2009

Four-country surveillance of intestinal intussusception and diarrhoea in children

Shally Awasthi
King George Medical University

Girdhar Agarwal
Lucknow University

Vikas Mishra
King George Medical University

Vijay Laxmi Nag
Sanjay Gandhi Postgraduate Institute

Hesham Fathey El Sayed
Suez Canal University

See next page for additional authors

Authors

Shally Awasthi, Girdhar Agarwal, Vikas Mishra, Vijay Laxmi Nag, Hesham Fathey El Sayed, Antonio Da Cunha, Alvaro Madeiro, Dipty Jain, William Macharia, James Ndung'u, Saumya Awasthi, and Ashish Wakhlu

doi:10.1111/j.1440-1754.2008.01434.x

ORIGINAL ARTICLE

Four-country surveillance of intestinal intussusception and diarrhoea in children

Shally Awasthi,[1] Girdhar G Agarwal,[2] Vikas Mishra,[1] Vijay Laxmi Nag,[3] Hesham Fathey El Sayed,[4] Antonio Jose Ledo da Cunha,[5] Alvaro Madeiro,[6] Dipty Jain,[7] William M Macharia,[8] James Ndung'u,[8] Saumya Awasthi[1] and Ashish Wakhlu[9]

[1]Department of Paediatrics, King George Medical University, [2]Department of Statistics, Lucknow University, [3]Department of Microbiology, SGPGI, [9]Department of Paediatrics Surgery, King George's Medical University, Lucknow, [7]Department of Paediatrics, Government Medical College, Nagpur, India, [4]Department of Paediatrics, Suez Canal University, Ismailia, Egypt, [5]Universidade Federal do Rio de Janeiro, [6]International Clinical Epidemiology Network, Brazil, and [8]University of Nairobi, Kenya

Aim: Establishment of baseline epidemiology of intussusception in developing countries has become a necessity with the possibility of reintroduction of rotavirus vaccine. The current study assessed the seasonal trend in cases admitted with intussusceptions and dehydrating acute watery diarrhoea in children aged 2 months to 10 years.

Methods: In a prospective surveillance study, teaching and research hospital sites in India (Lucknow and Nagpur), Brazil (Fortazela), Egypt (Ismailia) and Kenya (Nairobi) established a surveillance where a network of hospitals with surgical facilities catered to a reference population of about 1–2 million for reporting of intussusception. One large hospital per site also recruited admitted cases of acute watery diarrhoea.

Results: From April 2004 to March 2006, 173 and 2346 cases of intussusception and diarrhoea, respectively, were recruited. Cases of intussusception had no apparent seasonality. Most cases of intussusception (61.3%) (107/173) were in the ≤1 year age group, with males comprising 68.8% (119/173) of all cases. Hospital mortality of intussusception was 4.2% (4/96). Cases of diarrhoea peaked in March, with 56.6% (1328/2346) of admitted cases being males. Majority (83.1%) of cases of diarrhoea had received antibiotics, and the hospital mortality was 0.8% (18/2280).

Conclusion: Intussusception in the four participating countries exhibited no seasonal trend. We found that it is feasible to establish a surveillance network for intussusception in developing countries. Future efforts must define population base before the introduction of rotavirus vaccine and continue for some years thereafter.

Key words: diarrhoea; intussusception; rotavirus; seasonality.

Diarrhoea is a common cause of childhood morbidity and mortality in developing countries.[1–3] Rotavirus, particularly group A, is a major cause of dehydrating gastroenteritis.[4] It is estimated that each year, rotavirus accounts for 140 million cases of gastroenteritis leading to 800 000 deaths in developing countries and accounting for 20–70% of hospitalised cases of diarrhoea in children between the ages of 6 months and 2 years.[5,6] Worldwide, rotavirus accounts for an estimated two-fifths of all severe diarrhoea cases and causes up to a third of the 1.9 million deaths a year because of diarrhoea.[7] Ninety per cent of these deaths occur in the developing countries, where access to lifesaving treatment is limited and where a vaccine would offer the best hope for preventing countless deaths.[7] Prior to introduction of rotavirus vaccine, there is a need to establish epidemiology of intussusception as the earlier rhesus reassortant tetravalent vaccine was withdrawn in 1999 after reports of intussusception after administration.[8,9]

Key Points

1. There is a need to establish a surveillance network for intussusception in developing countries for a longer period before and after introduction of rotavirus vaccine.
2. We found no inherent association between 'seasonality of diarrhoea' and 'seasonality of intussusception'.
3. There are regional differences in incidence and age of presentation of intussusception that may be due to genetic, ethnic, infectious or environmental factors. Baseline information provided in this study may play a role in the post-licensure rotavirus vaccine surveillance for intussusception.

Correspondence: Professor Shally Awasthi, Department of Pediatrics, King George's Medical University, Lucknow (UP), India – 226003. Fax: +91 522 225 7674; email: sawasthi@sancharnet.in

Accepted for publication 22 July 2008.

Materials and Methods

The current study was carried out with the primary objective of assessing the seasonal trend in cases admitted with intestinal intussusceptions and dehydrating acute watery diarrhoea. The secondary objectives were to assess (i) hospital mortality rates of diarrhoea and intussusception; and (ii) the use of antibiotics and

antidiarrhoeals and duration of hospitalisation in cases admitted with intussusception and acute watery diarrhoea.

This was a four-country and five-site prospective surveillance study, conducted from April 2004 to March 2006, after institutional ethical clearance from all the participating sites. The participating sites were India (Lucknow: 26°51′N, 80°55′E, altitude 123 m and Nagpur: 21°9′N, 79°7′E, altitude 310 m), Brazil (Fortazela: 3°46′S, 38°3′W, altitude 94 m), Egypt (Ismailia: 30°35′N, 32°16′E, altitude 13 m) and Kenya (Nairobi: 1°16′S, 36°48′E, altitude 1500 m). We established a hospital surveillance network (HSN) with hospitals having operating facilities for the reporting of intestinal intussusception in a population of about 1–2 million in each city. Before inclusion of a hospital in the HSN, an informed, written consent of hospital authorities as well as physicians and surgeons was taken.

Also, in each city, an index hospital that was a part of large teaching, training and research medical school/universities was selected for recruiting cases of acute watery diarrhoea of <7 days duration and admitted with severe dehydration requiring intravenous fluids. This included Government Medical College and Hospital, Nagpur; King George's Medical University, Lucknow; Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; Suez Canal University, Ismailia, Egypt; and University of Nairobi, Kenya with paediatric bed strengths of 160, 100, 270, 40 and 250, respectively.

Project teams comprised paediatricians, paediatric and general surgeons. Reports of cases admitted with intussusception in children aged 2 months to 10 years were collected from all hospitals of the HSN weekly. Similarly, all cases of diarrhoea, aged 2 months–10 years, admitted to the index hospital, were invited for participation. Written informed consent was obtained from the parents or legal guardians of children prior to recruitment in the study. Excluded were those whose parents refused to participate in the study.

In the index hospital at every site, all hospital admissions were screened within 48 h to identify cases of acute watery diarrhoea. Diarrhoea was defined as the passage of three or more abnormally loose or watery stools per 24 h or a change in the number or consistency of stools.[10] The severity of dehydration caused by diarrhoea was assessed by symptomatic clinical examination as recommended by the World Health Organization[10] and was categorised as severe, some or no dehydration. Cases of dysentery (diarrhoea with blood in the stool, with or without mucus)[10] and persistent diarrhoea (diarrhoeal duration of 14 days or more)[10] were excluded from the study. Inclusion and exclusion criteria were the same across all five settings. Written informed consent was obtained from the parents or legal guardians of children suffering from diarrhoea prior to recruitment in the study.

The demographic and socio-economic variables were measured and history was taken for dietary practices, clinical symptoms with their duration, details of hospitalisation including the use of antidiarrhoeals and antibiotics in cases of diarrhoea and findings of clinical examination for the presence of dehydration. In cases of intussusception, other clinical examinations such as presence of intestinal tenderness, supraumbilical lump, blood in rectal examination and results of pertinent investigations, such as barium studies and ultrasound, were also noted.

Statistical Analysis

SPSS Version 11.0 (SPSS Inc., Chicago, IL, USA) was used in statistical analysis. Univariate analysis was performed for baseline variables. The characteristics of children with diarrhoea and intussusception were compared using chi-square test for categorical and Student's *t*-test for continuous variables. All statistical tests were two-tailed, and a *P*-value of <0.05 was considered significant. Because Brazil is in the Southern Hemisphere, for assessment of seasonal trends of diarrhoea and intussusception, data from the month of January for this site was added to data from June of all other sites, and this was sequentially followed for all other calendar months. We pooled data by month for all sites for the entire duration of the study. We are extremely limited in making direct comparisons in terms of raw frequencies of diarrhoea and intussusception for the reason that raw score scales are arbitrary and unique. We use standard *Z*-scores as a common scale for making a fair comparison. A standard *z*-score is obtained from a raw score by means of the formula:

$$z = \frac{X - \bar{X}}{S} \quad (1)$$

where X is the raw score for each month, $\bar{X}$ is the mean of raw scores and S is the standard deviation of raw scores.

Results

A total of 173 cases of intussusception and 2346 cases of diarrhoea were recruited from five sites during the period from April 2004 to March 2006. Among cases of intussusception, 119 (68.8%, 95% confidence interval: 61.9–75.7%) were males. There were 101 (58.4%, 95% confidence interval: 51.0–65.7%) cases of intussusception who also had diarrhoea. However, cases of intussusception that had diarrhoea were not counted among cases of diarrhoea alone. Among cases of intussusception, barium enema was done in 27.7% (48/173) and ultrasound abdomen in 15.0% (26/173), which confirmed the diagnosis, while in the remaining diagnosis, cases of intussusception was confirmed during surgery. Clinical signs associated with intussusception were abdominal tenderness (124/173, 71.7%), supraumbilical lump (55/171, 32.2%) and blood in rectal examination (72/173, 41.6%). The median duration of hospital stay for intussusception was 6.0 days (inter-quartile: 6.0), while the mean duration was 9.2 days (standard deviation (SD): 21.5), and the hospital mortality rate was 4.2% (4/96).

Age and sex distribution of cases for intussusception and diarrhoea are given in Tables 1 and 2, respectively. In Brazil, 93.7% (15/16) cases of intussusception were in infants as compared with 61.3% (106/173) when data from all sites were combined.

We also report the educational status of mothers as a surrogate for the socio-economic status across all the five sites in Table 3.

Among cases of diarrhoea, the mean duration of symptoms was 3.3 days (SD: 1.9), because most of the cases (80%) were in the age group 2 months to 18 months. We have reported median and inter-quartile range for duration of hospital stay in Table 4. The median duration of hospital stay was 5.0 days

Table 1 Distribution of intussusception cases by age group and sex among five sites

Site	Age groups (months)				Sex	
	0–6	7–12	13–24	25+	Female	Male
	n, %					
Brazil (*n* = 16)	9, 56.3	6, 37.5	0	1, 6.3	2, 12.5	14, 87.5
Egypt (*n* = 63)	20, 31.7	12, 19.0	12, 19.0	19, 30.2	22, 34.9	41, 65.1
Nagpur (*n* = 41)	10, 24.4	12, 29.3	7, 17.1	12, 29.3	14, 34.1	27, 65.9
Lucknow (*n* = 34)	13, 38.2	9, 26.5	4, 11.8	8, 23.5	8, 23.5	26, 76.5
Kenya (*n* = 19)	7, 36.8	8, 42.1	2, 10.5	2, 10.5	8, 42.1	11, 57.9
Overall (*n* = 173)	59, 34.1	47, 27.2	25, 14.5	42, 24.3	54, 31.2	119, 68.8
χ^2, *P* value	16.3, *P* = 0.2				5.2, *P* = 0.3	

Table 2 Distribution of diarrhoea cases by age group and sex among five sites

Site	Age groups (months)				Sex	
	0–6	7–12	13–24	25+	Female	Male
	n, %					
Brazil (*n* = 86)	22, 25.6	28, 32.6	25, 29.1	11, 12.8	37, 43.0	49, 57.0
Egypt (*n* = 361)	129, 35.7	124, 34.3	77, 21.3	31, 8.6	147, 40.7	214, 59.3
Nagpur (*n* = 209)	25, 12.0	36, 17.2	42, 20.1	106, 50.7	88, 42.1	121, 57.9
Lucknow (*n* = 266)	86, 32.3	73, 27.4	45, 16.9	62, 23.3	96, 36.1	170, 63.9
Kenya (*n* = 1424)	524, 36.8	532, 37.4	254, 17.8	114, 8.0	650, 45.6	774, 54.4
Overall (*n* = 2346)	786, 33.5	793, 33.8	443, 18.9	324, 13.8	1018, 43.4	1328, 56.6
χ^2, *P* value	334.2, *P* < 0.001				9.9, *P* = 0.04	

Table 3 Association of mother's education with diarrhoea and intussusception

Level of maternal education	Diarrhoea (*n* = 2331)	Intussusception (*n* = 111)
	n, %	
Uneducated	489, 21	20, 18
Literate, but no schooling	90, 3.9	6, 5.4
1–12 years of schooling	1545, 66.3	67, 60.4
>12 to <graduate level schooling	133, 5.7	8, 7.2
Graduation	55, 2.4	8, 7.2
Postgraduation	19, 0.8	2, 1.8
χ^2, *P* value	20.3, 0.001	14.1, 0.02

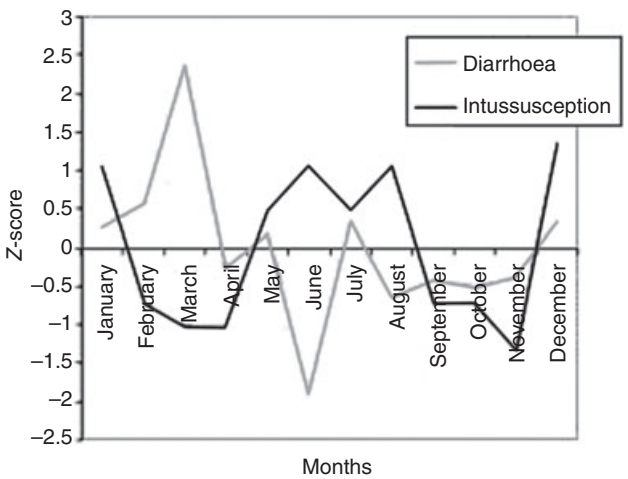

Fig. 1 Standardised *z*-score of intestinal intussusception and acute watery diarrhoea cases by month.

(inter-quartile: 5.0 days), while the mean duration was 7.4 days (SD: 10.8 days). Among cases of acute watery diarrhoea, the use of antidiarrhoeals and antibiotics is given in Table 4. Hospital mortality rate in cases of acute watery diarrhoea was 0.8% (18/2280).

Seasonal variations for each month, based on standardised *z*-scores of diarrhoea and intussusception occurrences, are shown in Fig. 1. Acute watery diarrhoea had a peak incidence in March (which corresponds to October in the actual calendar month of Brazil), but intussusception has no apparent seasonality. There is no intrinsic relationship between 'seasonality of diarrhoea' and 'seasonality of intussusception'.

Table 4 Use of antibiotics, antidiarrhoeal and duration of hospital stay for acute watery diarrhoea cases in five sites

Site	Antibiotic	Antidiarrhoeal†	Both	Duration of hospital stay
	n, %			*n*, median, inter-quartile
Brazil (*n* = 86)*	8, 9.3	0	0	12, 1.0, 0.0
Egypt (*n* = 361)*	272, 75.3	9, 2.4	1, 0.27	349, 2.0, 3.0
Nagpur (*n* = 209)*	161, 77.0	26, 12.4	26, 12.4	179, 5.0, 2.0
Lucknow (*n* = 266)*	190, 71.4	8, 3.0	3, 1.1	266, 3.0, 2.0
Kenya (*n* = 1424)*	1318, 92.5	13, 0.9	12, 0.8	1419, 6.0, 8.0
Overall (*n* = 2346)*	1949, 83.1	56, 2.3	42, 1.7	2225, 5.0, 5.0

*For columns 1–3 the denominator is *n*. †Metronidazole preparations, antisecretory and anti-emetic drugs.

Discussion

In this four-country and five-site study, we found about 74 cases of intussusception per 1000 admissions for acute watery diarrhoea. For intussusception, there was no apparent seasonality. However, there was a single peak in cases of diarrhoea in the month of March. In our study, we did not find any association between seasonal variation in occurrence of diarrhoea and intussusception.

As reported by others,[11,12] intussusception occurred most frequently in males and was most common below 1 year (61.3%) of age . However, there was a wide site-to-site variation in the age of children admitted with intussusception. We cannot explain this variation, which may be related to the cause of intussusception, which was not ascertained by us. Published estimates of number of cases and incidence of intussusception in infants also show a discrepancy, and as such, no trend can be ascertained between developed and developing countries.[13]

Like our findings, no such seasonal association has been reported from Australia[11] and Venezuela.[14] However, increased rates of intussusceptions in summer and winter months have been reported from India and African countries (South Africa and Nigeria) in previous studies.[15] Taking maternal educational status as a surrogate marker of socio-economic status, we did not find increased incidence of intussusception among the low socio-economic status, unlike in previous reports.[16] As reported from Venezuela,[14] majority of cases of intussusception were corrected surgically in our study.

Cases of dehydrating diarrhoea peaked in March in our study. Rotavirus, particularly group A, is a major cause of dehydrating gastroenteritis.[4] Rotavirus infection does not have a distinct seasonality in countries of temperate region.[17] In India, rotavirus infection has been reported to occur all the year round with a peak in winter months.[18,19] However, in Vellore, southern India, rotaviruses that were detected throughout the study period had a second peak from June to August (southwest monsoon season).[19] In Brazil[20] and Egypt,[21] the highest incidence of rotavirus diarrhoea were reported in winter months like in the USA[22] and unlike in Kenya, where rotavirus peak incidences were observed in the January–March periods, which are times of hot, dry weather, with low relative humidity.[23]

In the present study, maximum numbers of cases of diarrhoea were from Kenya and minimum numbers were from Brazil. This may be due to differences in the incidence of diarrhoea in two sites as well as variations in health care seeking, which is a complex personal and cultural behaviour. According to a United Nations Children's Fund report, in Africa and Asia, about half of children with diarrhoea may end up at a health facility, whereas in northeastern Brazil, where Fortazela is situated, only 14% of children with diarrhoea are taken to a health facility.[24]

In the present study, we found that majority (83.1%) of hospitalised cases of diarrhoea received at least one antibiotic, with a wide variation in its use across the sites. Because antibiotics are not recommended for cases of acute watery diarrhoea,[10] we are highlighting irrational use of drugs from participating sites. This is unlike much lower reported use of antibiotics when zinc was coadministered to children with diarrhoea and no or some dehydration was treated at the outpatient facility in all of the participating sites, except Kenya.[25] This was a unique, prospective surveillance of cases of intussusception and diarrhoea in the four developing countries. Because the population enumeration was not done and it was a passive surveillance at just one hospital facility per site, we are not able to report incidence rates for either diarrhoea or intussusception. Reporting of intussusception is likely to be more accurate because they were usually referred to paediatric surgeons, who were part of the HSN established for the study. We are also not able to report secular trends in the incidence rates of intussusception as the study lasted for about one calendar year.

Intussusception in the four participating countries had no seasonal trend. However, after the introduction of rotavirus vaccine, post-marketing surveillance for intussusception has been recommended.[26] We found that it is feasible to establish a surveillance network for intussusception in developing countries and future endeavours must define population and continue for a longer period before and after introduction of rotavirus vaccine.

Acknowledgement

This study was funded by the US Agency for International Development's unmet needs program 2003 through the International Clinical Epidemiology Network (INCLEN), and conducted through the INCLEN-Childnet. Professor Robert Black, Johns Hopkins' Bloomberg School of Public Health, USA, and

Dr Mark Miller, National Institutes of Health, USA, are acknowledged for technical advice during manuscript writing.

References

1 Bern C, Martines J, de Zoysa I, Glass RI. The magnitude of the global problem of diarrhoeal disease: a ten-year update. *Bull. World Health Organ*. 1972; **70**: 705–14.
2 Parashar UD, Bresee JS, Gentsch JR, Glass RI. Rotavirus. *Emerg. Infect. Dis*. 1998; **4**: 561–70.
3 De Zoysa I, Feachem RV. Interventions for the control of diarrhoeal diseases among young children: rotavirus and cholera immunisation. *Bull. World Health Organ*. 1985; **63**: 569–83.
4 Kapikian AZ, Wyatt RG, Greenberg HB, Kalica AR, Kim HW, Brandt CD. Approaches to immunization of infants and young children against gastroenteritis due to rotaviruses. *Rev. Infect. Dis*. 1980; **2**: 459–69.
5 Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. *Emerg. Infect. Dis*. 2003; **9**: 565–72.
6 Parashar UD, Alexander JP, Glass RI; Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm. Rep*. 2006; **11**: 1–13.
7 Parry J. New vaccines to boost child care in developing countries. *Bull. World Health Organ*. 2007; **85**: 426–7.
8 Haber P, Chen RT, Zanardi LR *et al.* An analysis of rotavirus vaccine reports to the vaccine adverse event reporting system: more than intussusception alone? *Paediatrics* 2004; **113**: 353–9.
9 Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA. Intussusception among infants given an oral rotavirus vaccine. *N. Engl. J. Med*. 2001; **344**: 564–72.
10 World Health Organization. Technical updates of the guidelines on Integrated Management of Childhood Illness (IMCI). Evidence and recommendations for further adaptations. Geneva. 2005. Available from: http://www.who.int/child-adolescent-health/New_Publications/IMCI/ISBN_92_4_159348_2.pdf [accessed 9 June 2007].
11 Justice F, Carlin J, Bines J. Changing epidemiology of intussusception in Australia. *J. Paediatr. Child Health* 2005; **41**: 475–8.
12 Boudville IC, Phua KB, Quak SH *et al.* The epidemiology of paediatric intussusception in Singapore: 1997 to 2004. *Ann. Acad. Med. Singap*. 2006; **35**: 674–9.
13 Bines JE, Liem NT, Justice FA *et al.* Risk factors for intussusception in infants in Vietnam and Australia: adenovirus implicated, but not rotavirus. *J. Pediatr*. 2006; **149**: 452–60.
14 Perez-Schael I, Escalona M, Salinas B, Materan M, Perez ME, Gonzalez G. Intussusception-associated hospitalization among Venezuelan infants during 1998 through 2001: anticipating rotavirus vaccines. *Pediatr. Infect. Dis. J*. 2003; **22**: 234–9.
15 Bines J, Ivanoff B. *Acute intussusception in infants and children: incidence, clinical presentation and management: a global perspective*. Department of Vaccines and Biologicals, World Health Organization (WHO). Document WHO/V&B/02.19. Geneva: WHO, 2002.
16 Stringer MD, Pablot SM, Brereton RJ. Paediatric intussusception. *Br. J. Surg*. 1992; **79**: 867–75.
17 Cook SM, Glass RI, LeBaron CW, Ho MS. Global seasonality of rotavirus infections. *Bull. World Health Organ*. 1990; **68**: 171–7.
18 Bahl R, Ray P, Subodh S *et al.* Incidence of severe rotavirus diarrhoea in New Delhi, India, and G and P types of the infecting rotavirus strains. *J. Infect. Dis*. 2005; **192**: S114–9.
19 Brown DW, Mathan MM, Mathew M, Martin R, Beards GM, Mathan VI. Rotavirus epidemiology in Vellore, south India: group, subgroup, serotype, and electrophoretype. *J. Clin. Microbiol*. 1988; **26**: 2410–4.
20 Pereira HG, Linhares AC, Candeias JA, Glass RI. National laboratory surveillance of viral agents of gastroenteritis in Brazil. *Bull. Pan Am. Health Organ*. 1993; **27**: 224–33.
21 Wierzba TF, Abdel-Messih IA, Abu-Elyazeed R, Putnam SD, Kamal KA *et al.* Clinic-based surveillance for bacterial- and rotavirus-associated diarrhea in Egyptian children. *Am. J. Trop. Med. Hyg*. 2006; **74**: 148–53.
22 Kramarz P, France EK, Destafano F. Population-based study of rotavirus vaccination and intussusception. *Pediatr. Infect. Dis. J*. 2001; **20**: 410–16.
23 Mutanda LN, Kinoti SN, Gemert W, Lichenga EO. Age distribution and seasonal pattern of rotavirus infection in children in Kenya. *J. Diarrhoeal Dis. Res*. 1984; **2**: 147–50.
24 Enzley S, Barros F. *A Global Review of Diarrhoeal Disease Control*. UNICEF staff working papers: Evaluation, Policy and Planning series, Number EVL-97-002. New York, NY: UNICEF, 1997. Available from: http://rehydrate.org/diarrhoea/diarrhoea-global-review.pdf [accessed 9 June 2007].
25 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 leads to less use of other medications: a randomized trial in five countries. *J. Pediatr. Gastroenterol. Nutr*. 2006; **42**: 300–5.
26 Dabbagh A, Eggers R, Cochi S, Dietz V, Strebel P, Cherian T. A new global framework for immunization monitoring and surveillance. *Bull. World Health Organ*. 2007; **85**: 904–5.