Economic evaluation of zinc and copper use in treating acute diarrhea in children: A randomized controlled trial
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Abstract

Background: The therapeutic effects of zinc and copper in reducing diarrheal morbidity have important cost implications. This health services research study evaluated the cost of treating a child with acute diarrhea in the hospital, the impact of micronutrient supplementation on the mean predicted costs and its cost-effectiveness as compared to using only standard oral rehydration solution (ORS), from the patient's and government's (providers) perspective.

Methods: Children aged 6 months to 59 months with acute diarrhea were randomly assigned to receive either the intervention or control. The intervention was a daily dose of 40 mg of zinc sulfate and 5 mg of copper sulfate powder dissolved in a liter of standard ORS (n = 102). The control was 50 mg of standard ORS powder dissolved in a liter of standard ORS (n = 98). The cost measures were the total mean cost of treating acute diarrhea, which included the direct medical, the direct non-medical and the indirect costs. The effectiveness measures were the probability of diarrhea lasting ≤ 4 days, the disability adjusted life years (DALYs) and mortality.

Results: The mean total cost of treating a child with acute diarrhea was US $14 of which the government incurred an expenditure of 66%. The factors that increased the total were the number of stools before admission (p = 0.01), fever (p = 0.01), increasing grade of dehydration (p = 0.00), use of antibiotics (p = 0.00), use of intra-venous fluids (p = 0.00), hours taken to rehydrate a child (p = 0.00), the amount of oral rehydration fluid used (p = 0.00), presence of any complications (p = 0.00) and the hospital stay (p = 0.00). The supplemented group had a 8% lower cost of treating acute diarrhea, their cost per unit health (diarrhea lasting ≤ 4 days) was 24% less and the incremental cost-effectiveness ratio indicated cost savings (in Rupees) with the intervention [-452; 95%CI (-11306, 3410)]. However these differences failed to reach conventional levels of significance.

Conclusion: An emphasis on the costs and economic benefits of an alternative therapy is an important aspect of health services research. The cost savings and the attractive cost-effectiveness indicates the need to further assess the role of micronutrients such as zinc and copper in the treatment of acute diarrhea in a larger and more varied population.
Background

Diarrhea remains a major cause of morbidity and mortality in developing countries with a significant proportion experiencing a depletion of zinc and copper micronutrient stores. Community-based randomized controlled trials have shown a beneficial effect of zinc supplementation in reducing the severity and duration of diarrhea. However, zinc supplementation has the potential to aggravate marginal copper deficiency, which in turn may impact negatively on the diarrheal morbidity [1]. This health services research study evaluated the economic impact and benefits of zinc and copper supplementation for treatment of acute diarrhea in a randomized, double blind, clinical trial.

The magnitude of the therapeutic effects of these micronutrient supplementation in reducing either the duration or the severity of diarrhea could compare favorably with other health interventions being implemented in developing countries to improve child health and survival. A decrease in severity and duration reduces costs, which may partly or totally, in the case of a dominant intervention, offset the costs of supplementation and also improve quality of life. Adding supplements of micronutrients to the standard management of diarrhea requires a change in treatment practices. Although this appears to be minimal and feasible from a cost perspective, in the face of limited resources, the effectiveness of this intervention must be considered to ensure that the opportunity costs incurred are minimized.

To date the cost-effectiveness of zinc and copper supplementation in the treatment of diarrhea has not been established. An essential element of this research is therefore to ascertain the efficiency of this supplementation. It is hypothesized that zinc and copper supplementation for treatment of acute diarrhea will be dominant compared to standard treatment from the provider's and patient's perspective (i.e. it will be both more efficacious and less costly). Our research questions were: What does it cost to treat a child of acute diarrhea in the hospital? Does the supplementation of zinc and copper to the oral rehydration solution (ORS) have an impact on the mean predicted costs of treating acute diarrhea and what is its incremental costs-effectiveness as compared to standard ORS?

Methods

Patient enrollment

This is a clinical trial that evaluated the therapeutic effect of zinc and copper supplementation added to standard oral rehydration solution (ORS) for treating acute diarrhea at the Nagpur city's Government Medical College and Hospital, India. This study was conducted in children aged 6 months to 59 months who presented to the hospital with more than three unformed stools in 24 hours and diarrheal duration of < 7 days. Any child with intractable vomiting, pre-renal or renal failure, respiratory distress, altered sensorium or any such co-morbid condition that precludes the use of oral rehydration solution (ORS) were excluded from the trial. Children with clinical signs of severe malnutrition such as kwashiorkor and marasmus were also excluded. Baseline assessment included diarrheal duration, character of the stool, degree of dehydration, age, gender, maternal education, number of children in the family, monthly parental income, diet of the child, immunization status, history of fever or vomiting, prior use of ORS, prior use of medications and the nutritional status. Children who had severe dehydration or inability to drink were temporarily excluded for 4 hours during which they received standard treatment. At the end of this time period they were reassessed for possible inclusion in the trial.

Intervention

The treatment was randomized at an individual level using a fixed randomization scheme with equal allocation of patients to the intervention and control group. The patients and the caregivers were blinded to the subject's treatment status. Two identical coded waterproof sachets of the intervention or the control were administered to the patient and the control group only once in a day. The intervention sachet contained 40 mg of Zinc sulfate and 5 mg of Copper sulfate powder. The control sachet contained 50 mg of standard ORS powder. These sachets were dissolved in one liter of ORS by the nurse. Each day a fresh solution was prepared till the diarrheal episode lasted. The children were encouraged to take their routine feeds. Patients were also provided with other usual supportive care with antipyretics and antibiotics for bloody diarrhea. Children needing intravenous fluids were randomized after they were able to take orally. If a child was dehydrated after 6 hours of oral rehydration or if signs of severe dehydration appeared despite appropriate ORS administration then they were administered intravenous fluids and this was recorded as an "unscheduled intravenous fluid".

Measurement of clinical outcomes

The children were assessed at the same time every 24 hours till discharge. The time taken to rehydrate the child from time of admission, episodes of vomiting, use of intravenous fluids during rehydration and the use of unscheduled intravenous fluids during the maintenance of hydration was measured daily. Any complications such as pre-renal or renal failure, convulsions, electrolyte imbalance, bronchopneumonia and septicemia were recorded. The use of other medication such as antibiotics was also recorded. Weight was recorded on admission and at discharge. A child was discontinued from the study if
the child experienced any of the above complications, died or if the parent withdrew consent.

The primary clinical outcome was the duration of diarrhea from the time of onset. A diarrheal day was defined as a 24-hour period with passage of at least four unformed stools and this episode was considered terminated on the last day of diarrhea followed by a 24-hour diarrheal free period. The number and proportion of patients with diarrhea > 4 days and the mean length of hospital stay was also estimated. The proportion of children with diarrhea > 4 days was estimated based on the results of the Indian community-based study of zinc supplementation, which indicated that the reduction in the duration of diarrhea was evident on the fourth day [2].

The severity of diarrhea was measured by the use of unscheduled intravenous fluids expressed as the number of subjects who received intravenous fluid at any time after randomization, weight loss at discharge, presence of complications or mortality.

Identifying and Measuring Costs

The cost data was collected to identify the direct medical, the direct non-medical and the indirect costs [3]. We used the actual financial and not economic costs and the rupee was valued in the year 1996 (1 $ = Rs. 36). The price paid for a service is a good reflection of the costs of producing the service in competitive markets which prevent both excess profits and negative expected profits [4]. Average variable costs were measured as a proxy for true marginal costs.

The resources utilized for the management of acute diarrhea and their unit costs were measured in order to determine three categories of costs (direct medical costs, direct non-medical costs, and indirect costs). We enumerated every input consumed by the patient and then its unit cost. This is known as "micro-costing" [5]. The direct medical costs were calculated from the patient’s and the government (provider’s) perspective. The measurement of the resources utilized was from the time of onset of diarrhea and during the study period. The direct medical cost to the patient included any out of pocket expenditures for medicines or the fees paid to the physician prior to seeking treatment at the government hospital. The direct medical cost to the ministry of health was the expenditure incurred by the hospital administration after randomization. The direct non-medical and the indirect costs were from the patient’s perspective. The protocol-driven costs were deducted from the total costs. The resource utilization was measured in a standard case-report form.

The direct medical costs included the services provided by the medical personnel, the medications, the type of service provided (general or intensive care) and the laboratory investigations. In the United States hospital cost accounting systems (data base for Disease related groups or DRGs, cost to charge ratios, etc) reimbursement systems for managed care and insurance allow assignment of costs to resources used, a process known as "gross accounting" [6]. In India, there is no established database of costs of medical services, investigations and the cost of hospital stay. These costs vary with respect to the type of medical services and hospital category. The government hospitals are subsidized, the charges at private and corporate hospitals overestimate costs whereas charges to the patients in non-for-profit hospitals are most likely to resemble the true costs. The unit charges account for the unit costs of the medical service rendered, the overhead and the administrative costs of that medical service and that of the supporting units. We calculated the unit costs of each patient visit at the outpatient clinic from the salaries of the staff working at this clinic times the proportion of their time spent rendering out-patient services, divided by the average number of attending patients. The cost was 1.5 times the amount actually charged to the patient by the government and resembled the cost structure of the non-for-profit hospitals. We therefore verified the other direct medical costs calculated by us by comparing it to the charges of non-profit hospitals. Similarly the cost of a day's stay for a patient, at the diarrhea treatment and training center or at the hospital ward, was calculated by summing the average per diem cost of stay in with the daily average per-patient labor charges of the doctors, the nurses and ward attendants. The per diem cost included the cost of subsidized meals. We estimated laboratory investigations in consultation with the laboratory administrators based on average labor costs of technicians, the costs of supplies, overheads and administration. The costs of drugs were the manufacture's wholesale price.

The direct non-medical cost of traveling to the physician or the hospital for the patient and the family, cost of food to the family and patient (only if it were not included in the per-diem hospital stay cost) during hospitalization and other incidental cost to the family but attributed to the illness were measured.

The indirect costs were measured by the wages lost of employed parents or guardians attending to the child with diarrhea. This is a conservative estimation, as monetary value is not assigned for the loss time of unemployed parents. We did not estimate intangible costs like pain, suffering and lost of leisure time.

Economic analysis

The mean (± SD) of the direct medical costs and its cost components such as the visit fees, costs of antibiotics, of intravenous fluids, of laboratory tests, of ORS, of length of
stay in the hospital, of out-patient visits were estimated. We also calculated the mean (± SD) of the direct non-medical and indirect costs in the study groups. The mean (± SD) of the total costs in the study groups was determined and the univariate and multivariate linear regression was used to determine the impact of the interventions, the pre and post randomization variables in predicting the total mean costs.

The cost-effectiveness of trace minerals was determined by 1) the total cost (Rs) per case of diarrhea > 4 days averted, 2) the total cost per death averted, and 3) the incremental cost effectiveness ratio (ICER), which is the ratio of difference (of the intervention and the control group) in total mean of costs in the numerator and the difference in the proportion of patients of diarrhea less than four days in the denominator. We constructed the 95% confidence intervals for the incremental cost effectiveness ratio. We used the non-parametric boot-strap method to assess the normality of this ratio and then constructed the confidence intervals [6].

We also calculated the ratio of the total mean cost and the mean number of patients with diarrhea less than 4 days (CE) for the intervention and the control group for the boot strap sample. This measured the mean cost per patient cured less that 4 days in each group. We then measured the relative cost-effectiveness (RCE) of the treatment group relative to that of the control with its 95% confidence intervals (CEtreatment / CEcontrol). STATA Version 5 was used for these statistical analyses.

Table 1: Base-line Demogrpahic Characteristics and Features of the Diarrheal Episode with Respect to Study Group*

| Characteristics                      | Treatment group (N = 102) | Control (N = 98) | P value |
|--------------------------------------|--------------------------|-----------------|---------|
| Age in months                        | 21.2 ± 14.2              | 21.4 ± 13.7     | 0.8     |
| Male sex (%)                         | 58.8                     | 49.9            | 0.16    |
| Monthly income Rs.                   | 1497 ± 1719              | 1436 ± 1428     | 0.62    |
| No. of children in the family        | 2.0 ± 0.9                | 2.1 ± 0.9       | 0.4     |
| Educational status of mother         |                          |                 |         |
| Illiterate(%)                        | 12.7                     | 23.4            | 0.11    |
| Primary                              | 7.8                      | 12.2            |         |
| Middle                               | 14.7                     | 14.2            |         |
| High                                 | 42.1                     | 37.7            |         |
| College                              | 22.5                     | 12.2            |         |
| Child’s diet (%)                     |                          |                 |         |
| Predominantly breast fed             | 15.6                     | 21.4            | 0.4     |
| Predominantly formula fed            | 5                        | 3               |         |
| Both                                 | 1                        | 3               |         |
| Other solid foods                    | 78.4                     | 72.6            |         |
| Immunization status (%)              |                          |                 |         |
| Unimmunized                          | 3.9                      | 7.1             | 0.4     |
| Incomplete                           | 14.7                     | 10.2            |         |
| Complete                             | 81.3                     | 82.6            |         |
| Weight (KG)                          | 8.2 ± 2.2                | 7.8 ± 2.1       | 0.2     |
| Height (CMS)                         | 77.3 ± 10.9              | 75.8 ± 9.9      | 0.3     |
| Wasting (%)                          | 58.2                     | 51              | 0.3     |
| Duration of diarrhea before enrollment(days) | 2.2 ± 1.4            | 2.2 ± 1.3       | 0.8     |
| No. of stools in the previous 24 hr  | 9.9 ± 6.3                | 9.3 ± 7.1       | 0.5     |
| Vomiting in 24 hr before enrollment (%) | 61.7                  | 55.1            | 0.3     |
| Fever during this episode(%)         | 39.2                     | 37.6            | 0.8     |
| Dehydration (%)                      |                          |                 |         |
| No                                   | 85.2                     | 82.6            | 0.8     |
| Some                                 | 11.7                     | 14.2            |         |
| Severe                               | 2.9                      | 3               |         |
| Type of stool                        |                          |                 |         |
| Watery or mucoid                     | 89.3                     | 87.8            | 0.2     |
| Bloody                               | 10.7                     | 12.2            |         |
| Hospitalized (%)                     | 57.8                     | 66              | 0.2     |

* Plus-minus values are mean ± SD
Disability adjusted life years (DALYs) are an indicator of the time lived with a disability and the time lost due to premature mortality [7]. This was calculated for all children in the study using their actual age, the number of days spent with diarrhea, and disability weights ranging from 0.4 to 0.6 (based on the severity of illness) with death weighted as 1. The discount rate was 5 %. We then calculated the mean (± SD) of DALYs lost in the two study groups.

**Results**

**Clinical Outcomes**

A total of 220 children (non-participation rate was 9 %) were enrolled in the study and were randomized to treatment (n = 102) and control (n = 98) groups. The baseline characteristics of the children in the two groups were similar (Table 1). The health outcomes in the study group were favorable but failed to reach significant levels. The study group also showed clinically important reductions in rate of complications and mortality (Table 2).

**Costs and Effectiveness Outcomes**

The average total cost of treating a patient with acute diarrhea was Rs. 500 (US$14). The patient and their families incurred 34% (direct medical cost: 4%, direct non-medical cost: 20%, and, the indirect cost: 10%) and the government incurred 66% of the total cost of treating a patient with acute diarrhea (Table 3). The mean cost of treating diarrhea incurred by the patient and the ministry of health in the treatment and the control group were not significantly different. Similarly the mean non-medical costs, the indirect costs and the total costs (medical, non-medical and the indirect costs) were similar in both groups (Table 3).

Univariate analysis showed that increasing age (p = 0.03), weight (p = 0.001), height (p = 0.002), and mid-arm circumference (p = 0.001), the intake of solid foods (p = 0.07), and if the child was completely immunized (p < 0.001) were associated with lower mean total cost for treating acute diarrhea. The variables that increased mean total costs were the number of stools before admission (p = 0.01), fever (p = 0.01), increasing grade of dehydration

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### Table 2: Clinical outcomes in the treatment and control group.

| Health Outcomes                  | Treatment | Control | Odds ratio [95%CI] | P value |
|----------------------------------|-----------|---------|--------------------|---------|
| Mean duration of diarrhea (m ± SE) | 4.34 ± 0.2 | 4.48 ± 0.2 |                     | 0.3     |
| Length of hospital stay (m ± SE)  | 1.6 ± 0.2 | 2 ± 0.2 |                     | 0.2     |
| Diarrhea > 4 days (%)            | 39        | 46      | 0.83 (0.63, 1.1)    | 0.2     |
| Unscheduled IV use(%)            | 2         | 5       | 0.37 (0.07, 1.9)    | 0.2     |
| Weight loss(%)                   | 34        | 44      | 0.7 (0.4, 1.2)      | 0.2     |
| Complications                    | 1         | 6       | 0.15 (0.02, 1.2)    | 0.05    |
| Mortality                        | 0         | 2       |                     |         |

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### Table 3: The costs incurred in treating patients of acute diarrhea in treatment and control group, in Rupees ($1 = 36 Rs, 1996)

| Cost Components                      | Treatment (mean ± SE) | Control (mean ± SE) | P value |
|--------------------------------------|-----------------------|---------------------|---------|
| Direct medical cost (Patient)        | 23.6 ± 7              | 17.3 ± 6            | 0.5     |
| - Visiting fees                      | 15.9 ± 6              | 6.9 ± 5             | 0.2     |
| - Medicines                          | 8 ± 4                 | 9.1 ± 5             | 0.5     |
| Direct medical cost (Government)     | 309.4 ± 34            | 351.7 ± 39          | 0.4     |
| - Cost of out-patient visits         | 3.5 ± 1               | 2.6 ± 1             | 0.2     |
| - Cost of hospital stay              | 195.3 ± 25            | 238.7 ± 32          | 0.2     |
| - Cost of ORS used                   | 15.7 ± 6              | 15 ± 4              | 0.7     |
| - Cost of antibiotics used           | 11.1 ± 4              | 18.6 ± 6            | 0.4     |
| - Cost of Intravenous fluids used    | 10.8 ± 3              | 17.7 ± 6            | 0.3     |
| - Cost of laboratory test            | 90.2 ± 11             | 93.4 ± 9            | 0.6     |
| Direct non-medical cost              | 100.7 ± 11            | 97.5 ± 12           | 0.7     |
| - Travel costs                       | 85.9 ± 10             | 76.8 ± 8            | 0.4     |
| - Other costs                        | 14.7 ± 4              | 20.7 ± 6            | 0.3     |
| Indirect costs                       | 47.5 ± 11             | 53.9 ± 12           | 0.7     |
| Total cost of diarrhea               | 481.25 ± 44           | 520.6 ± 54          | 0.6     |
(p < 0.001), use of antibiotics (p < 0.001), use of intravenous fluids (p < 0.001), hours taken to rehydrate a child (p < 0.001), the amount of oral rehydration fluid used (p < 0.001), presence of any complications (p < 0.001) and the hospital stay (p < 0.001). The best subset linear regression showed that there was a reduction in total cost by the use of micronutrients but failed to reach levels of significance (Table 4).

Th cost-effectiveness of the treatment is shown in Table 5. Boot-strap method was used to estimate the robustness of these estimates. The bootstrap estimate of the total mean cost of treatment group [Rs. 481; 95% CI (403, 577) versus Rs. 521; 95%CI (425, 623)] was less and the effect size of diarrhea ≤ 4 days was larger [63; 95%CI (52, 72) versus 52; 95%CI (42, 61)]. The intervention was dominant, with net cost saving of Rs. 40 and a net health gain 9 cases of diarrhea >4 days averted, but failed to reach level of statistical significance. The bootstrap re-sampling (1000 times) of incremental cost effectiveness ratio (ICER) showed a normal distribution (Figure 1). The cost-effectiveness plane and the scatter of the boot strap estimates of the ratio of cost difference and the effect difference are shown in Figure 2. Although the scatter overlapped zero it tended to be predominantly in the quadrant where the treatment group dominates (i.e. less cost and better effects). Similarly the relative cost effectiveness (RCE) 0.76 (95% CI 0.5,1), i.e. the cost per patient with diarrhea less than 4 days, was 24% less in the group with micronutrient supplementation. The DALY’s lost due to two deaths in the control group were 32.6 and 34.6. The DALYs (m; 95% CI) lost in the remaining patients of the treatment group (2.3; 2.1, 2.4) and control group (2.4; 2.2,2.5), showed a difference of 0.1.

Discussion
Oral rehydration therapy (ORT) is a well established and a cost-effective strategy for reducing diarrheal mortality [8]. It is also widely accepted. Micronutrient mix or trace minerals during the diarrheal episode could be of benefit in reducing not only case fatality rate but also diarrheal duration and morbidity. Any changes recommended in the composition of ORS from its traditional constituents to include trace minerals needs reasonable justification in terms of efficacy and costs. Our study showed that micronutrient supplementation had beneficial effects on rate of complications and mortality. Although it reduced the proportion of patients with diarrhea ≤ 4 days it failed to reach traditional significance levels. However this had important costs implications.

There is substantial variability in the costs of treating acute diarrhea between different countries. In India, there is little information on the costs associated with acute diarrhea. In this study, the cost of treating acute diarrhea was $14 per episode in children attending a government hospital where the government spent 66% of the costs per child. The average cost of treating diarrhea documented in another study in rural India in 1985–88 was $1.25 with a range of $0.13–$2.7 [9]. If the costs of treatment in this

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**Table 4: Predictors of total cost of treating acute diarrhea on best subset Linear regression**

| Variables          | Coefficient | Std Error | Student's T | P value |
|--------------------|-------------|-----------|-------------|---------|
| Treatment          | -19.1       | 28.7      | -0.66       | 0.5     |
| Age ≥ 1 yr.        | -13.6       | 13.9      | -0.98       | 0.3     |
| Complications      | 25.6        | 15.9      | 1.6         | 0.10    |
| Dehydration        | 166.1       | 40        | 4.14        | 0.000   |
| Total stool output | -0.02       | 0.01      | -1.45       | 0.14    |
| Use of IV fluids   | 131.1       | 88.5      | 1.48        | 0.14    |
| Length of hospital stay | 154.8 | 8.1     | 18.9       | 0.000   |

**Table 5: Cost-effectiveness of trace minerals**

|                        | Treatment (A) | Control (B) | Change in condition (A-B) |
|------------------------|--------------|-------------|---------------------------|
| No. of cases averted   | 63           | 52          | -9                        |
| No. of deaths          | 0            | 2           | -2                        |
| Total cost             | 481          | 521         | -40                       |
| Cost-effectiveness     |              |             |                           |
| Rs. per case averted   |              |             | -4.4                      |
| Rs. per death averted  |              |             | -20                       |
study are discounted for a 10 year period with an inflation-adjusted discount rate of 20% (average inflation rate of 7% and discount rate of 12% = 1.7 × 1.12 = 1.198 or 19.8%), the present value would be $2 (in 1986) as compared to $1.25 [10]. This was a hospital-based study with sicker children and therefore the cost of treatment is likely to be more. In Indonesia the average costs was $2.27 per child of which the community paid 46% [11]. In the United States the cost was US$289 per episode in <36-month old ambulatory population and the costs of hospitalization of 250,000 patients was US$ 560 million or $2240 per case. The contribution of direct medical costs (costs of medical services, medications and laboratory services), of travel costs and of indirect costs (missed work) in our study were 70%, 16% and 10% respectively as compared to 39%, 5% and 49% in <36-month old ambulatory population with acute diarrhea in the United States, showing vast variations in costs and their types between these two settings. The cost of treatment in developing countries is considerably less because of diverse health care systems, different hospital capacity, their scope and their sources of funding, price discrimination by pharmaceuticals and differences in the per capita income, which impacts on their medical care spending [14–16].

The severity of the illness, i.e. the grade of dehydration and the length of hospital stay were the most important predictors of total cost. Hospitalization accounted for 62% of the direct medical costs and is comparable to costs of rotavirus hospitalizations described by Tucker et al [17]. It costs less to treat well-nourished immunized children since these children are less likely to experience a severe episode requiring hospitalization. As expected, the use of intravenous fluids and antibiotics inflated the costs of treatment.

The total costs of treatment in the intervention group were 8% less than the total costs in the control group. There was a reduction of 8% in costs of hospitalization and a 6% reduction in costs of antibiotics in the supplemented group. Although these differences failed to reach conventional levels of significance, they translate into large national savings. The under-five population in India experiences 105 million episodes per year, of which 15–22.5 million are moderate to severe diarrheal episodes [18]. The mean cost of treating diarrhea was $14. Hence the
burden of medical costs per year would be $1.47 billion and an 8% saving would be $117.6 million. According to estimates from the United States, acute intestinal infectious diseases amount to a minimum of $23 billion a year which includes loss of productivity ($21.76 billion) and medical costs ($1.25 billion)[13]. We do not have estimates of loss of productivity caused by acute diarrhea in India.

The cost-effectiveness ratio (the incremental costs and effects of adding micronutrients to ORS) was calculated as the difference in costs between the two alternatives (net costs) divided by the difference in health outcomes (net effectiveness) [19]. The unit of health of interest and the effectiveness measure for this study was the proportion of children with diarrhea ≤ 4 days, since mortality is an infrequent outcome and would require a large sample size. We believe that it is a pragmatic and good proxy measure for diarrheal morbidity and mortality for assessing cost-effectiveness. The incremental cost-effectiveness estimate was negative because of the savings in the total costs of treatment with fewer morbid events. The intervention was not only more cost-effective, but it paid for itself. The cost per unit health with the use of trace minerals in ORS was 24% less than when only ORS was used. Therefore it could be judged as a more cost-effective intervention. These data were stochastic and not deterministic, i.e. both costs and effects were determined from data sampled from the same patients in a study. A sensitivity analysis or the confidence interval of the results helps to determine its robustness and its performance in a dynamic environment, where variations in costs and benefits occur due to variation in measurements and implementation of the intervention [20]. We determined the 95% confidence interval for the incremental cost-effectiveness ratio (ICER) using the non-parametric bootstrap method [21]. The CI yielded the magnitude of the observed difference, which favored the intervention because 62% of the bootstrap replications were in the quadrant where the treatment with the supplements dominated.
The effectiveness of the intervention was also measured in the number of DALYs. The loss of DALYs from morbidity was 0.1 and from mortality was 33.6 because of two deaths in the control group. A DALY translates into 481 episodes of acute diarrhea [22]. Therefore a saving of 0.1 DALY by using the micronutrients along with ORT saves 48 episodes of diarrhea and its costs.

This study had several limitations. The resources used were measured from the start of diarrhea and during the hospital stay. It did not capture downstream resources such as re-hospitalization or resources used after discharge of the treatment or the disease. Therefore the total cost of acute diarrhea in this study may have been underestimated. Also an assumption was that the course of the patient’s illness in the intervention group would be no different from that in routine care after discharge. Secondly, the measurement of the outcome in the study i.e. the proportion of diarrhea ≤ 4 days, is an intermediate and a proxy measure of diarrheal morbidity. Mortality is a definite outcome and perhaps the gold standard in terms of measurement. However the very large sample size needed for this outcome was not feasible. Though the outcome in this study was a pragmatic one it may restrict the generalizability and external validity of the study.

Although there were substantial economic cost savings, there were no statistical differences in costs and effects when tested to the null hypothesis. Medical cost data tend to be skewed in distribution with no ceiling effects on outliers. Appropriate transformations of the data are difficult. The heterogeneity of data on resource use is such that to show a difference between two groups for the same level of type I error (p < 0.05), a much larger sample size is needed for the economic question than for the clinical question [20,23]. However decision maker’s preferences regarding acceptable levels of risks for inferential error (type I error) in economic data may vary.

In conclusion, this study shows that the cost of treating acute diarrhoea in the developing world was less than in the developed countries and dependant on its severity. There was a reduction of 8% in costs of hospitalization and a 6% reduction in costs of antibiotics in the supplemented group which translated into large national savings. Favorable economic outcomes were observed with the use of trace minerals, which may have failed to reach these traditional levels of significance for the want of a larger sample. Therefore it is important that there is a further assessment of their use in a larger and more varied population.

Authors’ contributions
AP participated in the design of the study, its coordination, performed the statistical analysis and drafted the manuscript. LD participated in study design and performed the data collection. MSR conceived of the study, participated in its design and coordination. All authors read and approved the final manuscript.

Meeting where paper was presented
INCLEN (International Clinical Epidemiology Network) Global Meeting XV Querétaro, Mexico 1998.

Acknowledgments
We thank the management, the pediatric department and the clinical Epidemiology unit of Government Medical College, Nagpur, India for assisting in the data collection and data management. We are thankful to the patients and their parents for their participation in the trial. Finally we thank the International Clinical Epidemiology Network who funded the writing of this manuscript under the able guidance of Dr. Stephen Walter and Dr. Kate D’Este at University of Newcastle, Australia.

References
1. Allen LH: Zinc and micronutrient supplements for children. Am J Clin Nutr 1998, 68:4935-4985.
2. Sazawal S, Black RE, Bhan MK, Ghandhari N, Sinha A and Jalla S: Zinc supplementation in young children with acute diarrhoea in India. N Engl J Med 1995, 333:839-44.
3. Drummond MF, Stoddart GL and Torrance GW: Methods for the economic evaluation of health care programmes. Oxford, Oxford University Press; 1990:21-25.
4. Manheim LM: Health services research clinical trials. Issues in the evaluation of economic costs and benefits. Controlled Clinical Trials 1998, 19:149-158.
5. Luce BR, Manning WG, Siegel JE and Lipscomb L: Estimating Costs in Cost-Effectiveness Analysis. In: Cost-Effectiveness in Health and Medicon Edited by: Gold MR, Siegel JE, Russel LB, Weinstein MC. New York, Oxford University Press; 1996.
6. Briggs A and Fenn P: Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ 1998, 7:723-740.
7. Murray CJL: Quantifying the burden of disease : the technical basis for disability-adjusted life years. Bull World Health Organ 1994, 72:439-445.
8. Gutiérrez GR, Tapia-Conyer R, Guiscafré H, Reyes H, Martinez H and Kumate J: Impact of oral rehydration and selected public health interventions on reduction of mortality from childhood diarrheal diseases in Mexico. Bull World Health Organ 1996, 74:189-197.
9. Balaji LN and Court A: Epidemiology of acute diarrhea in children, its policy implications and management. Bulletin of sub-speciality chapter of pediatric gastroenterology of Indian Academy of Pediatrics 2000, 1:3-5.
10. Drummond MF, Stoddart GL and Torrance GW: Methods for the economic evaluation of health care programmes. Oxford, Oxford University Press; 1990:49-52.
11. Lerman SJ, Shepard DS and Cash RA: Treatment of diarrhea in Indonesian children: what it costs and who pays for it. Lancet 1985, 21:651-654.
12. Avendano P, Matson DO, Long J, Whitney S, Matson CC and Pickering LK: Costs associated with office visits for diarrhea in infants and toddlers. Pediatr Infect Dis J 1993, 12:897-902.
13. Garthright WE, Archer DL and Kvenberg JE: Estimates of incidence and costs of intestinal infectious diseases in the United States. Public Health Rep 1988, 103:107-115.
14. Phelps CE: International comparisons of health care systems. In: Health Economics New York, Harper Collins Publishers Inc; 1992:483-509.
15. Mohaghan MJ and Mohaghan MS: Do market components account for higher U.S. prescription prices? Ann Pharmacother 1996, 30:1489-1494.
16. Phelps CE: International comparisons of health care systems. In: Health Economics New York, Harper Collins Publishers Inc; 1992:234-235.
17. Tucker AW, Haddix AC, Brease JS, Holman MS, Parashe UD and Glass RI: Cost-effectiveness analysis of a rotavirus immunization program for the United States. JAMA 1998, 279:1371-1376.

18. Udani PM: Acute Diarrheal Diseases. In: Text book of Pediatrics (with special reference to problems of child health in developing countries) 1st edition. New Delhi, Jaypee Brothers; 1998:700.

19. Garber AM, Weinstein MC, Torrance GW and Kamlet MS: Theoretical foundations of cost-effectiveness analysis. In: Cost-effectiveness in health and medicine Edited by: Gold MR, Siegel JE, Russel LB, Weinstein MC. New York, Oxford University Press; 1996:25-53.

20. Manheim LM: Health services research clinical trials. Issues in the evaluation of economic costs and benefits. Controlled Clinical Trials 1998, 19:149-158.

21. Chaudhary MA and Stearn SC: Estimating confidence intervals(CI) for cost-effectiveness ratios: An example from a randomized trial. Statistics in Medicine 1996, 14:1447-1458.

22. Varley RC, Tarvid J and Chao DN: A reassessment of the cost-effectiveness of water and sanitation interventions in programmes for controlling childhood diarrhoea. Bull World Health Organ 1998, 76:617-631.

23. O’Brien and Drummond MF: Statistical versus qualitative importance in the socio-economic evaluation of medicines. Pharmacoeconomics 5:389-398.