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Prevalence and Genetic Diversity of Human Norovirus Diarrhoea Among Children With Gastroenteritis in Africa: (Systematic Review and Meta-Analysis)

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Abstract

Background

Africa has the highest burden of norovirus associated gastroenteritis. This review aims to estimate norovirus prevalence and the distribution of circulating genogroups, genotypes and GII.4 variants among children under 5 years with acute gastroenteritis in Africa.

Methods

A literature search was conducted using PubMed, biomed search.com, Ovid search, Cochrane and Popline. The inclusion criteria were study duration of at least 2months and diagnosis by RT-PCR . The data retrieved from articles included in this review included prevalence, sample size, norovirus positives, genotypes and genogroups. Data were computed for meta-analysis to estimate the prevalence and genetic diversity of norovirus among Africans children with acute gastroenteritis.

Results

The literature search containing Norovirus and Africa using the above stated databases produced 170 published articles. Out of the searched

Human norovirus is associated with 18% (95% CI: 17-20%) of diarrhoeal diseases and is one of the major causes of acute gastroenteritis in children worldwide. Noroviruses account for about one fifth of acute gastroenteritis cases in the world . Norovirus is an enteric virus known to play an important role in acute gastroenteritis in children. Noroviruses have been associated with the hospitalisation of children with acute gastroenteritis with the highest burden in children under five years of age.

Noroviruses are small non-enveloped single stranded RNA viruses in the calciviridae family. It has a genome size of about 7.5kb, organised into three open reading frames (ORF) ORF1 to ORF3. The genome is highly liable to mutation and recombination which causes emergence of new strains and high genetic diversity in noroviruses . Noroviruses have different strains whose genome can easily recombine that could lead to diverse mixed infections. .

Noroviruses are classified into six genogroups (GI-GVI) and genogroups GI, GII and GIV are known to infect humans. Among the genogroups that are known to infect humans, GII is the most predominant genogroup and also causes more than 70 articles, 33 articles from 15 countries met the inclusion criteria. Studies conducted in countries that did not meet the inclusion criteria were included in the discussion. The majority of the studies included in this review mainly focused on children less than 5 years of age hospitalized with acute gastroenteritis. Genotypic data from 15 countries revealed 31 genotypes and 13 GII.4 variants with Sydney 2012 as the most common circulating variant across the continent. Norovirus genogroup 2 (GII) and norovirus genotype GII.4 had remained the most dominant genogroup and genotype detected in the majority of studies conducted.

Conclusion

Norovirus genogroup 2 (GII), genotype GII.4 and Sydney 2012 GII.4 variant are commonly associated with childhood diarrhea in Africa however, only few studies were conducted within the region with limited data. The analysis revealed norovirus genetic diversity among genogroups, genotypes and variants. Norovirus surveillance should be implemented in Africa to assess the prevalence and genetic diversity of human noroviruses in children with acute gastroenteritis.

Keyword: Norovirus; Genogroup; Genotype; Genetic diversity, Africa; Gastroenteritis; Meta-analysis

Introduction

Each of the norovirus genogroups are further divided into genotypes based on the capsid sequences (. Norovirus capsid is a protein that contain a major and a minor structural proteins that surround the viral RNA and a putative neutralisation sites that interacts with histo-blood group antigens (HBGA) .

Globally the GII.4 genotype is associated with the majority of norovirus outbreaks and GII.4 variants are also associated with the majority of norovirus gastroenteritis since in the 1990's [1].

In developing countries, acute gastroenteritis is a public health concern and it continues to be an important cause of morbidity and mortality. In Africa, acute gastroenteritis has remained an important cause of mortality and morbidity among children under five years of age and viral agents tend to be the major etiology of acute gastroenteritis.

Norovirus is a common pathogen in Africa found in children with acute gastroenteritis and healthy children (symptomatic and asymptomatic). However the burden of norovirus associated with acute gastroenteritis in Africa has not been fully characterised [2].

Norovirus is detected by standardised laboratory techniques such as Enzyme Immunoassay (EIA), Reverse Transcriptase polymerase Chain Reaction (RT-PCR) and Quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT_PCR). Few norovirus studies have been conducted in Africa and they vary widely in terms of diagnostic techniques implemented, study duration, inclusion of asymptomatic controls, study population and sample size [3].

In many African countries the prevalence and genetic diversity of norovirus is still unknown, although few studies have indicated widespread prevalence of the pathogen (WHO 2015). Global Enteric Multicenter Study (GEMS), A 3-year prospective, age-stratified matched case-control study of moderate to severe diarrhea in children aged 0-59 months conducted in sub-Saharan Africa and South Asia to identify the etiology and population-based burden of diarrhea in children with acute moderate-to-severe diarrhea (MSD) [4].

The results have shown that norovirus has a smaller distribution but was significantly associated with diarrhea in certain age stratum . The reanalysis of the GEMS dataset with molecular detection techniques by further showed that norovirus is associated with diarrhea [5].

Reports on norovirus prevalence in Africa are always under estimated due to the limited use of molecular diagnostic tools and lack of norovirus surveillance in Africa [6]. Moreover, different assays using specific primers are found to have different sensitivities for different norovirus genotypes [7].

Despite of all the interventions taken to control acute gastroenteritis, it remains as the second leading cause of death among children less than 5 years of age [8] . Presently there is no licensed norovirus vaccine and antivirals for the treatment of norovirus associated acute gastroenteritis. Post introduction of the rotavirus vaccine, norovirus is becoming the major cause of viral gastroenteritis in children under 5 years [9].

This review provides a summary of studies conducted in Africa regions to assess the role of human noroviruses infections in association to diarrhoeal diseases, in addition to other studies that estimates norovirus infections in gastroenteritis cases in Africa [10]. This review reports on the norovirus prevalence, circulating genogroups and genotypes, predominant genotypes and GII.4 variants in Africa [11].

Material and methods

A systematic literature search was performed on articles that investigated norovirus infections in Africa from 2006-2018 [12]. The methods of this systematic review were set according to the 2015 preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) [13] .

Article search strategy and selection criteria

A systematic search was performed to search and select published articles from 2006-2018 using PubMed, Ovid, Biomedsearch.com™, Cochrane and Popline [14]. The searched terms used were: "norovirus", "Norwalk-like virus", "stomach viruses", "prevalence", "Africa", "genetic diversity", "norovirus epidemiology" and "genetic variation". Articles were assessed and selected based on the following inclusion criteria:

Study participants were children 5 years of age and below, mixed age (under 5years and above 5years mixed) studies that used RT-PCR for detection, sample size of at least 51 samples, study performed in Africa and study duration of at least 2months [15]. Articles that did not have the total number of samples screened, total positives, prevalence, dominant genogroups and genotypes were excluded. Articles that have participants more than 5 years old were also included in this review [16].

Data extraction

The following information were obtained from articles that were selected for this review: Author, year of publication, country, study period and duration, total number of samples, total number of samples tested positive, prevalence percentage, peak periods, predominant genogroups and genotypes, detection methods, GII.4 variants and type of study [17].

Data from studies that included the detection of noroviruses and other enteric pathogens like rotavirus, astrovirus, adenovirus were extracted and analyzed so as not to introduce bias against studies that did not test samples for other pathogens [18].

For studies that tested for only norovirus among participants who were tested negative for other pathogens, we use the total sample size of acute gastroenteritis recruited in the study [19].

Data were stratified by age and settings. For age, we grouped studies into two categories: children at 5years and younger than 5 years, older than 5 years and mixed (studies that did not report age stratified at age 5 years) [20]. We restricted the main analyses to these two age groups because of inconsistencies in age stratification and inclusion criteria between studies [21].

Studies that included inpatients, outpatients in hospitals, primary care clinics, dispensaries and community studies were also included in the review. Community based studies capture full range of disease severity, however because most individuals with norovirus do not seek care and care seeking is associated with severity [22].

We assume that community cases of acute gastroenteritis were on average less severe than individuals with acute gastroenteritis who were medically attended, because all those with severe diarrhea usually report to the health facility for treatment [23]. Different norovirus Gll.4 variants have been detected in some African countries [24].

We hypothesized that Gll.4 variants in Europe and Asia might be in circulation in many parts of Africa and increase the prevalence of Gll. 4 new variants [25]. We extracted the Gll.4 variants in studies included in this review to determine the common Gll.4 variants in Africa and to see the prevalent of Gll.4 variants in Africa [26].

Statistical Analysis

The data organized in excel were directly imported to Stata (version 14) for the calculation of pooled random effect and estimated prevalence rates [27]. The Stata package was also used to calculated heterogeneity as an estimate of variance between studies and to generate forest plots [28].

Heterogeneity was assessed by observing the forest plots for variation in results from various studies. To determine the norovirus prevalence Stata was used to calculate the pooled effect of the various studies [29]. Genetic diversity was calculated by estimating the pooled prevalence of Gl, Gll and GlV and the pooled individual genotypes detected in the various studies [30]. The pooled Gll.4 variants was calculated to observe the different Gll.4 variants that circulated in Africa during the period 2006-2018 [31].

Results

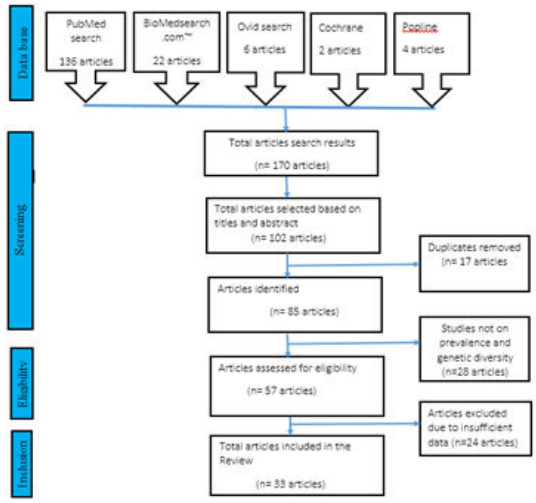

Figure 1: Literature search and article selection flowchart. The databases PubMed, Biomed search.com, Ovid Search, Cochrane and Popline were used as search tools. Articles wrere then screened for eligibility and inclusion criteria.

We performed a literature search using 5 electronic databases and we selected 170 articles. We excluded 68 articles that do not have the variables of total patients, Nov positives, detection method, genogroups, genotypes and predominant genotypes through the assessment of their titles, abstracts and results [32]. We removed 17 articles due to the reporting of the same information. We assessed and identified 85 full-text articles. From these articles 28 articles did not report on norovirus prevalence or genetic diversity in Africa. We assessed and identified 57 articles for eligibility [33]. From these articles 24 articles were excluded due to insufficient data [34]. The final database consisted of 33 articles from 15 countries with South Africa, Tunisia and Burkina Faso with more studies than the other countries included in the review. From the articles included in the review 28 studies use RT-PCR norovirus detection method, 3 studies used both EIA and RT-PCR methods and only two studies used EIA diagnostic method. The summary of selected studies on human norovirus prevalence and genetic diversity in Africa (Table 1) reveals 33 studies of acute gastroenteritis. These studies included 20 Hospital-based case studies (HBC), 5 Hospital and community based cases and controls studies (HCBCC), 5 hospital based cases and controls studies (HBCC) and 3 community based cases studies (CBC) [35].

No	Country	Study Duration	Age group	Number of Patients	Positives	Peak Periods	Norovirus Prevalence	Detection methods	Genogroups/ genotypes	Predominant genotypes	G11.4 variants	Study Type	References	Year of Publication
1	Ghana	1year	<15mths	82	13	May-June	15.90%	Reverse Transcriptase Polymerase Chain Reaction	GII(76.9%) n=10 GI (23.1%) n=3 GI. 5(n=2) GI.1 (n=1)	GII.4 (60%) n=6	N/A	HBC	Armah	2016

								(RT-PCR)	Noguchi-5/2000/GH Noguchi-6/2000/GH Noguchi-8/2000/GH Ghana-1/2000/GH Ghana-2/2000/GH Accra/2000/GH					
2	Ghana	1yr 6mths	≤13yrs	1234	139	May-August	11.30%	RT-PCR	No genotyping	N/A	N/A	HBCC	Krumkamp	2015
3	Libya	1year	<5years	520	91	May-August	17.50%	EIA&RT-PCR	GI (n=1)GII (n=90) no genotypes	GII.4 (n=26)		HBC	Abugalia	2011
4	Burkinaf aso	1year	<5years	433	79	Nov-May &June-Oct.	18.20%	RT-PCR	N/A	GII.4 (n=14)	N/A	HBC	Ouedraogo	2017
5	Burkinaf aso	1year	<5years	313	58	Nov-Feb	20.90%	RT-PCR	GI,(n=7) GII(n=51) GI.I (n=1) GI.3 (n=2) GII.4 (n=14) GII.16 (n=2) GII.2 (n=1) GII.c (n=3)	GII.4 (n=14)	2012 Sydney 2014 Hunter	HBCC	Ouedraogo	2016
6	Burkinaf aso	2mths	<11years	418	93	N/A	22.20%	RT-PCR	GI (n=37) GII (n=44) GI.2 (n=1) GI.3 (n=2) GI.7 (n=1) GII.4 (n=2) GII.12 (n=2) GII.8 (n=1)	GII/GI.d(G.3)	N/A	HBCC	Huynen	2013

									GII.7 (n=1)					
7	Morocco	1year	<5years	335	54	June	16.10%	RT-PCR	GI (n=12) GII (n=42) GII.4 (n=27) GII.3 (n=2) GII.16 (n=1) GII.13 (n=2) GII.17 (n=1)	GII.4 (27, 81.8%)	GII.4 Variant Sydney 2012	HBC	Qazoui	2014
8	Tunisia	1year	<6years	114	42	June	42/114(36.8%)	RT-PCR	GII.3 (n=29) GII.1 (n=6) GII.4 (n=5) GII.7 (n=2)	GII.3	Variant 2012 and variant 2010	HBC	Belliot	2015
9	Tunisia	4years	<12years	788	128	June-Dec	16.20%	RT-PCR	GII.4 (n=83) GI.2 (n=10) GI.4 (n=1) GII.I (n=5) GII.8 (n=4) GII.14 (n=4) GIIb/GII.2 (n=11) GIIb/GII.3 (n=24) GI (n=11) GII (n=103)	GII.4	2004 variant Hunter	HBC	Loulizi	2008
10	Tunisia	3years	<13years	407	38	winter	9.30%	Rt-PCR	GIIb/II.3 (n=15) GII.4 (n=12) G1b/1.6(n=5) GII.6 (n=3) GII.8 (n=1) GI.2 (n=1) GII (n=32) GI (n=6)	GII.4 and GII.b	2006b and Hunter 2004	HBC	Zaafrane	2013

11	Tanzania	1year	<5years	270	37	N/A	13.70%	IDEIA, RT-PCR	No genotyping data	N/A	N/A	HBC	Moyo	2007
12	Ethiopia	4mths	All ages	213	54	N/A	25.30%	Rt-PCR	GI,(n=4) GII, (n=17) GIV(n=1) GII. 4(n=5) GII. 12(n=4) GII. 17(n=8) GI. 4(n=1) GI. 8(n=1) 5595-ETH 5379-ETH GI. 5(n=2)	GII.17	Sydney 2012	HBC	Berthe	2016
13	Kenya	3Year 10mths	All ages	858	244	Nov/ April	28.40%	RT-PCR	GI (n=120) GII (n=214) No genotype data	GII	GII.4 variant	HBC	Kabue	2016
											Name of variant not given			
14	Kenya	4years	<5years	787	14	N/A	1.80%	RT-PCR	GII (n=14)	GII	N/A	HBCc	Liu	2016
15	South Africa	9mths	<5years	303	122	October	40.20%	RT-PCR	GI (n=18) GII (n=71) GII.4 (n=2) GII.14 (n=1) GI.4 (n=2) GI.5 (n=1)	GII	GII.4 variant Name of variant not given	HBC	Kabue	2016
16	South Africa	3years	<5years	3103	452	Nov	15%	RT-PCR	GI (n=94) GII (n=377) GII. 1(n=1) GII.4 (n=2) GII.6 (n=1)	GII	N/A	HBC	Page	2017

									GII.7 (n=1) GII. 10(n=1) GII. 13(n=1) GII14(n=1) GII. 16(n=1) GII. 2(n=1) GII. 3(n=1) GII. 12(n=1) GII. 17(n=1)					
17	South Africa	5years	<5years	5950	837	N/A	14.10%	RT-PCR	GI (n=54) GII (n=350) GI.2 (n=1) GI.3 (n=2) GI.6 (n=1) GI.7 (n=2) GI.5 (n=1) GII.4 (n=32) GII.3 (n=8) GII.2 (n=3) GII.12 (n=2) GII.13 (n=1)	GII.4 & GII.3	Osaka 2007,New Orleans 2009, Sydney 2012	HBC	Mans	2015
18	South Africa	16mths	Waste water	51	35	N/A	68%	RT-PCR	G1 (n=15) G11(n=32) GI.I (n=6) GI.3 (n=2) GI.4 (n=3) GI.8 (n=4) GII.2 (n=12) GII.4 (n=13)	GII.4	N/A	ENV	Murray	2013

									GII.17 (n=9)					
19	South Africa	1year	≤13 years	245	35	April-August	14.30%	RT-PCR	GII (n=31) GI (n=4) GI. 2(n=1) GI. 7(n=1) GI.8 (n=1) GII.4 (n=4) GII.6 (n=3) GII.1 (n=1)	GII.4	GII.4 2008 GII.4 2004	HBC	Mans	2010
20	Zambia	1year 4mths	<5years	454	52	Sept	11.50%	Rt-PCR	GII(32 GI (12 GII.p2(n =4) GI.p7 (n=6) GI.p2 (n=2) GI.p5 (n=1) GII.p4 (n=19) GII.pe (n=4)	GII.4	N/A	HBC	Howard	2017
21	Nigeria	8mths	<5years	55	14	August	25.50%	RT-PCR	GI (n=2) GII (n=13) GI.3 (n=2)	GII	N/A	CBC	Japhet	2012
22	Nigeria	7mths	<5years	188	61	Feb/April	32.50%	EIA & RT-PCR	GI (n=5) GII (n=8) GI+GII (n=3)	GII	N/A	HBCC	Ayolabi	2010
23	Angola	4mths	<5years	334	58	June-October	17.40%	RT-PCR	GII.7 (n=6) GII.I (n=3) GII.2 (n=1) GII.3 (n=3) GII.9 (n=1) GII.14 (n=2) GII.16 (n=1) GII[b] (n=9)	GII.4	New Orleans 2009 Sydney 2012	HBC	Esteves	2018

									GI.5 (n=1) GI.[b] (n=4) GI (n=12) GII (n=47) GII.4 (n=12) GII.6 (n=9) GI.3 (n=7)					
24	Cameroon	1year	1-69 years	2484	100	June-Agust	(1-16%)	RT-PCR	GI (n=45) GII (n=55) No genotyping data	GII	N/A	CBC	Ayukekbong	2013
25	Malawi	10years	<5years	1941	220	March	11.30%	Rt-PCR	GII.4 (n=67) GII.2 (n=6) GII.6 (n=4) GII.12 (n=4) GI. 5 (n=2) GI.7 (n=9) GI. 14 (n=2) GII (n=96) GI (n=19) GI/GII (n=2)	GII.4	Farmington Hill,Yerseke s38, Camberwell	HBC	Gomara	2013
26	Botswana	2yrs5mths	<5yrs	484	45	Dec-march	9.30%	RT-PCR	GII.4 (n=23) GII.2 (n=3) GII.6 (n=1) GII.12 (n=3) GI.9 (n=2) GII.10 (n=1) GII (n=31) GI (n=2)	GII.4	Sydney 2012	HBC	Makhaola	2018
27	Central African Republic	2yrs	<5yrs	666	47	May-Oct & Nov-April	7%	EIA	N/A	N/A	N/A	HCBCC	Breurec	2016
28	Uganda	7 years	<6 yrs	797	1yr=611	N/A	1yr=76.6 %	ELISA	GII	GI.I and GII.4	N/A	CBC	Thorne	2018

					2yr=753		2yrs=94.5%							
29	Sudan	8 months	<5years	437	12	dry season	2.70%	RT-PCR	GI (n=4)	GII	N/A	HBC	Adam	2018
30	Gambia	4years	<5years	685	16		2.30%	RT-PCR	GII (n=16)	GII	N/A	HCBCC	Liu	2016
31	Mali	4years	<5years	834	17		2.00%	RT-PCR	GII (n=17)	GII	N/A	HCBCC	Liu	2016
32	Mozambique	4years	<5years	484	10		2.10%	RT-PCR	GII (n=10)	GII	N/A	HCBCC	Liu	2016
33	Egypt	1year	<18years	230	31		13.40%	RT-PCR	GI (n=9) GII (n=22) GI.I (n=3) GI. 9(n=3) GII.4 (n=14) GII. 15(n=1) GI. 3(n=1) GI.4 (n=1) GI. 5(n=1) GII.3 (n=4) GIIb(n=3)		Bristol, hunter Sakai Cairo 2006a 2006b	HCBCC	Belliot	2009

Table 1 : Summary of studies for the detection and genotyping of human norovirus from different African countries (2006-2018).

The number of articles included in this review is relatively low, which is a reflection of the limited number studies on noroviruses infections in Africa. Most of the data represented patients less than 5 years and few mixed ages. Most studies are hospital-based cases 15% (95% CI: 0.12-0.18). A pooled meta-analysis of all the 33 articles revealed an estimated norovirus prevalence among 26,497 samples with 3859 positive samples in mixed ages and ages less than 5 years. The pooled prevalence for all the studies included in this analysis was 16% (95%CI: 0.12-0.21) among mixed ages and 12% (95% CI: 0.09-0.16) in children less than 5 years. The P-value was <0.01 and test for heterogeneity is high in both mixed ages and those <5 years of age as shown in forest plot (Fig1 and 2). In this analysis we found no significant difference in prevalence amongst mixed age group and <5 years age group (I^2=98.9% P<0.01 and I^2=97.6% P<0.01 respectively).

For norovirus genotype diversity, the genotype data from 15 African countries (fig 8) were analysed to determine the most prevalent norovirus genogroups circulating in Africa and the distribution of norovirus genotypes and GII.4 variants in Africa. The pooled analysis of norovirus genogroups in this review revealed a higher prevalence of norovirus genogroup 2 (GII) 80% (95% CI: 0.75-0.85) in mixed age group with 86% I squared (variation in the estimated prevalence attributable to heterogeneity). The GII prevalence in <5 years age group was 84% (95% CI: 0.79-0.89) with I squared 77% (Fig1 and 2). The GII prevalence is higher than GI 20% (95% CI: 0.15-0.25) in the mixed age group with I squared 86%. The GI prevalence in <5 years group was 16% (95% CI: 0.11-0.21) with I squared 77%. Although the prevalence of GII and GI are different in the mixed age group and the <5 yeas age group, however the I squared of both GI and GII are the same.

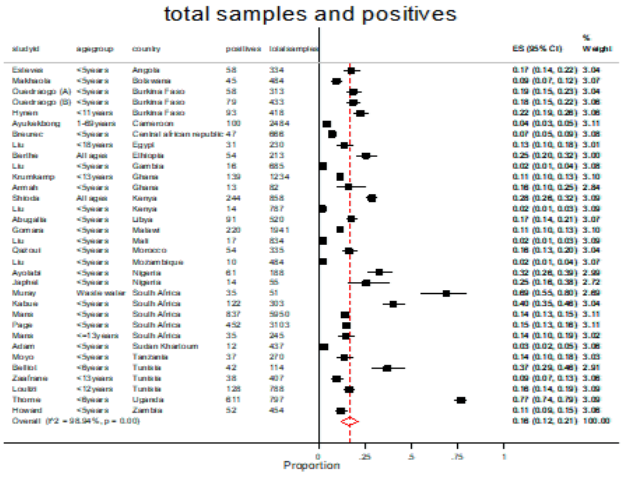

Figure 2: Forest plot for the prevalence of human norovirus by proportions of samples positive for norovirus in mixed age group.

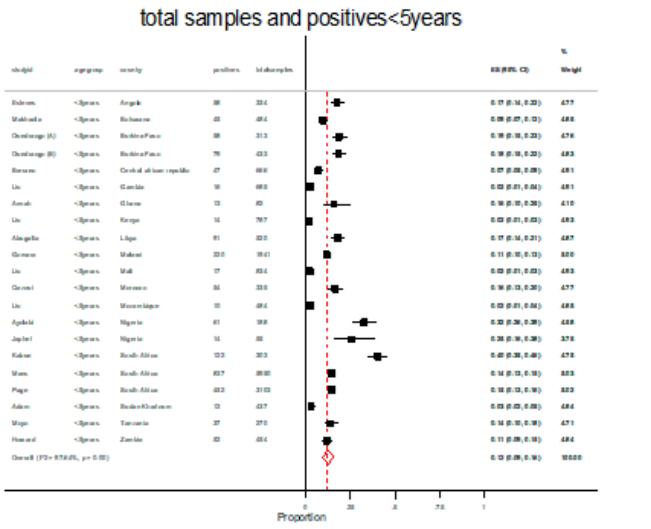

Figure 3: Forest plot for the prevalence of human norovirus by proportions of samples positive for norovirus in <5 years age group from 21 articles showing the estimated percentages and 95% confidence interval of each study With the Overall percentage and I squared (I^2) .

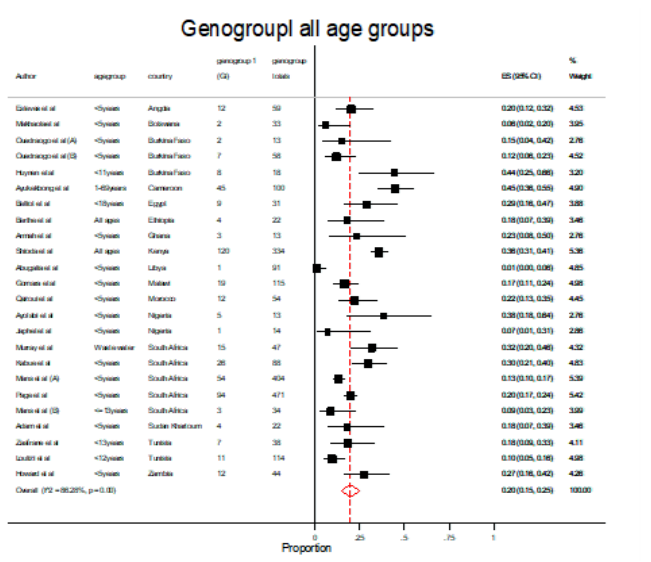

Figure 4: Forest plot for the prevalence of human norovirus by proportions of samples positive for norovirus (Gl) in all age groups.

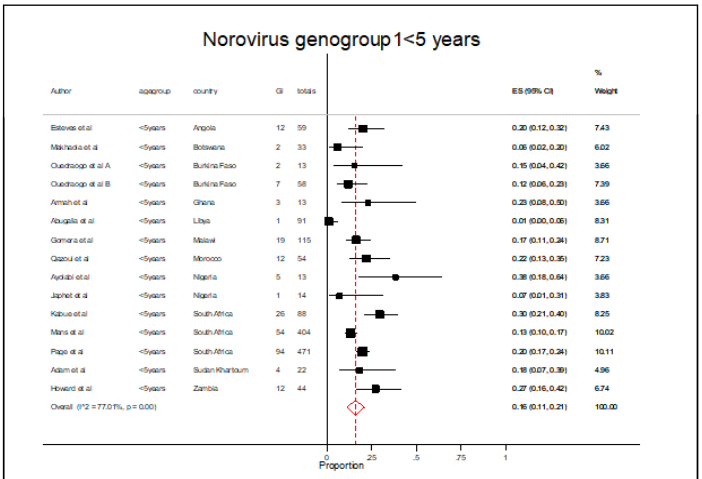

Figure 5: Norovirus genogroup 1 (Gl) among children <5 years of age showing the individual study percentages, overall percentages and I squared percentages.

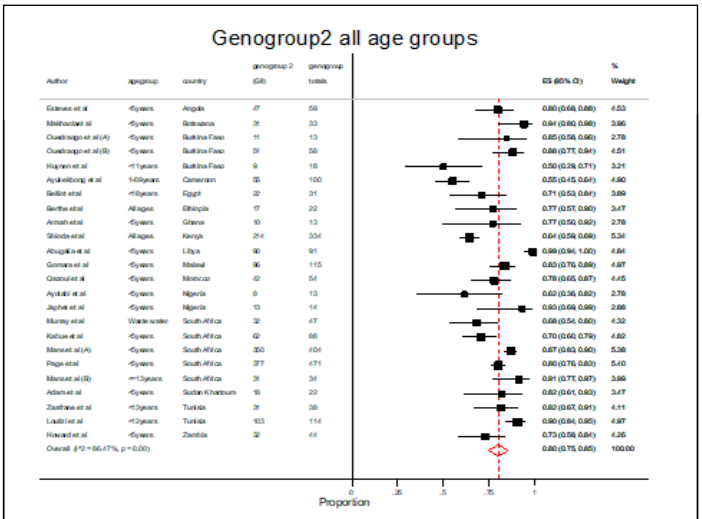

Figure 6: Forest plot for the prevalence of human norovirus by proportions of samples positive for norovirus (Gll) in mixed age group.

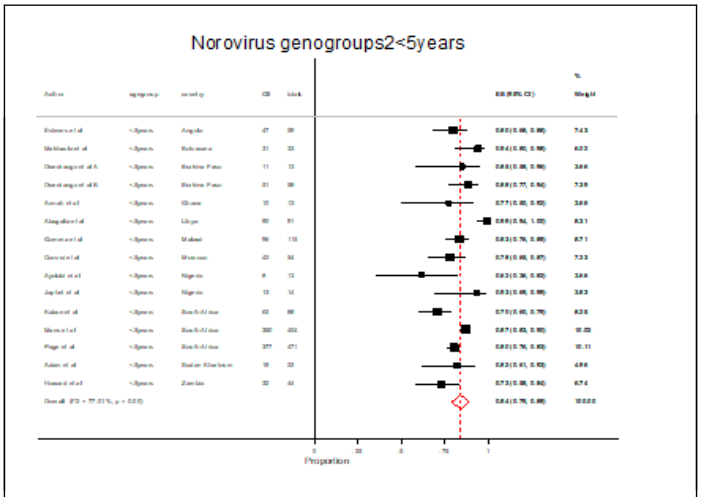

Figure7: Forest plot for the prevalence of human norovirus by proportions of samples positive for norovirus (GII) in <5 years age group.

GII overall represented 80% (95% CI: 0.75-0.85) as the most predominant genogroup and GI 20% (95% CI: 0.15-0.25) from combined data of all the studies that conducted genotyping. GII has been the most predominant genogroup across all the studies and in both age groups included in this review (fig 3 and 4). When analysis was restricted to studies that included only community based cases or hospital and community based cases and controls, or hospital based cases, or hospital based cases and controls in the age group less than 5 years both the pooled overall I squared and the estimated prevalence did not markedly change, (97.64%,p-0.00, and 12% (95% CI: 0.09-0.27 respectively). The analysis of individual studies have shown the predominance of GII across all the studies included in this review (fig 7 and 8).

Figure 8: The prevalence of human norovirus GI and GII from 21 studies conducted in 15 African countries.

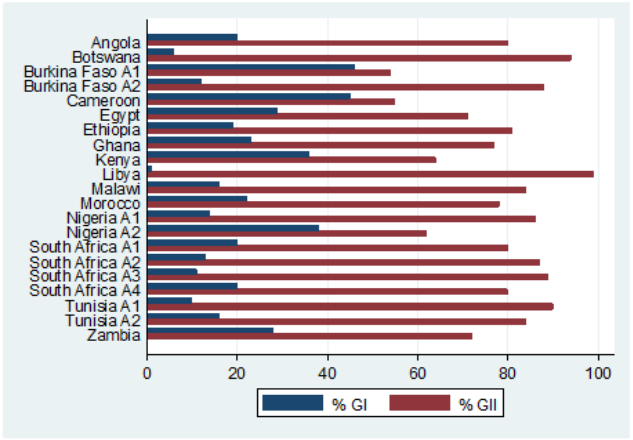

Figure 9: The prevalence of Human norovirus genogroup 1 (GI) and genogroup 2 (GII) per study conducted in 15 different African countries.

All the studies that performed genotyping revealed the circulation of GI genotypes and GII genotypes. The analysis showed the circulation of 12 GI genotypes and 20 GII genotypes in 9 African countries included in this review. Among all the genotypes from GI and GII included in this analysis, GII.4 genotypes presented the dominant variants followed by GII.3 genotype during the period reviewed (fig 9).

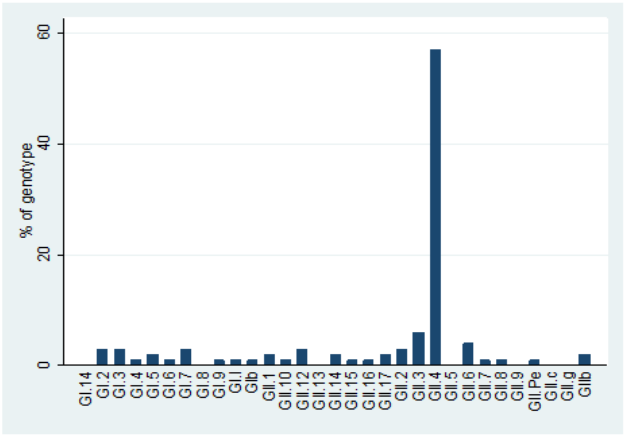

Figure 10: Prevalence of norovirus genotypes genotyped by various studies from the proportions of samples positive for norovirus.

GII.4 variants were mostly seen in studies with GII.4 as the predominant genotype with variant Sydney 2012 as the most widely circulating variant in Africa according to the genotyped data from the

studies reviewed and the study period (fig 10).

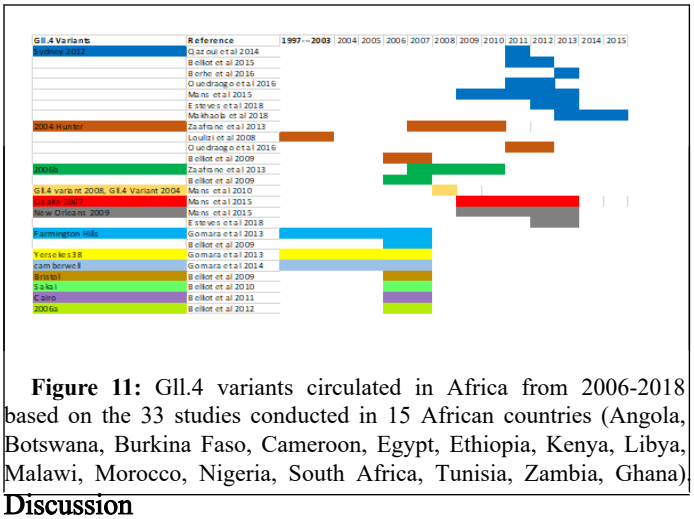

Figure 11: Gll.4 variants circulated in Africa from 2006-2018 based on the 33 studies conducted in 15 African countries (Angola, Botswana, Burkina Faso, Cameroon, Egypt, Ethiopia, Kenya, Libya, Malawi, Morocco, Nigeria, South Africa, Tunisia, Zambia, Ghana).

Discussion

This review and meta-analysis provides a summary of human norovirus detection and genotyping studies in different African countries from 2006-2018. The analysis demonstrated huge diversity of human norovirus genotypes with 31 genotypes belonging to human norovirus genogroups 1 and 2 as well as 13 variants of the Gll.4 genogroup. This trend of widespread diversity has been noted in other studies conducted in Brazil, China, India and Sweden. The results of the analysis on human norovirus prevalence among all cases of gastroenteritis (16%) is consistent with the updated estimate of global prevalence of norovirus (18% (95% CL: 17-20) in all cases of acute gastroenteritis . We confirm the genetic diversity in norovirus Gl and Gll genogroups and genotypes observed in other studies conducted in Africa.

The summary of the studies included in this review confirms the predominance of Gll as the most predominant human norovirus genogroup associated with acute gastroenteritis which is in line numerous other studies . Genotype data from 24 studies done in 15 African countries were analyzed to determine the circulating norovirus genogroups, genotypes and Gll.4 variants in Africa (Fig 10 and the distribution of the genotypes and the most predominant genotype in Africa. This is consistent with the review on the epidemiology of norovirus in Africa 509/832 NoV Gll. Our analysis confirms the observation that genotypes Gll.4 as the most frequently genotype characterized in Africa but showed Nov Gll.3 as the second genotype widely reported in Africa instead of Gl.3 as the second widely reported genotype. Our analyses has shown the circulation of 13 variants with Sydney 2012 and Hunter 2004 as the two common variants found in many of the studies with Sydney 2002as the most predominant variant in Africa from 2005-2015

In China the novel Gll.17 strain surpassed Gll.4 as the most predominant genotype causing norovirus gastroenteritis outbreaks in 2014/2015 . This shows that noroviruses are dynamic and rapidly evolving to the extent that the predominant genotypes can be replaced by other genotypes. The original Gll.17 strain had been detected in various parts of Africa in gastroenteritis cases, but recently the novel Gll.17 strain has been reported in Morocco . Due to limited norovirus studies conducted in Africa and the lack of norovirus surveillance network, it is unclear whether the novel Gll.17 norovirus strain is under-reported and may emerged as the next predominant strain.

Conclusion

The findings from this systematic review and meta-analysis has shown that norovirus is one of the important pathogens detected among children with diarrhoea in Africa. Two noroviruses genogroups (Gl and Gll) are the major causes of acute gastroenteritis associated with norovirus in Africa including different norovirus genotypes and variants. The analysis has shown norovirus Gll as the most predominant norovirus genogroup and Gll.4 the predominant genotype in Africa. Moreover, 13 variant strains have also circulated during the period reviewed with Sydney 2012 as the most widely distributed variant across the continent. In Africa only few studies on diarrheal diseases includes norovirus, this may be likely due to Diagnostic challenges for the detection of the virus. Therefore, results of this analysis would encourage the establishment of norovirus surveillance network in Africa to better assess the prevalence, mortality and genetic diversity of norovirus genogroups, genotypes and variants in Africa. The Africa rotavirus surveillance network should be utilized to implement Africa norovirus surveillance network across all African countries to measure the role of norovirus in acute gastroenteritis and norovirus genetic diversity among African children especially those under 5 years of age.

The estimates for the prevalence and genetic diversity of norovirus infection from this review could be used in the development of the data on the burden of norovirus gastroenteritis in Africa. More studies on diarrheal diseases e.g GEMS (Liu et al 2016) that report on the prevalence of noroviruses are needed.

This systematic review and meta-analysis has some important limitations. Age grouping was highly variable in the articles reviewed and this has made it difficult to categorize the studies into age categories. We restricted ourselves to <5 years age group and mixed age group. Only few studies reported data for mixed age group (<5 years and above 5 years). Although the review included 33 studies conducted in Africa, still there is a clear data gap for norovirus prevalence and genetic diversity in Africa. Therefore, quality network on norovirus surveillance is crucial in increasing studies on norovirus and improving the data for the true representation for the burden of norovirus disease in Africa. The heterogeneity of our meta-analysis for all the studies was 86% for all the ages and 77% for studies with ages <5years. This was not surprising because the studies included in this analysis are different in many ways. The studies were conducted in different settings, have different aims and objectives, have used different age groups, duration of the studies differ and have use different study types. The high heterogeneity is a reflection of the different results obtained from the different studies. The range of prevalence between individual studies is also wide among studies on mixed ages and studies on <5 years and below (02%-77%nand 02%-40% respectively). We also observed two outliers in the mixed aged group with a prevalence of 77% and 69% and two in the <5 years age group 32% and 40%. The big difference in prevalence between the individual studies and the outliers in both groups may be due to the high detection of human norovirus positives in those studies. As a result they differ from the majority of the studies dada set and resulted to high heterogeneity percentages.

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