SYSTEMATIC REVIEW

Promoting Appropriate Management of Diarrhea: A Systematic Review of Literature for Advocacy and Action: UNICEF-PHFI Series on Newborn and Child Health, India

DHEERAJ SHAH, *PANNA CHOUDHURY, PIYUSH GUPTA, #JOSEPH L MATHEW, $TARUN GERA, **SIDDHARTHA GOGIA, ##PAVITRA MOHAN, ‡RAJMOHAN PANDA AND ‡SUBHADRA MENON

*From the Department of Pediatrics, University College of Medical Sciences (University of Delhi), New Delhi, ¶Advanced Pediatrics Center, PGIMER, Chandigarh; *Child Health Foundation; $Sunder Lal Jain Hospital, New Delhi; **Max Hospital, Gurgaon, Haryana; ##UNICEF, India; and ‡Public Health Foundation of India, New Delhi, India.*

Correspondence to: Dr Dheeraj Shah, Associate Professor, Department of Pediatrics, University College of Medical Sciences and GTB Hospital, Dilshad Garden, Delhi 110 095, India. shahdheeraj@hotmail.com

Background: Scaling up of evidence-based management and prevention of childhood diarrhea is a public health priority in India, and necessitates robust literature review, for advocacy and action.

Objective: To identify, synthesize and summarize current evidence to guide scaling up of management of diarrhea among under-five children in India, and identify existing knowledge gaps.

Methods: A set of questions pertaining to the management (prevention, treatment, and control) of childhood diarrhea was identified through a consultative process. A modified systematic review process developed *a priori* was used to identify, synthesize and summarize, research evidence and operational information, pertaining to the problem in India. Areas with limited or no evidence were identified as knowledge gaps.

Results: Childhood diarrhea is a significant public health problem in India; the point (two-weeks) prevalence is 9-20%. Diarrhea accounts for 14% of the total deaths in under-five children in India. Infants aged 6-24 months are at the highest risk of diarrhea. There is a lack of robust nation-wide data on etiology; rotavirus and diarrheogenic *E.coli* are the most common organisms identified. The current National Guidelines are sufficient for case-management of childhood diarrhea. Exclusive breastfeeding, handwashing and point-of-use water treatment are effective strategies for prevention of all-cause diarrhea; rotavirus vaccines are efficacious to prevent rotavirus specific diarrhea. ORS and zinc are the mainstay of management during an episode of childhood diarrhea but have low coverage in India due to policy and programmatic barriers, whereas indiscriminate use of antibiotics and other drugs is common. Zinc therapy given during diarrhea can be upscaled through existing infrastructure is introducing the training component and information, education and communication activities**.**

Conclusion: This systematic review summarizes current evidence on childhood diarrhea and provides evidence to inform child health programs in India.

Key words: *Communication barriers, Diarrhea, National Health Programs, Operations Research, Oral rehydration therapy, Zinc.*

Diarrhea is one of the top five causes of death among infants and under-five children in India [1], despite the availability of easily implementable interventions and existence of National Guidelines for management at the community level. Oral rehydration therapy (ORT) with oral rehydration salt (ORS) solution remains the cornerstone of appropriate case management of diarrheal dehydration and is considered the single most effective strategy to prevent diarrheal deaths in children. However, data from United Nations Children's Fund (UNICEF) coverage evaluation survey (CES) [2] and the third National Family Health Survey (NFHS-3) [3] show that ORS usage rates are still unacceptable; while unwarranted anti-diarrheal drugs and injections continue to be prescribed frequently. Moreover, there is lack of knowledge and awareness amongst care providers on how to implement and achieve greater coverage of existing cost-effective interventions.

This systematic review of literature was undertaken to provide evidence-based guidance for advocacy and action towards better management of childhood diarrhea in India. This exercise was a part of the combined initiative of Public Health Foundation of India (PHFI), UNICEF India, and a team of independent researchers for advocacy and action focused on locally relevant issues [4]. The specific objective was to identify, synthesize and summarize

evidence pertaining to diarrhea (disease burden, etiology, preventive interventions, client practices and prescription practices) in children aged less than five years, with particular reference to the Indian context. The review further aimed to identify knowledge gaps and operational bottlenecks that plague the current program concerning prevention and control of diarrhea for under-five children in India.

METHODS

The methodology for this systematic review has been presented earlier [4]. A set of key questions for review were finalized through consensus building, and categorized as 'Technical Issues' and 'Operational Issues' [4]. The details of the search strategy for each question have been presented in ***WebTable I***. Literature searches were initially carried out during April 2010, and updated on 10 January 2012.

RESULTS

1. Diarrheal Morbidity and Mortality in India

According to 'SRS Report (2009) on Causes of Death (2001-2003)', diarrhea is the third most common cause of death in under-five children in India, responsible for 14% deaths in this age group [1]. Diarrheal illnesses are the leading causes of childhood deaths beyond infancy; it is responsible for 24% of the deaths in children aged 1-4 years, and 17% of all deaths in children 5-14 years.[1]. World Health Organization (WHO) estimates of mortality from 34 studies published between 1992 and 2000 suggest that 4.9 children per 1000 per year in developing countries died as a result of diarrheal illness in the first 5 years of life [5]. This has declined over the years from 13.6 (1982) and 5.6 (1992) per 1000 per year [6,7]. The decrease was most pronounced in children aged under 1 year. Diarrhea accounted for a median of 21% of all deaths of children aged under 5 years in these areas and countries, being responsible for 2.5 million deaths per year. *Lancet* child survival series, using a prediction model, estimated that 22% (14-30%) of all under-five deaths are attributable to diarrhea in 42 countries, where 90% of all under-five deaths occur [8]. Most recent prediction modeling data also conclude that diarrheal diseases globally are responsible for most under-five child deaths beyond neonatal age. This model predicts that 14% of under-five child deaths totaling to about 0.24 million in India occur due to diarrhea [9]. This figure is similar to the SRS verbal autopsy estimates. Further, there was marked regional variation with mortality rate from diarrheal diseases in Central India was three times that in the West. Girls in Central India had four times higher diarrheal disease mortality rate compared to boys in the West [10].

According to NFHS-3 report, 9% of all under-five children were reported to be suffering from diarrhea in last 2 weeks [3]. The corresponding figures for NFHS-2 and NFHS-1 were 19.2% and 10%, respectively [11,12]. These figures are not truly comparable as these datasets were obtained from mothers of children with different age groups (< 4 yr in NFHS-1, < 3 yr in NFHS-2 and < 5 yr in NFHS-3). On comparing the different age groups, the prevalence was more or less similar in NFHS-1 and NFHS-3 whereas it was significantly higher in all age groups up to three years in NFHS-2 survey. The reasons for a worsening trend between NFHS-1 and NFHS-2 followed by a decline in NFHS-3 are not clear. Surprisingly, states with some of the worst health indicators like UP, MP and Rajasthan reported a very low prevalence of diarrhea in NFHS-1; it increased by 2-3 times in NFHS-2. Another surprising finding from NFHS-1 was that almost 50% of the prevalence of diarrhea in previous two weeks was contributed by prevalence during last 24 hours. This may suggest a significant recall bias in using two week prevalence as an indicator. The second and third survey did not present any data on 24 hour prevalence. Overall, there appears to be decrease in prevalence from NFHS-2 to NFHS-3. However, all this data have to be interpreted with caution as these reported prevalence levels reflect mother's perception of the illness and not the medically certified illness.

More recent data from UNICEF 10-district survey report that 19.8% children (2-59 months) suffered from diarrhea in the two weeks preceding the survey [13]. However, this UNICEF data was from some districts in states with higher child mortality rates, and therefore not representative for the whole country. Countrywide UNICEF coverage evaluation survey reported 14.3% of children (< 2 yrs) to be suffering from diarrhea in the two weeks preceding the survey [2].

The maximum risk of diarrhea was in the age group of 6-12 months across all the surveys [2,3,11,12]. Blood was reported to be present in stools in around 10% of the diarrheal episodes in all the national health surveys [3,11,12]. Proportion of diarrheal episodes with visible blood in stools was least in infants (2% in < 6 mo and 5% in 6-12 mo; NFHS-3). No major rural/urban or gender differences were found, except for dysentery, which was more common in rural children. Prevalence of dysentery also had a negative correlation with mother's educational status and family's wealth or standard of living index [2,3].

Very few studies have attempted to find the incidence of diarrhea among children through well-designed longitudinal studies. Analysis of 27 studies from

developing countries, including three from India, suggested that the median incidence of diarrhea for under-five children was 3.2 episodes per child-year [5], with maximum incidence at 6-12 months (4.8 episodes per child year). More recent data suggested that a child (<4-6 years) suffers from average of 2-3 episodes of diarrhea per year [14-16]. ***Web Table* II** presents the summary of all such studies conducted in India.

Conclusion and Comments: BOX 1

Knowledge gaps and directions for future research: Reliable information regarding the contribution of diarrhea to total deaths is missing because of absence of medical certification of cause of death in majority of cases. The risk factors and profile of children dying of diarrhea in the community are not known. Whether most diarrheal deaths in the community are occurring in outbreak situations or occurring in isolation? Large scale incidence studies are not available. Most of the studies, and even the national databases, have estimated the incidence and prevalence of diarrhea in under-five children. Similar data in neonates and older children are scarce.

2. Etiology of Childhood Diarrhea in India

There is no large-scale nationally representative community based study in last two decades regarding etiology or trends of diarrhea from India. Most studies have been either designed to specifically evaluate the contribution of a single etiological agent or are based on isolation of microbes from stool samples of hospitalized patients without their clinical details. Moreover, the frequent presence of enteric pathogens in healthy children from developing countries makes it more difficult to determine their true etiological role in causation of diarrhea. The seasonality of some agents also preclude valid analysis from studies reporting cases within a short duration.

BOX 1

- Diarrheal illnesses are the third most common cause of death amongst under-five children, and is the leading cause beyond infancy.
- A child below five years of age suffers from average of 2-3 episodes of diarrhea per year.
- The point-prevalence (last two weeks) of diarrhea among under-five children is about 9-20%.
- A child is at maximum risk of diarrhea between 6-12 mo of age.
- About 10% of the diarrheal episodes are dysentry; there has been no change in this trend over last two decades.
- There are no major rural/urban or gender differences in prevalence of diarrhea.
- Dysentry is more common in rural areas, and in children from poorer families.
- There seems to be a positive trend of decrease in diarrheal morbidity and mortality.

A multicentric (China, India, Mexico, Myanmar and Pakistan), hospital-based study in 1991 evaluated the etiology of acute diarrhea (including those with presence of blood or mucus in stools) in children (0-35 months) [20]. The study attempted to eliminate the role of seasonality by enrolling comparable number of patients each week throughout the two-year study-period. The study also evaluated the presence of microorganisms in healthy controls to further increase the validity. An enteric pathogen could be detected in 68% cases. The organisms more prevalent in cases than in controls were rotavirus, *Shigella* spp. and enterotoxigenic *E. coli* (ETEC). From India (*N*=5,862), rotavirus was detected in 18%, Enterotoxigenic *E. coli* (ETEC) in 14% and *Shigella* spp. in 20%. Enteropathogenic *E. coli* (EPEC), *Salmonella spp*., *Clostridium jejuni* were equally prevalent in cases and controls. *Vibrio cholerae* was isolated from 2% of cases (0.2% of controls) whereas *E. histolytica* was detected only in 0.1% of cases (0.2% of controls). Rotavirus was isolated most frequently during the first year of life whereas *Shigella spp.* was the most common isolate in children aged 12-35 months.

A recent study [21] amongst subjects (including under-five children) hospitalized with acute diarrhea, reported rotavirus (48%), diarrheogenic *E. coli*, *Vibrio* (19% each), *Giardia* (14%), adenovirus (12%), and *Cryptosporidium* (11%) to be the most common organisms isolated from under-five children. Further, this study documented mixed infections in a substantial (48%) proportion of children.

There has not been any similar attempt to evaluate the etiology of diarrhea from the community. Most studies have concentrated on the role of a specific etiological agent, especially rotavirus, in causation of diarrhea (***WebTable* III**). It is apparent from these studies that rotavirus is the most frequent etiological agent, being responsible for about 15-30% of episodes in hospitalized children, and 7-15% in community. Almost all episodes of rotaviral diarrhea leading to hospitalization are reported in children less than two years of age. In an analytical review of 46 Indian studies, rotavirus positivity was detected in 20% of hospitalizations, 35% of neonatal infections, 15% of symptomatic infections in the community, and 23% of nosocomial infections. The modeling data extrapolating the prevalence of rotavirus in diarrhea hospitalizations to total

deaths are not valid as most diarrhea deaths occur in community, and probably in malnourished children. Among diarrhea hospitalizations, the commonest G types were G1 and G2 while commonest P types were P8, P6 and P4.

Diarrheagenic *E. coli*, esp. Enteroaggregative *E. coli*, is the most common bacterial pathogen isolated in most studies. However, it has also been isolated frequently in controls. *Vibrio cholerae* predominantly occurs in outbreaks, and most affected children are 2-5 yr olds. *V. cholerae* O1 is the predominant serogroup among diarrheal patients. The high isolation rate of *Vibrio cholerae* from studies utilizing methodology of analysis of samples sent to the microbiology department for culture is likely to be related to the patient profile as it is likely that samples would be sent more commonly in children having rice watery stools and severe dehydration to specifically look for *V. cholerae*.

Conclusions and Comments: BOX 2

Knowledge gaps and directions for future research: There is need for large scale community based studies evaluating the etiology of diarrhea, rather than concentrating on identification of one pathogen. Studies need to determine etiology of diarrhea, and correlates of diarrheal deaths in malnourished children compared to well-nourished children. Studies need to evaluate the contribution of rotavirus and other factors in causation of diarrheal deaths. However, as deaths from diarrhea primarily occur in settings where access to medical care is limited, collection of appropriate clinical specimens to perform a microbiologic evaluation is extremely challenging.

BOX 2

- There is no large-scale comprehensive community based study regarding etiology of diarrhea from India.
- Rotavirus is responsible for about 15-30% of episodes in hospitalized children; 7-15% in community. Almost all episodes leading to hospitalization are reported in children < 2 years. It is also the most commonly isolated agent in neonatal infections.
- Diarrheogenic *E. coli* is the most common bacterial pathogen.
- *Shigella spp*. is responsible for about 10-20% of episodes. Visible blood is present in stools in half to two-thirds of these episodes.
- *Vibrio cholerae* predominantly occurs in outbreaks. Most affected children are 2-5 yr olds.

3. National Guidelines for Diarrhea Control

In India, National diarrhea control program (CDD) was implemented from 1980 as a part of Sixth Five Year Plan (1980-85) with the primary thrust of improving the knowledge and practices of appropriate case management among caretakers and health care providers, and primary objective of preventing deaths due to dehydration. This program was integrated within Child Survival and Safe Motherhood (CSSM) program, which evolved into Reproductive and Child Health (RCH-I and RCH-II) programs. These programs with more funding and stronger management systems included integrated management of childhood illness (IMCI) as a central strategy for child health and survival. Under IMCI, frontline workers and health professional are trained in integrated management of newborns and sick children, including for diarrhea. In addition, RCH-II proposed to strengthen availability of ORS at community level through making them available at *Aanganwadis*, sub-centers and through alternate approaches such as social marketing and Public Distribution System. It also talks of improving families' practices on home management of diarrhea through Behavior Change Communication. The mainstay of the case management approach during acute diarrhea included oral rehydration therapy (ORT), continued breastfeeding, continued semisolid feeding in children older than 6 months of age and use of appropriate antimicrobials in cholera and bloody diarrhea. Although there has been a decrease in diarrheal mortality over last three decades, the ORS use rates during diarrhea have hardly changed. The practices of continued feeding and increase in fluids during diarrhea also are sub-optimal.

The current Government of India guidelines recommend low osmolarity ORS, zinc and continued feeding of energy dense feeds in addition to breastfeeding for management of diarrhea [41,42]. Antimicrobials are recommended only for gross blood in stools or *Shigella* positive culture, cholera, associated systemic infection, or severe malnutrition. The first line antibiotic recommended for treatment of dysentery is oral ciprofloxacin [41,42]. Measures for prevention of diarrhea include promoting exclusive breastfeeding, use of safe water, handwashing, food safety, safe disposal of excreta, and immunization against measles. These recommendations take into account new research findings while building on past recommendations. Two recent advances in managing diarrheal disease: (*i*) reduced osmolarity oral rehydration salts (ORS) containing lower concentrations of glucose and salt, and (*ii*) zinc supplementation as part of the treatment; have the potential to further reduce diarrheal morbidity and mortality by reducing the duration and

severity of diarrheal episodes and lower their incidence.

National Expert Group formulated by the Ministry of Health, Government of India proposed that a single universal ORS solution containing sodium 75 mmol/L and glucose 75 mmol/L, and with osmolarity 245 mOsmol/L was acceptable for all ages and all types of diarrhea. The revised formulation was approved by the Drug Controller of India and the Government formally launched it in June 2004. Similarly, based on the WHO/UNICEF/IAP recommendations, the Ministry of Health, Government of India has recommended that 20 mg of elemental zinc should be given to all children older than 6 months with diarrhea, and should be started as soon as diarrhea starts and continued for a total period of 14 days [41,42]. Children aged 2-6 months should be advised 10 mg per day of elemental zinc for 14 days.

Zinc dispersible tablets and liquid formulations are now available widely in the private sector. Zinc dispersible tablets are also being supplied in the RCH kits. Efforts are on for making them available at most peripheral centers, and as over the counter (OTC) drug [41]. Currently, there are no studies available on the operationalization of zinc treatment through government sector.

Knowledge gaps and directions for future research: The current diarrhea management guidelines mainly discuss the technical issues with very little emphasis on operationalization. The key strategies for IEC, and distribution system for reduced osmolarity ORS, zinc and ciprofloxacin have not been given adequate emphasis. Although National Guidelines recommend ciprofloxacin for dysentery and resistant cholera cases, there are issues related to its approval by Drug Controller General of India for use in children.

4. Preventive Interventions

A. *Breastfeeding*

Breastfeeding has the potential of preventing 13% of under-five deaths in developing countries [8,43]. ***Web Table* IV** presents a summary of studies reporting effect of breastfeeding on diarrhea morbidity or mortality. A pooled analysis of six studies from developing countries (Brazil, The Gambia, Ghana, Pakistan, the Philippines, and Senegal) documented a significant reduction in diarrhea related mortality with breastfeeding [51]. In the first 6 months of life, protection against diarrhea was substantially greater (OR 6·1 [95% CI 4·1–9·0]) than for infants aged 6–11 months (OR 1·9 [95% CI 1·2–3·1]). Protection was highest when maternal education was low.

The benefits of breastfeeding are greater when it is exclusive. In a study from Bangladesh [50], partial or no breastfeeding was associated with a 3.94-fold higher risk of deaths attributable to diarrhea in comparison to exclusive breastfeeding in the first few months of life. Subsequent studies from all settings have consistently documented the protective effect of exclusive breastfeeding on diarrhea morbidity (incidence and prevalence).

The evidence in favor of breastfeeding is of intermediate quality as randomized controlled trials directly evaluating breastfeeding *versus* no breastfeeding are not available due to ethical reasons. However, observational studies and breastfeeding promotion trials conclusively support the protective role of exclusive breastfeeding in prevention of diarrheal morbidity and mortality.

Conclusions and Comments: BOX 3

B. *Handwashing*

As pathogens causing diarrheal diseases are mostly transmitted through the feco-oral route, handwashing is proposed as an important prevention strategy. Epidemiological evidence shows that the important risk behaviors that encourage human contact with fecal matter include lack of handwashing after defecation, after handling feces, and before handling food. Handwashing aims to decontaminate the hands and prevent cross transmission. Washing with soap and water removes pathogens mechanically as well as by chemical microbicidal action. Hand washing may require infrastructural, cultural, and behavioural changes, which take time to develop, as well as substantial resources (eg trained personnel, community organization, provision of water supply and soap).

Several systematic reviews have attempted to address the issue of prevention of diarrhea by promoting handwashing interventions (***Web Table* V**). The Cochrane Review [52] included all randomized controlled trials which assessed interventions promoting handwashing after defecation or after disposal of children's feces and before preparing or handling foods. These activities

BOX 3

- Exclusive breastfeeding for six months reduces diarrheal morbidity and mortality.
- The preventive effect of breastfeeding on diarrhea incidence is most marked among children from lower socio-economic classes.
- The preventive effect is highest in the first six months but continues beyond six months if breastfeeding is continued along with complementary foods.

included promotion strategies such as small group discussions and larger meetings, multimedia communication campaigns with posters, radio/TV campaigns, leaflets, comic books, songs, slide shows, use of T-shirts and badges, pictorial stories, dramas, and games. All institution-based trials were from high income countries (except one from China) with adequate provision of water supply and soap. Community-based trials included five cluster-randomized controlled trials that used entire communities (generally villages or neighborhoods, except one trial, which used households) as units of randomization. These trials were conducted in low-and middle-income countries in Asia (*N*=4) and Africa (*N*=1). In three out of these five trials, soap was provided to the community by researchers. Three trials evaluated hand washing as the only intervention, and other two trials used multiple hygiene interventions that included hand washing with soap (the type of soap used is not described). Participants were mainly mothers or caregivers as well as children. The outcome of diarrhea was assessed only in children in all the trials included in this review. From Institution-based trials, the incidence of diarrhea was assessed in 7711 children aged less than seven years in 161 day-care centres and 87 schools in the eight trials. The two trials that adjusted for clustering and confounders, showed a reduction in the incidence of diarrhea by 39% (IRR 0.61, 95% CI 0.40 to 0.92). The five trials with rate ratios that did not adjust for clustering also showed a benefit from the intervention. In Community based trials, the intervention reduced the incidence of diarrhea by 32% (IRR 0.68, 95% CI 0.52 to 0.90; 4 trials) in trials that adjusted for clustering and confounders. The single trial which did not adjust for clustering effects also showed a similar benefit. The reduction in the risk of diarrhea was greater in the trials which provided soap to the communities (IRR 0.49, 95% CI 0.39 to 0.62) than in the trials that did not provide soap and promoted multiple hygiene interventions. Overall, the trials documented a significant benefit of interventions promoting handwashing in the institutions or communities [52]. It is important to note that the control group in most cases received quite frequent monitoring, which may itself have influenced hand washing behavior. This might have lowered the estimate of the quantum of benefit from handwashing. Overall, this review provided strong evidence that handwashing interventions reduce diarrheal morbidity by about one-third. However, most trials in this review had short-term follow up, and it is unclear if their level of effectiveness would be maintained if they were scaled up to larger regions with less intensive monitoring over a longer time-period.

In another systematic review of published studies (cohort, case-control and RCTs) assessing the water sanitation and hygiene interventions to reduce diarrhea in the less developed countries, all studied interventions were found to reduce significantly the risks of diarrheal illness [53]. Most of the interventions had a similar degree of impact on diarrheal illness, with the relative risk estimates ranging between 0·63 and 0·75 [53]. Hygiene interventions, including promotion of handwashing reduced diarrheal illness (RR 0·63, 95% CI 0·52–0·77; 11 studies). Re-analysis of the data after exclusion of poor quality studies lowered the risk further (RR 0·55, 95% CI 0·40–0·75). Hygiene interventions were typically of two types, those concentrating on health and hygiene education, and those that actively promoted handwashing (usually alongside education messages). In general, education was aimed at the mothers, although the outcome was measured in children. Separate meta-analyses examining the effectiveness of each of these specific interventions resulted in pooled estimates of RR of 0·56 (0·33–0·93) and 0·72 (0·63–0·83) for the effects of handwashing and education, respectively. In water quality interventions, point-of-use water treatment was found to be more effective than targeting the water source [53]. Multiple interventions (consisting of combined water, sanitation, and hygiene measures) were not more effective than interventions with a single focus. This is likely to be the result of piecemeal implementation of more ambitious intervention programs, which may result in an overall lack of focus or lack of sufficient attention on important components such as handwashing and water treatment at source.

Curtis and Cairncross [54] reported a systematic review focusing on handwashing studies as opposed to general hygiene interventions and also combined results from developed and less developed countries. The pooled relative risk of diarrheal disease associated with not washing hands was 1·88 (95% CI 1·31–2·68), implying that handwashing could reduce diarrhea risk by 47%. When all studies, when only those of high quality, and when only those studies specifically mentioning soap were pooled, risk reduction ranged from 42–44% [54].

Almost all studies included in the systematic reviews utilized soap (plain or anti-bacterial) for handwashing or did not report the proper technique. The only study reporting use of ash or soil in handwashing did not document any benefit of same in the reduction of diarrhea.

In the Lancet series of publications related to child survival [43], meta-analysis indicated that the relative risk of diarrhea with hand washing is 0.70 (95% CI 0.56-0.89).

The long term follow-up data from these studies are mostly not available. In an earlier study in Karachi, Pakistan, households that received free soap and

handwashing promotion for 9 months reported 53% less diarrhea than controls [55]. Eighteen months after the intervention ended, these households were enrolled in a follow-up study to assess sustainability of handwashing behavior. Upon re-enrollment, mothers in households originally assigned to the intervention were more likely to have a place with soap and water to wash hands, and more likely to demonstrate the correct procedure [55]. However, in the ensuing 14 months, former intervention households reported a similar proportion of person-days with diarrhea (1.59% versus 1.88%, P = 0.66) as controls [55]. Although intervention households showed better handwashing technique after 2 years without intervention, their soap purchases and diarrhea experience was not significantly different from controls.

Conclusions and Comments: Box 4

Knowledge gaps and directions for future research: Although the interventions promoting handwashing and other hygiene measures clearly show a reduction in diarrheal risk in the short term, the sustainability of handwashing-behavior in the communities require investigation. Also, the evidence of reduction in risk of diarrheal illnesses after scaling up the intervention in uncontrolled situations is not available. India-specific data on handwashing are scarce.

C. Vaccination

Rotavirus vaccine

In a recent systematic review of randomized controlled trials [56], available rotavirus vaccines were efficacious in reducing rotavirus-specific diarrhea by 72-73% at one year and 62-67% at two years following the vaccination. The efficacy in preventing severe rotaviral diarrhea was greater (80-93% at one year and 84-89% at two years) (***Table* I**). There was no significant effect of one type of vaccine (Rotarix) on all-cause diarrhea whereas the other brand (RotaTeq) resulted in reduction of all-cause diarrhea by about half. There was no effect of either vaccine on mortality. The only study from India included in this review was an immunogenecity and safety study [67]. This study documented that the seroconversion rate one month after receiving two doses of vaccine was 58.3% [95% CI: 48.7-67.4] as against 6.3% [95% CI: 2.5-12.5] in the placebo group. Efficacy in terms of reduction of diarrheal episodes or any other functional parameter was not assessed in this study.

BOX 4

- Interventions promoting handwashing can reduce diarrheal episodes by about one-third.
- Washing hands with soap and water is the most effective hygiene intervention to prevent diarrhea.
- Water treatment at point-of-use also reduces the risk of diarrhea by about one-third.
- Programs addressing multiple components (e.g. hygiene, sanitation, water quality and source) are not more effective than those focusing on individual components such as handwashing and water treatment at source.

Well-controlled effectiveness studies of rotavirus vaccine are non-existent. Studies from South American countries and USA documented a reduction in rotaviral diarrhea incidence, and associated hospitalizations, after introducing rotavirus vaccine [57-63]. Data from Mexico [61,63] documented a small reduction in diarrhea related mortality before and after introduction of rotavirus vaccine. However, these studies have limited validity due to a large time gap between the two comparison groups. The cost-efficacy for reducing mortality is likely to be extremely low as about 11,900 vaccinations were required to prevent one diarrheal death in the Mexican study [61]. Recent data from Brazil also suggest that the effectiveness of vaccination program may reduce over the years [57] as vaccinated children had more severe episodes 18 months after vaccination although all-cause diarrhea episodes were more severe in unvaccinated children in the first year of age [57]. Data from USA also documented a 15% increase in number of rotavirus positive cases in the second year over the immediate year following the vaccination program [62].

Podewils, *et al*. [68] projected that a universal rotavirus vaccination program could avert about 0.1 million deaths, 1.4 million hospitalizations, and 7.7 million outpatient visits among an Asian birth cohort till it reaches 5 years of age. These estimates for rotaviral deaths are crude, and do not represent a true picture as these models assume that rotavirus would be responsible for about one-fourth of diarrheal deaths in India. There is no direct estimate for this figure, and it merely reflects the rotavirus detection rates in hospitalized children in big cities. Most deaths due to diarrhea occur in communities where medical care is limited whereas etiologic picture derived from in-hospital deaths due to diarrhea would be biased toward agents that are less likely to respond to medical care. Moreover, most deaths occur in malnourished children where the role of rotavirus in causation of diarrhea is not clear, and there is likely to be significant role of systemic infections and other co-morbidities [69].

Cholera vaccine

Most vaccines against cholera have not been found to be

TABLE I SYSTEMATIC REVIEWS AND STUDIES* OF VACCINES IN PREVENTION OF DIARRHEA

Study Year [Ref.]	*Participants*	*Study type*	*Results*	*Comment*
Rotavirus			Rotarix	
Soares-Weiser, *et al.* 2011 [56]	175,944 children (age 1 mo- 6 mo) from 34 RCTs comparing rotavirus vaccines with placebo. Rotarix (26 trials; 99,841 participants, RotaTeq (8 trials, 76,103 participants). Most trials had multiple sites, often in several countries. The only trial from India was a safety study.	Systematic Review of RCTs	RR of diarrhea: 0.28 (95% CI 0.17 to 0.48; 11,121 participants, 6 trials) during first year and RR 0.33 (95% CI 0.21 to 0.50; 7293 participants, 5 trials) during second year of follow-up. RR for severe episodes after one year: RR 0.20 (95% CI 0.11 to 0.35; 35,004 participants, 7 trials) and after two years: RR 0.16 (95% CI 0.12 to 0.22; 32,106 participants, 7 trials). *RotaTeq* RR for diarrhea after one year : 0.27 (95% CI 0.22 to 0.33; 7614 participants, 4 trials) and during the second year: RR 0.38 (95% CI 0.26 to 0.55; 1569 participants, 1 trial) RR for severe episodes: first year 0.07 (95% CI 0.01 to 0.50; 1485 participants, 2 trials) and for two years: RR 0.11 (95% CI 0.03 to 0.47; 1569 participants, 1 trial). Rotarix was not better than placebo in reducing the number of cases of all-cause diarrhea but RotaTeq reduced the number of cases of all-cause diarrhea at one year (RR 0.41, 95% CI 0.28 to 0.60; 1030 participants). No statistically significant difference in the number of deaths in children using Rotarix or RotaTeq.	All the 34 trials (15 unpublished) were sponsored by companies manufacturing or licencing respective vaccines. Reporting of trial methods was poor in most. The allocation concealment, blinding and analysis were unclear or inadequate in most studies.
Vieira, *et al.* 2011 [57]	Two cohort of 250 children (vaccinated and unvaccinated)in Northeast Brazil	Cohort study	The mean numbers of all-cause diarrhea episodes/child in the first year were similar (0.87 and 0.84) in vaccinated and unvaccinated children. During the second year, the number of episodes/child decreased to 0.52 and 0.42. All-cause diarrhea episodes were more severe in unvaccinated children in the first year of age whereas these were more severe in vaccinated children 18 months after vaccination.	A very low (4.9%) prevalence of rotavirus positivity was seen in both groups indicating changing disease epidemiology rather than effect of any vaccination program
Molto, *et al.* 2011 [58]	Diarrhea-associated hospitalizations among under-five children in 2007 and 2008 vs. mean of 2003-05 from five health regions in Panama.	Historical control (Before-after) study	After the vaccine introduction, there was a decrease in diarrhea-associated hospitalizations of 22% in first year and 37% in second year.	Likely contribution of overall development and better diarrhea management practices. Increase in vaccination coverage could be the reason for better results in second year.
Quintanar-Solares, *et al.* 2011 [59]	Diarrhea-related hospitalizations during the 2008 and 2009 rotavirus seasons with the median of 2003-06 in hospitals of Mexico	Historical control (Before-after) study	Diarrhea-related hospitalizations decreased by 11% in first year and by 40% in second year.	Maximum decline in hospitalization was seen in infants.

contd...

de Palma *et al.* 2010 [60]	323 children (< 2 yr) admitted with rotaviral diarrhea and 969 healthy matched controls	Matched case-control study.	Effectiveness of two doses of vaccination against diarrhea requiring hospital admission was 76%. Admissions for diarrhea among children under 5 declined by 40% in 2008 and by 51% in 2009 from the prevaccine year 2006.	
Richardson, *et al.* 2010 [61]	Diarrhea related mortality in under-five children during 2008 and 2009 rotaviral seasons vs. baseline of 2003-06 levels.	Historical control (Before-after) study	Reduction in diarrhea-related mortality from an annual median of 18.1/100,000 children at baseline to 11.8/100,000 children in 2008 (rate reduction, 35% [95% CI, 29 to 39; P<0.001].	Likely contribution of overall development and better diarrhea management practices. Absolute risk reduction of death is 6.3/100,000 children; NNT 15874 for preventing one death. With 74% coverage, corrected NNT 11904
CDC 2009 [62	Rotavirus positivity in 2008-09 vs. 2000-06 (pre-vaccine) in USA	Historical control (Before-after) study	2007-08 and 2008-09 seasons were shorter and later than the median during 2000-2006. The 2008-09 season had 15% more positive rotavirus test results than the 2007-08 season.	Setting of developed country.
Esparz, *et al.* 2009 [63]	Mortality due to diarrhea in under-five children in Mexico	Historical control (Before-after) study	From 2000-07, deaths due to acute diarrhea in under-five children dropped 42%. Diarrhea mortality decreased between 2006-07; 15.8% in <1 yr and 22.7% in 1-4 year old.	Likely contribution of overall development and better diarrhea management practices.
Cholera				
Sinclair, *et al.* 2011 [64]	Four trials from Peru, Bangladesh and India reported outcomes of vaccine efficacy in children	Systematic Review of RCTs	Protective efficacy of oral cholera vaccines in under-five children was 38% (95% CI 20% to 53%; four trials) in comparison to older children and adults (Efficacy 66%, 95% CI 57% to 73%). Protective efficacy diminished after two years and was lost in the fourth year of follow-up. No clinically significant increase in adverse events.	Significant heterogeneity of vaccine preparations. Vaccine efficacy too low for routine use. May find use in places with high cholera endemicity.
Graves, *et al.* 2010 [65]	Studies enrolling children and adults who had received injectable cholera vaccine vs. placebo or no intervention	Systematic Review of RCTs	In under-five children, vaccine efficacy was 55% (RR 0.45, 95% 0.35 to 0.59; 250,941 participants) in first year and 17% (RR 0.83, 95% CI 0.52 to 1.31; 42,039 participants) in the second year of follow up.	Most of these vaccines are not in clinical use anymore making results of this review redundant.
Measles Reddaiah, *et al.* 1993 [66]	Children aged 9-24 months in Rural Haryana	Longitudinal study	Attack rates of diarrhea in immunized children (1.6/child/yr) was no different to that in the non-immunized (1.5/child/yr). The mean duration of diarrhea in both groups was 2.3 days. The prevalence of diarrhea in immunized and non-immunized was 3.85 and 3.67 respectively.	Measles vaccination had no impact on diarrheal morbidity.

**Studies included in systematic reviews have been de-duplicated in preparing this table*

very effective. Injectable vaccines are no longer in clinical use, and their protective efficacy lasted only for one to two years [65]. A recent systematic review of oral cholera vaccines reported a protective efficacy of 38% (95% CI 20% to 53%; four trials) in under-five children. This was lesser in comparison to older children and adults. Moreover, the efficacy gradually declined over two years, and was completely lost after three years. An Indian trial included in this review reported 67% efficacy of a modified killed-whole-cell oral vaccine against clinically significant cholera in an endemic setting [70]. The vaccine has the potential to be used in communities with the highest risk of cholera epidemics.

Measles vaccine

Although measles vaccination is promoted as a diarrhea prevention strategy, there are not enough studies to support its role. A single published study on the role of measles vaccine in prevention of diarrhea did not document any benefit [66]. Attack rate of diarrhea in immunized children (1.6/child/yr) was no different to that in the non-immunized (1.5/child/yr).

Conclusions: Box 5

Knowledge gaps and directions for future research: As most data regarding rotavirus related deaths and rotavirus vaccine in India are based on modeling methods and efficacy studies in other settings, respectively, these cannot be used to start large scale vaccination programs in India. There is an urgent need to generate India specific data on rotavirus vaccine effectiveness by evaluating functionally important outcomes such as incidence/ prevalence of diarrhea and related mortality. The effect of an operational program on other vaccines' coverage, and also on other child survival interventions need to be carefully evaluated in any future studies. Community acceptance, cost factors and logistics also need to be studied carefully. Utility and acceptability of cholera vaccine need to be studied in outbreak situations.

D. *Vitamin A*

Results from a systematic reviews (***Table* II**) indicated that vitamin A supplementation has no consistent protective effect on the incidence of diarrhea or diarrhea-related mortality in neonates and infants less than 6 months. However, there was some evidence of benefit in children aged 6-59 months in low and middle, income countries. A systematic review examining the role of vitamin A given during measles episode documented a significant reduction in duration of diarrhea [76]. However, even this review did not document any reduction in incidence of diarrhea. Overall, the evidence related to benefit of vitamin A in prevention of diarrhea is conflicting, and thus it is not recommended as a diarrhea prevention strategy, except in case of measles.

BOX 5

- Rotavirus vaccine is efficacious in prevention against severe rotaviral diarrhea (80-93%) and any rotaviral diarrhea (62-73%).
- There is no well controlled study evaluating the effectiveness of rotavirus vaccine as a public health strategy implemented in India or similar settings.
- Existing cholera vaccines are not effective enough for implementation on a large scale level.

Conclusions

Vitamin A supplementation does not reduce incidence of diarrhea or diarrhea-related mortality in neonates and children < 6 months but there is a benefit in children aged 6-59 months.

E. Zinc

A large body of evidence from India and other developing countries shows important therapeutic benefits with zinc administration during an episode of diarrhea [77]. In addition, many studies have examined the role of zinc supplementation as a preventive strategy to reduce diarrhea morbidity in the subsequent months (***Table* III**).

A meta-analysis of 17 randomized controlled trials of zinc supplementation (for ≥3 months) for under-five children reported fewer episodes of diarrhea (rate ratio: 0.86), and significantly fewer attacks of severe diarrhea or dysentery (rate ratio: 0.85), and persistent diarrhea (rate ratio: 0.75) with zinc supplementation in comparison to placebo [81]. Zinc-supplemented children also had significantly fewer total days with diarrhea (rate ratio: 0.86). The review concluded that zinc supplementation reduced significantly the frequency and severity of diarrhea and the duration of diarrheal morbidity. However, the relatively limited reduction in morbidity, and the presence of significant heterogeneity and publication bias indicate the need for larger, high-quality studies to identify sub-populations most likely to benefit. Other recent systematic reviews [78,79] concluded that there is a significant reduction in the incidence and prevalence of diarrhea with zinc supplementation but effect on mortality reduction is minimal. Zinc supplementation given during neonatal period also does not seem to reduce diarrheal morbidity in next one year [80].

Conclusions

Zinc supplementation for at least 2 weeks leads to 15-25% fewer episodes of diarrhea in under-five children in

TABLE II SYSTEMATIC REVIEWS OF VITAMIN A IN PREVENTION OF DIARRHEA

Study Year	*Participants*	*Study type*	*Results*
Gogia, *et al*. 2011 [71]	Infants (< 6 mo) from 6 studies conducted in low and middle income countries	Systematic Review of randomized and quasi-randomized trials	No reduction in risk of diarrhea (pooled risk ratio 1.02; 95% CI 0.99 to 1.06, P = 0.19; 24802 participants, 6 studies) or diarrhea related mortality (RR 1.01; 95% CI 0.72 to 1.41; 47998 participants, 7 studies) during first year of life.
Mayo-Wilson *et al*. 2011 [72]	Children aged 6 mo- 5 yrs who received synthetic oral vitmin A supplements or placebo/no intervention.	Systematic Review of RCTs	Seven trials reported a 28% reduction in mortality associated with diarrhea (0.72, 0.57 to 0.91). Vitamin A supplementation was also associated with a reduced incidence of diarrhoea (0.85, 0.82 to 0.87)
Imdad, *et al*. 2011 [73]	Children < 5 years of age	Systematic Review of RCTs	Vitamin A supplementation reduced diarrhea specific mortality by 30% [RR 0.70; 95 % CI 0.58-0.86] in children 6-59 months. No significant benefit was seen in children <6 mo of age.
Gogia, *et al*. 2009 [74]	neonates (<1 mo) receiving prophylactic vitamin A supplementation from 6 trials from developing countries	Systematic Review of RCTs (including quasi or cluster)	No reduction in risk of diarrhea with neonatal vitamin A supplementation.
Grotto, *et al*. 2003 [75]	9 RCTs dealing with morbidity from diarrhea in 6 mo- 7 yr olds	Systematic review of RCTs	No consistent overall protective effect on the incidence of diarrhea (RR, 1.00; 95% CI, 0.94-1.07)
D'Souza, *et al*. 2002 [76]	Vitamin A for preventing morbidity in measles 6mo-13yrs (492 vit A, 536 placebo)	Systematic Review of RCTs	No significant reduction in the incidence of diarrhea. There was a significant decrease in the duration of diarrhea.

the subsequent 2-3 months. There is no benefit of providing zinc in the neonatal period.

5. Health Care Practices in Management of Diarrhea (*WebTable VI*)

A. Care-Seeking

In NFHS-3 [3], treatment for diarrhea was sought from a health provider for 60% under-five children. The proportion of mothers who sought care was similar to NFHS-2 (63%) and NFHS-1 (61%) data [11,12]. Urban children, boys, children of educated mothers and children in households belonging to the higher wealth quintiles were more likely than other children to be taken to a health facility or provider for advice or treatment. In the UNICEF ten district survey [13] and CES [2], almost three-fourths of caregivers reported seeking care outside the home for diarrhea in children. In the Ministry of Health and Family Welfare-UNICEF rural India survey [83] conducted almost 20 years back, the proportion who sought care from a health provider was 65%. From these nationwide surveys, it is apparent that two-thirds to three-fourths of mothers seek care outside home when their child (below the age of five years) suffers from diarrhea. It is striking to note that care-seeking behavior does not seem to have changed over last twenty years, with almost 30-40% children never seeking care outside home

Few surveys have provided information about the profile of health workers visited by mothers. In the UNICEF ten-district survey (2009) [13], a large majority (79% total, 82% urban and 77% rural) of mothers sought treatment from private medical sector. Private service providers (doctor) and private hospitals were the most common sources of consultations. Only 22% of mothers sought care from public health sector. Among the public sector health facilities; government hospitals, PHCs, CHCs, and rural hospital were more popular. Anganwadi and sub-centres were least used for diarrhea treatment. In the UNICEF coverage evaluation survey [2], 48% mothers sought care from private sector and 21% from government sector during an episode of diarrhea in their child.

Similarly, in the MoHFW-UNICEF rural survey (1990) [83], 83% of mothers sought treatment from private practitioners, mostly practicing allopathy (not necessarily licensed). Only 12% sought care from government health center or health worker. The profile of rural doctors was also assessed in this survey. It was found that 62% had no medical qualification and only 3% had a MBBS degree.

In view of the foregoing, it is apparent that any intervention to improve the diarrhea management practices must target the private doctors, including

TABLE III SYSTEMATIC REVIEWS OF ZINC IN PREVENTION OF CHILDHOOD DIARRHEA

Author Year [Ref.]	*Participants*	*Study type*	*Results*	*Comment*
Patel, *et al.* 2011 [78]	RCTs reporting use of zinc supplementation for prevention of childhood diarrhea	Meta-analysis of RCTs	Zinc supplementation resulted in 19% reduction in prevalence and 9% reduction in incidence of diarrhea. It also reduced recurrent diarrhea by 28%. Effects on prevention of persistent diarrhea, dysentery or mortality were not significant.	Heterogeneity of studies was an issue. Quality assessment and methodology of reporting of this review is not rigorous.
Yakoob, *et al.* 2011 [79]	CTs on zinc supplementation Rfor children (3 mo-5yr) in developing countries and its effect on mortality	Meta-analysis and Modelling	In the random effect model, there was no significant effect of preventive zinc on diarrhea-specific mortality (RR = 0.82; 95% CI: 0.64, 1.05) or all cause mortality (RR = 0.91; 95% CI: 0.82, 1.01). After application of CHERG rules, a 13% reduction in diarrhea mortality was seen.	
Gulani, *et al.* 2011 [80]	RCTs and quasi-RCTs evaluating effect of neonatal zinc supplementation	Systematic Review	No significant effect on the number of episodes of diarrhea (RR 0.87, 95% CI 0.65-1.16; 2 trials) or number of children having diarrhea (RR 0.97, 95% CI 0.90-1.04, 2 trials) during first year.	Only two trials reported diarrhea related outcome. Data inadequate for any definite conclusion.
Aggarwal, *et al.* 2007 [81]	RCTs of zinc supplementation for > 3 months conducted in under-five children	Systematic Review of RCTs	Zinc supplementation led to fewer episodes of diarrhea (RR: 0.86) and significantly fewer attacks of severe diarrhea or dysentery (RR: 0.85), persistent diarrhea (RR: 0.75, and lower duration of diarrhea (RR: 0.86)	Limited reduction Heterogeneity Publication bias
Bhutta, *et al.* 1999 [82]	RCTs dealing with zinc supplementation in < 5 yrs. At least 50% of RDA for at least 2 weeks	Systematic review of RCTs	Pooled ORs for diarrheal incidence and prevalence were 0.82 (95% CI 0.72 to 0.93) and 0.75 (95% CI 0.63 to 0.88) respectively. Results similar in short-course and continuous trials	15-25% reduction in incidence of diarrhea in the short-term with zinc supplementation

unlicenced and unqualified practitioners.

B. ***Oral Rehydration Therapy***

National Diarrheal Disease Control Program has been operational in the country since 1980s, and oral rehydration therapy (ORT) is the key element. Recently, the Government of India introduced the low osmolarity Oral Rehydration Solution (ORS), recommended by WHO for the management of diarrhea. Zinc has also been approved as an adjunct to ORS for the management of diarrhea. Emphasis is also placed on continued feeding, including breastfeeding during diarrhea. One major goal of this program is to increase awareness among mothers and communities about the causes and treatment of diarrhea. ORS packets are made widely available and mothers are taught how to use them.

NFHS-3 asked mothers of under-five children who suffered from diarrhea within two weeks preceding the survey, a series of questions about feeding practices during diarrhea, the treatment of diarrhea, and their knowledge and use of ORS. Sixty percent of the mothers reported consulting a health care provider during the episode of diarrhea [3]. However, only 26% of children used ORS. Another disturbing fact was that caregivers of only one in ten children gave increased fluids during diarrhea. Twenty-seven percent of children were given less to drink, 10 percent were given much less to drink, and 4 percent were not given anything to drink, resulting in 4 in 10 children with diarrhea having their fluids decreased while suffering from diarrhea. More than half (57 percent) of children received neither oral rehydration therapy nor increased fluids when sick with diarrhea. Use of ORS and ORT was even less likely among children living in rural areas, children of mothers with little or no education, and children belonging to households in the lower wealth quintiles. These figures indicate poor implementation of proper diarrhea treatment practices not only among mothers but also among health-care providers.

All three National family health surveys [3,11,12] also assessed the knowledge of mothers of under-five children regarding ORS. NFHS-3 reported that 73% of women knew about ORS packets. Knowledge of ORS packets was considerably higher among urban mothers (86%) than rural mothers (70%). The proportion of women who knew of ORS packets increased with education and increasing wealth index. Knowledge of ORS packets was lowest among mothers belonging to the lowest wealth quintile (59%). Knowledge of ORS packets was lowest among mothers who were not regularly exposed to any mass media. There was a clear

dichotomy between knowledge and practice. Despite three-fourth of women knowing about ORS, only one-fourth used it when their child suffered from diarrhea. This difference can not be explained only on the basis of use of other home available fluids as only 43% mother used either ORS or increased fluids (including home available fluids) during diarrhea.

The trends related to management practices related to diarrhea in the communities are not very encouraging. ***Table* IV** shows that ORS use rates have not improved significantly in the seven years from NFHS-2 (1998-99) to NFHS-3 (2005-06) despite improvement in knowledge. The figures of ORS use rates in NFHS-1 are not strictly comparable as these were related to 'ever use of ORS' in comparison to 'ORS use during current episode of diarrhea' in NFHS-2 and NFHS-3. UNICEF surveys report a better ORS use rates (38%-43%) in comparison to NFHS surveys.

Health providers' practices for management of diarrhea was assessed in UNICEF ten-district survey [13]. 85-100% of doctors practicing modern medicine claimed that they prescribed ORS. However, as earlier stated, mothers' reports suggested low level of ORS prescription. In the MoHWF-UNICEF rural India survey [83], most practitioners were aware of ORS; only few actually prescribed it. Only 26% stocked ORS with them, out of which almost half had open packets, and were probably re-dispensing it as medicine in smaller pouches. In other small-scale prescription surveys, ORS use rates was also unsatisfactory.

The results underscore the need for informational programs for mothers and supplemental training for health-care providers that emphasizes the importance of ORS, ORT, and increased fluid intake during episodes of diarrhea.

C. *Feeding during diarrhea*

Continued feeding during a diarrheal episode helps in faster recovery and reduces the chances of getting malnourished. In the NFHS-3 survey, only 37% of children were given the same as usual to eat when recently suffering from diarrhea [3]. Two percent children were given more to eat, 31% were given 'somewhat less than the usual' amount of food, 11% were given much less than the usual amount of food, and 4% were not given any food. Rural mothers were more likely to reduce feeding during diarrhea. Behavior contrary to recommendations for proper management of diarrhea suggests the need for public education program on proper feeding practices during diarrhea.

The practice of giving semi-solids to children during diarrhea showed a marginal improvement from 15% in NFHS-2 to 20% in NFHS-3. However, this could be related to more number of older children in NFHS-3 rather than an improvement in diarrhea management practice as the NFHS-3 catered to mothers having children less than five years in comparison to NFHS-2, which surveyed mothers having children less than three years of age.

D. *Zinc*

As zinc has been introduced in the National Program only recently, the data evaluating use of zinc in diarrhea are scarce. NFHS-3 attempted to obtain the data on zinc treatment given during diarrhea [3]. Only 0.3% of the mothers reported the use of zinc during the preceding episode of diarrhea. However, 30% of mothers reported use of unknown drugs which might have included zinc. In the UNICEF ten-district survey [13], around 1% of mothers had knowledge of zinc and a similar proportion utilized zinc in the management of their child suffering from diarrhea. The awareness regarding zinc is presently negligible in the community. However, government and private practitioners of modern medicine have begun to prescribe zinc. In UNICEF ten-district survey, 30% of government and 36% of private practitioners of modern medicine claimed to prescribe zinc to a child suffering from diarrhea. In a prescription audit from a tertiary care

TABLE IV TEMPORAL TRENDS IN ORAL REHYDRATION THERAPY

Indicator	*Survey (Year)*					
	MoHFW, IMRB, UNICEF Rural India survey (1990)	*NFHS-1 (1992-93)*	*NFHS-2 (1998-99)*	*NFHS-3 (2005-06)*	*UNICEF 10-district survey (2009)*	*UNICEF coverage evaluation survey (2009-10)*
Knowledge of ORS	37%	43%	62%	74%	70%	NA
ORS use rate	6%	26%*	27%	26%	38%	43%
Increasing fluids	NA	10%	22%	10%	10%	10%

**Ever use of ORS in NFHS-1; use during most recent episode in other surveys; ORS: Oral rehydration solution; NFHS: National Family Health Surveys; MoHFW: Ministry of Health and Family Welfare; Data from references [83,3,11,12].*

center in Chennai [87], 65% of children hospitalized with diarrhea received zinc therapy.

E. Other medications/ antibiotics/ antidiarrheals

In NFHS-3 survey, significant proportion of children were treated with drugs (mostly unnecessary), including 30 percent who were treated with 'unknown' drugs and 16 percent who were treated with antibiotics [3]. Irrational use of antibiotics was particularly common for children of more educated mothers and for children in households belonging to the higher wealth quintiles. Use of antimotility drug was fortunately rare with only 1.5% reporting their use. However, the validity of this data is limited because of ignorance of mothers in a significant proportion about the type of drugs given to their children. NFHS-3 did not provide information about receipt of injections during diarrheal episode. However, in NFHS-2 and NFHS-1, 14-15% of mothers reported that injections were given to their child to treat diarrhea [11,12]. In the recent UNICEF ten-district survey [13], the proportion receiving injections during a diarrheal episode was 23%. In the MoHFW-UNICEF rural India survey [83], 80% of private health providers believed antibiotics to be the most useful drugs in management of diarrhea, and 40% of children received injections during an episode of diarrhea.

Prescription audits of doctors have consistently shown very high usage rates of antibiotics in diarrhea (***WebTable* VI**). More than two-thirds of prescriptions given to children suffering from diarrhea had antibiotics. Fixed drug combination (antibacterials + antiprotozoals) are also very commonly used in treatment of diarrhea.

Overall, the practices of healthcare providers in management of diarrhea are far from satisfactory. Use of ORS is low, and antibiotics and other drugs are used irrationally and indiscriminately.

Conclusions: BOX 6

BOX 6

- Three-fourth seek care during diarrhea; a large majority from private providers.
- Knowledge of ORS/ORT amongst mothers of under-five children is good (~70-75%) but there is a big gap between knowledge and practice as reflected in poor ORS usage rates (25-40%).
- The knowledge regarding ORS has shown a positive trend but the use rates have been consistently poor.
- Provider's knowledge of ORS is universal but this again does not translate commonly into practice.
- Knowledge and use of zinc is negligible, though appears to be improving.
- Practice of advising increased fluids and continued feeding during diarrhea needs improvement.
- Irrational use of antibiotics, other drugs and injections to treat diarrhea is common.
- Use of antisecretory agents is rare.

F. Barriers to appropriate health practices

Information on why ORS is not prescribed or why it is not used commonly by mothers is very scarce. There is hardly any published information on this aspect. It is apparent from the prescription audits that the prescription rate of ORS is poor amongst health providers whose care is sought most commonly by the communities. As almost three-fourth of the mothers seek care from health providers for their child during diarrhea, and in majority ORS was not prescribed, the ORS usage rate is bound to be low.

As most users and providers have the knowledge of ORS, but do not make efforts to use it, it reflects low salience of the product in the mind of target group. The MoHFW-UNICEF survey addressed some of these issues in the 1990 survey [83]. The mothers mostly did not use ORS as it was not prescribed by the doctor. Those who reduced the fluid intake during episode of diarrhea did so because either the child rejected fluids (30%), or they believed that the cooling effect of fluids can exacerbate diarrhea (21%) and water content in the fluid can aggravate diarrhea (17%). Fortunately, there were no cultural barriers to the adoption of ORS and ORT, and the level of satisfaction was high amongst the mothers who used it. Rural doctors perceived the medication (capsules/tablets) to be the most important element in diarrhea management, and ORS only as an adjunctive treatment. Sixty-five percent did not rank ORS among the 3 most important elements of treatment in the early stages of diarrhea. In the qualitative survey, the reasons for not prescribing ORS were mentioned as (*i*) it does not stop diarrhea, (*ii*) it is indicated only in dehydration, and (*iii*) presence of perceived contraindications such as vomiting, cough/cold and fever. The reasons for high antibiotic usage were (*i*) strong belief on its benefit in diarrhea, (*ii*) expectation of patient of receiving a medicine from health practitioner, and (*iii*) regular interaction with chemists about new available drugs. Reasons for prescribing antibiotics in UNICEF ten-district survey [13] were presence of dehydration, very frequent loose motions and vomiting. In some other small scale studies, presence of fever prompted the doctor to

prescribe antibiotics in cases of diarrhea.

Regarding stocking ORS, the majority (79-90%) of service providers working in the government sector (practitioners of modern medicine, ANMs/AWWs/ ASHAs) and private chemists stocked supplies of ORS [13]. In contrast, most private practitioners of modern medicine, unregistered medical practitioners and private/ government AYUSH practitioners kept no stock of ORS packets. Stock-outs of ORS were reported in 24-42% of government-sector community health functionaries (ANMs, AWWs and ASHAs). In the MoHFW-UNICEF rural India survey [83], stocking of ORS was reported by only 26% of rural doctors; almost half of them were probably opening the packets and re-dispensing as medicine in smaller paper-pouches (*pudiyas*).

Lack of adequate training in ORT has also been cited as one of the reasons for poor ORS usage in the UNICEF ten-district survey [13]. Although 72% of ANMs/AWWs/ ASHAs reported that they had received some training on management of childhood diarrhea, most (88%) reported having received training for less than eight hours.

An operational study for implementation of ORT was conducted in West Bengal through the existing health services facilities [92,93]. All the grassroot level health workers, including their supervisors at various levels were trained regarding the management of patients of diarrhea by ORT. Training was done for one working day (in batches of 30-40 health workers) using lectures with slides. After five months, the training was repeated for one day, in batches, using modern methods which included module-based approach, discussion, problem-solving exercises, and demonstrations. Another block in the same district with similar demographic features was not provided with this intervention, and served as control. After 22 months of observation, it was evident that despite adequate training, the performance of workers was not encouraging as there was low utilization of both home available fluids and oral rehydration solution in the study area [93]. Diarrhea associated mortality was also similar (2.8/1000 under-five children) between the study and control group. Though evaluation of training of workers using modern modular methods revealed a striking improvement in their knowledge regarding signs of dehydration, preparation and use of ORS etc., this did not translate into practice. The knowledge and level of skills also went down to a considerable extent after 12 months. In spite of providing necessary forms to maintain records, no CHGs or AWWs actually did so. There was no supervision at all at the PHC level. ORS supply was also grossly inadequate as it was not replenished. In spite of the elaborate training imparted to the community health guides and anganwadi workers, the overall usage rate in the study area was only 11% in comparison to 12% in control areas. Home available fluid (HAF) usage rates were also low in both the areas (27% in study *vs* 20% in control). Further, it was revealed that two-thirds of the mothers did not even know their village level worker in the study area. In spite of repeated training of health workers to educate mothers to use ORT earliest in an episode of diarrhea and in adequate amonts, the grassroot level health workers failed to do so even amongst the small poroportion of mothers (12.4%) educated by them. The reasons for failure cited in this study were: (i) logistic failure, (ii) lack of motivation of health workers, and (iii) lack of proper supervision at all levels, and (iv) absence of continued supply of ORS [93]. ***Box* 7** presents a compiled list of barriers to ORS/ORT use, and for preventing antibiotic use [83, 92-98].

A recent review has tried to address the problem of poor performance by community health workers [99]. Most schemes for these workers assume that there is a sufficient pool of volunteers to participate in the social service in rural areas and urban settlements. Most programs pay their community workers a salary or honorarium and there is no system of sustained community financing. Other financial incentives range from a small salary from the state to payments for attendance at training sessions. However, the costs entailed by lost economic opportunities may be too high even if they are working on part-time basis. A high attrition rate contributes to poor stability of the program and increases training costs because of the need for continuous replacement. Payments and commissions related to drug dispensing and sales may encourage inappropriate treatment at the expense of prevention and overuse of medications. Non-financial approaches to improving performance may have less potential to distort care than fee-for-service payments or those associated with drug sales. The review concluded that policymakers should consider using a mix of financial and non-financial incentives tailored to local circumstances to improve health workers' performance, training programs should be tailored to the literacy level of the community health workers, and well-organised supervisory systems should be developed to improve motivation and provide professional development [99].

G. Social Marketing of ORS

NFHS surveys reported that knowledge of ORS was consistently better in mothers who are exposed to any kind of mass media [3,11,12]. Attempts at social marketing of ORT through mass media have been done in past. Television has been effectively used impart knowledge in the communities regarding use of ORS and ORT.

BOX 7

Barriers in ORS Use

A. *System side barriers*

Lack of motivated staff at most peripheral level.

Lack of supervision

Lack of confidence of people in public health system

Lack of awareness of people about public health system

Health care providers are not convinced of benefits of ORS, and do not prescribe it despite knowing about it.

- Perception that it does not stop diarrhea
- Perception that it is only indicated in dehydration
- Preference of intravenous fluids in case of dehydration

ORS-stock outs common with govt. health functionaries

Lack of IEC material laying emphasis on ORT

Inadequate training and inadequate retention of the knowledge and skills about ORT

B. *Demand-side barriers*

Parents, caregivers and providers are not convinced of benefits of ORS.

(have knowledge of ORS but don't use it)

Perception that it is not a medicine (does not stop diarrhea)

Social beliefs (cooling effect of fluids, chances of exacerbation of illness)

C. Barriers to Preventing Antibiotic Use

Fever, dehydration and young age prompts caregiver to prescribe antibiotics

Health workers not convinced of absence of any benefit.

Demand for antibiotics by patients/parents is not common but expectation of a product/ medicine by parents is common.

A small-scale, questionnaire-based study from the slums of Delhi, evaluated the effectiveness of the Ministry of Health's mass media campaign to promote ORT use during diarrheal episodes [100]. The knowledge of 59 mothers who watched the television (TV) advertisement with celebrities delivering simple and clear messages were compared to 90 mothers who had received ORT messages from other sources such as health workers. Mothers in the first group were considerably more likely to know how to correctly prepare ORS than those who learned about ORT from other sources (62.7% *vs* 37.7%). However, no significant difference in use of ORT at home between the 2 groups existed (69.49% and 53.33%, respectively). TV advertisements were more likely to teach educated mothers how to correctly prepare and to use OR at home, than health staff (81.5% *vs* 35.5% and 81.5% *vs* 41.9%, respectively). These results showed that social marketing of ORS packets via TV was successful in increasing ORT acceptability, knowledge and use, and especially among educated mothers. Similar studies in Bangladesh [101] showed that education incites changes in attitude and behavior of mothers, which makes them more receptive of new knowledge and modern medicine. Another possibility for the education difference may be that TV was able to interest educated mothers better than health staff. These findings indicate a need to strengthen education programs in this area using effective media such as television for both mothers and health care providers [102-104].

Knowledge gaps and directions for future research

There is an urgent need to find out the reasons for low ORS use by the users as well as health providers through large scale representative qualitative studies in the community. The system-related barriers need to be urgently addressed by strengthening and overhauling the health system. Acceptability of different preparations of ORS such as flavoured and ready-made ones need to be compared to the standard packaging in the community. National Rural Health Mission is a welcome step in this direction, and its impact on care-seeking behavior and practices needs to be continuously monitored. The role of media in improving the practices needs to be evaluated in operational research programs. With the revolution in telecommunications, the role of mobile phones in community education need to be explored. Urgent operational research is needed to find out the ways to improve the community level workers' performance. Their capability in handling various programs (integrated *vs* vertical) also need to be explored.

6. Operational Research on Zinc Use in Diarrhea

The efficacy of zinc treatment during diarrhea has been proved by many randomized, placebo-controlled trials, and systematic reviews of randomized controlled trials. However, the effectiveness under real-life conditions is influenced by the community's knowledge, attitudes and perceptions, and the quality of training component and financing system. Data regarding scaling up of zinc use from effectiveness studies in communities need to be examined to evaluate its impact on diarrhea management (***Table* V**).

Bhandari, *et al*. [104] conducted a cluster-randomized trial in Haryana utilizing government providers (doctors,

TABLE V OPERATIONAL RESEARCH ON USE OF ZINC DURING DIARRHEA

Author Year [Ref.]	*Place*	*Sample size and characteristics*	*Profile of health worker*	*Type of training*	*Results*	*Comments*
Bhandari, *et al*. 2008 [104]	Primary Care setting, Haryana, India	Cluster randomized trial Six clusters of 30,000 people, each randomly assigned to intervention and control sites. *Intervention:* Zinc and ORS use promoted through trainings Control: Only ORS promotion	Government and private providers and village health workers	Standard training in diarrhea management and referral, including appropriate use of zinc. *Duration:* half a day for physicians and a full day for health workers. Education campaigns promoted zinc as 'tonic' for preventing future episodes.	After 3 months of intervention: zinc use during diarrheal episode: 36.5% ORS use: 34.8% vs. 7.8% Compliance with 14 day zinc: 70% Diarrhea in last two weeks: 13% vs. 18% Antibiotic use: 4% vs. 16% Diarrhea hospitalizations: *After 6 months of intervention*: zinc use during diarrheal episode: 59.8% ORS use: 59.2% vs. 9.8% Compliance with 14 day zinc: 62% Diarrhea in last two weeks: 14% vs. 23% Antibiotic use: 2% vs. 15%	Extensive IEC campaigns (posters, announcements) used in intervention areas. Continuous free supplies of zinc and ORS ascertained. Regular supervision. Motivation measures for health providers (if any) not clear. Injection usage and other drug usage remained high in both areas. Actual compliance with full 14 day course was 22-36%.
Bhandari *et al*. 2005 [105]	Primary health center of Tigaon in Faridabad district, Haryana, India.	Survey of 2364 households having under-five children served by primary health center.	government providers (physicians and auxiliary nurse midwives at the primary health center), private practitioners and community workers under the ICDS scheme.	Two day training in diarrhea management, zinc distribution and use, and referral criteria.	There was a shift in care-seeking from private providers to community health workers. The prescription and use rates of ORS during diarrhea increased markedly from 7% at baseline to over 40% at 3 to 6 months. Zinc was prescribed in more than half of episodes and 72-74% reported giving the complete 14-day course.	Pilot study; formed the basis of the later cluster-randomized trial.
Awasthi, *et al*. 2006 [106]	Outpatient health facilities in six centers in five countries (Brazil, Ethiopia, Egypt, India and Philippines	2,002 children aged 2 to 59 months Intervention: zinc (20 mg once daily for 14 days) with ORS Control: ORS alone Locally developed culturally specific messages for promoting zinc.	No details on profile of healthworkers; probably doctors as the study is done in outpatient health facilities	No details on training of healthworkers. Locally developed culturally specific messages emphasizing therapeutic and preventive benefits of zinc.	In five of six sites, ORS use in cases with continued diarrhea on days 3 to 5 was the same in the two groups or higher in zinc group, except in Brazil where it was lower in zinc group. Overall adherence to zinc supplementation was 83.8% (95% CI 81-86). Antibiotic/antidiarrheal use was lesser in the zinc group.	Quasi-randomized trial; unit of randomization being the day
Gupta, *et al.*	Rural area	Randomized double-	Village sur-	Modular training in the	Lower incidence of diarrhea in the	Evaluated zinc

contd...

Author Year	*Place [Ref.]*	*Sample size and*	*Profile of*	*Type of training*	*Results*	*Comments*
2007 [107]	comprising of 11 villages in West Bengal	blind placebo controlled community based study enrolling 1712 children aged between 6 and 48 months in a randomized double blind study	veillance officers (at least secondary school educated) selected in consultation with village Panchayat.	local language, including diarrhea management, preparation of ORS and referral.	supplemented group (RR 0.74, 95% CI 0.64-0.87) 96% of mothers administered syrup weekly to their children.	supplementation given routinely and not during diarrheal episodes.
Baqui,*et al.* 2004 [108]	Bangladesh	Community based cluster randomized trial 3,974 children in the intervention clusters and 4,096 in control clusters, Intervention: zinc and ORS promotion and distribution; Control: ORS distribution and emphasis on feeding	Community health workers and community volunteers	Standard training to community health workers	ORS use 75% vs. 50% Antibiotic prescription 13% vs. 34% Other medicines 15% vs 45%	Continuous free supplies of zinc and ORS ascertained. Regular supervision. Motivation measures for health providers (if any) not clear.

ANMs and *Aanganwadi* workers) and private practitioners (including unlicenced) as channels of delivery of intervention (provision of zinc and ORS along with caregiver education on their use) after a brief training in diarrhea management and zinc use. The earlier pilot work [105] by this group had demonstrated the feasibility to train various government and community channels to promote zinc as a treatment for acute diarrhea through the primary healthcare system. Information education and communication (IEC) activities involved posters and campaigns to promote zinc as a treatment for diarrhea, as well as a "tonic" that prevents diarrhea over the ensuing months, to ensure compliance with the full 14-day course. Uninterrupted supplies of ORS packets and zinc were ensured. The intervention resulted in reduction in the prevalence of diarrhea and hospitalizations. ORS use increased significantly in the intervention areas, and the intervention also resulted in reduction in the use of unwarranted oral and injectable drugs during diarrhea.

Operational feasibility of introducing zinc in the treatment of diarrhea has also been demonstrated from a multicentric study in outpatient health facilities of six centers in five countries [106] where zinc supplementation was taken by 84% of participants, and it resulted in reduction in antibiotic/antidiarrheal use. This study however, did not demonstrate a significant increase in ORS use with zinc supplementation. Operational feasibility of preventive zinc therapy has also been demonstrated from rural area of West Bengal [107]. Evidence from a communities of Bangladesh [108] also documented a significantly higher use of ORS and other home fluids in the zinc intervention areas than those in the comparison areas. The probability of use of an antimicrobial during diarrhea was only about one-third in the intervention children compared to that in the comparison children.

The improvement in ORS utilization and reduction in antibiotic use in the populations receiving zinc demonstrates that the benefits of zinc supplementation extend well beyond reducing the diarrheal morbidity and mortality. The reasons for reduction in antibiotic and other unknown drug usage could be a reflection of fulfilling the caregivers' expectation of medicine by dispensing zinc, and a shift in careseeking behavior from private provider to government functionary. Improvement in ORS use rates are likely to be the effect of enthusiastic IEC campaigns incorporating zinc messages along with ORS. Overall, the studies have demonstrated that an intervention to improve diarrhea management with ORS and zinc is feasible, acceptable and effective in rural Indian communities. Further scaling-up of this intervention should be given priority in India.

Conclusions: Box 8

Knowledge gaps and directions for future research: Zinc has now been introduced in the National diarrhea treatment guidelines. Efforts are on to promote its usage by involving organizations such as Indian Academy of Pediatrics. The providers' practices need to be continuously monitored to document any effect of these strategies. The efficacy of zinc and its effect on health-seeking behavior, and ORS and antibiotic use rates need to be monitored in real program based settings. Compliance with the use of zinc for 14 days needs to be evaluated in the communities. The preventive effects of using zinc in the program need to be monitored by conducting follow-up incidence and prevalence studies. The capability of the existing health system to deliver zinc along with other strategies in management of diarrhea need to be assessed by continuous monitoring and supervision.

DISCUSSION

This systematic review methodologically collected and collated evidence from a variety of sources (including but not restricted to peer reviewed publications), to guide the initiation and/or scaling-up of advocacy and actions for tackling the burden of childhood diarrhea in India. This review is a critical first-step in today's era of evidence-informed decision-making. The review concluded that diarrhea is widely prevalent at any point among under-five children in India, and accounts for 14% of the total deaths in this age group. Exclusive breastfeeding, handwashing and point-of-use water treatment were identified to be the most effective strategies for prevention of all-cause diarrhea. Rotavirus vaccines, though efficacious in preventing rotavirus specific diarrhea, need further evaluation for their efficacy and effectiveness in India or similar settings. The current use rates for ORS and zinc are unacceptably low. Incorporation of zinc therapy in the health programs can reduce antibiotic prescription and improves ORS utilization. Zinc therapy can be upscaled through existing infrastructure, introducing the training component and information, education and communication activities**.**

BOX 8

- Introduction of zinc in treatment of diarrhea reduces antibiotic prescription and increases ORS usage provided all health functionaries (including private providers) are involved in the program and uninterrupted supplies are maintained.
- Compliance with zinc is acceptable after IEC activities.
- Intervention of zinc treatment given during diarrhea can be upscaled through existing infrastructure, introducing the training component and IEC activities.

Results of this review are in consonance with the existing diarrhea prevention and control strategies. Recent analysis using Lives Saved Tool (LiST) estimated that diarrheal deaths can be drastically reduced (by 78%-92%) if key interventions (ORS, zinc, antibiotics for dysentery, rotavirus vaccine, vitamin A supplementation, basic water, sanitation, hygiene, and breastfeeding) were scaled-up in the 68 high child mortality countries [109].

Previous reviews tended to have methodological limitations such as incorporation of outdated data; or selective inclusion (or omission) of evidence supporting a particular viewpoint. Another strength of this review is that we could access current data relevant to India from multiple sources including Health Ministry documents, NFHS series, UNICEF surveys etc. Therefore, this systematic review can be regarded as current, comprehensive and oriented to facilitating informed decision making, especially at program level.

Nevertheless, some limitations of this review must also be recognized. We did not undertake detailed quality assessment of the included publications. Therefore we have not presented insights into the applicability, transferability or appropriateness of cited evidence with specific reference to the Indian context. Secondary analysis of the data presented in the included publications was also not undertaken. Therefore, we are unable to present a weighted average for numerical data or other meta-analyses. We have reported data as presented in the original publications, without filtering or treating them to fit a common reporting format. This can make it slightly difficult to compare outcomes presented in variable manner. Although we have accorded highest priority to recent systematic reviews, some conclusions presented in systematic reviews could stem from a limited number of trials (in some cases, even one RCT) and participants. It must also be noted that we have not undertaken literature search for some issues like efficacy and effectiveness of zinc and ORS in management of diarrhea as these are well established interventions, and the need of a re-appraisal on these was not identified in the finalization of questions for this systematic review.

Competing interests: None stated; *Funding*: UNICEF.

Disclaimer: The views expressed by authors are their own and do not reflect the Institutional policies, to which they belong.

REFERENCES

1. Sample Registration System: Special Survey of Deaths.

Report on Causes of Death: 2001-03, Office of Registrar General of India, Ministry of Home Affairs, New Delhi. 2009.
2. United Nations Children's Fund and Ministry of Health and Family Welfare, Government of India. 2009 Coverage Evaluation Survey. All India Report. New Delhi: UNICEF, 2010. Available from: URL: http://www.unicef.org/india/health_6679.htm. Accessed February 24, 2012.
3. International Institute for Population Sciences (IIPS) and Macro International. 2007. National Family Health Survey (NFHS-3), 2005–06: India: Volume I. Mumbai: IIPS.
4. Mathew JL, Shah D, Gera T, Gogia S, Mohan P, Panda R, *et al.* UNICEF-PHFI Newborn and Child Health Series – India. Systematic Reviews on Child Health Priorities for Advocacy and Action: Methodology. Indian Pediatr. 2011;48:183-9.
5. Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. Bull WHO. 2003;81:197-204.
6. Bern C, Martines J, de Zoysa I, Glass RI. The magnitude of the global problem of diarrhoeal disease: a ten-year update. Bull WHO.1992;70:705-14.
7. Snyder JD, Merson MH. The magnitude of the global problem of acute diarrhoeal disease: a review of active surveillance data. Bull WHO.1982;60:604-13.
8. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS, and the Bellagio Child Survival Study Group. How many child deaths can we prevent this year? Lancet. 2003; 362: 65-71.
9. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, *et al.*, for the Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet.2010;375:1969-87.
10. Million Death Study Collaborators, Bassani DG, Kumar R, Awasthi S, Morris SK, Paul VK, *et al.* Causes of neonatal and child mortality in India: a nationally representative mortality survey. Lancet. 2010;376:1853-60.
11. International Institute for Population Sciences (IIPS) and ORC Macro. 2000. National Family Health Survey (NFHS-2), 1998–99: India: Volume I. Mumbai: IIPS.
12. International Institute for Population Sciences (IIPS) and Macro International 1995. National Family Health Survey (NFHS-1), 1992–93: India: Volume I. Mumbai: IIPS.
13. UNICEF. Management Practices for Childhood Diarrhea in India: Survey of 10 Districts. New Delhi: UNICEF; 2009.
14. Anvikar AR, Dolla C, Dutta S, Rao VG, Gadge VS, Shukla GP, *et al.* Role of Escherichia coli in acute diarrhoea in tribal preschool children of central India. Paediatr Perinat Epidemiol. 2008 ;22:40-6.
15. Anand K, Sundaram KR, Lobo J, Kapoor SK. Are diarrheal incidence and malnutrition related in under five children? A longitudinal study in an area of poor sanitary conditions. Indian Pediatr. 1994;31:943-8.
16. Gupta N, Jain SK, Ratnesh, Chawla U, Hossain S, Venkatesh S. An evaluation of diarrheal diseases and acute respiratory infections control programmes in a Delhi slum. Indian J Pediatr. 2007;74:471-6.
17. Awasthi S, Pande VK. Cause-specific mortality in under fives in the urban slums of Lucknow, north India. J Trop Pediatr. 1998;44:358-61.
18. Grover VL, Chhabra P, Malik S, Kannan AT. Pattern of morbidity and mortality amongst under fives in an urban resettlement colony of East Delhi. Indian J Prev Soc Med. 2004;35:21-26.
19. Parashar UD, Burton A, Lanata C, Boschi-Pinto C, Shibuya K, Steele D, *et al.* Global mortality associated with rotavirus disease among children in 2004.J Infect Dis. 2009 Nov 1;200 Suppl 1:S9-S15.
20. Huilan S, Zhen LG, Mathan MM, Mathew MM, Olarte J, Espejo R, *et al.* Etiology of acute diarrhoea among children in developing countries: a multicentre study in five countries. Bull World Health Organ. 1991;69:549-55.
21. Nair GB, Ramamurthy T, Bhattacharya MK, Krishnan T, Ganguly S, Saha DR, *et al.* Emerging trends in the etiology of enteric pathogens as evidenced from an active surveillance of hospitalized diarrhoeal patients in Kolkata, India. Gut Pathog. 2010;2:4.
22. Kuttiat VS, Lodha R, Das B, Kohli U. Prevalence of cholera in pediatric patients with acute dehydrating diarrhea. Indian J Pediatr. 2010;77:67-71.
23. Ajjampur SS, Sarkar R, Sankaran P, Kannan A, Menon VK, Muliyil J, *et al.* Symptomatic and asymptomatic Cryptosporidium infections in children in a semi-urban slum community in southern India. Am J Trop Med Hyg. 2010;83:1110-5.
24. Nandy S, Mitra U, Rajendran K, Dutta P, Dutta S. Subtype prevalence, plasmid profiles and growing fluoroquinolone resistance in Shigella from Kolkata, India (2001-2007): a hospital-based study. Trop Med Int Health. 2010;15:1499-507.
25. Nayak MK, Chatterjee D, Nataraju SM, Pativada M, Mitra U, Chatterjee MK, *et al.* A new variant of Norovirus GII.4/2007 and inter-genotype recombinant strains of NVGII causing acute watery diarrhoea among children in Kolkata, India. J Clin Virol. 2009;45:223-9.
26. Samal SK, Khuntia HK, Nanda PK, Satapathy CS, Nayak SR, Sarangi AK, *et al.* Incidence of bacterial enteropathogens among hospitalized diarrhea patients from Orissa, India. Jpn J Infect Dis. 2008;61:350-5.
27. Ramani S, Sowmyanarayanan TV, Gladstone BP, Bhowmick K, Asirvatham JR, Jana AK, *et al.* Rotavirus infection in the neonatal nurseries of a tertiary care hospital in India. Pediatr Infect Dis J. 2008;27:719-23.
28. Ramani S, Kang G. Burden of disease & molecular epidemiology of group A rotavirus infections in India. Indian J Med Res. 2007;125:619-32.
29. Saha DR, Rajendran K, Ramamurthy T, Nandy RK, Bhattacharya SK. Intestinal parasitism and Vibrio cholerae infection among diarrhoeal patients in Kolkata, India. Epidemiol Infect. 2008;136:661-4.
30. Monica B, Ramani S, Banerjee I, Primrose B, Iturriza-Gomara M, Gallimore CI, *et al.* Human caliciviruses in symptomatic and asymptomatic infections in children in Vellore, South India. J Med Virol. 2007;79:544-51.
31. Banerjee I, Ramani S, Primrose B, Moses P, Iturriza-Gomara M, Gray JJ, *et al.* Comparative study of the

epidemiology of rotavirus in children from a community-based birth cohort and a hospital in South India. J Clin Microbiol. 2006;44:2468-74.
32. Bhattacharya R, Sahoo GC, Nayak MK, Ghosh S, Dutta P, Bhattacharya MK, *et al.* Molecular epidemiology of human astrovirus infections in Kolkata, India. Infect Genet Evol. 2006;6:425-35.
33. Bahl R, Ray P, Subodh S, Shambharkar P, Saxena M, Parashar U, *et al.* Incidence of severe rotavirus diarrhea in New Delhi, India, and G and P types of the infecting rotavirus strains. J Infect Dis. 2005;192 (Suppl 1):S114-9.
34. Ballal M, Ramamurthy T. Enteroaggregative Escherichia coli diarrhea in Manipal. Indian Pediatr. 2005;42:722-3.
35. Mishra D, Gupta VK, Yadav RB. Role of Entamoeba histolytica in acute watery diarrhea in hospitalized under-five children. Indian Pediatr. 2004;41:861-3.
36. Phukan AC, Patgiri DK, Mahanta J. Rotavirus associated acute diarrhoea in hospitalized children in Dibrugarh, north-east India. Indian J Pathol Microbiol. 2003;46:274-8.
37. Kaur R, Rawat D, Kakkar M, Uppal B, Sharma VK. Intestinal parasites in children with diarrhea in Delhi, India. Southeast Asian J Trop Med Public Health. 2002;33:725-9.
38. Ballal M, Shivananda PG. Rotavirus and enteric pathogens in infantile diarrhoea in Manipal, South India. Indian J Pediatr. 2002;69:393-6.
39. Saha MR, Saha D, Dutta P, Mitra U, Bhattacharya SK. Isolation of Salmonella enterica serotypes from children with diarrhoea in Calcutta, India. J Health Popul Nutr. 2001;19:301-5.
40. Jain V, Parashar UD, Glass RI, Bhan MK. Epidemiology of rotavirus in India. Indian J Pediatr. 2001;68:855-62.
41. Government of India: Ministry of Health & Family Welfare; Child Health Division. Minutes of the High Level Committee Meeting Held on 20.3.2007 to Discuss Role of Zinc in Management of Diarrhoea and New Guidelines for Treatment of Diarrhoea in Children. Available from: URL: http://www.whoindia.org/LinkFiles/Child_Health_in_India_Child_Health_GOI_Guidelines_002.pdf. Accessed January 26, 2012.
42. Bhatnagar S, Lodha R, Choudhury P, Sachdev HPS, Shah N, Narayan S, *et al.* IAP Guidelines 2006 on management of acute diarrhea. Indian Pediatr. 2007; 44:380-9.
43. Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, *et al.*, for the Maternal and Child Undernutrition Study Group. What works? Interventions for maternal and child undernutrition and survival. Lancet 2008;371:417–40.
44. Duijts L, Jaddoe VW, Hofman A, Moll HA. Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. Pediatrics. 2010;126:e18-25.
45. Ehlayel MS, Bener A, Abdulrahman HM. Protective effect of breastfeeding on diarrhea among children in a rapidly growing newly developed society. Turk J Pediatr. 2009;51:527-33.
46. Quigley MA, Cumberland P, Cowden JM, Rodrigues LC. How protective is breast feeding against diarrhoeal disease in infants in 1990s England? A case-control study. Arch Dis Child. 2006;91:245-50.
47. Khadivzadeh T, Parsai S. Effect of exclusive breastfeeding and complementary feeding on infant growth and morbidity. East Mediterr Health J. 2004;10:289-94.
48. Saleemi MA, Zaman S, Akhtar HZ, Jalil F, Ashraf RN, Hanson LA, *et al.* Feeding patterns, diarrhoeal illness and linear growth in 0-24-month-old children. J Trop Pediatr. 2004;50:164-9.
49. Bhandari N, Bahl R, Mazumdar S, Martines J, Black RE, Bhan MK; Infant Feeding Study Group. Effect of community-based promotion of exclusive breastfeeding on diarrhoeal illness and growth: a cluster randomised controlled trial. Lancet. 2003;361:1418-23.
50. Arifeen SE, Hoque DM, Akter T, Rahman M, Hoque ME, Begum K, *et al.* Effect of the Integrated Management of Childhood Illness strategy on childhood mortality and nutrition in a rural area in Bangladesh: a cluster randomised trial. Lancet. 2009;374:393-403..
51. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000;355:451-5.
52. Ejemot RI, Ehiri JE, Meremikwu MM, Critchley JA. Hand washing for preventing diarrhoea. Cochrane Database Syst Rev. 2008;23:CD004265.
53. Fewtrell L, Kaufmann RB, Kay D, Enanoria W, Haller L, Colford JM Jr. Water, sanitation, and hygiene interventions to reduce diarrhoea in less developed countries: a systematic review and meta-analysis. Lancet Infect Dis. 2005;5:42-52.
54. Curtis V, Cairncross S. Effect of washing hands with soap on diarrhoea risk in the community: a systematic review. Lancet Infect Dis. 2003;3:275-81.
55. Luby SP, Agboatwalla M, Bowen A, Kenah E, Sharker Y, Hoekstra RM. Difficulties in maintaining improved handwashing behavior, Karachi, Pakistan. Am J Trop Med Hyg. 2009;81:140-5.
56. Soares-Weiser K, MacLehose H, Ben-Aharon I, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev 2010;5:CD008521.
57. Vieira SC, Gurgel RQ, Kirby A, Barreto IP, Souza LD, Oliveira OC, *et al.* Acute diarrhoea in a community cohort of children who received an oral rotavirus vaccine in Northeast Brazil. Mem Inst Oswaldo Cruz. 2011 ;106:330-4.
58. Molto Y, Cortes JE, De Oliveira LH, Mike A, Solis I, Suman O, *et al.* Reduction of diarrhea-associated hospitalizations among children aged < 5 Years in Panama following the introduction of rotavirus vaccine. Pediatr Infect Dis J. 2011;30(1 Suppl):S16-20.
59. Quintanar-Solares M, Yen C, Richardson V, Esparza-Aguilar M, Parashar UD, Patel MM. Impact of rotavirus vaccination on diarrhea-related hospitalizations among children < 5 years of age in Mexico. Pediatr Infect Dis J. 2011;30(1 Suppl):S11-5.
60. de Palma O, Cruz L, Ramos H, de Baires A, Villatoro N, Pastor D, *et al.* Effectiveness of rotavirus vaccination

against childhood diarrhoea in El Salvador: case-control study. BMJ. 2010;340:c2825. doi:10.1136/bmj.c2825.
61. Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, Esparza-Aguilar M, Johnson B, Gomez-Altamirano CM, *et al.* Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. N Engl J Med. 2010;;362:299-305.
62. Centers for Disease Control and Prevention (CDC). Reduction in rotavirus after vaccine introduction—United States, 2000-2009. MMWR Morb Mortal Wkly Rep. 2009;58:1146-9.
63. Esparza-Aguilar M, Bautista-Márquez A, González-Andrade Mdel C, Richardson-López-Collada VL. Analysis of the mortality due to diarrhea in younger children, before and after the introduction of rotavirus vaccine. Salud Publica Mex. 2009;51:285-90.
64. Sinclair D, Abba K, Zaman K, Qadri F, Graves PM. Oral vaccines for preventing cholera. Cochrane Database Syst Rev. 2011;3:CD008603.
65. Graves PM, Deeks JJ, Demicheli V, Jefferson T. Vaccines for preventing cholera: killed whole cell or other subunit vaccines (injected). Cochrane Database Syst Rev. 2010;8:CD000974.
66. Reddaiah VP; Kapoor SK. Does measles immunization reduce diarrhoeal morbidity. Indian J Comm Med 1993;18:115-7.
67. Narang A, Bose A, Pandit AN, Dutta P, Kang G, Bhattacharya SK, *et al.* Immunogenicity, reactogenicity and safety of human rotavirus vaccine (RIX4414) in Indian infants. Hum Vaccin. 2009;5:414-9.
68. Podewils LJ, Antil L, Hummelman E, Bresee J, Parashar UD, Rheingans R. Projected cost-effectiveness of rotavirus vaccination for children in Asia. J Infect Dis. 2005;192(Suppl 1):S133-45.
69. Sachdev HP, Kumar S, Singh KK, Satyanarayana L, Puri RK. Risk factors for fatal diarrhea in hospitalized children in India. J Pediatr Gastroenterol Nutr. 1991;12:76-81.
70. Sur D, Lopez AL, Kanungo S, Paisley A, Manna B, Ali M, *et al.* Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. Lancet. 2009;374:1694-702.
71. Gogia S, Sachdev HS. Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less. Cochrane Database Syst Rev. 2011;2:CD007480.
72. Mayo-Wilson E, Imdad A, Herzer K, Yakoob MY, Bhutta ZA. Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis. BMJ. 2011;343:d5094. doi: 10.1136/bmj.d5094.
73. Imdad A, Yakoob MY, Sudfeld C, Haider BA, Black RE, Bhutta ZA. Impact of vitamin A supplementation on infant and childhood mortality. BMC Public Health. 2011;11(Suppl 3):S20.
74. Gogia S, Sachdev HS. Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials. BMJ. 2009;338:b919. doi: 10.1136/bmj.b919.
75. Grotto I, Mimouni M, Gdalevich M, Mimouni D. Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. J Pediatr. 2003;142:297-304.
76. D'Souza RM, D'Souza R. Vitamin A for preventing secondary infections in children with measles—a systematic review. J Trop Pediatr. 2002;48:72-7.
77. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2008;3:CD005436.
78. Patel AB, Mamtani M, Badhoniya N, Kulkarni H. What zinc supplementation does and does not achieve in diarrhea prevention: a systematic review and meta-analysis. BMC Infect Dis. 2011;11:122.
79. Yakoob MY, Theodoratou E, Jabeen A, Imdad A, Eisele TP, Ferguson J, *et al.* Preventive zinc supplementation in developing countries: impact on mortality and morbidity due to diarrhea, pneumonia and malaria. BMC Public Health. 2011 Apr 13;11 Suppl 3:S23.
80. Gulani A, Bhatnagar S, Sachdev HP. Neonatal zinc supplementation for prevention of mortality and morbidity in breastfed low birth weight infants: systematic review of randomized controlled trials. Indian Pediatr. 2011;48:111-7.
81. Aggarwal R, Sentz J, Miller MA. Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. Pediatrics. 2007;119:1120-30.
82. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, *et al.* Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. J Pediatr. 1999;135:689-97.
83. Vishwanathan H, Rhode JE. Diarrhea in Rural India: A Nationwide Study of Mothers & Practitioners, All India Summary. New Delhi: Vision Books; 1990.
84. Kumar R, Indira K, Rizvi A, Rizvi T, Jeyaseelan L. Antibiotic prescribing practices in primary and secondary health care facilities in Uttar Pradesh, India. J Clin Pharm Ther. 2008;33:625-34.
85. Awasthi S, Srivastava NM, Pant S. Symptom-specific care-seeking behavior for sick neonates among urban poor in Lucknow, Northern India. J Perinatol. 2008;28 (Suppl 2):S69-75.
86. S KI, Chandy SJ, Jeyaseelan L, Kumar R, Suresh S. Antimicrobial prescription patterns for common acute infections in some rural & urban health facilities of India. Indian J Med Res. 2008;128:165-71.
87. Balasubramanian S, Ganesh R. Prescribing pattern of zinc and antimicrobials in acute diarrhea. Indian Pediatr. 2008;45:701.
88. Chakrabarti A. Prescription of fixed dose combination drugs for diarrhoea. Indian J Med Ethics. 2007;;4:165-7.
89. Bharathiraja R, Sridharan S, Chelliah LR, Suresh S, Senguttuvan M. Factors affecting antibiotic prescribing pattern in pediatric practice. Indian J Pediatr. 2005;72:877-9.
90. Singh J, Bora D, Sachdeva V, Sharma RS, Verghese T. Prescribing pattern by doctors for acute diarrhoea in children in Delhi, India. Diarrhoeal Dis Res. 1995;

13:229-31.
91. Raghu MB, Balasubramanian S, Balasubrahmanyam G, Indumathy, Ramnath A. Drug therapy of acute diarrhoea in children—actual practice and recommendations. Indian J Pediatr. 1995;62:433-7.
92. Gupta DN, SenGupta PG, Sircar BK, Mondal S, Sarkar S, Deb BC. Implementation of ORT: some problems encountered in training of health workers during an operational research programme. Indian J Public Health. 1994;38:69-72.
93. Sircar BK, Deb BC, Sengupta PG, Mondal S, Gupta DN, Sarkar S, *et al.* An operational study on implementation of oral rehydration therapy in a rural community of West Bengal, India. Indian J Med Res. 1991;93:297-302.
94. Dua T, Bahl R, Bhan MK. Lessons learnt from Diarrheal Diseases Control Program and implications for the future. Indian J Pediatr. 1999;66:55-61.
95. Sengupta PG, Mondal SK, Ghosh S, Gupta DN, Sikder SN, Sircar BK. Review on development and community implementation of oral rehydration therapy. Indian J Public Health. 1994;38:50-7.
96. Suarez De Balcazar Y, Balcazar FE. Child survival in the Third World: a functional analysis of oral rehydration therapy dissemination campaigns. Behav Change. 1991;8:26-34.
97. Sarkar K, Sircar BK, Roy S, Deb BC, Biswas AB, Biswas R. Global review on ORT (oral rehydration therapy) programme with special reference to Indian scene. Indian J Public Health. 1990;34:48-53.
98. Kumar V, Kumar R, Khurana JL. Assessment of the effect of training on management of acute diarrhoea in a primary health care setting. J Diarrhoeal Dis Res. 1989;;7:70-6.
99. Haines A, Sanders D, Lehmann U, Rowe AK, Lawn JE, Jan S, *et al.* Achieving child survival goals: potential contribution of community health workers. Lancet 2007; 369: 2121–31.
100. Koul PB, Murali MV, Gupta P, Sharma PP. Evaluation of social marketing of oral rehydration therapy. Indian Pediatr. 1991;28:1013-6.
101. Green EC. Diarrhea and the social marketing of oral rehydration salts in Bangladesh. Soc Sci Med. 1986;23:357-66.
102. Meyer A, Foote D, Smith W. Communication works across cultures: hard data on ORT. IDev Commun Rep. 1985;51:3-4.
103. Rao KV, Mishra VK, Retherford RD. Mass media can help improve treatment of childhood diarrhoea. Natl Fam Health Surv Bull. 1998;11:1-4.
104. Bhandari N, Mazumder S, Taneja S, Dube B, Agarwal RC, Mahalanabis D, *et al.* Effectiveness of zinc supplementation plus oral rehydration salts compared with oral rehydration salts alone as a treatment for acute diarrhea in a primary care setting: a cluster randomized trial. Pediatrics. 2008 May;121:e1279-85.
105. Bhandari N, Mazumder S, Taneja S, Dube B, Black RE, Fontaine O, *et al.* A pilot test of the addition of zinc to the current case management package of diarrhea in a primary health care setting. J Pediatr Gastroenterol Nutr. 2005;41:685-7.
106. Awasthi S; INCLEN Childnet Zinc Effectiveness for Diarrhea (IC-ZED) Group. 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. Pediatr Gastroenterol Nutr. 2006;42:300-5.
107. Gupta DN, Rajendran K, Mondal SK, Ghosh S, Bhattacharya SK. Operational feasibility of implementing community-based zinc supplementation: impact on childhood diarrheal morbidity. Pediatr Infect Dis J. 2007;26:306-10.
108. Baqui AH, Black RE, El Arifeen S, *et al.* Zinc therapy for diarrhoea increased the use of oral rehydration therapy and reduced the use of antibiotics in Bangladeshi children. J Health Popul Nutr. 2004;22:440–2.
109. Fischer Walker CL, Friberg IK, Binkin N, Young M, Walker N, Fontaine O, *et al.* Scaling up diarrhea prevention and treatment interventions: a Lives Saved Tool analysis. PLoS Med. 2011;8:e1000428.