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Review

Enteropathogenic viruses associated with acute gastroenteritis among African children under 5 years of age: A systematic review and meta-analysis

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SUMMARY

Gastroenteritis viruses are the leading etiologic agents of diarrhea in children worldwide. We present data from thirty-three (33) eligible studies published between 2003 and 2023 from African countries bearing the brunt of the virus-associated diarrheal mortality. Random effects meta-analysis with proportion, subgroups, and meta-regression analyses were employed. Overall, rotavirus with estimated pooled prevalence of 31.0 % (95 % CI 24.0–39.0) predominated in all primary care visits and hospitalizations, followed by norovirus, adenovirus, sapovirus, astrovirus, and aichivirus with pooled prevalence estimated at 15.0 % (95 % CI 12.0–20.0), 10 % (95 % CI 6–15), 4.0 % (95 % CI 2.0–6.0), 4 % (95 % CI 3–6), and 2.3 % (95 % CI 1–3), respectively. Predominant rotavirus genotype was G1P[8] (39 %), followed by G3P[8] (11.7 %), G9P[8] (8.7 %), and G2P[4] (7.1 %); although, unusual genotypes were also observed, including G3P[6] (2.7 %), G8P[6] (1.7 %), G1P[6] (1.5 %), G10P[8] (0.9 %), G8P[4] (0.5 %), and G4P[8] (0.4 %). The genogroup II norovirus predominated over the genogroup I-associated infections (84.6 %, 613/725 vs 14.9 %, 108/725), with the GII.4 (79.3 %) being the most prevalent circulating genotype. In conclusion, this review showed that rotavirus remains the leading driver of viral diarrhea requiring health care visits and hospitalization among under-five years children in Africa. Thus, improved rotavirus vaccination in the region and surveillance to determine the residual burden of rotavirus and the evolving trend of other enteric viruses are needed for effective control and management of cases.

Introduction

Acute gastroenteritis continues to be a major public health concern across the globe, particularly in infants and young children before their fifth birthday.[1] Globally, diarrheal disease is ranked the 2nd leading etiology of infectious disease morbidity and one of the top ten leading

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causes of death.[2] According to World Health Statistics, gastroenteritis alone accounts for approximately 1.7 billion annual cases of childhood diarrheal morbidity, with death cases estimated at 525,000 among children < 5 years old.[3] Countries in Sub-Saharan Africa and South Asia with estimated mortality rates of 50 to 150 per 100,000 people, particularly bear the brunt of the diarrheic morbidity.[4] Of all causes of gastroenteritis, enteric viruses are responsible for most cases.[5,6] According to the Centers for Disease Control and Prevention, gastroenteritis infections associated with viral pathogens account for > 200,000 deaths of children each year worldwide.[6,7] Although acute diarrheal disease is generally self-limiting in industrialized nations, it can sometimes result in high morbidity for young and elderly patients. In low-and middle-income countries, diarrheal diseases attributable to viral pathogens are a significant cause of death, particularly in infants.[5,6] In these settings with significant burden, factors such as malnutrition, poor access to healthcare, wasting, early cessation of or not breastfeeding, poor sanitation and hygiene, and not receiving any dose or the full dose of viral vaccine (e.g., oral rotavirus vaccine) positively influence pediatric diarrheal mortality.[1]

Enteropathogenic agents causing childhood diarrhea include a variety of viruses, bacteria, helminths, and protozoa which are transmitted principally via ingestion of contaminated food, water, or objects, a result of poor overall hygiene.[8] Of the agents of acute gastroenteritis, viruses have recently been recognized through advancements in molecular detection techniques as major drivers of childhood diarrhea in developing countries in Africa.[9–12] Predominantly, rotavirus (family Reoviridae), norovirus (family Caliciviridae), and adenovirus (family Adenoviridae) have emerged as major viral etiologies of both endemic and epidemic childhood gastroenteritis worldwide, while human astrovirus (family Astroviridae), sapovirus (family Caliciviridae), and aichivirus (family Picornaviridae) are contributing viruses.[13,14]

Over the recent years, data on the epidemiology of rotavirus infection and the burden of disease have informed the design and implementation of the oral rotavirus vaccine currently in use both nationally and internationally. Notwithstanding the globally acclaimed effectiveness of the vaccine, there have been widespread reports of rotavirus vaccine underperformance in developing countries including Africa with poor socioeconomic conditions.[8,15] Beside rotaviruses, there is currently no licensed antivirals or vaccines to treat and prevent infection with enteropathogenic viruses.[16] Thus, early, and accurate diagnosis of viral diarrhea is key to the clinical management of cases and public health surveillance. Importantly, pooled epidemiologic data on the viral etiology of infectious diarrhea will serve as a proof of concept highlighting the need for sustained surveillance and to inform preventive measures through vaccinations and empirical treatments.

Successful enteric virus surveillance systems have been implemented in developed countries in the US, Europe, Asia, and Oceania resulting in a significant increase in epidemiologic data on enteric virus prevalence and diversity.[17] On the contrary, national surveillance programs for enteric viruses are either lacking or nonfunctional in most African countries. Therefore, this study reviewed several articles published within the last two decades (2003–2023) and summarizes the data from investigations on viral etiology of childhood diarrhea in Africa to estimate the overall prevalence for different enteric viruses across different sub-regions, identify key viruses to be targeted in tackling the burden of diarrhea and important data gaps needed to inform future research in Africa. Furthermore, the genetic diversity of rotaviruses and noroviruses for studies providing genotype data was assessed.

Methods

Literature search strategy

This review was carried out following the established guidelines in Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[18] Systematically, electronic databases comprising Google SCHOLAR, PubMed, Science Direct, Wiley Online Library, Embase, Cochrane Library, and African Journals Online (AJOL) were searched for peer-reviewed articles published over two decades (2003–2023). Published articles were identified engaging a range of search strings or terms “gastroenteritis in Africa”, “viral diarrhea in children”, “causes of diarrhea”, “prevalence of gastroenteritis”, “enteric viruses in Africa”, “diarrhea in under five years children”, “epidemiology of enteric virus disease”, “rotavirus” norovirus” astrovirus” sapovirus” aichivirus” adenovirus” Africa” and related terms. Further, all the references in the identified articles were screened for relevant publications.

Inclusion and exclusion of studies

We included community and hospital-based surveys, prospective or retrospective observational studies (cross-sectional and case-control studies) reported between 2003 and 2023. We included only articles reported in English on virus-associated gastroenteritis manifesting symptoms of diarrhea among infants and young children < 5 years old in Africa. Included studies must have used polymerase chain reaction alone or in combination with enzyme-linked immunosorbent assay (ELISA) for the identification of enteric virus in the diarrheic samples. Where duplicate studies were found, only the ones with full-text information were included. In cases where multiple publications emanated from the same study, information was retrieved only from the most recent available article. Excluded articles included those that focused on one virus pathogen alone, children > 5 years, asymptomatic populations, studies outside Africa, and children with immunocompromised disease. In addition, articles with no accessible quantitative data were excluded. Further, to assess the diarrheic burden attributable to viral enteropathogens, we excluded published articles with fewer than 38 diarrheic children and < 3 months duration of the study. Finally, rotavirus and norovirus genotype data were retrieved to assess the genetic diversity of both viruses.

Study selection

Titles and abstracts of papers were screened for eligibility by two independent reviewers (David Moses Adaji, DMA; Sunday Ocholi Samson, SOS), and the records for exclusion were confirmed by a third reviewer (Cornelius Arome Omatola, CAO). Subsequently, the full texts of potentially eligible studies were assessed by two reviewers (SOS and DMA) and discrepancies were settled by consensus between the reviewers (SOS, DMA, and CAO).

Data extraction

The data from all eligible publications were extracted into a Microsoft Office Excel database. Data extraction was carried out by two reviewers (SOS and DMA) who assessed the full texts and checked for any missing details or confirmed important data by the third researcher (CAO). Numbers were assigned to the articles to avoid being mixed up. Relevant information obtained from eligible publications included author details, the year the article was published, duration/period of study, country of study, African region (based on the United Nations demarcation), study setting/design, age band, sample size, case definition, inclusion criteria, method of detection, sampling strategy, study setting (outpatient department, or hospital-based), outcome virus (number and proportion), numbers genotyped for rotavirus and/or norovirus, and numbers of rotavirus G and P-genotype combinations.

Risk of bias assessment

The methodological qualities or risk of bias in individual articles were evaluated based on a modified 12-point scoring system developed by Downs and Black,[19] for assessing population-based prevalence. This critical appraisal tool had been previously adapted in a similar study.[20] The assignment of quality scores was based on the following checklists: clearly defined study objective, study design indicated, participants' representativeness in the sourced population, participants accumulated during the same period, sample size justified in the study, management of missing data, gender, age, and other relevant characteristics such as confounding variables reported, assay method for enteric viruses reported, potential biases identified in the study, and outcome of the study is clearly described. The quality assessment was carried out independently by authors (Cornelius Arome Omatola, CAO; Kehinde Charles Mofolorunsho, KCM) and any disagreement was resolved by discussion.

Data synthesis and statistical analysis

A chronicle approach was used to describe the number of studies and study designs. The metaprop function from the R package meta was used to calculate the pooled effect estimates using random-effects models. Due to anticipated heterogeneity, a random-effects meta-analysis was employed to estimate the overall effect size. DerSimonian-Laird random-effects method was applied to estimate the pooled between-study variance (heterogeneity)[21,22] and used metaprop command (R version 4.3.1) to pool prevalence. Individual and pooled estimates were graphically displayed using forest plots. Between-study heterogeneity was assessed with I^2 statistics, expressed as percent low (25 %), moderate (50 %), and high (75 %) and chi-square test statistic (Q) (*p-value* < 0.05). To investigate the sources of heterogeneity, subgroup analysis was performed by study designs and geographic area of the study,[23] which was categorized as East, West, North, and South according to the reported study location. We calculated the proportion of prevalence for different gastroenteritis virus infections in multiple enteric virus pathogen studies among children under-five years in Africa. We conducted meta-regression analyses to investigate potential moderators. The regression coefficient estimates how the prevalence effects of each subgroup differ from the specified reference subgroup. The year of study publication, age band, and sample size were examined as moderators in the meta-regression model. The results of the analyses were tested for statistically significant differences. Finally, potential bias was assessed qualitatively using funnel plots, by plotting the study effect size against standard errors of the effect size, and quantitatively using Egger's test. Results were reported as prevalence expressed as a percentage. All statistical analyses were performed with R software, version 4.3.1 (R, College Station, TX).

Results

Overview of selected studies

The initial search on electronic databases identified 1448 potentially relevant studies out of which 500 duplicates and 899 records that did not meet our research objectives were excluded. The excluded records included randomized controlled trials; studies that focused exclusively on asymptomatic individuals; and studies reported on outbreaks of diarrhea. Thirty-three studies were of satisfactory quality and thus, were included in the systematic review and meta-analytic study of the burden of enteric virus infection (Fig. 1 and Table 1) [8–10, 12–14, 24–50]. Cross-sectional studies constitute the largest proportion (94 %, 31/33) of eligible studies while the remaining which were case-control studies were just 6 % (2/33). Included in Table 1 are the characteristics and quality assessment scores for individual studies. Most of the studies received moderate (B=5–8; 12/33) to high-quality (A=9–12; 19/33) assessment scores. Two of the studies had a low assessment score due to reasons which included inadequate representativeness of participants in the sourced population, sample size inadequately justified, and inability to identify confounding variables. To understand the epidemiology of enteric virus infection in Africa, published studies from different countries were stratified by their geographical regions (i.e. West Africa, Central Africa, Southern Africa, East Africa, and North Africa) based on the United Nations demarcation. Most of the included studies were from West Africa (11/33) followed by East and North African regions (7/33 each), Central Africa (5/33), and Southern Africa (3/33) (Table 1). Overall, studies included in the analysis identified participants from outpatients (15 studies), hospitalized patients (11 studies), outpatients-hospital cases combined (5 studies), and community-based cases (2 studies). Out of the 33 studies, eleven studies documented rotavirus genotype profiles typed by the method of RT-PCR and were used for the analysis of the genotype diversity. Fifteen studies with information on norovirus genogroups and genotypes were used for the analysis of the circulating norovirus genotypes (Fig. 1).

Meta-analysis of prevalence of enteropathogenic viral infections among children ≤5 years old in Africa

The meta-analytic study identified a total of 9662 diarrheic samples from children under-five years in 33 studies. Rotavirus, sapovirus, norovirus, adenovirus, astrovirus, and aichivirus were detected in 2740, 174, 1018, 778, 297, and 27, respectively (Table 1). Across all studies, there was statistically significant heterogeneity (Figs. 2–6). Hence the pooled prevalence estimates of viral enteropathogens were based on the random effects model. Overall, rotavirus with an estimated pooled prevalence of 31.0 % (95 % CI 24.0–39.0) predominated in acute gastroenteritis among children younger than 5 years old in Africa, followed by norovirus with pooled prevalence estimated at 15.0 % (95 % CI 12.0–20.0), adenovirus 10 % (95 % CI 6–15), sapovirus 4.0 % (95 % CI 2.0–6.0) and astrovirus 4 % (95 % CI 3–6) (Figs. 2–6). Aichivirus with a prevalence of 2.3 % was the least detected.

Subgroup analysis based on regions

The proportion of acute gastroenteritis caused by enteric viruses among children ≤ 5 years old across African regions was executed to identify regions with significant diarrheic burden (Table 2). The subtotal random pooled estimate of rotavirus prevalence was 37 % (95 % CI: 21–57 %) for countries in West Africa, followed by 32 % (95 % CI: 23–43 %) for Central Africa, while Southern Africa with 22 % (95 % CI of 14–32 %) had the least prevalence of rotavirus attributable diarrhea. The prevalence of sapovirus significantly differed between the regions of Africa. It was higher among countries in Central Africa (n = 3, proportion = 0.06, 95% CI [0.02, 0.16]) compared to West Africa (n = 4, proportion = 0.03, 95 % CI [0.01, 0.12]). Regionally, norovirus prevalence was higher in Central and East Africa (18 % each), followed by West Africa (16 %) and North Africa (15 %) while Southern Africa (10 %) had the least. Sub-geographically, adenovirus was more frequently detected among diarrheic children in West Africa (16 %; 95 % CI 8.0–30 %) with a p-value less than 0.01 than in other African regions which indicated a close prevalence rate (7–9 %). Again, astrovirus was detected more frequently in West Africa (9 %; 95 % CI 5–13) than was reported in North Africa (7 %; 95 % CI 4–11), followed by Central Africa (5 %; 95 % CI 3–6), Southern and East Africa (2 % each). Overall, the output data (tau-square and I^2) related to each viral infection suggest high heterogeneity in the effect sizes. Furthermore, the Q test statistics indicated that the included studies in each category of viral infection did share a common effect size. Due

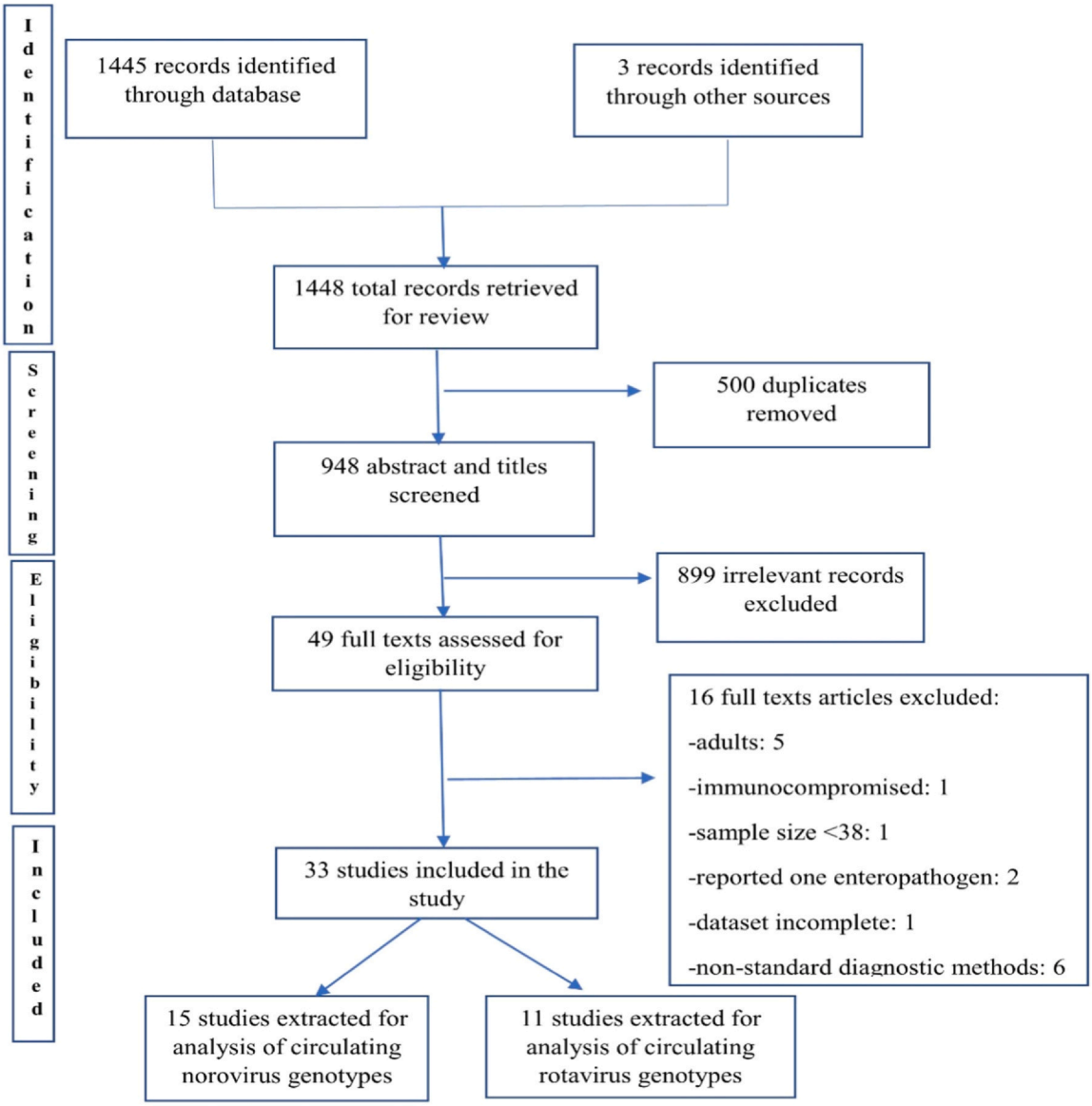

Fig. 1. Flow diagram of published studies included and excluded for this review.

to variations in sample size, studies, inclusion criteria, and methodology, heterogeneity examination in meta-analyses becomes inevitable.

Subgroup analysis based on hospital settings

The summary proportion of acute gastroenteritis caused by rotavirus, estimated from 30 studies was 29 % (95 %CI: 29–38 %) for inpatients alone, 32 % (95 %CI: 19–48 %) for outpatient alone, and 32 % (95 %CI: 30–35 %) for inpatient and outpatient combined (Suppl. Fig. 1). The summary proportion of acute gastroenteritis caused by norovirus, estimated from 25 studies was 12 % (95 %CI: 6–21 %) for inpatients alone, 19 % (95 %CI: 15–25 %) for outpatients alone, 11 % (95 %CI: 7–18 %) for inpatient and outpatient combined, and community-based 34 % (95 %CI: 30–40 %) (Suppl. Fig. 2). The summary proportion of acute gastroenteritis caused by adenovirus, estimated from 23 studies was 5 % (95 %CI: 3–8 %) for inpatients alone, 21 % (95 %CI: 14–30 %) for outpatients alone, and 3 % (95 %CI: 2–4 %) for inpatient and outpatient combined (Suppl. Fig. 3). The summary proportion of acute gastroenteritis caused by sapovirus, estimated from 14 studies was 4 % (95 %CI: 2–6 %) for inpatients alone, 6 % (95 %CI: 3–9 %) for outpatients alone, 1 % (95 %CI: 1–2 %) for inpatient and outpatient combined, and community-based 9 % (95 %CI: 6–13 %) (Suppl. Fig. 4). The summary proportion of acute gastroenteritis caused by astrovirus, estimated from 26 studies was 2 % (95 %CI: 1–8 %) for inpatients alone, 6 % (95 %CI: 4–8 %) for outpatients alone, 3 % (95 %CI: 2–5 %) for inpatient and outpatient combined, and community-based 8 % (95 %CI: 5–12 %) (Suppl. Fig. 5). Based on the meta-regression output, we can conclude that both years of study publication and the age band are not significant moderators of heterogeneity effects, which are also supported by the insignificant regression coefficient (Suppl. Docx). These suggest that they did not moderate the variability in individual virus prevalence at the study level.

Publication bias

Publication bias was assessed by funnel plot and Egger test for small-study effects. However, publication bias is not pertinent when the goal is to estimate a single summary proportion rather than a

Table 1
General characteristics of studies included in the analysis.

Study	Country	Region	Study duration	Design	Setting	Assay method	Age band	Sample size	Rotavirus positive n (%)	Norovirus positive n (%)	Human adenovirus positive n (%)	Human astrovirus positive n (%)	Sapovirus positive n (%)	Aichi virus positive n (%)	"Quality Score (A = 9–12) (B = 5–8) (C = 1–4)"
Manouana et al.[13]	Gabon	Central Africa	April 2018-Nov 2019	Cross-sectional	Outpatient	RT-PCR	< 5 years	177	26 (14.7)			13 (7.3)	6 (3.4)	2 (1.1)	A
Potgieter et al.[24]	South Africa	Southern Africa	2014-2016	Cross-sectional	Outpatient	Multiplex PCR	< 5 years	275	36 (13.0)	42 (15.0)	51 (19.0)	5 (2.0)	9 (3.0)		A
Mero et al.[8]	Guinea-Bissau	West Africa	Nov 2010-Oct 2012	Cross-sectional	Outpatient	RT-PCR	<5 years	228	53 (23.2)	62 (27.2)	40 (17.5)	30 (13.2)	19 (8.3)		A
Efunshile et al.[25]	Nigeria	West Africa	Dec 2016-April 2017	Cross-sectional	Outpatient	RT-PCR	<5 years	243	231 (95.1)		103 (42.4)	11 (4.5)	4 (1.6)		A
Ouedraogo et al.[9]	Burkina Faso	West Africa	Nov 2011-Sept 2012	Cross-sectional	Outpatient	RT-PCR	<5 years	263	167 (63.5)	55 (20.9)	82 (31.2)	13 (4.9)	27 (10.3)	2 (0.8)	A
El-Mosallamy et al.[26]	Egypt	North Africa	Jul 2013-Jan 2015	Cross-sectional	Outpatient + hospitalized	RT-PCR	0-2 years	100	37 (37.0)	14 (14.0)	7 (7.0)	3 (3.0)			A
Maina et al.[27]	Nigeria	West Africa	April-Nov, 2017	Cross-sectional	Outpatient	RT-PCR	<5 years	65	20 (30.8)	7 (10.8)					B
Shioda et al.[28]	Kenya	East Africa	Jun 2007-Feb 2009	Cross-sectional	Community	RT-PCR	<5 years	273		99 (36.3)		22 (8.1)	25 (9.2)		A
Aminu et al.[29]	Nigeria	West Africa	Jan - Mar, 2002	Cross-sectional	Outpatient	RT-PCR and ELISA	<5 years	134	12 (9.0)			7 (5.2)			B
Adam et al.[30]	Sudan	East Africa	April-Jun, Aug-Sept, 2014	Cross-sectional	Hospitalized	RT-PCR	<5 years	437	45 (10.2)	22 (5.0)	7 (1.6)	0 (0.0)			B
Ayolabi,[31]	Nigeria	West Africa	Aug 2006-July 2008	Cross-sectional	Hospitalized	RT-PCR and ELISA	<5 years	302	78 (25.8)	60 (19.9)	14 (4.6)	65 (21.5)			A
Gelaw and Liebert,[32]	Ethiopia	East Africa	Dec 2015-April 2016	Cross-sectional	Outpatient	RT-PCR	<5 years	38	4 (10.5)	5 (13.2)	7 (18.4)	2 (5.3)	3 (7.9)		B
Pelkonen et al.[33]	Angola	Central Africa	Dec 2013-Aug 2014	Cross-sectional	Outpatient	RT-PCR	<5 years	98	30 (31.0)	26 (27.0)	5 (5.0)	3 (3.0)	19 (19.0)		B
Japhet et al.[10]	Nigeria	West Africa	Aug 2012-Dec 2013	Cross-sectional	Outpatient + hospitalized	RT-PCR	<5 years	103	41 (39.8)	11 (10.7)		7 (6.8)	0 (0.0)	1 (0.97)	B
Mayindou et al.[34]	Congo	Central Africa	Jun 2012-Jun 2013	Cross-sectional	Hospitalized	RT-PCR and ELISA	< 5 years	655	304 (46.4)		31 (5.5)				B
Zaki and Kheir,[35]	Egypt	North Africa	Jan 2015-Jan 2017	Cross-sectional	Outpatient	RT-PCR	<5 years	100	44 (44.0)	30 (30.0)	20 (20.0)	14 (14)			A
Louya et al.[36]	Republic of Congo	Central Africa	Jun 2012-Jun 2013	Cross-sectional	Hospitalized	RT-PCR and ELISA	<5 years	461	172 (37.3)	96 (20.8)	14 (3.0)				A
Randremanana et al.[37]	Madagascar	East Africa	Nov 2011-Jan 2014	Case-control	Hospitalized	RT-PCR and ELISA	<5 years	198	86 (43.4)		6 (3.0)	5 (2.5)			C
Sdiri-Loulizi et al.[38]	Tunisia	North Africa	Jan 2003-Jun 2005	Cross-sectional	Outpatient + hospitalized	RT-PCR	0-2 years	632	142 (22.5)	110 (17.4)	17 (2.7)	26 (4.1)	6 (0.9)	22 (3.5)	A
Kabayiza et al.[39]	Rwanda	Central Africa	Nov 2009-Jun 2012	Cross-sectional	Outpatient	RT-PCR	< 5 years	880	325 (36.9)	98 (11.1)	216 (24.5)	36 (4.1)	33 (3.8)		A
Aminu et al.[40]	Nigeria	West Africa	Jul 2002-Jul 2004	Cross-sectional	Outpatient	RT-PCR and ELISA	<5 years	869	156 (18.0)		57 (6.6)	48 (5.5)			A
Benmessaoud et al.[41]	Morocco	North Africa	Mar 2011-Mar 2012	Cross-sectional	Hospitalized	RT-PCR	<5 years	122	21 (17.2)	1 (0.8)		6 (4.9)			B
Nhampossa et al.[42]	Mozambique	Southern Africa	Dec 2007-Oct 2011	Case-control	Outpatient + hospitalized	RT-PCR and ELISA	<5 years	784	246 (31.4)	33 (4.2)	23 (2.9)	14 (1.8)	10 (1.3)		A
Joseph and Godwin,[43]	Nigeria	West Africa	Jan 2013-Dec 2014	Cross-sectional	Outpatient	RT-PCR	<5 years	152	87 (57.2)		61 (40.1)				B
Rossouw et al.[44]	South Africa	Southern Africa	July 2016-Dec 2017	Cross-sectional	Hospitalized	Multiplex PCR	<5 years	205	46 (22.4)	32 (15.6)	15 (7.3)	3 (1.5)	9 (4.4)		A
Japhet et al.[10]	Nigeria	West Africa	Jun 2010-Jan 2011	Cross-sectional	Community	RT-PCR	<5 years	55	19 (34.5)	14 (25.5)					C
Gelaw et al.[45]	Ethiopia	East Africa	Nov 2015-April 2016	Cross-sectional	Outpatient	RT-PCR	<5 years	450			144 (32.0)	16 (3.6)			A

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Region	Study duration	Design	Setting	Assay method	Age band	Sample size	Rotavirus positive n (%)	Norovirus positive n (%)	Human adenovirus positive n (%)	Human astrovirus positive n (%)	Sapovirus positive n (%)	Aichi virus positive n (%)	"Quality Score (A = 9–12) (B = 5–8) (C = 1–4)"
Mashaly et al.[46]	Egypt	North Africa	Nov 2021-May 2022	Cross-sectional	Outpatient	RT-PCR and ELISA	< 5 years	100	39 (39.0)	27 (27.0)		12 (12.0)			B
Arowolo et al.[47]	Nigeria	West Africa	Feb 2015-April 2017	Cross-sectional	Hospitalized	RT-PCR	< 5 years	175	29 (16.6)	9 (5.1)	9 (5.1)	34 (19.4)			B
Qazoui et al.[48]	Morocco	North Africa	Jan-Dec 2011	Cross-sectional	Hospitalized	RT-PCR	< 5 years	335	89 (26.6)	54 (16.1)					A
Hugho et al.[12]	Tanzania	East Africa	Jul 2020-Feb 2022	Cross-sectional	Hospitalized	RT-qPCR	< 5 years	146	56 (38.4)	17 (11.6)	29 (19.9)	1 (0.7)	4 (2.7)		B
Abugalia et al.[49]	Libya	North Africa	Oct 2007-Sept 2008	Cross-sectional	Outpatient + hospitalized	RT-PCR and ELISA	< 5 years	520	164 (31.5)	91 (17.5)					A
Moyo et al.[50]	Tanzania	East Africa	Dec 2005-Feb 2006	Cross-sectional	Hospitalized	RT-PCR and ELISA	< 5 years	87	49 (18.1)	37 (13.7)	7 (2.6)	1 (0.4)			A

Note: RT-PCR: Reverse transcriptase polymerase chain reaction; RT-qPCR: Real-time quantitative polymerase chain reaction.

comparison of treatments, interventions, or methods. Therefore, we generated the funnel plots and used the Egger test to examine whether the distribution of effect size estimates follows what one would ordinarily anticipate (that is., less variation with a higher number of studies constructs a roughly symmetric dispersion about the mean) and to detect whether the small-study effect is present. The funnel plots (Suppl. Figure Y) show that small-study effects genuinely exist in this meta-analysis study. Further, we conducted a rank correlation test to examine the relationship between the sample size and the observed effect size of each study (Suppl. Figure X). Despite clear evidence to the contrary in the funnel plot, the rank correlation test fails to find a significant relationship between sample size and effect size. The reason could be attributed to the fact that the rank correlation test has low power when examining a small number of studies. Finally, Egger's regression test was conducted, and it was evident that it performed better than the rank correlation test when the number of included studies was small (Suppl. Docy). When the analysis was stratified by research design for each of the enteropathogenic viruses associated with acute gastroenteritis, the results of the Egger's test were not statistically significant for all the viruses: Rotavirus [(B = −0.6177 (CI: −1.4365, 0.2011), p = 0.6499), Sapovirus (B = −2.2279 (CI: −3.1804, −1.2755), p = 0.0356), Norovirus (B = −0.9852 (CI: −1.5359, −0.4345), p = 0.0057, Adenovirus (B= −0.7453 (CI: −1.6909, 0.2004), p = 0.0011; and patient-control studies (B = −1.8626 (CI: −2.4087, −1.3165), p < .0001). Although, there is clear evidence of heterogeneity and funnel plot asymmetry. There is also an indication of a small study effect, even though the effect was not very evident.

Rotavirus and norovirus genotype distribution in Africa

Information on rotavirus G/P genotype combinations was available for 743 isolates from 11 studies. Genotype G1P[8] accounting for a prevalence of 39 %, predominated in the acute diarrheal cases, followed by G3P[8] (11.7 %), G9P[8] (8.7 %), and G2P[4] (7.1 %). Reassortant and potentially zoonotic rotavirus strains such as G2P[6], G3P[4], G3P[6] (2.7% each), G8P[6] (1.7 %), G1P[6] (1.5 %), G12P[6], G10P[8] (0.9 %), G12P[8] (0.8 %), G8P[4] (0.5 %), and G4P[8] (0.4%) were reported less frequently (Fig. 7). Information on the circulating norovirus genotypes was available for 725 isolates from 15 studies. The genogroup II norovirus infections predominated over genogroup I and genogroup I/II associated infections (84.6 %, 613/725 vs 14.9 %, 108/725 vs 0.4 %, 3/725). Further, an analysis of five studies with information on the circulating norovirus GI and GII genotypes indicated a great diversity of norovirus genotypes in Africa. The relative frequencies of norovirus GI and GII genotypes in Africa are depicted in Fig. 8. Overall, the GII.4 (79.3 %) was the most prevalent genotype of norovirus associated with acute gastroenteritis in African children.

Discussion

Enteropathogenic viruses, since their first recognition in diarrheal cases in the early 1970s, have remained the leading cause of acute gastroenteritis worldwide.[51] According to world health statistics, every child before their fifth birthday practically has an episode of viral diarrhea irrespective of racial inclination and socioeconomic status and this has impacted significantly on both the economic burden of public health services and productivity loss.[52] The diarrheal mortality which disproportionately affects those living in low socioeconomic regions like Africa is noteworthy.[1] Therefore, to determine the contributions of individual viruses in diarrhea cases for comparison with global prevalence rates, we employed a meta-analysis to provide the pooled prevalence estimate of enteric viruses from multiple studies conducted among children ≤ 5 years with acute gastroenteritis in Africa. In addition, the study sought to

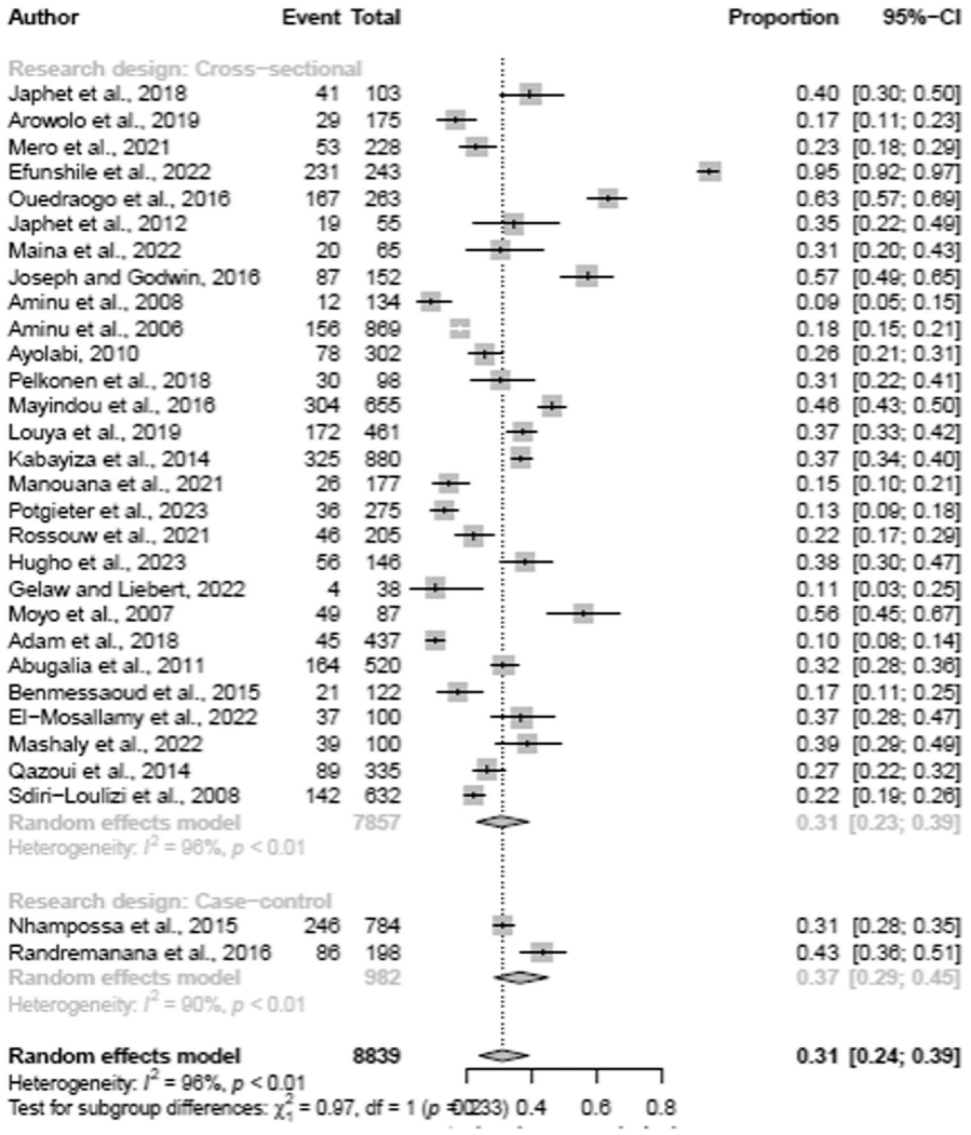

Fig. 2. Forest plot (stratified by research design) for the meta-analysis examining the overall prevalence of rotavirus in Africa.

know the genotype diversity of the two leading viral pathogens for prioritization of vaccine targets in the African continent. To our knowledge, this is the first meta-analytic study to describe the frequency of each viral enteropathogen concurrently with their genotype diversity in published studies that tested for multiple enteric viruses among diarrheic children ≤ 5 years old in the African continent.

In the current study, rotavirus with an overall pooled prevalence of 31.0 % (95 % CI 24.0–39.0) of all the gastroenteritis cases of hospitalizations and outpatients and an estimated prevalence of 22 % to 37 % across all geographical settings in Africa is the most common identified viral agent associated with acute childhood diarrhea. Our meta-analytic finding corroborates previously reported acute rotavirus gastroenteritis hospitalizations range of 30 %–72 % and the worldwide prevalence of community-associated infection of 4 %–24 %.[53] Further, the finding in the study supports the current body of knowledge which posited that rotavirus remains the leading etiology of viral diarrhea globally despite the widespread use of the oral rotavirus vaccine.[11,51] On the contrary, a similar meta-analytic study in South Korea [54] and a worldwide review of multiple pathogen studies reported an average rotavirus prevalence of 15.1 % and 20 %,[55] respectively, which are lower than the rate observed in our studies. Although regional disparities are difficult to interpret due to regional heterogeneity, nevertheless differences in mean income level, quality of health care, and cultural beliefs such as delay in seeking health care as well as stopping breastfeeding or feeding may explain the observed variations in diarrheal morbidity rates between regions. Previously in Africa, a review of 44 studies that tested multiple pathogens causing diarrheal disease, showed that rotavirus with increased detection rates from 58 % to 74 % to 89 % over 3 successive decades (1976–1985, 1986–1995, and 1996–2006) was the most prevalent cause of diarrheal disease.[56] Interestingly, the current rotavirus prevalence rate of 31 % in comparison with the above reports indicated that the diarrheic burden in Africa has reduced by 2–3 folds over the past 2 decades, a likely reflection of the impact of oral rotavirus vaccine performance widely evident in most licensure countries. Notwithstanding, the high attributable percentage in Waggie et al. [56] study as compared to the current study might be due to the study selection criteria as they included several studies with non-reliable pathogen detection procedures capable of amplifying false positive results.

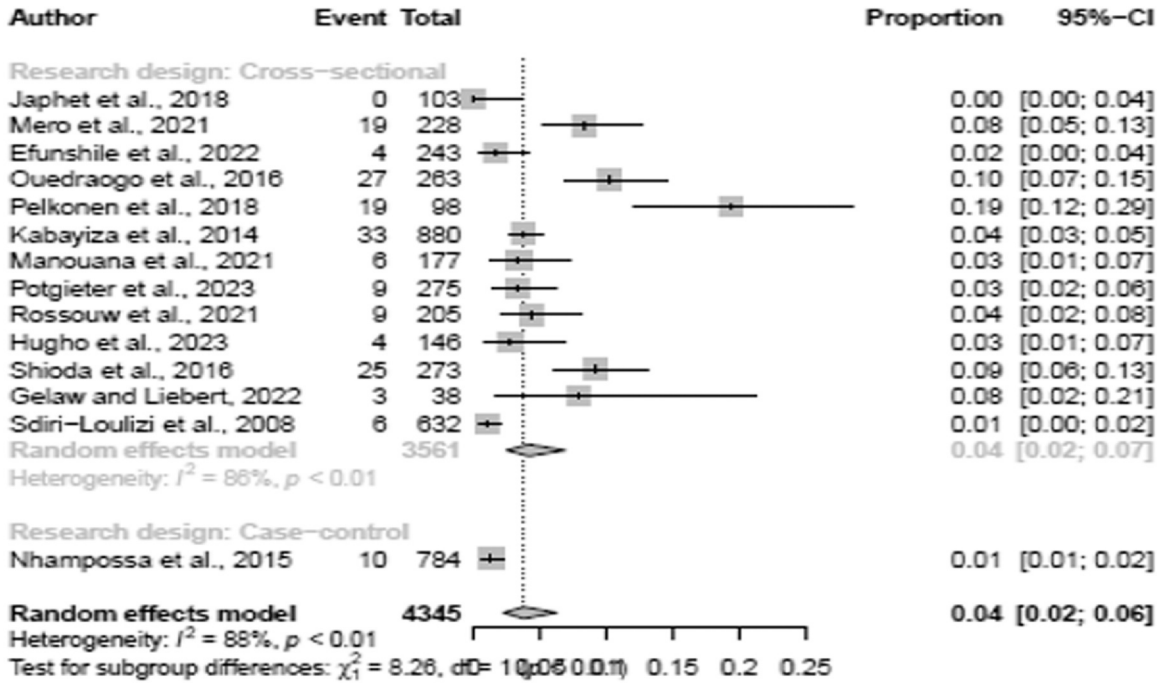

Fig. 3. Forest plot (stratified by research design) for the meta-analysis examining the overall prevalence of sapovirus in Africa.

The dominant circulating rotavirus G/P genotype combinations (G1P[8], G3P[8], G9P[8], and G2P[4]) observed in this study conform with the strains frequently infecting humans worldwide and that are associated with severe diarrheic infections requiring medical attention [51]. Overall, the G1P[8] genotype with the diarrheal attributable proportion of 39 % remains the most prevalent rotavirus strain worldwide despite the availability of effective rotavirus vaccine in most national immunization schedules.[11,57] Although, pre-and post-licensure evaluation was not ascertained in the study, the finding of high prevalence and the continuous predominance of the G1P[8] over the other strains in Africa could be attributed to the high antigenic and genetic heterogeneity character of the strains which have been previously credited to the global prevalence and the epidemiological fitness advantage of the variants.[57] In some countries like South Africa a shift in rotavirus genotype predominance and circulation pre- and post-vaccine are common due to either natural genotype cycling or vaccine-induced selective pressure.[20] In a particular season, most of the dominant circulating rotavirus strains may co-circulate, thereby creating the opportunities for emergence of reassortant strains such as the G3P[4] observed in the study. The circulation of unusual genotype combinations such as G3P[6], G1P[6], and G4P[8] similarly observed in the high- and low-income WHO-EMRO (World Health Organization defined as Eastern Mediterranean region) countries have been attributed to natural phenomenon worldwide.[57] Furthermore, the findings of unusual rotavirus strains such as G8P[4], G8P[6], and G10P[8] of bovine origin that can rapidly adapt to human populations, may be suggesting the existence of dynamic interaction and inter-host transmission events between bovine and human rotaviruses which could provide the mechanism for generating more genetic diversity via reassortment of genome segments. Thus, close and continuous monitoring of the presence of these genotypes is important to identify any change associated with the disease dynamics among the human population in Africa.

Norovirus with pooled prevalence ranging from 10 % to 18 % across all geographical regions and an overall pooled prevalence of 15.0 % (95 % CI 12.0–20.0) in African children ranks second most important viral etiology of childhood diarrhea in the region. Though the overall proportion of acute gastroenteritis caused by norovirus was half as high as rotavirus, the comparability of the rate with recent meta-analysis findings of 16.68 % (95 % CI 16.63–16.72) and 17.7 % (95 % CI: 16.3 %–19.2 %) reported for China and the world,[58,59] respectively is suggestive of widespread distribution and transmission risks of norovirus in different socioeconomic settings. In a previous review of single pathogen studies (between 1990–2013) in Africa, a pooled prevalence of 11 % (95 % CI 8–14 %), lower than the current rate, was reported.[60] The increased detection/prevalence observed in this study could be due to changes in the norovirus antigenic landscape or cumulative viral evolution which over time can lead to the domination of one strain over the others. The source of variation between studies might also be explained by the inclusion criteria. For instance, Kubue et al.[60] included older age groups with a lower risk of infection as compared to our review which only considered ages of significant vulnerability. In consideration of the widespread use of the effective oral rotavirus vaccine (ORV) that resulted in a reduction in the global trend of rotavirus and the realization of emerging norovirus dominance in several countries post ORV licensure,[51,61] it is suggested based on our meta-analytic findings for health care policymakers to continue to strengthen research focus on potential measures to prevent or treat norovirus infection which is emerging rapidly especially in regions like Africa with the significant diarrheal burden.

The overall detection rates of norovirus genogroup II (85 %) against the GI (15 %) among African children with acute gastroenteritis in this study was not unexpectedly high as it is comparable with findings from previously published pooled single studies which reported norovirus GII and GI rates of 88.5 % vs 3.4 % and 92.9 % vs 6.7 % for Africa[17] and the world,[59] respectively. Contrary to our finding, a lower prevalence of 81 % for GII and a higher prevalence of 18 % for GI has been reported previously among both children and adult populations in Africa.[60] Comparatively, the source of discrepancy might be due to the timing of published

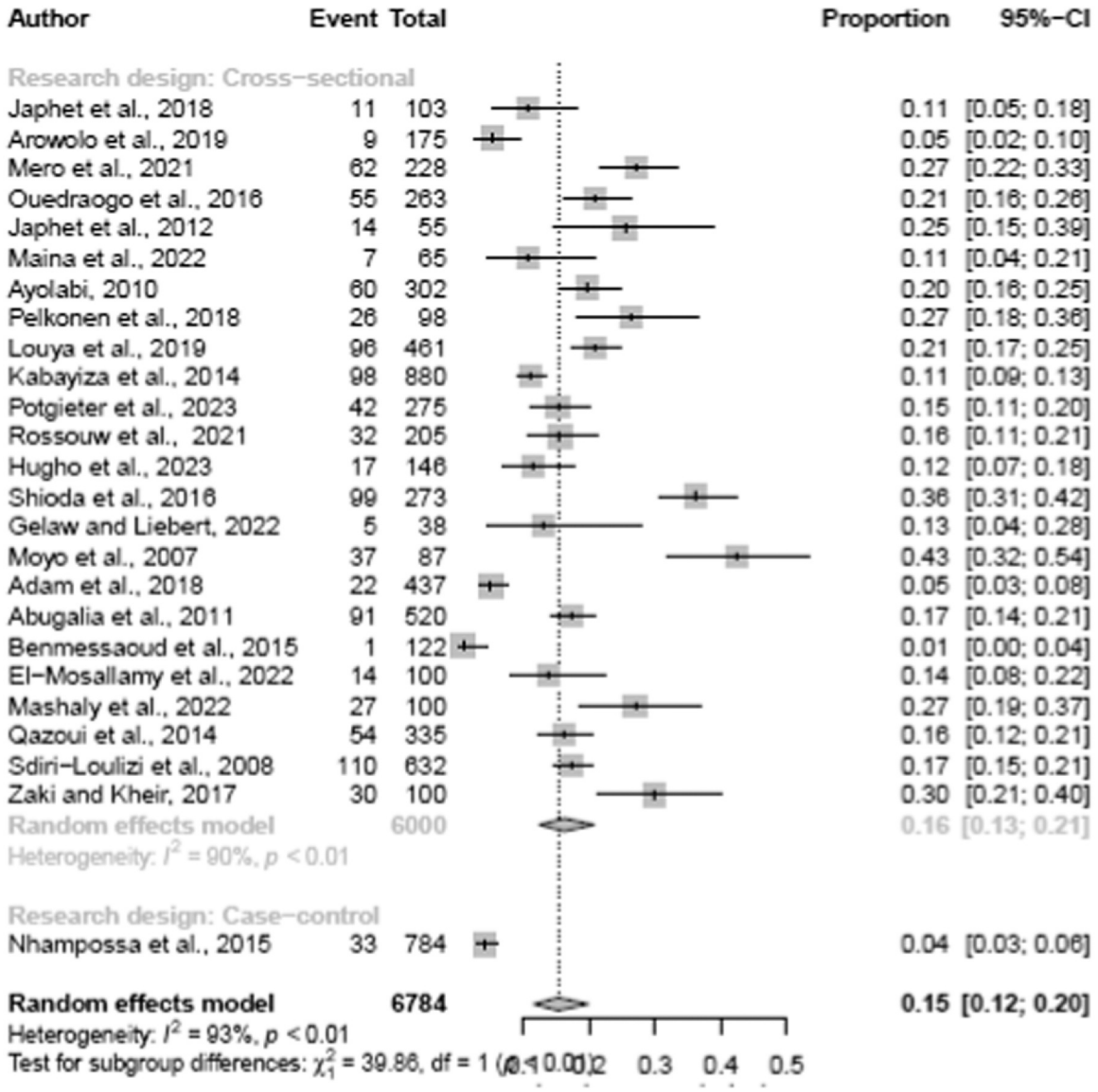

Fig. 4. Forest plot (stratified by research design) for the meta-analysis examining the overall prevalence of norovirus in Africa.

studies and the ages of subjects included in the review. Additionally, the analysis of norovirus genotype diversity revealed the GII.4 (79.3 %) predominance in acute diarrheal cases, corroborating the regional and global data which indicated the dominance of the genotype in acute gastroenteritis outbreaks and sporadic cases over the past two decades.[17,59,60] Characteristically, the GII.4 genotype has a high mutation rate, with new variants emerging every 2 to 3 years via epochal evolution.[51] Despite the comparability of GII.4 data with global prevalence rate, it is pertinent to say that most of the published studies reviewed in the study focused mainly on determining the genogroups of noroviruses of which there are several other types in Africa, where the predominance of GII.4 has been clearly demonstrated. Thus, the possibility of estimating the exact contribution of different genotypes of norovirus to acute gastroenteritis in the African pediatric population is far from being established.

Analysis by hospital settings showed that rotavirus was responsible for higher cases of childhood hospitalization (21–38 %) than norovirus (6–21 %), adenovirus (3–8 %), sapovirus (2–6 %), and astrovirus (1–8 %). This observation supports reports of Banyai et al.[51] who posited that rotavirus causes more severe gastroenteritis with a higher degree of dehydration in children than is caused by the other enteric viral pathogens. Our findings also suggest that the proportion of rotavirus infections detectable in diarrheic patients is more likely to increase with increasing disease severity requiring hospital admissions. The comparability of the estimated rotavirus hospitalization range in the study with a previously reported global rate of 35–40 % [51], singled out the virus as a common childhood enemy in different geographical settings. Worldwide, norovirus is associated with 11–17 % of emergency room or hospital cases,[62] corroborating findings in our study and equally suggesting lower severity of the virus as compared to rotavirus. The high rate of community-based norovirus cases as compared to the hospital-admitted cases and the 12–24 % rates in a similar setting previously reported for the world[62] further pinpoint the presence in the community of more individuals who may be suffering from a less severe disease not requiring medical attention. Unlike rotavirus, there was generally a decreasing trend in the prevalence of norovirus, sapovirus, and astrovirus-associated diarrheic infections from community to outpatient to inpatient groups, observations suggesting that these enteric viruses more commonly are associated with mild forms of

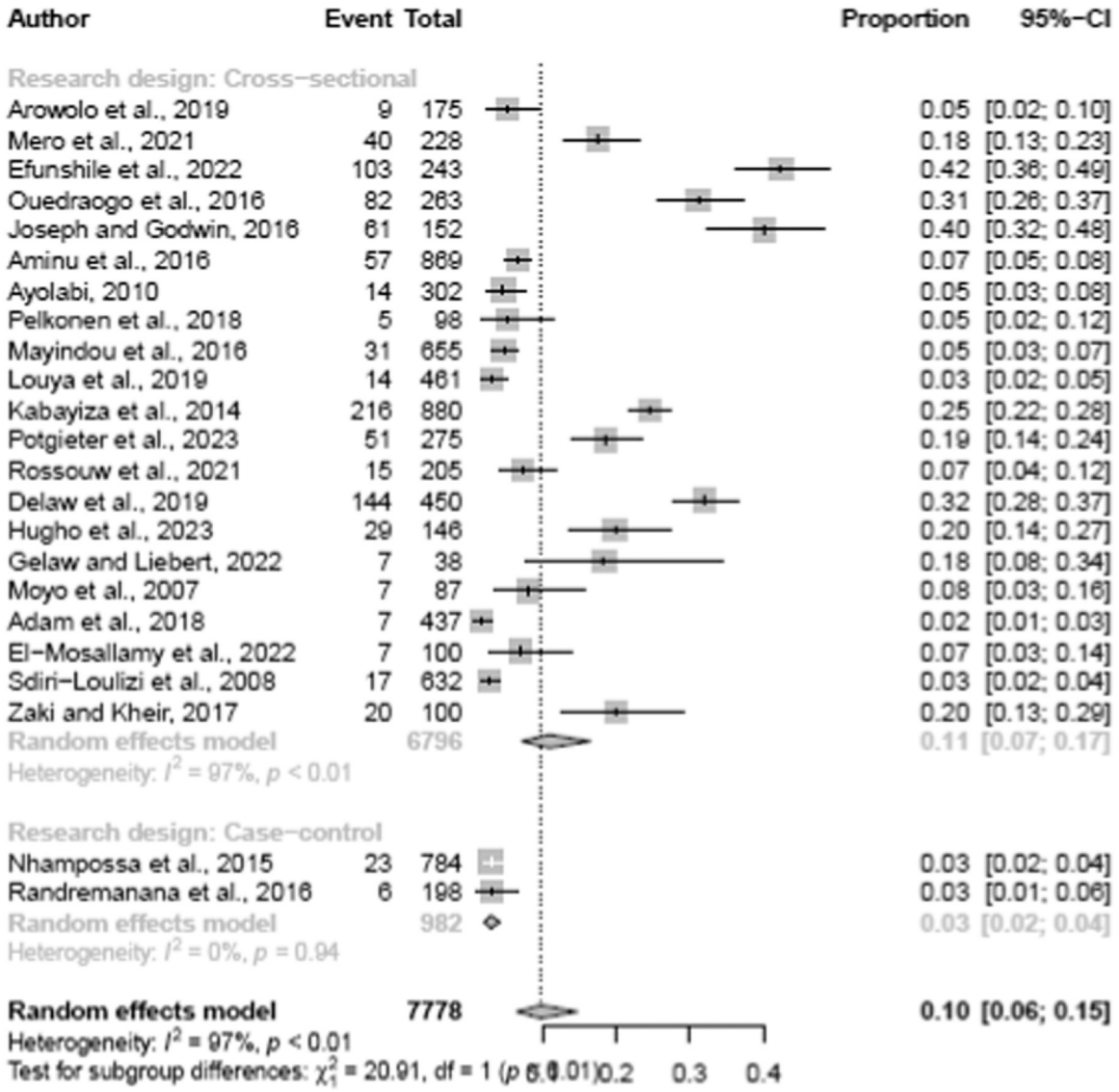

Fig. 5. Forest plot (stratified by research design) for the meta-analysis examining the overall prevalence of human adenovirus in Africa.

gastroenteritis. Even though norovirus proportionally contributes a greater share of infection to acute gastroenteritis in community and outpatient settings, disease outcomes such as hospitalization and death do arise, with approximately 70,000 and 800, respectively, annually in the US.[63]

In the current study, a human adenovirus pooled prevalence rate of 10 %, which ranged from 7 % to 16 % sub-geographically, suggests a moderate impact of the virus as an etiologic agent of acute gastroenteritis in Africa. Consistent with our findings, Alcala et al.[64] reported a prevalence of 11.5 % among children with acute gastroenteritis symptoms in Spain. On the contrary, lower (4.44 %) and higher (24.5 %) prevalence rates for human adenovirus have been reported in China[65] and Brazil,[66] respectively. The variations in epidemiological scenarios from different countries could be explained by the differences in socioeconomic parameters, PCR reaction primers, case definition, and molecular diagnostic efficiencies for enteric types F40/41.

The sapovirus, astrovirus, and aichivirus estimated pooled prevalence rates of 4.0 %, 4 %, and 2.3 % observed in the current study suggest a minor impact of these viruses as important drivers of severe gastroenteritis among children < 5 years in Africa. In the same age range, a worldwide review by Diaz-Valcarce et al.[67] reported a sapovirus prevalence of 4.4 %, which is similar to the prevalent rate estimated in the study. Further, Platts-Mills et al.[68] surveillance study covering 8 different low income-countries, identified sapovirus as the most frequent enteric viral pathogens among children with acute gastroenteritis, besides rotavirus, norovirus, adenovirus, or astrovirus. Even though the outcome of the Platts-Mills et al.[68] study included only a few sites in Africa, their findings of sapovirus predominance, which in this larger study, significantly drives childhood diarrhea highlight the potential emerging impact in diarrheal diseases and the tendency for dominance of this RNA virus in low-resource settings. Evidently, the rate of infection with astroviruses observed in the study has been corroborated by Olortegui et al.[69] and Stuempfig and Seroy[6] data which indicated astrovirus prevalence of 2 % to 9 % among children manifesting symptoms of diarrhea in ambulatory, clinical or hospital-based settings worldwide. Aichivirus, on the other hand, with the least attributable proportion across all geographical settings remained understudied in the area as only limited articles reported it. Although aichivirus prevalence observed in smaller studies may be enlightening, it is not generalizable. Therefore, improved surveillance for aichivirus in African countries may provide a more comprehensive understanding of the disease dynamics.

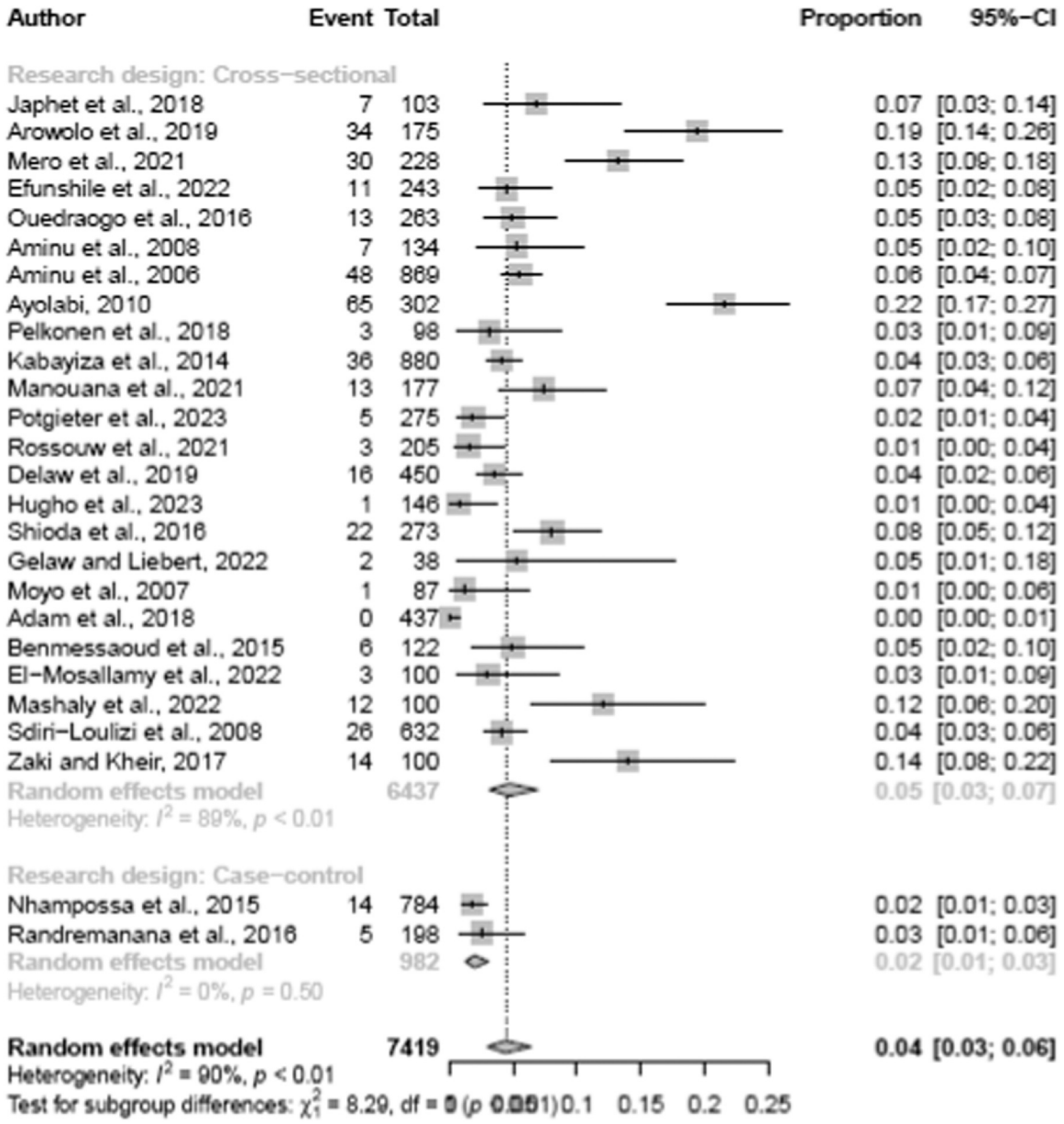

Fig. 6. Forest plot (stratified by research design) for the meta-analysis examining the overall prevalence of human astrovirus in Africa.

The current meta-analytic study has certain limitations. Firstly, only a few studies from the Central and Southern African regions met the criteria for inclusion, making it difficult to pinpoint the actual share of the diarrheic burden caused by individual viruses in multiple pathogen studies in those regions. Secondly, the use of different primer sets for enteric virus detection via polymerase chain reaction amplification could lead to differing results with respect to the reported viral enteropathogens in circulation. Thirdly, few studies failed to support the initial ELISA-based detection methods with the more sensitive PCR-based detection approach for all the samples during the entire study period. In such studies, data on the circulating genotypes, especially for rotavirus were not reported. Fourthly, some studies included in the review did not report on all the viral pathogens under review, making it difficult to evaluate the exact impact of those pathogens not reported. Finally, our search on the databases was limited to only studies reported in English, which may have resulted in the exclusion of studies published in local languages only.

In conclusion, rotavirus with a considerable number of healthcare visits and hospitalizations, is still the leading etiology of viral gastroenteritis among children under 5 years in Africa despite the widespread use of the vaccine. The rapidly emerging norovirus and adenovirus ranked as the 2nd and 3rd most important causes of diarrhea in African children, an observation pointing to the need for future studies to not only limit the focus to single pathogen detection but on all the epidemiologically relevant gastroenteritis pathogens. The high genotype diversity of the two leading viral pathogens in Africa highlights the need for continued surveillance of gastroenteritis viruses in the region with a view to providing relevant up-to-date epidemiological data that could guide policy-making processes for better management of preventive strategies such as vaccination. The findings from our study showed the introduction of affordable diagnosis for viral enteropathogens in our children's hospitals will improve patient care by reducing the unnecessary use of antibiotics.

Table 2
Subgroup analysis for comparison of enteropathogenic viral infections in African regions.

					Heterogeneity test	
Enteropathogenic viruses	Region	Number of studies	95 % CI	I %	Degree of freedom	p-value
Rotavirus	West Africa	11	0.37(0.21-0.57)	98	10	< 0.001
	Central Africa	5	0.32(0.23-0.43)	93	4	< 0.001
	Southern Africa	3	0.22(0.14-0.32)	94	2	< 0.001
	East Africa	5	0.28(0.14-0.49)	97	4	< 0.001
	North Africa	6	0.28(0.23-0.34)	83	5	< 0.001
	Overall	**30**	**0.31(0.24-0.39)**	**96**	**29**	**< 0.001**
Sapovirus	West Africa	4	0.03(0.41-0.12)	76	3	< 0.001
	Central Africa	3	0.06(0.02-0.16)	95	2	< 0.001
	Southern Africa	3	0.02(0.01-0.05)	76	2	< 0.001
	East Africa	3	0.06(0.03-0.11)	63	2	< 0.001
	North Africa	1	0.01(0.00-0.02)	-	0	< 0.001
	Overall	**14**	**0.04(0.02-0.06)**	**88**	**13**	**< 0.001**
Norovirus	West Africa	7	0.16(0.10-0.23)	84	6	< 0.001
	Central Africa	3	0.18(0.12-0.27)	94	2	< 0.001
	Southern Africa	3	0.10(0.05-0.19)	95	2	< 0.001
	East Africa	5	0.18(0.08-0.34)	97	4	< 0.001
	North Africa	7	0.15(0.08-0.26)	78	6	< 0.001
	Overall	**25**	**0.15(0.12-0.200**	**93**	**24**	**< 0.001**
Adenovirus	West Africa	7	0.16(0.08-0.30	98	6	< 0.001
	Central Africa	4	0.07(0.03-0.16)	98	3	< 0.001
	Southern Africa	3	0.07(0.03-0.17)	97	2	< 0.001
	East Africa	6	0.09(0.04-0.21)	96	5	< 0.001
	North Africa	3	0.07(0.03-0.18)	95	2	< 0.001
	Overall	**23**	**0.10(0.06-0.15)**	**97**	**22**	**< 0.001**
Astrovirus	West Africa	8	0.09(0.05-0.13)	93	7	< 0.001
	Central Africa	3	0.05(0.03-0.06)	50	2	< 0.001
	Southern Africa	3	0.02(0.01-0.03)	-	2	< 0.001
	East Africa	7	0.02(0.01-0.05)	52	6	< 0.001
	North Africa	5	0.07(0.04-0.11)	82	4	< 0.001
	Overall	**26**	**0.04(0.03-0.06)**	**90**	**25**	**< 0.001**

Note: The bold mentions the overall statistics show a significant heterogeneity between studies across subgroups based on the regions at p = 0.001.

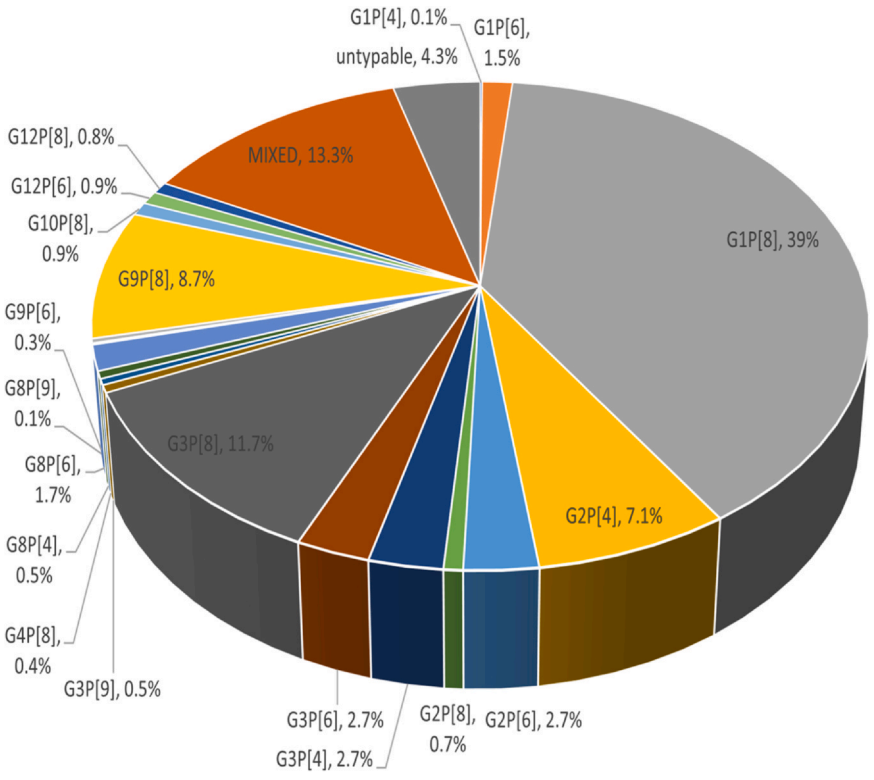

Fig. 7. Distribution of rotavirus G/P genotype combinations in diarrheal cases in Africa.

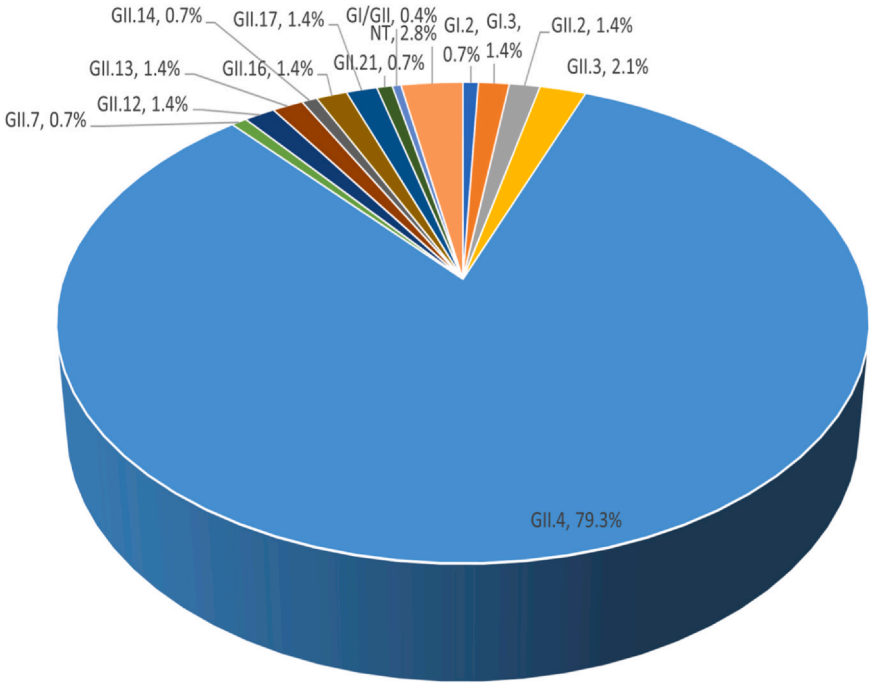

Fig. 8. Distribution of norovirus genotypes in diarrheal cases in Africa.

Author contributions

C.A.O. conceived of the study. C.A.O. developed the study protocol and carried out the literature review. S.O.S. and D.M.A. extracted the data. C.A.O. and C.K.M. performed the quality assessment. R.E.O. ad access to all obtained data, and conducted statistical analyses; and interpretation of results. All authors were involved in the original draft preparation, review, and editing of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Declaration of Competing Interest

Authors have no interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106169.

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