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PREVALENCE AND RELATIVE RISK OF ROTAVIRUS GASTROENTERITIS IN CHILDREN UNDER FIVE YEARS IN NIGERIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Rotavirus is responsible for most cases of gastroenteritis and mortality in children below five years of age, especially in developing countries, including Nigeria. Nonetheless, there are limited data on the nationwide estimate for the prevalence of rotavirus. This systematic review and meta-analysis sought to determine the pooled prevalence of rotavirus infections and its relative risk among children below five years of age in Nigeria. Eligible published studies between 1982 and 2021 were accessed from "PubMed", "Science Direct", "Google Scholar" and "African Journal Online", "Web of Science", "Springer", "Wiley" were systematically reviewed. The pooled prevalence, relative risk and regional subgroup analyses were calculated using the random effects model at 95% confidence interval (CI). A total of 62 selected studies, including 15 studies case-control studies, were processed in this review from pooled population of 18,849 children. The nationwide pooled prevalence of rotavirus among children below five years of age in Nigeria was 23% (CI 95%; 19-27). Regional subgroup analysis showed that the Southern region had a prevalence of 27% (CI 95%; 21- 32) while the Northern region had a 20% (CI 95%; 16%-25%) prevalence, although the difference was not significant (P = 0.527). Rotavirus was implicated in most cases of acute gastroenteritis with relative risk of 5.7 (95% CI: 2.9-11.2). The high prevalence and relative risk of rotavirus infections among children in Nigeria shows that rotavirus is an important cause of acute gastroenteritis in Nigeria. Thus, there is need for further surveillance, especially at community levels together with the introduction of rotavirus vaccines into the national immunization programme.

Key words: Rotavirus, prevalence, meta-analysis, gastroenteritis, relative risk

1. BACKGROUND

Diarrhoeal disease is the second leading cause of death in children under five years old globally. An estimated 1.7 billion cases and mortality of 525,000 in infants have been attributed to diarrhoea annually (WHO, 2017). According to the Global Enteric Multicentre Study (GEMS), a follow-up, age-grouped and case-control study conducted in seven Asian and sub-Saharan African countries, identified rotavirus, among all the agents responsible for diarrhoea, to be strongly associated with cases of moderate to severe diarrhoea in children under five years old (Kotloff *et al*., 2013; Liu *et al*., 2016).

Rotavirus is a member of the *Reoviridae* family with a size of 70 - 75 nm and is classified into ten serogroups (A-J) based on the outer protein (VP6). Among these serogroups, rotavirus group A is responsible for most gastroenteritis cases in human populations (Banyai *et al*., 2018). Rotavirus is transmitted via the faecal-oral route, through both fomites and close person-to-person contact. They are shed in enormous quantities in the stools of infected persons and few virions (<100 virions) are sufficient to cause disease in a susceptible host. Symptoms such as diarrhoea, malaise, vomiting and fever are associated with rotavirus infection and can result in dehydration in some cases (Crawford *et al*., 2017). The incubation period of gastroenteritis caused by rotavirus is one to three days and symptoms normally resolve in 3 to 7 days (Cortese & Parashar, 2009).

Majority of rotavirus-associated gastroenteritis occurs in Sub-Saharan Africa due to poor hygiene, malnutrition and lack of access to potable water. It has been estimated that about 215,000 infants die each year due to rotavirus-associated gastroenteritis and almost half of these deaths occur in four countries: Nigeria, Pakistan, India and Democratic Republic of Congo. Nigeria alone accounts for 14% (30,800) estimated rotavirus associated deaths in 2013 (Tate *et al*., 2016). A more recent

study estimated that rotavirus is responsible for about 47,898 deaths in children under five years old in Nigeria (Anderson *et al*., 2020).

Rotavirus vaccines have been introduced in more than 107 countries globally and their use has led to substantial reductions in morbidity and mortality (ROTA council, 2020). However, Nigeria is yet to introduce the rotavirus vaccine into its national immunization programme, despite the huge burden of rotavirus infection among children in Nigeria. For the most efficient health care and the distribution of rotavirus vaccine, information on the prevalence of rotavirus infections in different parts of the country is crucial. Therefore, this systematic review and meta-analysis seeks to provide the prevalence and relative risk of rotavirus infection in children ≤ 5 years of age in Nigeria. Our aim was to determine:

1. The pooled prevalence of rotavirus infection among children below five years of age with gastroenteritis in Nigeria.
2. The relative risk of rotavirus infection in case-control studies conducted among children below five years of age in Nigeria.

2. MATERIALS AND METHODS

The review was developed after searching Cochran and PROSPERO databases for availability of identical reviews to avoid repetition of any previously performed study. Presently, this is the first attempt at providing a pooled prevalence from several studies conducted on rotavirus-associated gastroenteritis in Nigeria. The protocol for this review was designed and registered on PROSPERO with registration number CRD42021261373.

2.1 Data Search

We identified primary studies on the prevalence of rotavirus infection in children below five years of age conducted in Nigeria using PubMed, Google Scholar and AJOL (African Journals Online), Web of Science, Springer, and Wiley databases. Grey literatures, such as conference papers, were also included to avoid publication biases. Publications were identified using keywords such as: "rotavirus Nigeria", "viral diarrh* in Nigeria", "prevalence", "infants", "children", "acute viral gastroenteritis Nigeria". Boolean operators such as (AND, NOT, OR) were also used. All the identified citations were downloaded into Zotero bibliographic management software for further processing. Last search for studies was conducted 17/12/2021. Further details on search methods are detailed in the Supplementary Material.

2.2 Eligibility Criteria for the Studies

Studies were included in the review when the following conditions were fulfilled:

1. The population of study were children under five years old with acute gastroenteritis/diarrhoea.
2. The numerators, i.e. the cases, were defined.
3. The denominators, i.e. the total number of population/participants sampled, were defined.
4. An arbitrary sample size of ≥ 50 to avoid publication bias in this review.
5. The study was conducted within Nigeria in any setting, such as hospital, clinics or community in Nigeria.
6. If the papers described co-infection studies and the prevalence of rotavirus in children below five years was clearly stated.
7. If children above five years of age were included in the studies but prevalence of those below five years old was separately calculated.

Studies that did not meet the eligibility criteria mentioned above were excluded.

2.3 Study selection and critical appraisal

Studies were selected from the first primary research on rotavirus-associated gastroenteritis among the population of interest in Nigeria for the past 39 years (from January 1982 to December 2021). Studies obtained were those that estimated the prevalence of rotavirus in the population using viral antigen detection methods, such as electron microscopy (EM), enzyme immunoassay (EIA), latex agglutination and lateral flow immunoassays (immunochromatography), nucleic acid detection on polyacrylamide gel or by polyacrylamide gel electrophoresis (PAGE), and nucleic acid amplification using reverse transcription PCR (RT-PCR) as stipulated in the guidelines for rotavirus detection and characterization (WHO, 2009).

Publications were assessed based on the Joanna Briggs Institute (JBI) critical appraisal tool for prevalence studies and each of the conditions were awarded 10 points for yes and zero for no. There was no moderate point. Two independent reviewers (D.D. and P.C) also reviewed the studies based on the criteria and discrepancies in selection were resolved by a third reviewer (V.C).

2.4 Subgroup Meta-analyses

Subgroup analysis was done based on the calculated sample size. Other subgroup analyses were performed based on the region of the country where the study was conducted. Subgroup meta-analyses were performed using the sample size obtained from the pooled prevalence of all the included studies in this review, using the Cochran's sample size calculation formula:

$$n = \frac{z^2 p(1-p)}{d^2}$$

Where n = sample size

Z = Z statistics for a level of confidence (1.96)

P = expected prevalence or proportion and (23% random effect pooled prevalence)

d = precision (margin of error, if its 5%, then d = 0.05)

$$n = \frac{1.96^2(1-23)}{0.05^2}$$

n =273.

2.5 Data Extraction

Information, such as author(s), region, patients' age, detection method(s), year of study, settings (hospital/clinic or community) and prevalence (sample size and cases) were collected from the selected studies. When a study was sampled across different regions of the country, it was excluded in the regional grouping.

2.6 Statistical Analysis

The data was analysed using MetaXL (v5.2) and MedCalc statistical software (v20). The random effects model was used to determine the pooled prevalence because of the heterogeneity in these primary studies such as sample size. The prevalence was calculated using the freeman-double arcsine transformation. The test for heterogeneity was done using Cochran's Q-test and I^2 test and was considered significant if the p value for Q test was ≤ 0.05. When the I^2 test is greater than 75%, the studies were considered highly heterogeneous (Barendregt and Doi, 2015). Tests for publication bias were evaluated using doi plots where Luis Frya-Kanamori (LFK) index is considered asymmetry if it has a value greater than ± 2, which indicates publication bias (Barendregt *et al*., 2013). Egger's and Begg's tests were also used to assess for publication bias in the study with *p*-value < 0.05 suggesting the presence of publication bias while *p*-value > 0.05 indicates the absence of publication bias in the studies (Begg and Mazumdar, 1994; Egger *et al*., 1997)

3. RESULTS

A total of 966 studies were accessed from Google Scholar, PubMed, African Journals Online (AJOL), Web of Science, Springer and Wiley online databases. Of these, 423 duplicate research articles were removed and another 469 articles were expunged after screening for study titles and abstracts because they are irrelevant to this review. Seventy-one full-text articles were eventually retrieved while 3 were inaccessible, i.e. both abstract and full-text article could not be found. Finally, during data extraction, nine articles were excluded because of the following reasons: four articles did not meet the age criteria, one used sample size < 50, one did not specify the age group of study and three were pure molecular studies lacking information on prevalence. Thus, 62 articles were accessed based on the specified criteria, as listed in Supplementary Table 1. All the 62 articles were also used for meta-analyses and studies that accessed both case control and prevalence were used for both analyses. The studies were reported using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol (Page *et al*., 2021) (Figure 1).

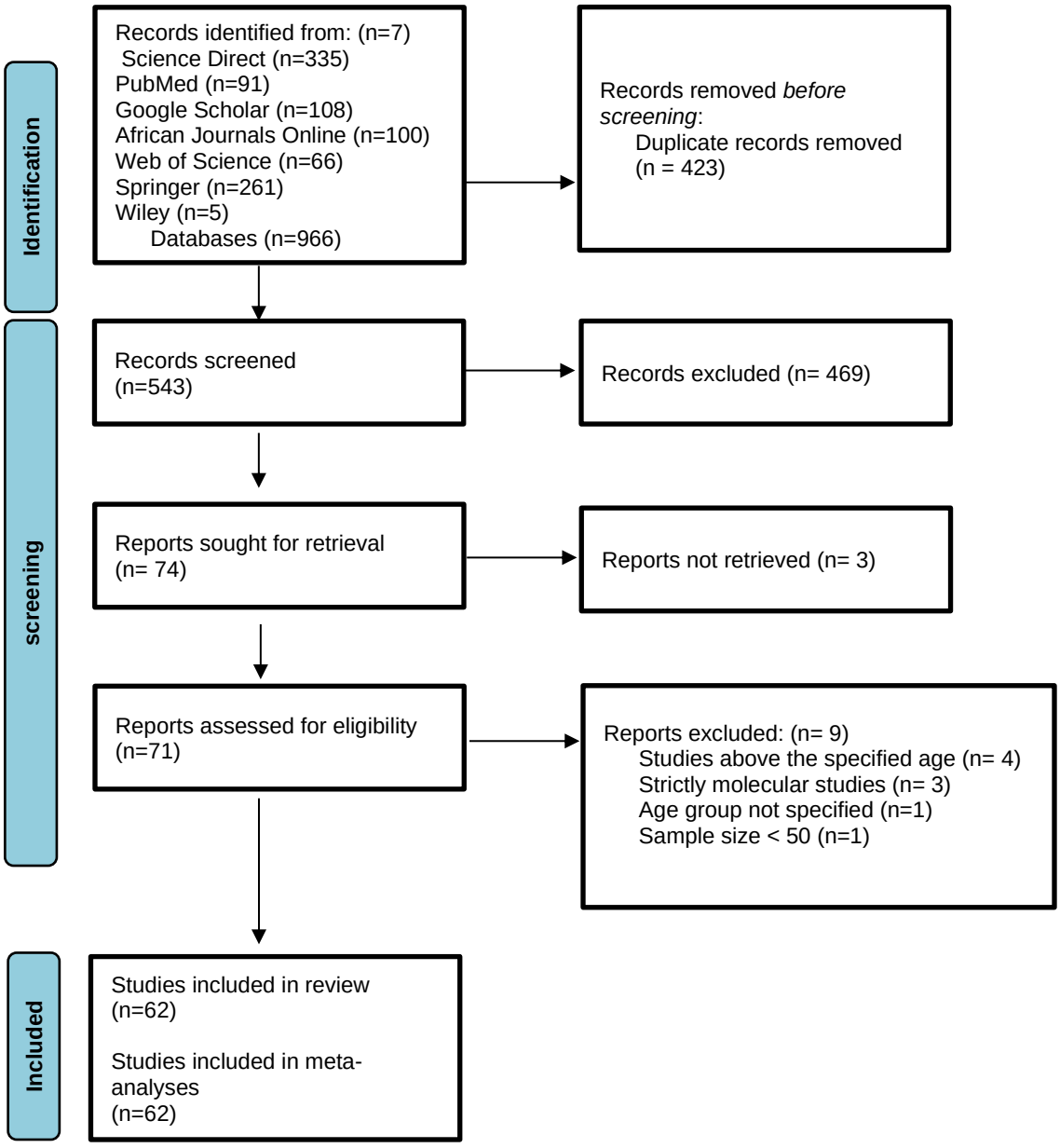

Figure 1: PRISMA flow chart for study assessments of rotavirus in Nigeria

3.1 Rotavirus detection methods used in selected studies

Among the included studies, the commonly used detection methods include EIA, PAGE, ICT and RT-PCR which were used in 52/62, 2/62, 3/62 and 17/62 (7 studies used RT-PCR for prevalence

while 10 studies performed secondary characterization using RT-PCR) of the studies, respectively. Case control study design was used in 15/62 of the studies while all the 62 studies also accessed the prevalence of infection within the target population. The number of studies carried out in the northern Nigeria (34/62) were greater than those in the southern part (26/62), while only 2/62 studies were carried out in both regions. Majority of the studies were conducted in a healthcare facility (60/62), while 2/62 was carried out in the community.

3.2 Prevalence of rotavirus associated gastroenteritis among under-five children in Nigeria

The 62 selected studies sampled a total of 18,849 diarrhoeal stool samples, out of which 4,947 samples were positive for rotavirus. In addition, the prevalence of rotavirus in Nigeria among the studies ranges from 5.3% to 57.2%. The pooled prevalence of rotavirus associated gastroenteritis among children below 5 years of age in Nigeria, based on the random effects model, was 23% (95% CI, 19.3% - 26.9%), as shown in Figure 2.

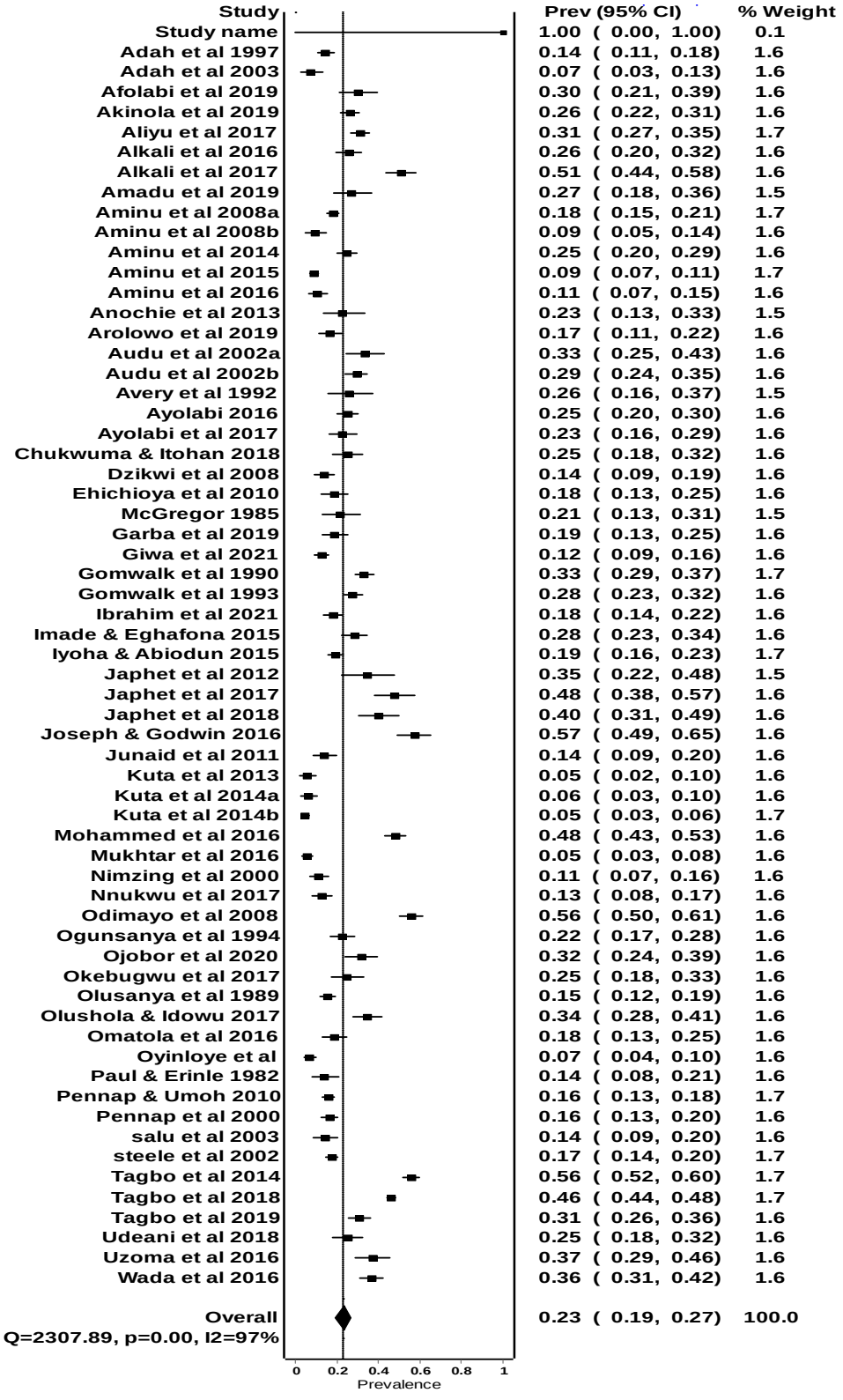

Figure 2: Forest plot of the pooled prevalence of rotavirus using the random effects model

Heterogeneity among the studies was determined using the Cochran's Q test and I^2 statistics. Cochran's Q test was 2307.8 and was statistically significant ($P< 0.001$) while I^2 showed 97.3% heterogeneity between the studies. In order to test for publication bias, doi plot with LFK index was used (Figure 3). The LFK index was -0.01 showing no asymmetry (publication bias). Egger's and Begg's test showed the absence of statistically significant publication bias ($p = 0.06$) and ($p = 0.20$)

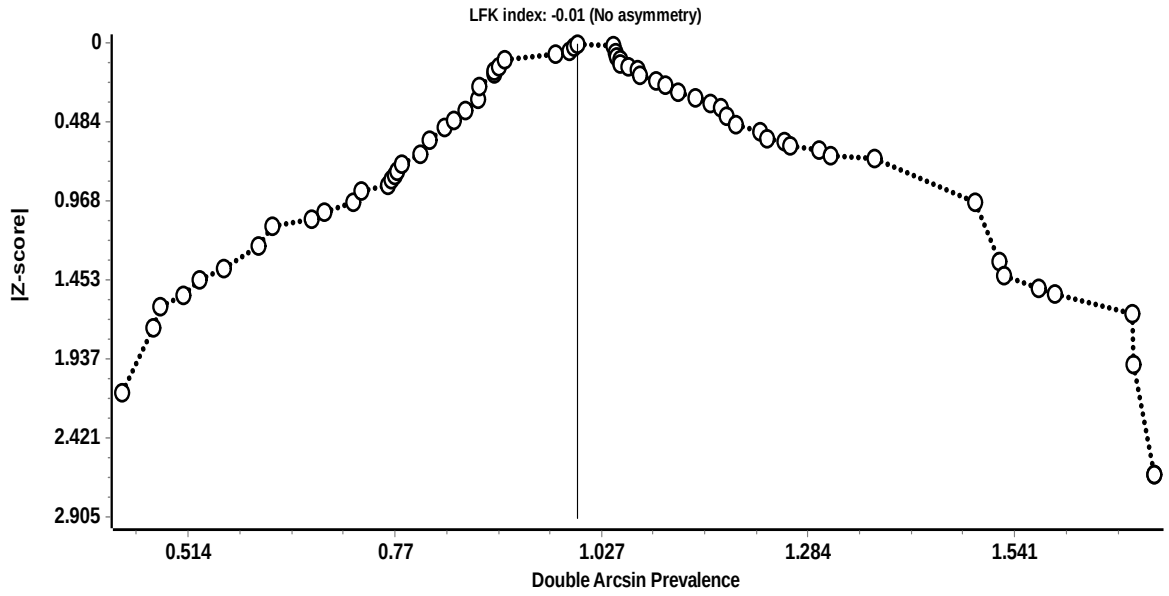

Figure 3: Doi plot of the rotavirus studies to evaluate publication bias.

3.3 Subgroup analysis

Based on the calculated sample size of 273, subgroup analysis of studies that used sample sizes ≥ 273 showed a prevalence of 23% (95% CI 17.4% - 29.7%). Regional subgrouping showed that

studies conducted in the southern part of the country had prevalence of 27% (95% CI 21% - 32%) than studies carried out in the northern part of the country with prevalence of 20% (95% CI 16% - 25%) as shown in Figures 4 and 5. However, this difference was not statistically significant (*P* = 0.5269). Subgroup analysis based on the viral detection methods showed that studies where RT-PCR was used for primary detection had prevalence of 21% (95% CI 14% - 30%) while studies that used EIA for detection had prevalence of 23% and this difference was statistically insignificant (*P* = 0.9065). Additional subgroup analysis based on study settings was performed which showed prevalence of 23% (95% CI 19% - 27%) for studies performed in healthcare facility (HF) while studies carried out in the community had prevalence of 24% (95% CI 9% - 42%). Similarly, this difference was not statistically significant (*P* = 0.9739).

The relative risk of rotavirus infection among case control studies was 5.7 (95% CI 2.9 – 11.2) with few studies showing little or no samples positive for rotavirus in their control (Figure 6, Supplementary Table 2). This implies that diarrhoea among children under 5 years of age in Nigeria is strongly associated with rotavirus.

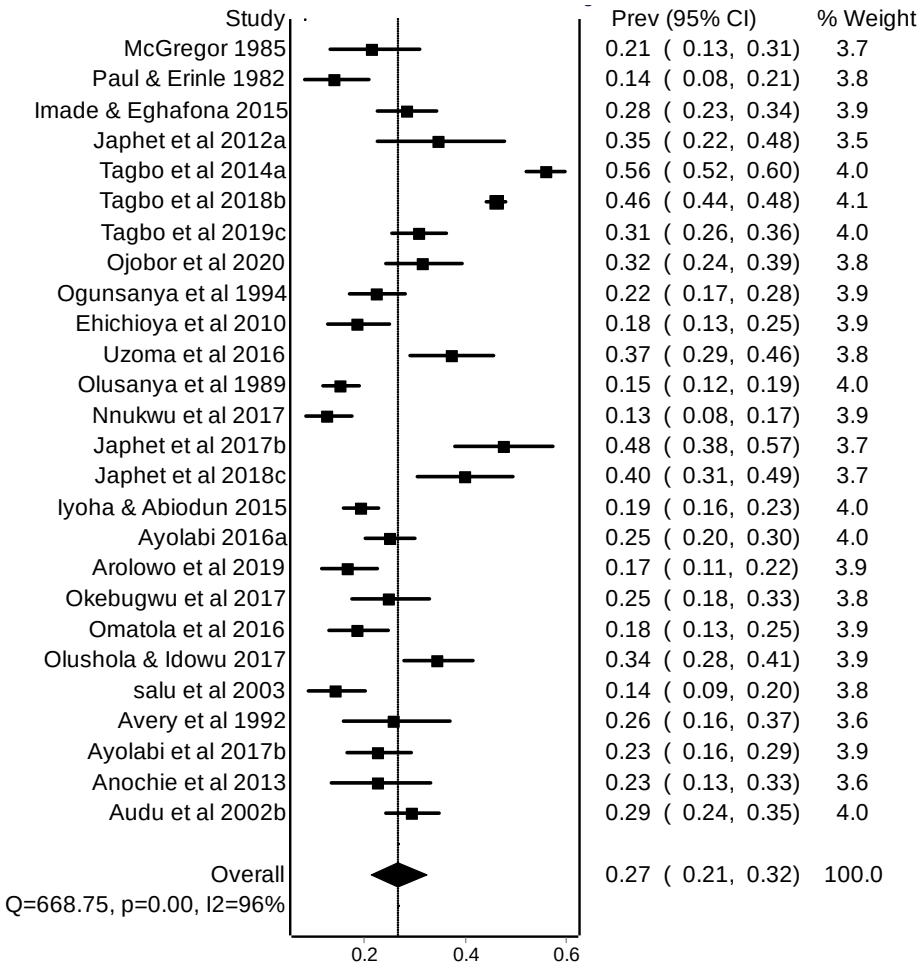

Figure 4: Forest plot of the prevalence of studies conducted in the Southern Nigeria

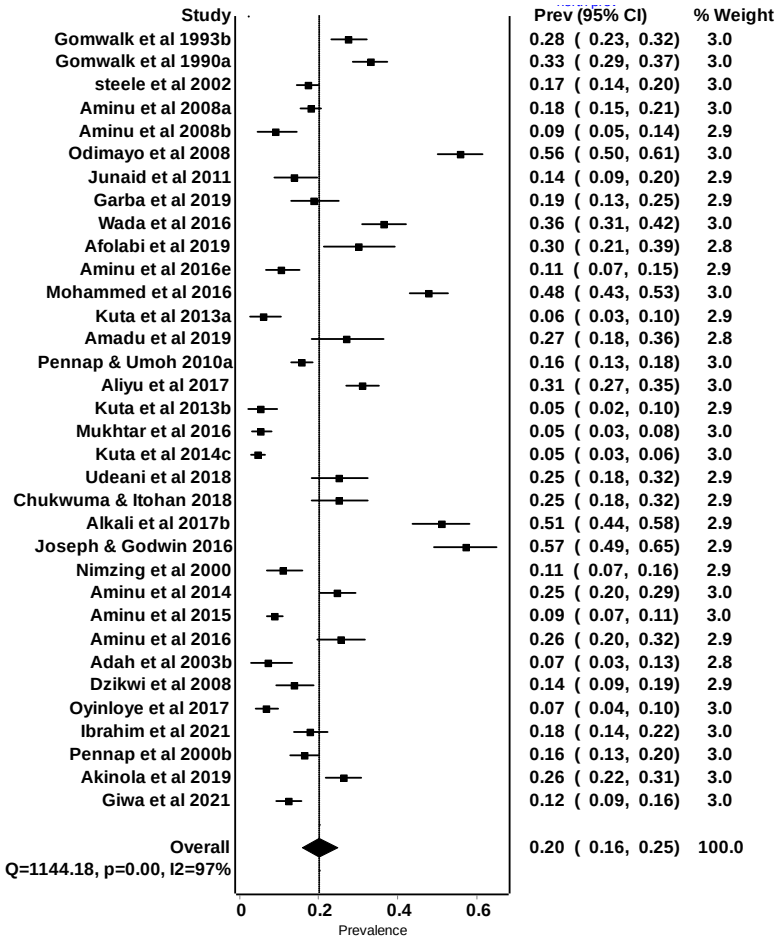

Figure 5: Forest plot of prevalence studies conducted in the Northern Nigeria

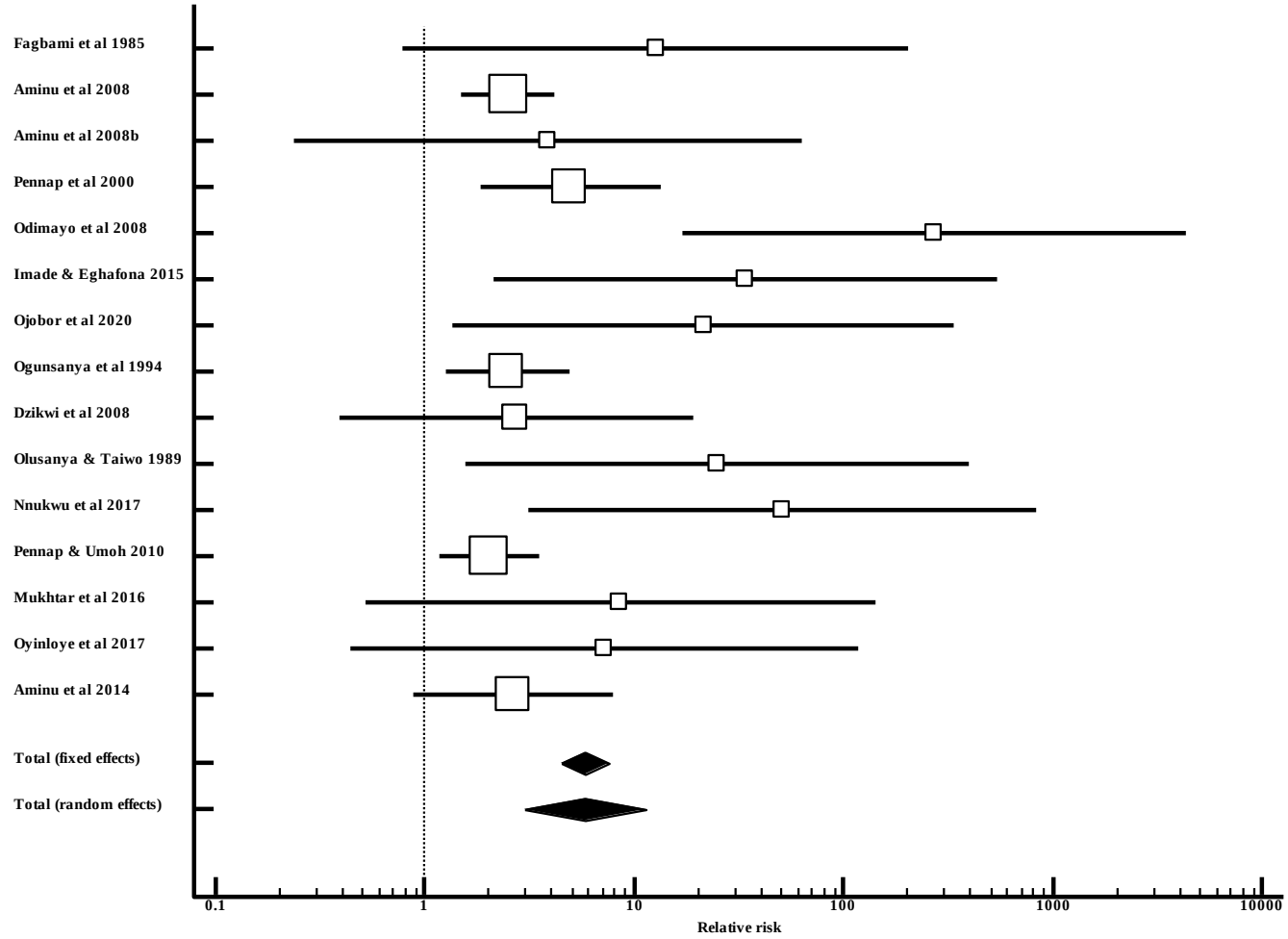

Figure 6: Forest plot of the relative risk of rotavirus gastroenteritis in Nigeria

4. DISCUSSION

The burden of rotavirus is high among children below five years of age living in resource poor countries in Sub-Saharan Africa due to poor hygiene, limited access to healthcare and malnutrition (Kotloff *et al*., 2013). This study is the first attempt at providing an estimate for rotavirus-associated gastroenteritis among children below five years of age in Nigeria. Our findings suggest that rotavirus is responsible for a substantial proportion of cases (19-27%) of acute gastroenteritis among children less than five years old in Nigeria. This is consistent with systematic reviews and

meta-analysis conducted in Ethiopia and LAC (Latin America and Caribbean countries) with a mean prevalence of 23% and 24.3%, respectively (Linhares *et al*., 2011; Damtie *et al*., 2020). However, higher rotavirus prevalence (35-39.9%) was noted amongst Iranian children (Moradi-Lakeh *et al*., 2014; Monavari *et al*., 2017). This might be attributed to study differences such as geographical location, sample sizes and viral detection methods. The majority of these studies used EIA method and only a few studies used RT-PCR for primary detection of the viruses, which is more sensitive than EIA (Ehichioya *et al*., 2010; Japhet *et al*., 2012; Anochie *et al*., 2013; Aminu *et al*., 2015; Iyoha and Abiodun, 2015; Arolowo *et al*., 2019; Japhet *et al*., 2019). These factors may contribute to the significant heterogeneity within the studies.

The pooled prevalence of 23% determined in this study was shown to be robust by testing for sensitivity through exclusion of studies with sample sizes below 273. This sensitivity analysis had a prevalence of 23%, which is the same with

the pooled prevalence. Regional subgroup analysis revealed that, even though greater numbers of studies were conducted in the north, its prevalence (16% - 25%) in the region is lower than that of the southern region of Nigeria which had a slightly higher prevalence (21% - 32%). Factors, such as age differences, climatic conditions and immune status of the children, can be responsible for these differences across the regions. Furthermore, there is a possibility that the health seeking practices of the people living in the various regions might have influenced the prevalence of the studies since most of the studies were conducted in health care facilities (Onwujekwe *et al*., 2011). On the other hand, there is a possibility of overestimation of the prevalence since only the most severe cases of gastroenteritis visit the hospital.

Based on the weight of evidence from the case-control studies with a relative risk of 5.7 (95% CI 2.9 – 11.2), there are indications that most diarrhoea cases among children under five years old is

attributable to rotavirus since there few asymptomatic cases of rotavirus infection among the samples. This is similar to the results of a pre-vaccination study carried out in Mozambique where rotavirus was detected in cases of moderate to severe diarrhoea with an odds ratio of 6.4 (Acácio *et al*., 2021).

5. CONCLUSIONS AND RECOMMENDATIONS

The weight of evidence presented in this systematic review and meta-analysis showed that rotavirus is responsible for a considerable proportion of acute gastroenteritis among children in Nigeria. This reinforces the need for the implementation of rotavirus vaccine in the national immunization program to reduce this huge burden in children. Furthermore, these findings reveal the need for more prospective and case-control research to access the rotavirus disease burden. Most studies reviewed here were carried out in healthcare and clinical settings, however very limited information is available on viral diseases in community settings. More importantly, future studies should adopt more sensitive acute gastroenteritis diagnostic techniques for accurate and valid estimation of viral burden among the study population.

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