ELSEVIER

Journal of Clinical Epidemiology 60 (2007) 560–566

Journal of Clinical Epidemiology

Zinc supplementation reduced cost and duration of acute diarrhea in children

Germana V. Gregorio[a,b,*], Leonila F. Dans[a,b], Cynthia P. Cordero[b], Carlo A. Panelo[b]

[a]Department of Pediatrics, University of the Philippines College of Medicine Philippine General Hospital, Taft Avenue, Manila, Philippines

[b]Department of Clinical Epidemiology, University of the Philippines College of Medicine Philippine General Hospital, Taft Avenue, Manila, Philippines

Accepted 21 August 2006

Abstract

Objective: To determine whether zinc with oral rehydration solution (ORS) is more cost effective than ORS alone in the treatment of acute diarrhea.

Study Design and Setting: Cost-effectiveness analysis among patients consulting the emergency room of a government institution.

Method: Cost of treatment and outcome of participants of a randomized trial of zinc + ORS vs. ORS alone for acute diarrhea were investigated. Included were subjects 2–59 months with diarrhea <7 days and no dehydration. The direct medical, nonmedical and indirect costs were obtained, using the societal perspective. The incremental cost-effectiveness ratio (ICER) was calculated.

Results: Sixty patients were given zinc + ORS and 57 were given ORS alone. Mean duration of diarrhea was 17 hours shorter and mean total cost of treatment was 5% cheaper in the zinc than ORS group .The ICER showed that with use of zinc, the society saves $ 2.4 per day of diarrhea <4 days and spends $ 0.03 per case of diarrhea averted <4 days from consult, although the confidence interval included the null value of zero.

Conclusion: Use of zinc with ORS reduced the total cost and duration of acute diarrhea. The ICER suggests cost effectiveness of zinc supplementation but there is a need to further assess the role of zinc supplementation in a larger population.

Keywords: Oral rehydration solution; Incremental cost effectiveness ratio; Cost effectiveness analysis; Zinc; Diarrhea

1. Introduction

Diarrheal diseases are a leading cause of childhood mortality and morbidity in developing countries and an important cause of malnutrition [1]. The majority of diarrheal deaths are caused by dehydration that can be treated with oral rehydration solution (ORS). However, ORS is unable to reduce the volume, frequency, and duration of diarrhea.

It is not clear why some episodes of diarrhea persist for a longer duration but host factors, such as nutritional deficiencies [2], which may increase susceptibility to enteric infections and delay mucosal recovery would be expected to contribute to this effect. Two well-documented determinants of diarrheal duration are low weight-for-age and decreased cell-mediated immunity. Common to both these factors is zinc deficiency [3].

Zinc is an essential trace element for humans [4]. Zinc supplementation improves immune function and reduces the incidence of diarrhea among children in developing countries [5–7]. In a meta-analysis [8] that included children <5 years old with acute diarrhea given at least 1.5 times the recommended daily allowance for zinc, those who received zinc had a 15% (95% confidence interval (CI): 8–22%) risk reduction of having diarrhea on a certain day and a 16% (95% CI = 7–26) lower probability of having an episode of diarrhea lasting >7 days Possible role of zinc includes regulation of water and electrolyte transport, improvement in the enzymatic functions of the brush borders, and enhancement of the repair of the intestinal mucosa [9,10]. While these results are encouraging, the therapeutic efficacy of zinc has important cost implications.

There are two cost effectiveness analyses that have been reported on the use of zinc in acute diarrhea. The first was done in India [11], in the context of a randomized controlled trial wherein an 8% lower cost of treatment was observed with zinc supplementation compared with ORS alone. However, both the cost of zinc and copper were

* Corresponding author. Tel.: +632-5240892; fax: +632-5260150.
E-mail address: germana1@hotmail.com (G.V. Gregorio).

0895-4356/07/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi: 10.1016/j.jclinepi.2006.08.004

considered as both were used for supplementation. The second study [12] used secondary data and compared the expected clinical outcomes and costs with the use of zinc + ORS vs. ORS alone. This study considered the direct medical cost alone and showed that the mean incremental cost effectiveness ratio (ICER) was reduced from US$113 for ORS alone to US$73 per disability adjusted life year (DALY) averted when ORS is combined with zinc. The results of these studies could not be directly transposed to the local setting because the cost levels differ in different settings. Furthermore, the cost may vary depending on whose perspective the cost of resources was derived.

In 2003, our institution was one of the participating sites of a randomized controlled study that assessed the acceptability of zinc supplementation in children with acute diarrhea. One group was randomized to zinc and ORS and another to ORS alone. An economic evaluation was simultaneously conducted among the patients included in our institution. This determined whether the use of zinc + ORS is more cost effective than ORS alone in the treatment of acute diarrhea.

2. Methods

This cost effectiveness analysis (CEA) was conducted in 2003 using 117 of 138 patients included in the randomized controlled trial (RCT). Both the RCT and CEA obtained ethics committee approval from the independent ethics review board of the institution. Patients were recruited at the Emergency Room (ER) of the institution and from two satellite centers (San Andres and Paco local health units) within 5 km from study site. Those recruited in the satellite centers were sent to the ER and if necessary, hydration and all laboratory work-ups were done there.

Included were children between 2 and 59 months old with diarrhea <7 days duration and no evidence of dehydration. Excluded were those with other medical illness, severe malnutrition (weight for height <-3 SD, National Center for Health Statistics) and with current intake of antibiotics or zinc supplements. After informed consent, baseline features were taken. The subjects were then randomized by block randomization with use of sealed envelopes containing the treatment assignment for each day. The day of randomization was considered day 0 of the study. The *study group* received 20 mg zinc sulfate tablet per day for 14 days along with standard WHO-ORS. The *control group* received WHO-ORS only. The zinc tablets, taken 2 hours after food intake, were dissolved in water or milk before administration or were taken as is by older children. The WHO-ORS was provided in sachet to be dissolved in a liter of clean water and consumed in 24 hours.

During follow-up visits between days 3–5 and 14–17, the presence or absence of diarrhea was ascertained through interview of caregivers. The exact day on which the stools returned to normal frequency and consistency was asked. The duration of diarrhea was computed from the day of consultation up to the time the bowel movement has returned to its normal frequency and consistency followed by a 24-hour diarrhea free period. The study personnel inspected the blister pack of zinc and counted the number of tablets left. Mothers were also asked if they have given the zinc tablets to anyone aside from the patient.

A patient was considered cured if there is cessation of diarrhea within 10 days after consult. Treatment failure was defined as the presence of any adverse drug reactions to zinc or if the duration of diarrhea was >10 days from consultation. A patient was withdrawn if he develops other medical conditions requiring antibiotic therapy or noncompliance with intake of zinc ($<80\%$ intake of recommended dose).

2.1. Cost effectiveness analysis

The prevailing cost in 2003 was used, using the local currency, pesos (P) [US$ 1 = 53 pesos, 2003). The costs considered were direct medical and nonmedical costs and indirect costs. The cost values for the components of the direct medical cost were derived mostly from the different departments of the institution.

The original cost of the hospital's ER is no longer available. Thus, the cost of the building space per patient per day was computed based on the 2003 estimate of the annual rental cost per square meter where the site of the ER is located, which is P48, 750 (US$ 92), multiplied by the approximate land area of 75 m^2 and divided by the annual number of consults (11,315). This was estimated at P323.13 (US$ 6.10) per patient per day. Cost of diagnostics was based on the charge of the institution for charity patients category B [patients with annual family income between P10,000–20,000 (US$ 189–$377)]. This was used based on an interview with the Head of the Laboratory that the charge for category B patients approximates the cost taking into consideration the operating expenses (cost of reagents and supplies) in the performance of the investigation, the use of equipment and machines and the salary of the personnel doing the procedure. The cost of medications was based on the price list of the UP-PGH Pharmacy and was used based on an interview with the Chief Pharmacist that the charge for medications in the pharmacy approximates the cost. The use of the facilities and the salary of the employees are subsidized by the government and were not considered in the computation of the cost of the drugs. The cost of personnel time was estimated based on the annual residents' (P213, 588)/nurses' (P159, 600) salary divided by the approximate time that each personnel devotes for a patient. Slack time was not accounted for. Based on informal interviews and actual observations, a resident physician spends 1 hour per patient with the time allocated as follows: history and physical examination (20 minutes), performance of necessary laboratory tests and instructions for treatment (15 minutes), reassessment after 1st and 2nd hour of hydration (10 minutes), and reassessment at end of hydration and discharge orders (15 minutes).

A nurse spends 15 minutes per patient with the time allocated as follows: endorsements (2 minutes), patient care (10 minutes), and charting (3 minutes). The cost of personnel time was then estimated as P68.13 [P48.37 (US $ 0.91) for resident physician and P19.18 (US $ 0. 36) for 15 minutes for nurse].

The overhead costs such as water, electricity, cleaning, and security were not accounted for due to technical difficulties in obtaining these costs. The hospital does not compute the use of the utilities in this manner and thus no data is available.

The direct nonmedical cost while the child was in the ER was estimated at P140 (US$ 2.64) per day based on the cost of two meals, transportation fare, and incidental expenses while in the hospital. The indirect cost was estimated at P280 (US $ 5.30) per day based on the lowest allowable legislated wage in 2003 for urban laborers in the country. It was assumed that even if there is no real wage payment at household level, that is, for volunteer caregivers or unemployed mothers, there is still a cost attached to the care giving services rendered. Furthermore, whatever number of hours that a child gets sick in the course of the day, it was assumed that the care giving would be compensated for the day.

Overall, the cost per patient was obtained by taking the sum of the direct medical and nonmedical costs and indirect cost. The mean total cost for each group was then obtained.

2.2. Data analysis

Differences between the two groups were tested using chi-square or Fisher's exact test for qualitative variables and student's *t*-test for continuous variables. All hypothesis testing was done at $\alpha = 0.05$, two-tailed.

To determine the ICER, the difference between the two groups in the mean total cost of treatment was divided by the difference in their effectiveness. The effectiveness measures were the following: (1) per *day* of diarrhea averted less than 4 days from consult, obtained by subtracting from 4 days the mean duration of diarrhea of each group and then getting the difference between the two groups, and (2) per *case* of diarrhea averted less than 4 days from consult, as the duration of diarrhea after consult with ORS alone is usually 4 days.

The confidence limits of the ICER were determined by Fieller's theorem [13,14] and/or by bootstrap sampling using STATA version 7.0 (Stata Corporation, Texas, USA) [15]. Bootstrap samples of 116, corresponding to the size of the original data were drawn with replacement from the original samples. The process was repeated 1,000 times to generate the 95% CI of the ICER. Using data generated by bootstrap sampling, a cost effectiveness (CE) plane was constructed. An acceptability curve was also done by plotting the cumulative density of the cost-effectiveness on the y-axis and the ICERs generated from the bootstrap sampling on the x-axis.

Sensitivity analysis was performed by altering the input values of the direct medical costs and indirect costs and by considering different durations of diarrhea to assess the effects of uncertainties. Based on the cost that was derived after different permutations were considered, the difference in the cost between the zinc and ORS and the ORS groups was obtained and point estimates for ICER were calculated.

2.3. Sample size estimate

Sample size estimate was based on cost and duration of diarrhea and was computed at $\alpha = 0.05$, two tailed and with a power of 80%. In a previous unpublished study, the mean cost incurred if a child develops an acute diarrhea and consults an urban, government hospital is P3,271 ± 1,741. Thus, to detect a 30% difference in the cost of treatment between the two groups, at least 49 patients per group are needed. To detect a 33% difference in the duration of diarrhea wherein the mean (±SD) duration of diarrhea was 5.4 ± 3.4 days in patients treated with ORS, 56 patients per group are needed.

3. Results

The data collection for the CEA started from patient number 22 of the clinical trial after ethics approval was obtained for the CEA.

3.1. Baseline characteristics (Table 1)

No difference was observed in the baseline characteristics of the two groups except for the mean duration of diarrhea that was 11 hours shorter in the zinc group.

3.2. Clinical outcomes

A significantly shorter duration of diarrhea from the time of consultation was noted in the zinc than in the ORS group (mean ± SD, 2.98 ± 0.92 days vs. 3.67 ± 1.63, $P = 0.009$) with a difference of 0.69 days (16.6 hours). There were more

Table 1
Baseline characteristics of the two study groups investigated

	Zinc + ORS ($n = 60$)	ORS ($n = 57$)	P
Mean age (months)	13.20 ± 10.38	14.82 ± 11.41	0.41
Males, n (%)	35 (58)	27 (47)	0.24
Mean (±SD) duration of diarrhea before consult (days)	2.45 ± 1.16	2.91 ± 1.17	0.034*
Mean (±SD) number of stools in the past 24 hours before consult	6.52 ± 3.60	6.72 ± 4.10	0.78
Patients with some dehydration at consult, n (%)	14 (23)	11 (19)	0.95
Currently breastfed, n (%)	21 (35)	14 (25)	0.22

* Statistically significant.

patients in the zinc group with duration of diarrhea <4 days from admission [54/59 (92%) vs. 43/57 (75%), $P = 0.780$]. One patient in the zinc group was withdrawn on day 3 because of measles and then was lost to follow-up, thus the duration of diarrhea of this patient is unknown. Another patient in the ORS group was considered a treatment failure because the duration of diarrhea was >10 days. The percentage of clinical cures in both groups is the same [59/60 (98%) vs. 56/57 (98%), $P = 1.0$].

3.3. Cost outcomes (Table 2)

A higher cost for drugs was noted in the zinc group while a higher indirect cost was seen in the ORS group. The breakdown of the total cost for the direct medical, direct nonmedical, and indirect costs was 35%, 10%, and 55%, respectively, for the zinc and 28%, 9%, and 63%, respectively, for the ORS group. The cost driver in both groups is the indirect cost. Overall, the total cost of treatment is less in the zinc group, with a cost difference of P87.16 (US$ 1.6).

3.4. Incremental cost-effectiveness ratios

Two measures of effectiveness were used in the computation of the ICER (1) per *day* of diarrhea averted <4 days from consult, which was obtained by subtracting from 4 days the mean duration of diarrhea of each group, and (2) per *case* of diarrhea averted <4 days from consult.

The computed ICER (Table 3) suggests that with zinc supplementation, the society saves P127.50 ($ 2.4) for each day that the diarrhea is averted <4 days from consult and spends P1.48 ($ 0.03) for each case of diarrhea <4 days from consult, although the CIs include the null value of zero.

The bootstrap re-sampling was used to construct the CE plane (Fig. 1). The bootstrap estimates of the cost and effect differences showed that most of the estimates are in the quadrant where the zinc group is dominant, that is, less costly and more effective, although there are few estimates in the other quadrants.

Fig. 2 presents the cost-effectiveness acceptability curve. Different ceiling ratios were hypothesized reflecting the maximum value that decision makers are willing to invest for a unit of effectiveness. As seen, if a ceiling ratio of P70.00 (~US$ 1.32) is assumed, which is the amount of zinc tablets for 14 days, the probability of the intervention to be effective is approximately 27%. At P90.00(~US$ 1.70), based on the mean of the amount that parents are willing to spend for zinc tablets, as seen in the local RCT on the acceptability of zinc, the probability is increased by 34%. For a 90% probability for the zinc intervention to be cost effective, the society should spend P200.00 (~US$ 3.80) for every day that the diarrhea is averted <4 days from consult.

3.5. Sensitivity analysis

Sensitivity analysis showed that if the mean and upper limit of the duration of diarrhea is considered, under the best (decreased 50% direct medical cost and decreased 50% daily wage lost) and worst (increased 200% direct medical cost and increased 200% daily wage lost) scenarios, zinc supplementation is cheaper and more effective, resulting in a net saving of P59–578 (US$ 1.11–10.91) per day of diarrhea averted <4 days. On the other hand, if the lower limit of the duration of diarrhea is considered as the outcome, zinc supplementation after adjustment of direct medical costs and indirect costs is more costly and less effective than no supplementation, and clearly ORS treatment is preferred.

4. Discussion

The present study showed that zinc supplementation in addition to ORS is less costly and more effective than ORS alone in the treatment of acute childhood diarrhea. This important finding could translate to significant national savings for a developing country like the Philippines where each child <5 years succumbs from two to three episodes of diarrhea per year [16].

Table 2
Comparison of costs in Philippine pesos (mean ± SD) between the two study groups

	Zinc + ORS ($n = 59$)	ORS ($n = 57$)	P
Direct medical cost			
Hospital cost	328.61 ± 42.07	328.8 ± 42.80	0.98
Personnel	68.69 ± 8.79	68.74 ± 8.95	0.98
Diagnostics	34.25 ± 78.96	27.81 ± 71.95	0.65
Drugs and medical supplies	94.51 ± 47.79	21.24 ± 34.08	<0.001
Direct nonmedical cost			
Out-of-pocket expenditure	142.37 ± 18.27	142.46 ± 18.54	0.98
Indirect cost	835.25 ± 257.32	992.28 ± 439.77	0.020
Total cost	1,500.83 ± 311.08	1,587.66 ± 499.71	0.26

Table 3
Computation of ICER and 95% CI based on the difference in cost and difference in effect between the two groups

	Per day of diarrhea averted[a]			Cases of diarrhea averted <4 days		
	Cost (Pesos)	Effect[a]		Cost (Pesos)	Effect	
Zinc + ORS	1,500.50	1.02		1,446.45	54	
ORS	1,587.66	0.33		1,430.38	43	
Difference in cost			−87.16			16.27
Difference in effect			0.684			11
ICER			−127.44			1.48
95% CI of ICER						
Fieller's theorem			−300.6 to 228.2			−9.45 to 9.70
Bootstrap sampling			−275.1 to 225.5			

[a] Per day of diarrhea averted <4 days from consult was determined by subtracting from 4 the mean duration of diarrhea of each group.

The mean duration of diarrhea observed in this study, which is 3.67 and 2.98 days in the ORS and zinc group, respectively, is within the range of 2.7−7.1 days for ORS treated and 2.3−6.1 days for zinc supplemented patients observed in other trials [9,10,17−25]. On consult, the duration of diarrhea was 11 hours shorter in the zinc group but it is debatable whether this is clinically significant. For the caregiver, this is probably trivial, as they would have consulted earlier if there were signs that should alarm them. However, for the society, this might be important if the parents or guardians missed a day of work to attend to the patient. The data on the duration of diarrhea though is only an estimate and thus, subject to recall bias.

For comparison of costs obtained in the present study with other local and international reports, constant pricing was done using 2003 as the base year, the year the study was conducted [26]. We showed that the mean cost of treatment of acute diarrhea is P1,544 (US$ 29) and is lower than the cost of P3,271 (US$ 73) in a local study reported in 2000 (L.F.D., unpublished data) (P4,134 [US$ 78] in 2003). Both studies considered the society's perspective. However, the earlier report was based on review of medical records of hospitalized patients, while the present study included patients consulting at the ER but not requiring hospital admission.

There is a substantial difference in the cost of treatment of acute diarrhea cases between countries with a lower cost in developing countries than in developed countries. In India [11], the cost in 1996 was US$ 14 per episode among hospitalized patients (equivalent to $16.41 in 2003) while in Indonesia [27] this was estimated at $2.27 in 1985 ($3.90 in 2003). In the United States [28], the average cost per episode of diarrhea was $289 in 1991 ($391 in 2003) among infants consulting an outpatient clinic and the median cost of a diarrhea associated hospitalization among children <5 years was $2,307 in 1999 ($2,549 in 2003) [29]. Since the daily wage lost is the cost driver in the present and other studies [11,27,28], the difference in the per capita income may account for the difference in the medical costs among different countries.

The favorable outcome observed with zinc supplementation in this study is similar to the finding of Patel et al. [11] in Nagpur, India and the report of Robberstad et al. [12] in United Republic of Tanzania. In all these studies, the

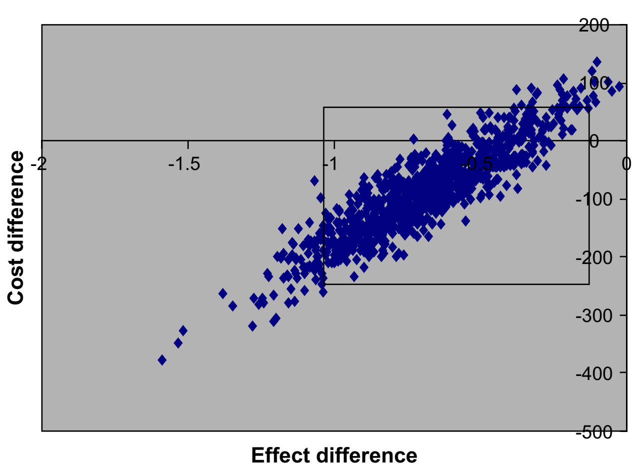

Fig. 1. Cost effectiveness plane of the cost and effect difference between the zinc + ORS and ORS group. The box is defined by the 95% confidence interval of the cost difference (y axis) and effect difference (x axis).

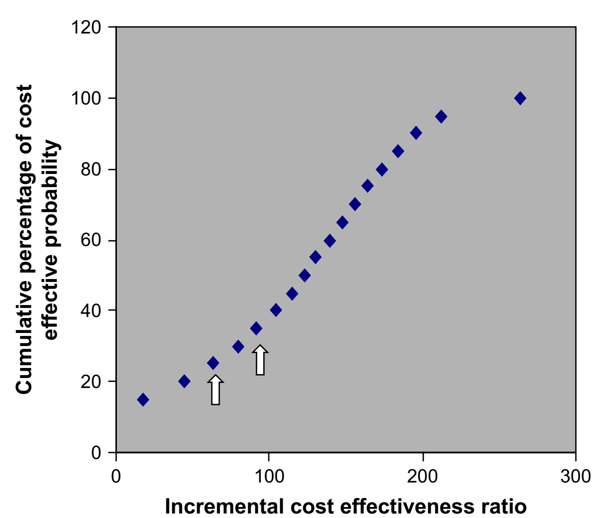

Fig. 2. The cost-effectiveness acceptability curve shows that with a ceiling ratio of P70.00 (left arrow) and P90.00 (right arrow), the probability for the intervention to be cost effective is 27% and 34%, respectively.

intervention group was dominant, as the cost was less and the effect was better. The ICER in the Indian study is a cost savings of Rupees 452 ($12.50) for every case of diarrhea <4 days while the ICER in this study is P127.50 ($ 2.41) using per day of diarrhea averted <4 days from consult. In both these studies, however, the confidence limits of the ICERs are not significant, and thus, could be interpreted as a loss or a gain to society for every unit of effectiveness. In Robberstad's study [12], the mean cost effectiveness ratio per DALY averted was reduced by one third when ORS was combined with zinc using a Tanzanian life expectancy of 46 years. The results of the present study, however, could not be compared with this, as it is difficult to express our findings as DALYs based on the outcomes that were measured in the trial.

It is clear in Patel's [11] and in this study that the lesser cost of treatment with zinc supplementation translates into larger national savings. In India, where there are 105 million episodes of diarrhea per year in children less than 5 years old and with a mean cost of treatment of US$ 14 per case, the burden of medical illness is $1.47 billion. An 8% savings would be $117 million. In the Philippines [16], there are 30 million episodes of diarrhea per year in children <5 years of age and the mean cost is $29 per case. This is equivalent to $870 million and a 5% savings would amount to $4.35 million or approximately P231 million. A further beneficial effect of zinc supplementation is the reduction in the incidence of persistent diarrhea and dysentery [30] and in the episodes of recurrent diarrhea [31].

As this study was done from a societal perspective, the final decision whether to implement the results will depend on the amount that society is willing to spend for every unit of effectiveness, thus, an acceptability curve was constructed [13,14]. For a 90% probability for the zinc intervention to be effective, decision makers must be willing to spend approximately P200.00(~$3.80) for every day of diarrhea that is averted less than 4 days from consult. If this value is multiplied with 30 million, corresponding to the number of diarrhea cases per year in the Philippines in children less than 5 years of age, this amounts to P 6 billion (US$ ~113 million). This amount is about 3% of the total national health spending and is one third of the health department's budget. Financing for this need not come from a single source, and this cost requirement is feasible if it can be rationally distributed across various payers. Thus, despite the wide CIs of the computed ICER, it is still useful in constructing an acceptability curve that predicts the probability of the intervention to be effective depending on the health resources of the society.

This study has several limitations. First, although the CEA was done in the context of an RCT, the objective of the RCT was not to determine the efficacy of supplementation but to assess the acceptability of zinc and its effect on the use of ORS and antibiotics. Thus, the objective of determining the duration of diarrhea was only a clinical outcome of interest for the CEA but not for the RCT. It would have been ideal if the patients in the RCT, who were also used for the CEA, were followed up more closely to have a more precise estimate of the duration of diarrhea. However, this might affect the compliance on the use of zinc tablets, which is the main outcome of interest of the RCT. This could have over- or underestimated the cost of illness and over- or underestimated the duration of diarrhea. Recall bias is also possible if the mothers fail to report exactly the day that the diarrhea stopped. The interval between the first and second follow-up is 8–12 days and it is possible that mothers could have forgotten the exact day when the diarrhea ceased. Second, the study was conducted in an urban, government, tertiary hospital. The treatment of patients with acute diarrhea in our setting may be different from other government or private institutions. The results of this study may be an overestimate if the setting was in a health sector with a lower cost of health care delivery, like a local health center but may be an underestimate if the study was done in a private setting. Ideally, the sample of patients for a CEA should be drawn from a sufficiently heterogeneous population across different types of institutions to increase the generalizability of the results. Third, selection bias may have occurred as patients with a higher risk of developing complications related to the diarrheal illness and who require hospital admission were excluded, thus, could have underestimated the cost and the duration of diarrhea. Lastly, over- or underestimation of the cost of illness may have happened, as in some instances, the exact cost is unknown and only assumptions were made. The overhead cost for water, electricity, cleaning, and security was not considered, as we have no access to this data. This could have underestimated the cost of the use of the ER, pharmacy, and laboratory facilities of the institution. On the other hand, an indirect medical cost was attached even for household labor, whether a child is sick for a day or a fraction thereof, and this could have overestimated the cost. Despite these limitations, however, the sensitivity analysis performed which altered the duration of diarrhea and the direct medical costs and indirect costs did not change our basic conclusion, thus, increasing the validity of our results.

In conclusion, the use of zinc with ORS reduces by 5% the total cost of treatment and by 17 hours the duration of acute diarrhea. The ICER suggests cost saving for society but there is a need to further assess the role of zinc supplementation in a larger population.

Acknowledgment

This cost effectiveness analysis was funded by the Research and Implementation Development Office of the University of the Philippines College of Medicine. The World Health Organization supported the randomized controlled trial.

References

[1] Kosek M, Bern C, Guerrant RL. The global burden of diarrheal disease, as estimated from studies published between 1992 and 2000. Bull World Health Organ 2003;81:197–204.

[2] Yoon PM, Black RE, Moulton LH, Becker S. The effect of malnutrition in the risk of diarrheal and respiratory mortality in children <2years of age in Cebu, Philippines. Am J Clin Nutr 1997;65:1070–7.

[3] Black RE. Zinc deficiency, infectious disease and mortality in the developing world. J Nutr 2003;133(Suppl):1485S–9S.

[4] International Zinc Nutrition Consultative Group. Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull 2004;25:91–204.

[5] Allen LH. Zinc as a micronutrient for children. Am J Clin Nutr 1998;68(Suppl):495S–8S.

[6] Fuchs GK. Possibilties for zinc in the treatment of acute diarrhea. Am J Clin Nutr 1998;68(Suppl):480S–3S.

[7] Hambridge M, Cousins RJ, Costello RB. Zinc and health: current status and future directions. J Nutr 2000;130(Suppl):341S–520S.

[8] Zinc Investigators' Collaborative Group. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 2000;72:1516–22.

[9] Strand TA, Chandyo RK, Bahl R, Sharma PR, Adhikari RK, Bhandari N, et al. Effectiveness and efficacy of zinc for the treatment of acute diarrhea in young children. Pediatrics 2002;109:898–903.

[10] Sazawal S, Black RE, Bhan MK, Bhandari N, Sinha A, Jalla S. Zinc supplementation in young children with acute diarrhea in India. N Engl J Med 1995;333:839–44.

[11] Patel AB, Dhande LA, Rawat MS. Economic evaluation of zinc and copper use in treating acute diarrhea in children: a randomized controlled trial. Cost Eff Res Alloc 2003;1:1–10.

[12] Robberstad B, Strand T, Black RE, Sommerfelt H. Cost effectiveness of zinc as adjunct therapy for acute childhood diarrhea in developing countries. Bull World Health Organ 2004;82:523–31.

[13] Briggs A, Fenn P. Confidence intervals or surfaces. Uncertainty on the cost-effectiveness plane. Health Econ 1993;7:723–4.

[14] Briggs AH, O'Brian BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health 2002;23:377–401.

[15] Stata 7 user's guide 2001. Bootstrap sampling and estimation. Texas: Stata Press; 2001. pp. 157–167.

[16] http://www.doh.gov.ph/. 2005.

[17] Bhandasi N, Bahl R, Taneja S, Strand T, Molbak K, Ulvik RJ, et al. Substantial reduction in severe diarrheal morbidity by daily zinc supplementation in young north Indian children. Pediatrics 2002;109:1–7.

[18] Roy SK, Tomkins AM, Akramuzzaman SM, Behrens RH, Haider R, Mahalanabis D, et al. Randomized controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. Arch Dis Child 1997;77:196–200.

[19] Hidayat A, Achadi A, Sunoto S, Soedarmo SP. The effect of zinc supplementation in children under 3 years of age with acute diarrhea in Indonesia. Med J Indonesia 1998;7:237–41.

[20] Sachdev HPS, Mittal NK, Yadav HS. A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. J Pediatr Gastroenterol Nutr 1988;7:877–81.

[21] Faruque AS, Mahalanabis D, Haque SS, Fuchs GJ, Habte D. Double-blind, randomized, controlled trial of zinc or vitamin A supplementation in young children with acute diarrhea. Acta Paediatr 1999;88:154–60.

[22] Dutta P, Mitra U, Niyogi SK, Dutta S, Manna B, Basak M, et al. Impact of zinc supplementation in malnourished children with acute watery diarrhea. J Trop Pediatr 2000;46:259–63.

[23] Baqui AH, Zaman K, Persson LA, El Arifeen S, Yunus M, Begum N, et al. Simultaneous weekly supplementation of iron and zinc is associated with lower morbidity due to diarrhea and acute lower respiratory infection in Bangladeshi infants. J Nutr 2003;133:4150–7.

[24] Al-Sonboli N, Gurgel RQ, Shenkin A, Hart CA, Cuevas LE. Zinc supplementation in Brazilian children with acute diarrhea. Ann Trop Pediatr 2003;23:3–8.

[25] Bhatnagar S, Bahl R, Sharma PK, Kumar GT, Saxena SK, Bhan MK. Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial. J Pediatr Gastroenterol Nutr 2004;38:34–40.

[26] http://stats.bls.gov/cpi/home.htm#data US Bureau of Labor Statistics, 2005.

[27] Larman SJ, Shephard DS, Cash RA. Treatment of diarrhea in Indonesian children: what it costs and who pays for it. Lancet 1985;21:651–4.

[28] Avendano P, Matson DO, Long J, Whitney S, Matson C, Pickering LN. Costs associated with office visits for diarrhea in infant and toddlers. Pediatr Infect Dis J 1993;12:897–902.

[29] Zimmerman CM, Bresee JS, Parashar UD, Riggs TL, Holman RC, Glass RI. Cost of diarrhea-associated hospitalizations and outpatient visits in an insured population of young children in the United States. Pediatr Infect Dis J 2001;20:14–9.

[30] Sazawal S, Black RE, Bhan MK, Jalla S, Bhandari N, Sinha A, et al. Zinc supplementation reduces the incidence of persistent diarrhea and dysentery among the socioeconomic children in India. J Nutr 1996;126:443–50.

[31] Bhandari N, Bahl R, Taneja S, Strand T, Molbak K, Ulvik RJ, et al. Substantial reduction in severe diarrheal morbidity by daily zinc supplementation in young north Indian children. Pediatrics 2002;109:86–93.