71–73.
5. Curtis V (2003) Talking dirty: how to save a million lives. Int J Environ Health Res 13 Suppl 1: 78–79.
6. Forsberg BC, Petzold MG, Tomson G, Allebeck P (2007) Diarrhoea case management in low- and middle-income countries: an unfinished agenda. Bull World Health Organ 85: 42–48.
7. WHO/UNICEF (2004) WHO/UNICEF joint statement: clinical management of acute diarrrhea. Geneva, Switzerland: WHO/UNICEF. pp 1–8.
8. Winch PJ, Gilroy KE, Fischer Walker CL (2008) Effect of HIV/AIDS and malaria on the context for introduction of zinc treatment and low-osmolality ORS for childhood diarrhea. J Health Popul Nutr 26: 1–11.
9. Bhutta ZA, Bird SM, Black RE, Brown KH, Gardner JM, et al. (2000) Therapeutic effects of oral zinc in acute and persistent diarrheal children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 72: 1516–1522.
10. Black RE (1998) Therapeutic and preventive effects of zinc on serious childhood infectious diseases in developing countries. Am J Clin Nutr 68: 4768–4788.
11. Black RE (2000) Zinc deficiency, infectious disease and mortality in the developing world. J Nutr 133: 1405S–1409S.
12. Black RE, Sarazaw N (2001) Zinc and childhood infectious disease morbidity and mortality. Br J Nutr 85 Suppl 2: S125–129.
13. Fischer Walker C, Black RE (2004) Zinc and the risk for infectious disease. Annu Rev Nutr 24: 235–273.
14. Bhatnagel N, Mazumder S, Taneja S, Dude B, Agarwal RG, et al. (2008) Effectiveness of zinc supplementation plus oral rehydration salts compared with oral rehydration salts alone as a treatment for acute diarrhoea in a primary care setting: a cluster randomized trial. Pediatrics 121: e1279–1283.
15. Haider BA, Bhutta ZA (2009) The effect of therapeutic zinc supplementation among young children with selected infections: a review of the evidence. Food Nutr Bull 30: S41–S59.
16. Lazzarini M, Ronfani L (2008) Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev: CD005456.
17. Lukasik M, Thomas RL, Aranda JV (2008) A meta-analysis of the effects of oral zinc in the treatment of acute and persistent diarrheaa. Pediatrics 121: 326–336.
18. Patro B, Gelicki D, Sajzewiwa H (2008) Meta-analysis: zinc supplementation for acute gastroenteritis in children. Aliment Pharmacol Ther 20: 713–725.
19. Salvatore S, Hausser B, Devreker T, Vietri MC, Lumi C, et al. (2007) Probiotics and zinc in acute infectious gastroenteritis in children: are they effective? Nutrition 23: 498–506.
20. Aggarwal R, Senet J, Miller MA (2007) Role of zinc administration in prevention of childhood diarrheas and respiratory illnesses: a meta-analysis. Pediatrics 119: 1120–1130.
21. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, et al. (1999) Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators Collaborative Group. J Pediatr 135: 689–697.
22. Canani RB, Cirillo P, Baccigrossi V, Rustolo S, Passariello A, et al. (2005) Zinc inhibits cholera toxin-induced, but not Escherichia coli heat-stable enterotoxin-included, ion secretion in human enterocytes. J Infect Dis 191: 1037–1047.
23. Long KZ, Rosado JL, Monroya Y, de Lourdes Solano M, Hertzmark E, et al. (2007) Effect of vitamin A and zinc supplementation on gastrointestinal parasitic infections among Mexican children. Pediatrics 120: e184–853.
24. Roy SK, Rasgh R, Khattan W, Azim T, Chowdhury R, et al. (2000) Zinc supplementation in the management of shigellosis in malnourished children in Bangladesh. Eur J Clin Nutr 62: 849–853.
25. Valery PC, Tizollio PJ, Boyce NC, White AV, Stewart PA, et al. (2005) Zinc and vitamin A supplementation in Australian Indigenous children with acute diarrhoea: a randomised controlled trial. Med J Aust 182: 530–535.
26. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21: 1539–1558.
27. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177–188.
28. Thompson SG, Higgins JP (2002) How should meta-regression analyses be undertaken and interpreted? Stat Med 21: 1593–1573.
29. Fajolobu E, Enolopae A, Odowole AO, Silva BO, Abidey RO, et al. (2008) Zinc supplementation in children with acute diarrhoea. Niger J Hosp Med 18: 101–103.
30. Nahreed A, Walker Fischer CL, Moundal D, Ahmed S, Arifeen SE, et al. (2009) Zinc therapy for diarrhoea improves growth among Bangladeshi infants 6 to 11 months of age. J Pediatr Gastroenterol Nutr 48: 89–93.
31. Patel AB, Dibley MJ, Mamanti MR, Badhoninya N, Kulkarni H (2009) Zinc and copper supplementation in acute diarrhoea in children: A double-blind randomized controlled trial. BMC Medicine 7: 25.
32. Roy SK, Hosain MJ, Khattan W, Chakrabartty B, Chowdhury S, et al. (2008) Zinc supplementation in children with cholera in Bangladesh: randomised controlled trial. BMJ 336: 266–268.
33. Al-Nasiboli N, Graggel RJ, Sheiran A, Hart CA, Caeve LE (2003) Zinc supplementation in Brazilian children with acute diarrhoea. Ann Trop Paediatr 23: 3–4.
34. Bahl R, Bhandari N, Saxena M, Strand T, Kumar GT, et al. (2002) Efficacy of zinc-fortified oral rehydration solution in 6- to 35-month-old children with acute diarrhoea. J Pediatr 141: 677–682.
35. Bhatnagar S, Bahl R, Sharma PK, Kumar GT, Saxena SK, et al. (2004) Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial. J Pediatr Gastroenterol Nutr 38: 34–40.
36. Boran P, Tokuc G, Vagas E, Oktene S, Gokulum M (2006) Impact of zinc supplementation in children with acute diarrhoea in Turkey. Arch Dis Child 91: 295–299.
37. Brooks WA, Santosham M, Roy SK, Faruque AS, Wahed MA, et al. (2005) Efficacy of zinc in young infants with acute watery diarrheaa. Am J Clin Nutr 82: 605–610.
38. Dutta P, Mitra U, Dutta A, Niyogi SK, Dutta S, et al. (2000) Impact of zinc supplementation in malnourished children with acute watery diarrheaa. J Trop Pediatr 46: 258–269.
39. Faruque AS, Mahalanabis D, Haque SS, Fuchs GJ, Hadte D (1999) Double-blind, randomized, controlled trial of zinc or vitamin A supplementation in young children with acute diarrhoea. Acta Paediatr 88: 154–160.
40. Fischer Walker CL, Bhutta ZA, Bhandari N, Tekn T, Shafih F, et al. (2006) Zinc supplementation for the treatment of diarrhea in infants in Pakistan, India and Ethiopia. J Pediatr Gastroenterol Nutr 43: 337–363.
41. Gregorio GV, Dams LF, Cordero CP, Pascual CA (2007) Zinc supplementation reduced cost and duration of acute diarrhees in children. J Clin Epidemiol 60: 560–566.
42. Hidayat A, Achadi A, Sunoto, Soedarmo SP (1998) The effect of zinc sulfate supplementation in children under three years of age with acute diarrhea in Indonesia. Med J Indonesia 7: 237–241.
43. Patel AB, Bhande LA, Rawat MS (2005) Therapeutic evaluation of zinc and copper supplementation in acute diarrhea in children: double blind randomized trial. Indian Pediatr 42: 433–442.
44. Polat TB, Uysal M, Çetinkaya F (2003) Efficacy of zinc supplementation on the severity and duration of diarrhea in malnourished Turkish children. Pediatr Int 45: 535–539.
45. Roy SK, Tomkins AM, Akramuzzaman SM, Behrens RH, Haider R, et al. (1997) Randomized controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. Arch Dis Child 77: 196–200.
46. Sachdev HP, Mittal NK, Mittal SK, Yadav HS (1988) A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. J Pediatr Gastroenterol Nutr 7: 877–881.
47. Sazawal S, Black RE, Bhan MK, Bhandari N, Sinha A, et al. (1995) Zinc supplemented young children with acute diarrhea in India. N Engl J Med 333: 839–844.
48. Strand TA, Chandyo RK, Bahl R, Sharma PR, Adhikari RK, et al. (2002) Effectiveness and efficacy of zinc for the treatment of acute diarrhea in young children. Pediatrics 109: 890–903.
49. Awasti S (2006) Zinc supplementation in acute diarrhea is acceptable, does not interfere with oral rehydration, and reduces the use of other medications: a randomized trial in five countries. J Pediatr Gastroenterol Nutr 42: 300–305.
50. Khatun U, Malek MA, Black RE, Sarkar NR, Wahed MA, et al. (2001) A randomized controlled clinical trial of zinc, vitamin A or both in undernourished children with persistent diarrhea in Bangladesh. Acta Paediatr 90: 376–380.
51. Larson CP, Roy SK, Khan AI, Rahman AS, Qadri F (2008) Zinc treatment to under-five children: applications to improve child survival and reduce burden of disease. J Health Popul Nutr 26: 356–365.
52. Roy SK, Tomkins AM, Akramuzzaman SM, Chakraborty B, Ara G, et al. (2007) Impact of zinc supplementation on subsequent morbidity and growth in Bangladeshi children with persistent diarrhoea. J Health Popul Nutr 25: 67–74.
53. Roy SK, Tomkins AM, Mahalanabis D, Akramuzzaman SM, Haider R, et al. (1998) Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children. Acta Paediatr 87: 1255–1259.
54. Friedich JO, Adhikari NK, Beyer J (2008) The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: a simulation study. BMC Med Res Methodol 8: 32.
55. Bhutta ZA, Nizami SQ, Imani Z (1999) Zinc supplementation in malnourished children with persistent diarrhea in Pakistan. Pediatrics 103: e42.
56. Penny ME, Peerson JM, Marin RM, Duran A, Lanata CF, et al. (1999) Randomized, community-based trial of the effect of zinc supplementation, with and without other micronutrients, on the duration of persistent childhood diarrhea in Lima, Peru. J Pediatr 135: 208–217.
57. Sachdev HP, Mittal NK, Yadav HS (1990) Oral zinc supplementation in persistent diarrhoeas in infants. Ann Trop Paediatr 10: 63–69.
58. Brown KH, Baker SK (2009) Galvanizing action: conclusions and next steps for mainstreaming zinc interventions in public health programs. Food Nutr Bull 30: S79–184.
59. Khan AM, Larson CP, Faruque AS, Saha UR, Hoque AB, et al. (2007) Introduction of routine zinc therapy for children with diarrhoea: evaluation of safety. J Health Popul Nutr 25: 127–133.
60. Dewey KG, Cohen RJ (2007) Does birth spacing affect maternal or child nutritional status? A systematic literature review. Matern Child Nutr 3: 151–173.
61. Fischer Walker CL, Black RE (2007) Functional indicators for assessing zinc deficiency. Food Nutr Bull 28: S454–479.
62. King JC, Hambidge KM, Westcott JL, Kern DL, Marshall G (1994) Daily variation in plasma zinc concentrations in women fed meals at six-hour intervals. J Nutr 124: 508–516.
63. McMillan EM, Rose DJ, Halberg F (1987) Diurnal stage of circadian rhythm of plasma zinc in healthy and pneumoni volunteers. Prog Clin Biol Res 227B: 295–303.
64. Raqib R, Roy SK, Rahman MJ, Azim T, Ameer SS, et al. (2004) Effect of zinc supplementation on immune and inflammatory responses in pediatric patients with diarrhea. Ann J Clin Nutr 79: 444–450.
65. Thompson SG, Higgins JP (2005) Treating individuals 4: can meta-analysis help target interventions at individuals most likely to benefit? Lancet 365: 341–346.
66. Baqui AH, Black RE, El Arifeen S, Yunus M, Chakraborty J, et al. (2002) Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. Brmj 325: 1059.
67. Larson CP, Hoque AB, Larson CP, Khan AM, Saha UR (2005) Initiation of zinc treatment for acute childhood diarrhoea and risk for vomiting or regurgitation: a randomized, double-blind, placebo-controlled trial. J Health Popul Nutr 23: 311–319.