Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization

N.A. Cunliffe,[1] P.E. Kilgore,[2] J.S. Bresee,[3] A.D. Steele,[4] N. Luo,[5] C.A. Hart,[6] & R.I. Glass[7]

Rapid progress towards the development of rotavirus vaccines has prompted a reassessment of the disease burden of rotavirus diarrhoea in developing countries and the possible impact of these vaccines in reducing diarrhoeal morbidity and mortality among infants and young children. We examined the epidemiology and disease burden of rotavirus diarrhoea among hospitalized and clinic patients in African countries through a review of 43 published studies of the etiology of diarrhoea. The studies were carried out from 1975 through 1992, and only those in which a sample of more than 100 patients with diarrhoea were specifically screened for rotavirus by using an established diagnostic test were included.

Rotavirus was detected in a median of 24% of children hospitalized for diarrhoea and in 23% who were treated as outpatients; 38% of the hospitalized patients with rotavirus were <6 months and 81% were <1 year of age. Rotavirus was detected year-round in nearly every country and generally exhibited distinct seasonal peaks during the dry months. In 5 countries where rotavirus strains had been G-typed, 74% of strains were of one of the four common serotypes (G1 to G4), G1 was the predominant serotype, and 26% were non-typeable. This cumulative experience from 15 African countries suggests that rotavirus is the most important cause of severe diarrhoea in African children and that most strains in circulation today belong to common G types that are included in reassortant vaccines. Wherever large numbers of cases of rotavirus diarrhoea occur early in infancy, immunization at birth may protect the children before their first symptomatic infection.

Introduction

In developing countries, diarrhoea is a major cause of disease among under-5-year-olds, with an estimated 2.4–3.3 million deaths each year (*1*, *2*). Rotavirus is the single most important etiological agent implicated in severe dehydrating diarrhoea, and is responsible each year for an estimated 600000 to 870000 childhood deaths (*3*, *4*). Improvements in water supplies and excreta disposal may reduce the transmission of enteric bacteria and parasites, but are unlikely to reduce the incidence of rotavirus diarrhoea. Vaccines are therefore being developed as the primary public health intervention to reduce the burden of diarrhoea caused by rotavirus (*5*, *6*).

Gastroenteritis is a major cause of childhood morbidity and mortality in Africa (*1*, *7*). Although many studies have documented the high prevalence of rotavirus among African children with mild or severe diarrhoea, these have never been analysed to

[1] Wellcome Research Training Fellow, Viral Gastroenteritis Section, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA. Current address: Malaria Project and Wellcome Trust Centre; and Department of Paediatrics, College of Medicine, Blantyre, Malawi.

[2] Medical Officer, Child Vaccine-Preventable Diseases Branch, National Immunization Program, Centers for Disease Control and Prevention, Atlanta, GA, USA.

[3] Medical Officer, Viral Gastroenteritis Section, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA.

Reprint No. **5892**

[4] Department of Virology, Medical University of South Africa (MEDUNSA), Pretoria, Republic of South Africa.

[5] Deputy Minister, Ministry of Health, Republic of Zambia, Lusaka, Zambia.

[6] Professor, Department of Medical Microbiology and GenitoUrinary Medicine, University of Liverpool, Liverpool, England.

[7] Chief, Viral Gastroenteritis Section, MS G-04, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA. Requests for reprints should be sent to Dr R.I. Glass, Mailstop G-04, CDC, 1600 Clifton Road NE, Atlanta, GA30333, USA.

provide a broader picture of the importance of rotavirus in this region. The objectives of this review of published studies of rotavirus diarrhoea in northern, southern and sub-Saharan Africa are as follows: to estimate the disease burden and assess of the need for a rotavirus immunization programme; to examine the age distribution of severe cases to determine an optimal schedule for immunization; to evaluate the circulating rotavirus strains to identify unusual types that could be incorporated into a vaccine; and to determine the seasonal patterns of rotavirus infection and their links with possible routes of transmission or regional trends relevant to immunization strategies.

Methods

Papers were identified for this review from a multilingual MEDLINE search of publications from 1975 to 1996 using the keywords of "rotavirus" and the name of each African country, or from citations noted in studies found in the MEDLINE search. Excluded were studies in which data on fewer than 100 children were reported and surveys of less than 3 months' duration. The studies were grouped by setting (hospital, outpatient, combined in- and outpatient, and community based) and analysed separately, since rotavirus is detected more frequently among children with severe disease (i.e., hospitalized) than in a community setting (*8*). For each study, the prevalence of rotavirus diarrhoea among all patients with diarrhoea was examined by age group. The prevalence of neonatal rotavirus infections and of mixed rotavirus/bacterial or parasitic infections was examined where data were available.

Seasonal and geographical trends in rotavirus diarrhoea were reviewed from studies presenting data on monthly rotavirus detections for at least one year. Climatic information supplied in each publication was used to define months as rainy or dry. For each report, we determined the peak season for rotavirus transmission by plotting the monthly detection rates and comparing them with the median monthly value for rotavirus detection for the year or for the study period. To test the hypothesis that rotavirus peaks were associated with dry seasons, we performed a stratified analysis by region because previous studies had identified differences in the seasonality of rotavirus detection with changes in latitude (*9*). Finally, we reviewed studies in which rotavirus strains were characterized for G-types (VP7 genes) and P-types (VP4 genes) to examine the distribution of rotavirus strains in circulation.

Results

Overview of inpatient and outpatient studies

A total of 27 inpatient and 16 outpatient studies from 15 countries met the criteria for inclusion in this review. The inpatient studies (Table 1), which were conducted between 1975 and 1992, included children aged ≤15 years. Twelve studies lasted for a full year; 6 studies were continued longer. Faecal specimens were screened by enzyme-linked immunosorbent assay (ELISA) in 18 studies, by latex agglutination (LA) in 3, electron microscopy (EM) in 4, viral culture in 2, and immunoelectro-osmophoresis (IEOP) in 1 study. Rotavirus was detected in a median of 24% (range, 13–55%) of children hospitalized for diarrhoea.

The 16 outpatient studies (Table 2), which were conducted between 1977 and 1992, included children up to 14 years of age. Eight studies lasted 12 months and none continued for more than 2 years. Faecal specimens were screened by ELISA in 11 studies and by EM, IEOP and LA in the others. Rotavirus was detected in a median of 23% (range, 7–40%) of children. These investigations contrast with 9 community-based surveys of diarrhoea, where rotavirus was detected in fewer than 10% (range, 2.3–8%) of children with diarrhoea (*10–18*). Of 23 inpatient and outpatient studies that tested for pathogens other than rotavirus, 19 (83%) identified rotavirus as the most common diarrhoeal pathogen.

Age of patients with rotavirus diarrhoea

Of the 27 inpatient studies, 11 surveyed infants and children <2 years of age and 19 included infants and children <5 years of age (Table 1). The median rates of rotavirus detection did not differ significantly between studies of younger versus older children in either the inpatient (26% versus 29%) or outpatient settings (25% versus 20%).

Data from 10 inpatient and 6 outpatient studies indicated the age distribution of rotavirus diarrhoea in patients <2 years of age, the age group with the highest morbidity and mortality from rotavirus diarrhoea. Children hospitalized for rotavirus diarrhoea tended to be younger than those seen as outpatients (median age, 6 months versus 9 months). Moreover, 81% of children hospitalized (compared with 61% of those treated as outpatients) were <1 year of age; 97% of the cases among inpatient children occurred by the age of 18 months. In 3 inpatient studies where detailed age data were available, a median of 38% of patients with rotavirus diarrhoea were <6 months of age.

Table 1: **Rotavirus detection rates from 27 inpatient studies of paediatric gastroenteritis in Africa**[a]

Country or area	Reference	Study characteristics: Years	Study characteristics: Duration (months)	Study characteristics: Detection assay[b]	Patient characteristics: Number	Patient characteristics: Age (years)	Patient characteristics: % with rotavirus
Northern Africa							
Egypt	*87*	1982–83	12	ELISA	137	<1.5	34
Morocco	*48*	1982–83	12	ELISA + LA	327	<4	20
Sub-Saharan Africa							
Benin	*88*	1991–92	8	LA	220	<5	29
Ethiopia	*89*	1979	4	IEOP	175	<2[c]	49
Ethiopia	*90*	1983–84	12	ELISA	496	<3	22
Gabon	*91*	1984–85	12	ELISA	237	<10	21
Kenya	*23*	1975–76	12	Culture	160	<6	41
Kenya	*92*	1981–83	18	ELISA	360	<1.5[c]	40
Kenya	*93*	NR[d]	NR[d]	Culture	363	<6	29
Nigeria	*94*	1985–86	6	ELISA	192	<4	20
Nigeria	*95*	1980–82	20	ELISA	139	<8	20
Nigeria	*96*	1989–90	6	ELISA	185	<10	32[e]
Senegal	*97*	1983–88	60	LA	111	<15	14
United Republic of Tanzania	*98*	1976	7	EM	123	<4[c]	31
Zambia	*99*	1992	12	ELISA	1067	<5	24
Zimbabwe	*69*	1974–75	12	EM	256	<2[c]	32
Southern Africa							
Durban	*70*	1985–87	31	ELISA	1142	<12	55
Durban	*44*	1981	9	ELISA	126	<2	20
Johannesburg	*100*	1974–75	12	EM	104	<2	14
Johannesburg	*49*	1982–83	8	ELISA	616	<1.5	14
Johannesburg	*101*	1981	6	EM	114	<2	34
KaNgwane	*102*	1985–86	12	ELISA	310	<2[c]	13
Pretoria	*103*	1983–85	24	ELISA	788	<2	23
Pretoria	*71*	1983–86	36	ELISA	1316	<5	24
Pretoria	*59*	1989	12	ELISA	292	<3[c]	33
Pretoria	*60*	1989	12	ELISA	605	<12	16[e]
Transkei	*56*	1988–89	12	ELISA	216	<2[c]	33
Median (range)			12 (4–60)		237 (104–1316)		24 (13–55)

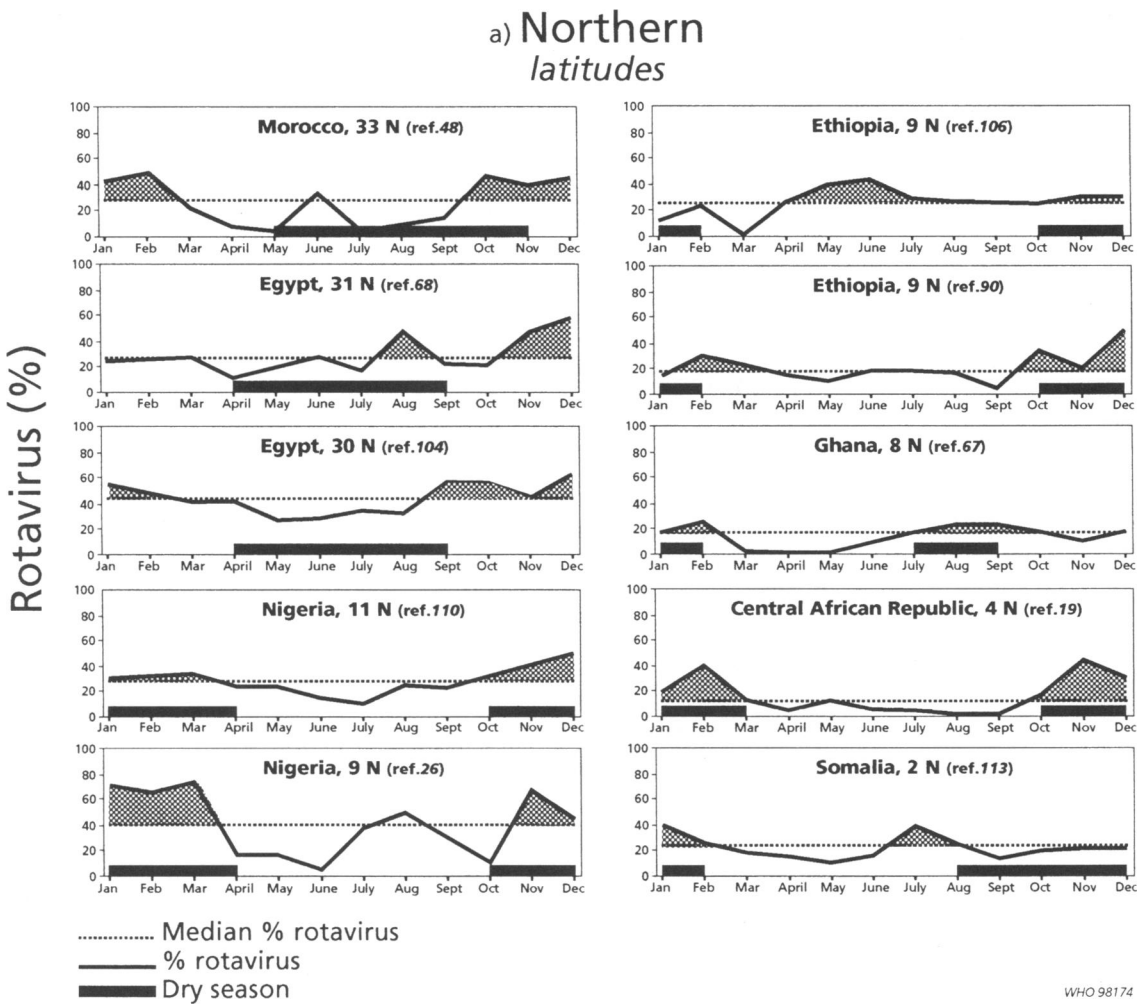
[a] Includes studies with > 100 children.
[b] ELISA = enzyme-linked immunosorbent assay; LA = latex agglutination; EM = electron microscopy; IEOP = immunoelectro-osmophoresis.
[c] Age selection criteria not given, but majority of cases less than the stated age.
[d] NR = not reported.
[e] Includes nosocomial rotavirus infections.

Potential bias. To examine potential bias introduced by our selection criteria, we examined detection rates from additional studies excluded from this review because they included a mixture of both inpatients and outpatients, enrolled fewer than 100 children, or lasted less than 3 months. The 8 investigations from 4 countries (*19–26*) that enrolled both inpatients and outpatients had a median detection rate of 20% (range, 11–33%), not significantly different from studies that included only outpatients (23%) or inpatients (24%) (data not shown here). In addition, 19 other studies from 8 countries were excluded because of small numbers of patients and their short duration. In 12 inpatient studies (*27–38*) the median proportion of cases attributable to rotavirus infection was higher (32%; range, 4–61%), compared with 7 outpatient studies (*29, 39–44*) in which the median detection was lower (10%; range, 0–44%).

Seasonality of rotavirus infection

We examined the seasonal patterns of disease by plotting the monthly detections of rotavirus and comparing them with the local wet and dry seasons (Fig. 1). In all countries except Ghana, rotavirus detections occurred throughout the year. Seasonal peaks were commoner during dry seasons than wet

Fig. 1. **Percentage monthly rate of diarrhoeal cases excreting rotavirus in 12 African countries.** a) Northern countries, b) Southern countries. The yearly median is marked; the shaded areas indicate peaks above the median value.

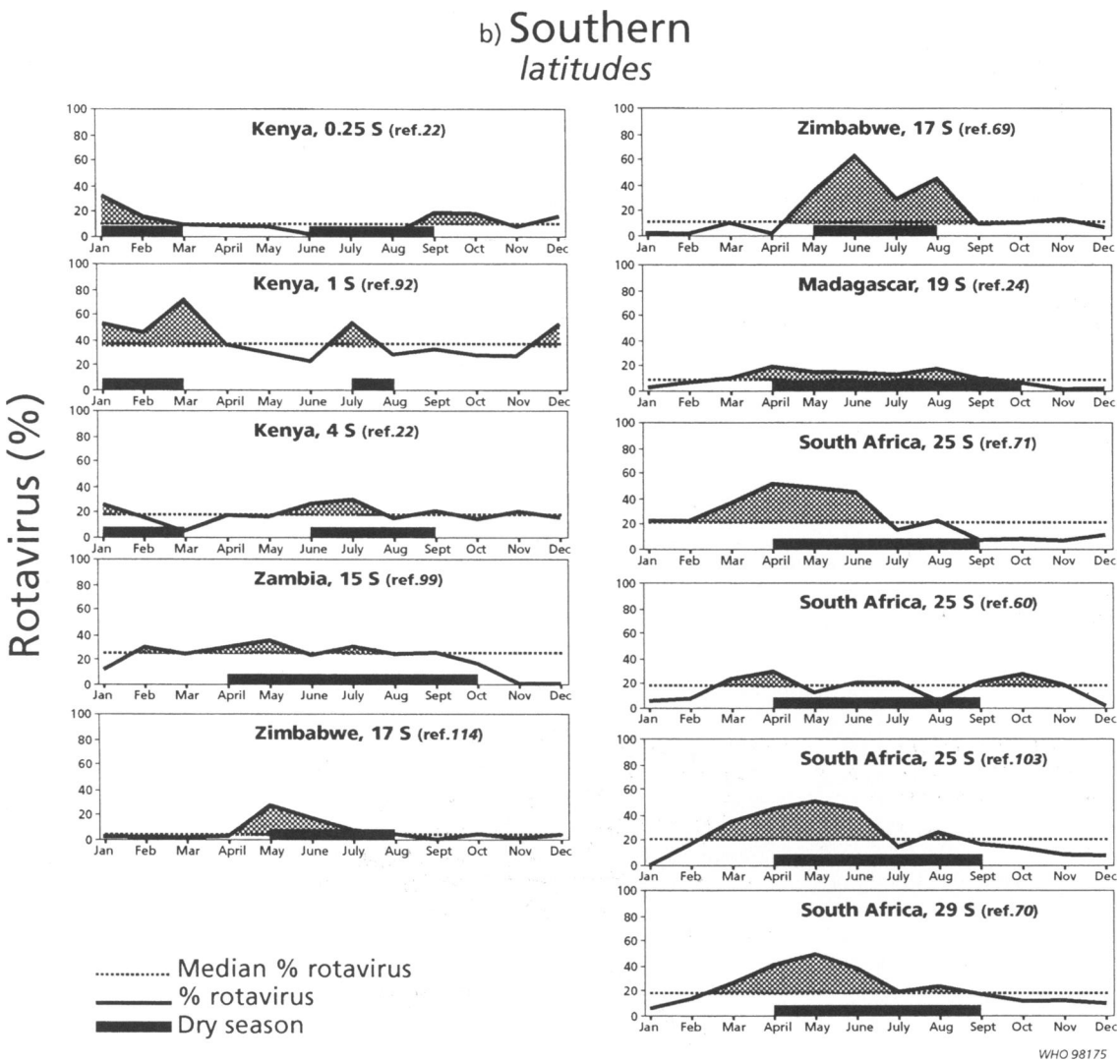


seasons, but this pattern was not consistent for every country. We stratified countries by latitude into three regions — northern, sub-Saharan, and southern Africa — to determine whether large differences in climate were associated with peaks in rotavirus activity. In northern Africa (Egypt and Morocco), rotavirus had a single peak in the autumn and winter, but not during the dry season. In southern Africa (South Africa, Madagascar, Zambia and Zimbabwe), rotavirus generally had a single peak in the autumn and winter, which overlapped with the dry seasons. In sub-Saharan Africa (Central African Republic, Ethiopia, Ghana, Kenya, Nigeria and Somalia), rotavirus detections were 6 times more likely to have peaks during the dry season ($P < 0.0001$), but the seasonality of virus detection was not clearly defined by the onset or end of the dry season alone.

Rotavirus strain characteristics

Rotavirus strains were characterized for G serotype in 8 studies from 5 countries and for P genotype in

Fig. 1. *Continued*



3 studies from South Africa (Table 3). The G1 serotype was commonest (42%), followed by G2 (16%), G4 (12%) and G3 (4%); the G serotypes of 26% of strains could not be determined. The P genotype of 68% of strains could be determined; P[8] was the commonest (44%), followed by P[4] (15%), P[6] (6%), P[12] (0.7%) and P[9] (0.6%). Mixed rotavirus infections (either G or P type) were identified in 1.8% of specimens. In early studies, strains were characterized by electropherotype or subgroup. Strains with long electropherotypes and/or subgroup II specificity were predominant in most countries (Central African Republic, Egypt, Ethiopia, Gambia, Ghana, Kenya, Malawi, Morocco, Senegal, and South Africa (*40*, *45–65*), but short electropherotypes were common in the United Republic of Tanzania (*30*), Madagascar (*24*), and Gambia (*62*, *63*). Rotaviruses with atypical combina-

Table 2: **Rotavirus detection rates from 16 outpatient studies of paediatric gastroenteritis in Africa**[a]

Country	Reference	Study characteristics			Patient characteristics		
		Years	Duration (months)	Detection assay[b]	Number	Age (years)	% with rotavirus
Northern Africa							
Egypt	*104*	1986	12	ELISA	200	<2	40
Egypt	*68*	1983–84	20	ELISA	350	<5	29
Egypt	*87*	1982–83	12	ELISA	131	<1.5	31
Sub-Saharan Africa							
Cameroon	*105*	1989–90	18	LA	204	<6	20
Ethiopia	*106*	1977–78	12	IEOP	962	<14	28
Gabon	*107*	1980–81	12	EM	156	<10	10
Ghana	*108*	1987–88	12	LA	196	<5	7
Ghana	*67*	1991–92	12	EM	447	<4	15
Kenya	*109*	NR[c]	NR[c]	ELISA	153	<5	22
Nigeria	*15*	1985–86	12	ELISA	115	<6	25
Nigeria	*110*	1986–87	12	ELISA	392	<5	27
Nigeria	*111*	1989–90	6	ELISA	215	<5	22
Nigeria	*94*	1985–86	6	ELISA	184	<4	10
Senegal	*112*	1982	3	ELISA	212	<5[d]	16
Somalia	*113*	1983–84	24	ELISA	1667	<14	25
Zimbabwe	*114*	1987–88	13	ELISA	225	<2	24
Median (range)			12 (3–24)		208 (115–1667)		23 (7–40)

[a] Includes studies with > 100 children.
[b] ELISA = enzyme-linked immunosorbent assay; LA = latex agglutination; EM = electron microscopy; IEOP = immunoelectro-osmophoresis.
[c] NR = not reported.
[d] Age selection criteria not given, but majority of cases less than the stated age.

tions of subgroup and electropherotype indicative of natural reassortment between genetically distinct rotaviruses were detected in Kenya (*53*) and South Africa (*55*). Strains with additional RNA segments indicative of genomic rearrangement were found in Kenya (*53*) as well as among South African neonates (*66*). Non-group A rotaviruses were detected in 15% of rotavirus-positive stools from a study in Ghana, and included 3 strains with RNA patterns indicative of group C rotavirus (*67*).

Mixed rotavirus infections

Data on mixed infections from 7 studies that each included more than 50 children with rotavirus diarrhoea (*17, 20, 21, 68–71*) identified at least one other potential enteropathogen in a median of 23% of rotavirus cases (range, 14–64%). In several studies, these mixed infections were associated with malnutrition (*21*) and prolonged diarrhoea (*70, 72*).

Neonatal rotavirus infections

Eight studies from three countries (Table 4) identified rotavirus in a median of 14% of newborns (range, 9–38%), most of whom were <1 week old (*66, 73–79*). These infections were predominantly asymptomatic, and in Kenya were associated with diarrhoea in pre-term newborns (*73*). Neonatal infections have also been detected in the Gambia between seasonal epidemics (*62*). In South Africa, neonatal strains were characterized to be P[6]G4 (*60, 80–82*).

Discussion

Diarrhoea remains a major contributor to the high rates of childhood mortality in Africa. Of the 25 million children born each year in sub-Saharan Africa, 4.3 million (about 1 in 6) will die by the age of 5 years and about one-fifth of these deaths (850000) will be from diarrhoea. This review of 43 studies from 15 African countries has examined the etiology of acute gastroenteritis in children, and found rotavirus to be the single most common cause of diarrhoea, responsible for about one-fourth of all diarrhoea cases identified in both hospital patients and outpatients. If 20–25% of these diarrhoeal deaths are due to rotavirus, an effective properly administered rotavirus vaccine could potentially prevent 170000–210000 childhood deaths every year, or

Table 3: **Summary of rotavirus G and P types in Africa**[a]

Country	Reference	Years	No. tested	Typing method[b]	G type				P type					Predominant strain type	Mixed types	Non-typeable
					G1	G2	G3	G4	P[4]	P[8]	P[6]	P[9]	P[12]			
Sub-Saharan Africa																
Central African Republic	*45*	1983–85	152	ELISA	102	22	19	—[c]	—	—	—	—	—	G1	0	9[c]
Gambia[d]	*62*	1982–84	24	ELISA	9	8	5	0	—	—	—	—	—	G2, G1	0	2
Kenya	*52*	1982–83	16	FFN	7	4	2	0	—	—	—	—	—	G1	0	3[e]
Kenya	*53*	1989–91	95	ELISA	28	13	0	8	—	—	—	—	—	G1	0	46
Nigeria	*115*	1989	13	ELISA	8	0	0	0	—	—	—	—	—	G1	0	5
Southern Africa																
Ga-Rankuwa	*58*	1989	94	ELISA	40	12	0	9	—	—	—	—	—	G1	1 (G)	32
Pretoria	*116*	1984–93	227	HYB	—	—	—	—	35	95	13	—	6	P[8]	8[f] (P)	70
Pretoria	*60*	1989	14	HYB	6	3	0	4	3	8	2[g]	—	—	P[8]G1	1 (G and P)	0
Multicentre[h]	*81*	1988–89	572	HYB	214	91	9	98	83	253	37[i]	5	—	P[8]G1	6 (G) 5 (P)	G 154 P 189
Total			980 (G types)		414	153	35	119	121	356	52	5	6	—	—	—
			813 (P types)		(42)[j]	(16)	(4)	(12)	(15)	(44)	(6)	(0.6)	(0.7)	—	—	—

[a] P genotype designations as recommended by Rotavirus Nomenclature Working Group (*117*).
[b] ELISA = enzyme-linked immunosorbent assay; FFN = fluorescent-focus-neutralization; HYB = hybridization.
[c] G4 serotyping not performed.
[d] G2 was the most common serotype in the first year, which was replaced by G1 the following year.
[e] Antigenic mosaic strains.
[f] Includes three mixed infections with P[9] genotype.
[g] Includes a single neonatal strain.
[h] Includes strains from Pretoria, Ga-Rankuwa, Johannesburg, Umtata and Port Elizabeth.
[i] Includes 28 neonatal strains.
[j] Figures in parentheses are percentages.

Table 4: **Summary of clinical studies of neonatal infections among hospitalized infants in Africa**

Country	Reference	No. of patients	Rotavirus infection (%)	Age at infection	Detection assay[a]	Comment
Kenya	*73*	128	9	NR[b]	ELISA	Pre-term
Nigeria	*74*	213	11	71%, <1 week	ELISA	Hospital stay <48 hrs
Nigeria	*75*	84	38	75% nosocomial infections, >10 days stay	ELISA	24% nosocomial
South Africa	*76*	122	34	63%, <1 week	EM	1 case with necrotizing enterocolitis
South Africa	*77*	125	15	80%, <5 days	ELISA	Re-infection in 4/14 at follow-up
South Africa[a]	*78*	86	13	NR[b]	ELISA	—
South Africa	*79*	324	32	Peak, 4–5 days	EM	—
South Africa	*66*	78	13	1–2 weeks	EM	Collected in community
Median (range)		124 (78–324)	14 (9–38)			

[a] ELISA = enzyme-linked immunosorbent assay; EM = electron microscopy.
[b] NR = not reported.

about one in 20 deaths (4–5%). In other terms, between 1 in 120 and 1 in 150 children would die by age 5 years from rotavirus diarrhoea. While previous public health efforts to decrease diarrhoea mortality focused on early treatment with oral rehydration salts, the availability of rotavirus vaccine in the near future may provide an important new public health tool to address the problem of child survival in Africa.

This study provides several insights into the role that rotavirus vaccine might play in preventing diarrhoeal morbidity and mortality, while underscoring the challenges and pitfalls to vaccine development that may lie ahead. In this review, 81% of hospitalizations for rotavirus occurred in children during their first year of life, and 38% of cases occurred before 6 months of age — figures quite different from those for children in industrialized countries, where more disease occurs at an older age. Rotavirus vaccine would have to be administered very early and with high coverage in the first few months of life to prevent disease. The effectiveness of rotavirus vaccines in infants and children is likely to be influenced, in some areas, by neonatal rotavirus infections that appear to be asymptomatic, may protect children against subsequent disease, and could influence the efficacy of the vaccine as measured in clinical trials.

A majority of the serotypes of rotavirus strains in circulation in Africa appear to be like those common in the rest of the world, i.e. G serotypes 1–4, which are components of the first tetravalent vaccine. At the same time, 26% of strains in this review were considered non-typeable, leaving open the prospect that the vaccine may fare less well against this unknown antigenic challenge.

The legacy of testing rotavirus vaccines in Africa has been negative since neither of the two candidate vaccines tested in three trials had proven efficacy (Table 5) (*83–85*). While these studies suggest that live, oral rotavirus vaccines may not work well in African children, the low efficacy may reflect problems of study design. All three trials enrolled relatively small sample sizes compared to rotavirus trials done elsewhere, and their analysis did not include coding for the severity of diarrhoea, an important observation since the vaccine protects best against severe disease which is less common and would require a larger sample size in a vaccine trial. The absence of stratification by the severity of diarrhoea may have inadvertently diluted the observed impact of the vaccine in preventing severe rotavirus diarrhoea, which is the primary goal of current vaccines. In this review, the early peak age of rotavirus diarrhoea suggests that immunization in the three trials may have occurred too late to avoid natural infection, thus decreasing the power of the trial to detect significant vaccine efficacy. In view of these critical problems of trial design and status of natural immunity in the host, the results of these early trials provide little information about how current candidate vaccines might fare if they were administered to African infants in a timely fashion (i.e. at a very young age) and in a trial setting where an adequate number of episodes of severe rotavirus diarrhoea could be effectively monitored. New vaccine trials in Africa will be needed to examine the potential efficacy of current reassortant vaccines to protect

Table 5: **Summary of rotavirus vaccine trials in Africa**

Country	Reference	Year	Vaccine strain	Dosage schedule	No. of infants enrolled		No. with rotavirus diarrhoea		Efficacy (%)	Strain characteristics	Comments
					Vaccine	Placebo	Vaccine	Placebo			
Central African Republic	*83*	1988–89	WC3	2 doses at age 3 and 4 months	237	235	58	59	nil	G1 (n = 8); G3 (n = 3)	Milder disease among vaccinees
Gambia	*84*	1985	RIT 4237	3 doses at age 10, 14 and 18 weeks	185	91	47	34	33	92% short electropherotype (n = 73)	Severe rotavirus diarrhoea poorly defined; high pre-vaccination neutralizing antibody titres
Rwanda	*85*	1985	RIT 4237	1 dose at age 3–8 months	122	123	6	6	nil	NR[a]	Few rotavirus diarrhoea cases

against the four major G serotypes. A recent trial in Venezuela suggests that if the trials are large and children are immunized early, live oral rotavirus vaccines can be effective in developing countries (*86*).

This review was conducted to learn about the epidemiology of rotavirus in Africa from the many published etiological studies. Its scope was limited because of the lack of countries with published data, differences in the methods and populations sampled, and the requirement to include only papers that met our selection criteria. Despite these limitations, the weight of evidence confirms the major role played by rotavirus as a cause of severe diarrhoea in African children. Unassessed is the role of concurrent infections with human immunodeficiency virus (HIV), malaria, other enteric infections, and malnutrition as modulators of the severity of rotavirus disease. These cofactors, which may influence disease severity, could also affect the behaviour, immunogenicity, and efficacy of live oral vaccines.

Much more work is needed for the prevention of rotavirus diarrhoea in Africa through the use of vaccines. The safety, immunogenicity, and efficacy of new vaccines will have to be assessed in situations of malnutrition, HIV, concurrent enteric infections, unusual rotavirus serotypes, and early age of first infection, all of which could influence the vaccine's effectiveness. Once efficacy is established, the challenge to achieve good vaccine coverage in a timely fashion in sub-Saharan Africa will be great, since current levels of immunization coverage in this region are among the lowest in the world. However, the huge burden of rotavirus diarrhoea in Africa and the impact of a successful rotavirus vaccine could serve to boost vaccine coverage overall.

Acknowledgements

Dr N.A. Cunliffe is a Wellcome Research Training Fellow in Clinical Tropical Medicine (grant number 044337/Z/95/Z). We thank Mr John O'Connor for editorial assistance during preparation of this manuscript.

Résumé

Epidémiologie de la diarrhée à rotavirus en Afrique: évaluation des besoins en matière de vaccination antirotavirus

Les progrès rapides de la mise au point de vaccins antirotavirus ont conduit à réévaluer l'importance des diarrhées à rotavirus dans les pays en développement et la place éventuelle de ces vaccins dans la diminution de la morbidité et de la mortalité du nourrisson et du jeune enfant. L'épidémiologie et la charge de morbidité ont été analysées chez des patients des hôpitaux et des dispensaires de 12 pays africains à partir de 43 études sur l'étiologie de la diarrhée publiées dans la littérature. Les études ont été réalisées de 1975 à 1992, et seules ont été incluses dans l'analyse celles dont l'échantillon comptait plus de 100

patients diarrhéiques chez lesquels les rotavirus ont été recherchés au moyen d'une épreuve diagnostique classique.

Les rotavirus ont été décelés chez 24% (médiane) des enfants hospitalisés pour diarrhée et chez 23% (médiane) des patients ambulatoires; parmi les patients hospitalisés, 38% avaient moins de 6 mois et 81% moins d'un an. La présence de rotavirus est notée tout au long de l'année dans presque tous les pays, avec des pics saisonniers en saison sèche. Dans 5 pays où le sérotype G des souches a été déterminé, 74% des souches appartenaient à l'un des 4 sérotypes courants (G1-G4), avec une prédominance du sérotype G1, et 26% de souches étaient non typables. D'après l'ensemble de ces observations dans 15 pays africains, les rotavirus sont la cause principale de diarrhée grave chez l'enfant dans ces pays, et la plupart des souches en circulation aujourd'hui appartiennent aux types G courants inclus dans les vaccins réassortis. Quand le nombre de cas de diarrhée à rotavirus observé chez le jeune nourrisson est considérable, la vaccination à la naissance pourrait protéger l'enfant avant sa première infection symptomatique.

References

1. **Bern C et al.** The magnitude of the global problem of diarrhoeal disease: a ten-year update. *Bulletin of the World Health Organization*, 1992, **70**: 705–714.
2. **Murray CJ, Lopez AD.** Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet*, 1997, **349**: 1436–1442.
3. **De Zoysa I, Feachem RG.** Interventions for the control of diarrhoeal disease among young children: rotavirus and cholera immunization. *Bulletin of the World Health Organization*, 1985, **63**: 569–583.
4. **Institute of Medicine.** The prospects of immunizing against rotavirus. In: *New vaccine development: diseases of importance in developing countries*, Vol. 2. Washington, DC, National Academy Press. 1986: D13-1 to D13-12.
5. **Kapikian AZ et al.** Efficacy of a quadrivalent rhesus rotavirus-based human rotavirus vaccine aimed at preventing severe rotavirus diarrhea in infants and young children. *Journal of infectious diseases*, 1996, **174** (Suppl. 1): S65–S72.
6. **Clark HF et al.** The development of multivalent bovine rotavirus (strain WC3) reassortant vaccine for infants. *Journal of infectious diseases*, 1996, **174** (Suppl. 1): S73–S80.
7. **Kirkwood BR.** Diarrhoea. In: Feachem RG, ed. *Disease and mortality in sub-Saharan Africa*. Oxford, Oxford University Press, 1991: 134–154.
8. **Black RE et al.** Incidence and severity of rotavirus and *Escherichia coli* diarrhoea in rural Bangladesh. *Lancet*, 1981, **1**: 141–143.
9. **Cook SM et al.** Global seasonality of rotavirus infections. *Bulletin of the World Health Organization*, 1990, **68**: 171–177.
10. **Zaki AM et al.** The detection of enteropathogens in acute diarrhea in a family cohort population in rural Egypt. *American journal of tropical medicine and hygiene*, 1986, **35**: 1013–1022.
11. **Molbak K et al.** The etiology of early childhood diarrhea: a community study from Guinea-Bissau. *Journal of infectious diseases*, 1994, **169**: 581–587.
12. **Goh Rowland SGJ et al.** The etiology of diarrhoea studied in the community in young urban Gambian children. *Journal of diarrhoeal disease research*, 1985, **3**: 7–13.
13. **Oyejide CO, Fagbami AH.** An epidemiological study of rotavirus diarrhoea in a cohort of Nigerian infants. II. Incidence of diarrhoea in the first two years of life. *International journal of epidemiology*, 1988, **17**: 908–912.
14. **Georges MC et al.** Diarrheal morbidity and mortality in children in the Central African Republic. *American journal of tropical medicine and hygiene*, 1987, **36**: 598–602.
15. **Coker AO et al.** A study on the prevalence of rotavirus diarrhoeas in Ohaozara local government area, Imo State, Nigeria, and the Lagos University Teaching Hospital, Lagos, Nigeria. *East African medical journal*, 1987, **64**: 586–589.
16. **Georges-Courbot MC et al.** Prospective longitudinal study of rotavirus infections in children from birth to two years of age in Central Africa. *Annales de l'Institut Pasteur*, 1988, **139**: 421–428.
17. **Chunge RN et al.** Mixed infections in childhood diarrhoea: results of a community study in Kiambu District, Kenya. *East African medical journal*, 1989, **66**: 715–723.
18. **Chunge RN et al.** Comparative aetiology of childhood diarrhoea in Kakamega and Kiambu Districts, Kenya. *East African medical journal*, 1992, **69**: 437–441.
19. **Georges MC et al.** Parasitic, bacterial and viral enteric pathogens associated with diarrhea in the Central African Republic. *Journal of clinical microbiology*, 1984, **19**: 571–575.
20. **Georges-Courbot MC et al.** Rôle des rotavirus dans l'étiologie des diarrhées infantiles en République centrafricaine. *Bulletin de la Société de Pathologie exotique*, 1984, **77**: 32–38.
21. **Mutanda LN et al.** Aetiology of diarrhoea in malnourished children at Kenyatta National Hospital. *East African medical journal*, 1985, **62**: 835–841.
22. **Makino Y et al.** Virological survey of children in Nyeri and Mombasa: monthly survey of rotavirus in faeces. *East African medical journal*, 1983, **60**: 536–541.
23. **Mutanda LN.** Epidemiology of acute gastroenteritis in early childhood in Kenya. III. Distribution of the aetiological agents. *East African medical journal*, 1980, **57**: 317–326.
24. **Cassel-Beraud AM, Michel P, Garbarg-Chenon A.** Epidemiological study of infantile rotavirus diarrhoea in Tananarive (Madagascar). *Journal of diarrhoeal disease research*, 1993, **11**: 82–87.

25. **Paul MO, Erinle EA.** Rotavirus infection in Nigerian infants and young children with gastroenteritis. *American journal of tropical medicine and hygiene*, 1982, **31**: 374–375.
26. **Gomwalk NE, Gosham LT, Umoh UJ.** Rotavirus gastroenteritis in pediatric diarrhoea in Jos, Nigeria. *Journal of tropical pediatrics*, 1990, **36**: 52–55.
27. **Mutanda LN.** Epidemiology of acute gastroenteritis in early childhood in Kenya: aetiological agents. *Tropical and geographical medicine*, 1980, **32**: 138–144.
28. **Dossetor JFB, Chrystie IL, Totterdell BM.** Rotavirus gastroenteritis in Northern Nigeria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1979, **73**: 115–116.
29. **Fagbami AH, Johnson OA, David-West TS.** Rotavirus infection in children presenting with acute gastroenteritis in Ibadan, Nigeria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1985, **79**: 114–115.
30. **Sam NE et al.** Rotavirus infection in Tanzania: a virological, epidemiological and clinical study among young children. *Acta pathologica, microbiologica et immunologica Scandinavica*, 1992, **100**: 790–796.
31. **Schoub BD et al.** Viruses in acute summer gastroenteritis in black infants. *Lancet*, 1975, **1**: 1093–1094.
32. **Schoub BD et al.** Rotavirus and winter gastroenteritis in white South African infants. *South African medical journal*, 1977, **52**: 998–999.
33. **Robins-Browne RM et al.** Summer diarrhoea in African infants and children. *Archives of disease in childhood*, 1980, **55**: 923–928.
34. **Schoub BD et al.** A microbiological investigation of acute summer gastroenteritis in black South African infants. *Journal of hygiene*, 1977, **78**: 377–385.
35. **Geyer A et al.** The microbial aetiology of summer paediatric gastroenteritis at Ga-Rankuwa Hospital in South Africa. *East African medical journal*, 1993, **70**: 78–81.
36. **Dowling JM, Wynne H.** Role of enteric adenoviruses and rotaviruses in infantile gastroenteritis. *Lancet*, 1981, **2**: 305–306.
37. **Mhalu FS et al.** Prevalence of infection with rotavirus and enteric adenoviruses among children in Tanzania. *NIPH annals*, 1988, **2**: 3–7.
38. **Abiodun PO.** Incidence of rotavirus in acute childhood diarrhoea in the University of Benin Teaching Hospital, Benin. *Nigerian journal of paediatrics*, 1989, **16**: 31–34.
39. **De Mol P et al.** Enteropathogenic agents in children with diarrhoea in rural Zaire. *Lancet*, 1983, **1**: 516–518.
40. **Pavone R et al.** Viral gastro-enteritis in children in Malawi. *Annals of tropical paediatrics*, 1990, **10**: 15–20.
41. **Hassan EM et al.** Detection of enteropathogens in diarrhoeal diseases among malnourished Egyptian infants and children. *Journal of the Egyptian Public Health Association*, 1989, **64**: 461–474.
42. **Rowland MGM, McCollum JPK.** Malnutrition and gastroenteritis in the Gambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1977, **71**: 199–203.
43. **Rowland MGM et al.** Viruses and diarrhoea in West Africa and London: a collaborative study. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1978, **72**: 95–98.
44. **Mackerjee MKR et al.** Aetiology of diarrhoea in adequately nourished young African children in Durban, South Africa. *Annals of tropical paediatrics*, 1984, **4**: 183–187.
45. **Georges-Courbot MC et al.** Subgroups, serotypes, and electropherotypes of rotavirus isolated from children in Bangui, Central African Republic. *Journal of clinical microbiology*, 1988, **26**: 668–671.
46. **Georges MC et al.** Rotavirus isolated from infantile diarrhoea in the Central African Republic: study of the genome by electrophoresis. *Annals of virology*, 1983, **134E**: 533–537.
47. **Naguib T et al.** Cultivation and subgroup determination of human rotaviruses from Egyptian infants and young children. *Journal of clinical microbiology*, 1984, **19**: 210–212.
48. **Tazi-Lakhsassi L et al.** Epidemiological and clinical study and electropherotyping survey of rotavirus acute diarrhoea in a children's infectious disease unit in Casablanca, Morocco. *Annales de l'Institut Pasteur*, 1988, **139**: 205–215.
49. **Kidd AH et al.** Characterization of rotaviruses and subgroup F adenoviruses from acute summer gastroenteritis in South Africa. *Journal of medical virology*, 1986, **18**: 159–168.
50. **Steele AD, Alexander JJ.** Molecular epidemiology of rotavirus in black infants in South Africa. *Journal of clinical microbiology*, 1987, **25**: 2384–2387.
51. **Chiba Y et al.** Rotavirus infection of young children in two districts of Kenya from 1982 to 1983 as analyzed by electrophoresis of genomic RNA. *Journal of clinical microbiology*, 1984, **19**: 579–582.
52. **Urasawa T et al.** Antigenic characterization of rotaviruses isolated in Kenya from 1982 to 1983. *Journal of clinical microbiology*, 1987, **25**: 1891–1896.
53. **Gatheru Z et al.** Characterization of human rotavirus strains causing gastroenteritis in Kenya. *Epidemiology and infection*, 1993, **110**: 419–423.
54. **Cisse MF et al.** Electrophoretypes de génome de rotavirus isolés chez des enfants Sénégalais. *Bulletin de la Société de Pathologie exotique*, 1989, **82**: 637–644.
55. **Steele AD, Alexander JJ.** The relative frequency of subgroup I and II rotaviruses in black infants in South Africa. *Journal of medical virology*, 1988, **24**: 321–327.
56. **Griffiths FH, Steele AD, Alexander JJ.** The molecular epidemiology of rotavirus-associated gastroenteritis in the Transkei, Southern Africa. *Annals of tropical paediatrics*, 1992, **12**: 259–264.
57. **Steele AD.** Shift in genomic RNA patterns of human rotaviruses isolated from white children in South Africa. *South African medical journal*, 1991, **79**: 143–145.

58. **Mnisi YN, Williams MM, Steele AD.** Subgroup and serotype epidemiology of human rotaviruses recovered at Ga-Rankuwa, Southern Africa. *Central African journal of medicine*, 1992, **38**: 221–225.
59. **Bos P, Mnisi Y, Steele AD.** The molecular epidemiology of rotavirus infection in Ga-Rankuwa, Southern Africa. *Central African journal of medicine*, 1992, **38**: 286–290.
60. **Steele AD et al.** Electrophoretic typing of nosocomial rotavirus infection in a general paediatric unit showing the continual introduction of community strains. *Journal of medical virology*, 1993, **40**: 126–132.
61. **Tufvesson B.** Detection of a human rotavirus strain different from types 1 and 2 — a new subgroup? Epidemiology of subgroups in a Swedish and an Ethiopian community. *Journal of medical virology*, 1983, **12**: 111–117.
62. **Rowland M et al.** Epidemiological aspects of rotavirus infection in young Gambian children. *Annals of tropical paediatrics*, 1985, **5**: 23–28.
63. **Hanlon P et al.** Epidemiology of rotavirus in a periurban Gambian community. *Annals of tropical paediatrics*, 1987, **7**: 238–243.
64. **Bos P et al.** Monitoring of rotavirus infection in a paediatric hospital by RNA electrophoresis. *South African medical journal*, 1995, **85**: 887–891.
65. **Steele AD et al.** Variation in genomic RNA rotavirus electropherotypes isolated from white and black infants in Southern Africa. *South African medical journal*, 1988, **84**: 574–576.
66. **Besselaar TG, Rosenblatt A, Kidd AH.** Atypical rotavirus from South African neonates. *Archives of virology*, 1986, **87**: 327–330.
67. **Armah GE et al.** Seasonality of rotavirus infection in Ghana. *Annals of tropical paediatrics*, 1994, **14**: 223–230.
68. **Pazzaglia G et al.** *Campylobacter*-associated diarrhoea in Egyptian infants: epidemiology and clinical manifestations of disease and high frequency of concomitant infections. *Journal of diarrhoeal disease research*, 1993, **11**: 6–13.
69. **Cruickshank JG, Zilberg B.** Winter diarrhoea and rotaviruses in Rhodesia. *South African medical journal*, 1976, **50**: 1895–1896.
70. **Haffejee IE, Moosa A.** Rotavirus studies in Indian (Asian) South African infants with acute gastroenteritis. I. Microbiological and epidemiological aspects. *Annals of tropical paediatrics*, 1990, **10**: 165–172.
71. **Steele AD et al.** Enteropathogens isolated from children with gastroenteritis at Ga-Rankuwa Hospital, South Africa. *Annals of tropical paediatrics*, 1988, **8**: 262–267.
72. **Haffejee IE, Moosa A.** Rotavirus studies in Indian (Asian) South African infants with acute gastroenteritis: II. Clinical aspects and outcome. *Annals of tropical paediatrics*, 1990, **10**: 245–254.
73. **Mutanda LN et al.** Aetiology of diarrhoea in pre-term neonates at Kenyatta National Hospital nursery, Nairobi, Kenya. *East African medical journal*, 1990, **67**: 223–230.
74. **Fagbami AH, Oyejide CO, Enahoro F.** Neonatal rotavirus infection in urban and rural communities in Nigeria. *Tropical and geographical medicine*, 1987, **39**: 341–344.
75. **Omoigberale AI, Abiodun PO.** Nosocomial rotavirus infection in newborns. *East African medical journal*, 1995, **72**: 220–221.
76. **Steele AD, Steinhardt LS, Alexander JJ.** Viruses excreted in neonatal stools. *South African medical journal*, 1987, **72**: 198–200.
77. **Haffejee IE, Moosa A, Windsor I.** Circulating and breast-milk anti-rotaviral antibodies and neonatal rotavirus infections: a maternal–neonatal study. *Annals of tropical paediatrics*, 1990, **10**: 3–14.
78. **Haffejee IE, Windsor I, Moosa A.** Asymptomatic rotavirus infections among normal Indian children in Chatsworth, Durban. *South African medical journal*, 1989, **76**: 599–601.
79. **Oelofsen MJ, Venter EH, Smith MS.** Nosocomial rotavirus infections in a South African hospital nursery for white infants. *South African medical journal*, 1985, **68**: 394–396.
80. **Steele AD et al.** Further characterisation of human rotaviruses isolated from asymptomatically infected neonates in South Africa. *Journal of medical virology*, 1992, **38**: 22–26.
81. **Steele AD, van Niekerk MC, Mphahlele MJ.** Geographic distribution of human rotavirus VP4 genotypes and VP7 serotypes in five South African regions. *Journal of clinical microbiology*, 1995, **33**: 1516–1519.
82. **Steele AD, Sears JF.** Characterisation of rotaviruses recovered from neonates with symptomatic infection. *South African medical journal*, 1996, **86**: 1546–1549.
83. **Georges-Courbot MC et al.** Evaluation of the effiacy of a low-passage bovine rotavirus (strain WC3) vaccine in children in Central Africa. *Research in virology*, 1991, **142**: 405–411.
84. **Hanlon P et al.** Trial of an attenuated bovine rotavirus vaccine (RIT 4237) in Gambian infants. *Lancet*, 1987, **1**: 1342–1345.
85. **De Mol P et al.** Failure of live, attenuated oral rotavirus vaccine. *Lancet*, 1986, **1**: 108.
86. **Perez-Schael I et al.** Efficacy of the rhesus rotavirus-based quadrivalent vaccine in infants and young children in Venezuela. *New England journal of medicine*, 1997, **337**: 1181–1187.
87. **Shukry S et al.** Detection of enteropathogens in fatal and potentially fatal diarrhea in Cairo, Egypt. *Journal of clinical microbiology*, 1986, **24**: 959–962.
88. **Anagonou SY et al.** Gastroentérites à rotavirus en pédiatrie hospitalière au Centre national hospitalier et universitaire de Cotonou (Benin). *Médecine tropicale*, 1993, **53**: 105–107.
89. **Thoren A et al.** Aetiology and clinical features of severe infantile diarrhoea in Addis Ababa, Ethiopia. *Journal of tropical pediatrics*, 1982, **28**: 127–131.
90. **Muhe L, Fredrikzon B, Habte D.** Clinical profile of rotavirus enteritis in Ethiopian children. *Ethiopian medical journal*, 1986, **24**: 1–6.

91. **Mefane C et al.** Diarrhées du jeune enfant à Libreville (Gabon). *Archives françaises de Pédiatrie*, 1986, **43**: 813–816.
92. **Mutanda LN.** Age distribution and seasonal pattern of rotavirus infection in children in Kenya. *Journal of diarrhoeal disease research*, 1984, **2**: 147–150.
93. **Mutanda LN.** Epidemiology of acute gastroenteritis in early childhood in Kenya. VI. Some clinical and laboratory characteristics relative to the aetiological agents. *East African medical journal*, 1980, **57**: 599–606.
94. **Olusanya O, Taiwo O.** Rotavirus as an aetiological agent of acute childhood diarrhoea in Ile-Ife, Nigeria. *East African medical journal*, 1989, **66**: 100–104.
95. **Paul MO, Paul BD.** Rotavirus infection among children in hospital in Nigeria. *Journal of infection*, 1986, **12**: 39–47.
96. **Abiodun PO, Omoigberale A.** Prevalence of nosocomial rotavirus infection in hospitalized children in Benin City, Nigeria. *Annals of tropical paediatrics*, 1994, **14**: 85–88.
97. **Cisse MF et al.** Causes des gastro-entérites infectieuses de l'enfant à Dakar. *La presse medicale*, 1989, **18**: 1827–1830.
98. **Brookfield DSK et al.** Viruses demonstrated in children in Tanzania: studies in diarrhoea and measles. *Journal of infection*, 1979, **1**: 249–255.
99. **Mpabalwani M et al.** Rotavirus gastroenteritis in hospitalized children with acute diarrhoea in Zambia. *Annals of tropical paediatrics*, 1995, **15**: 39–43.
100. **Freiman I et al.** A microbiological study of gastroenteritis in black infants. *South African medical journal*, 1977, **52**: 261–265.
101. **Schoub BD et al.** Variance in rotavirus infection rates in different urban population groups in South Africa. *Journal of medical virology*, 1982, **10**: 171–179.
102. **Tiemessen CT et al.** Infection by enteric adenoviruses, rotaviruses, and other agents in a rural African environment. *Journal of medical virology*, 1989, **28**: 176–182.
103. **Steele AD, Alexander JJ, Hay IT.** Rotavirus-associated gastroenteritis in black infants in South Africa. *Journal of clinical microbiology*, 1986, **23**: 992–994.
104. **El-Mougi M et al.** Epidemiological and clinical features of rotavirus-associated acute infantile diarrhoea in Cairo, Egypt. *Journal of tropical pediatrics*, 1989, **35**: 230–233.
105. **Koulla-Shiro S, Loe C, Ekoe T.** Prevalence of *Campylobacter enteritis* in children from Yaoundé (Cameroon). *Central African journal of medicine*, 1995, **41**: 91–94.
106. **Stintzing G.** Seasonal fluctuations in the occurrence of enterotoxigenic bacteria and rotavirus in paediatric diarrhoea in Addis Ababa. *Bulletin of the World Health Organization*, 1981, **59**: 67–73.
107. **Sitbon M et al.** Rotavirus prevalence and relationships with climatological factors in Gabon, Africa. *Journal of medical virology*, 1985, **16**: 177–182.
108. **Nakano T et al.** Survey of enteropathogenic agents in children with and without diarrhoea in Ghana. *Journal of tropical medicine and hygiene*, 1990, **93**: 408–412.
109. **Kakai R, Wamola IA, Bwayo JJ.** Association of human rotavirus infection and intestinal rotavirus-specific immunoglobulin A in children with diarrhoea. *East African medical journal*, 1995, **72**: 217–219.
110. **Gomwalk NE et al.** Influence of climatic factors on rotavirus infection among children with acute gastroenteritis in Zaria, Northern Nigeria. *Journal of tropical pediatrics*, 1993, **39**: 293–297.
111. **Ogunsanya TI, Rotimi VO, Adenuga A.** A study of the aetiological agents of childhood diarrhoea in Lagos, Nigeria. *Journal of medical microbiology*, 1994, **40**: 10–14.
112. **Vargues F et al.** Etudes parasitologique, bactériologique et virologique de selles de 212 enfants diarrhéiques Dakarois non-hospitalisés, *Bulletin de la Societé de Pathologie exotique*, 1984, **77**: 97–103.
113. **Casalino M et al.** A two-year study of enteric infections associated with diarrhoeal diseases in children in urban Somalia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1988, **82**: 637–641.
114. **Tswana SA et al.** The incidence of rotavirus infection in children from two selected study areas in Zimbabwe. *Central African journal of medicine,* 1990, **36**: 241–246.
115. **Avery RM et al.** Viral agents associated with infantile gastroenteritis in Nigeria: relative prevalence of adenovirus serotypes 40 and 41, astrovirus, and rotavirus serotypes 1 to 4. *Journal of diarrhoeal disease research*, 1992, **10**: 105–108.
116. **Mphahlele MJ, Steele AD.** Relative frequency of human rotavirus VP4 (P) genotypes recovered over a 10-year period from South African children with diarrhea. *Journal of medical virology*, 1995, **47**: 1–5.
117. **Estes M.** Rotaviruses and their replication. In: Fields BN, Knipe DM, Howley PM, eds. *Field's virology*, 3rd ed., Vol 2. Philadelphia, Lippincott-Raven Press, 1996: 1625–1655.