

“Human Norovirus prevalence in Africa: a review of studies from 1990 to 2013”

Running Head: Human Norovirus in Africa

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ABSTRACT:

OBJECTIVES: Reliable estimates of Human Norovirus (NoV) prevalence in Africa are limited. This review aims to assess the contribution of Human NoV to diarrheal diseases in Africa. **METHODS:** We conducted a systematic review of the PubMed and EMBASE databases for published articles of Human NoV in Africa between 1990 and 2013. Data were extracted from selected studies and analysed.

RESULTS: A total of 208 eligible studies were identified, of which 55 (from 19 countries) met the inclusion criteria. Many cases were of sporadic gastroenteritis (70.4%) in children (82%), 65.4% of which were seen in an outpatient setting. Over half (59.4%) of affected children were under 5 years of age. The pooled prevalence rate of Human NoV was 11% (95% CI 8-14%) and the meta-analysis indicated significant heterogeneity between the studies. However, the conditional negative binomial regression could not clearly find the factors affecting the Human NoV prevalence rates reported. A close relationship was found between Human NoV strains from environmental and clinical samples. **CONCLUSION:** Unreported sporadic gastroenteritis cases of Human NoV are common in Africa. Most of them are community-associated infections. Possible environmental transmission routes have been documented. Combined environmental and clinical studies are required for targeted actions to control transmission of Human NoV in Africa. Furthermore, systematic surveillance of Human NoV is needed to measure the burden of NoV-induced gastroenteritis in Africa and support any requirements for vaccine development.

Key words: Human NoV, Africa, Sporadic gastroenteritis, Environment

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INTRODUCTION:

Globally, one in ten infant deaths (before the age of 5 years) are due to diarrheal disease, causing almost 800,000 mortalities worldwide, most of them occurring in Sub-Saharan Africa and South Asia (Kotloff *et al.* 2013; Liu *et al.* 2012). In Africa, 115 people die every hour due to diseases linked to poor sanitation, poor hygiene and contaminated water (UNICEF and WHO, 2012; WHO, 2011; UNICEF / WHO, 2009; Boshi-Pinto *et al.* 2008; UNICEF, 2006).

The viruses mainly involved in diarrheal diseases include rotavirus (Greenberg and Estes, 2009), NoV (Patel *et al.* 2009), astrovirus (Mitchell 2002) and adenovirus types 40 and 41 (Uhnnoo *et al.* 1990). NoVs (previously known as “norwalk-like viruses”) were first discovered by electron microscopic examination of human stools (Kapikian *et al.* 1972) and are part of the *Caliciviridae* family along with sapovirus, lagovirus and vesivirus (Green *et al.* 2000). They are single stranded, non-enveloped, positive-sense RNA viruses (Jiang *et al.* 1993; Xi *et al.* 1990). There are 5 genogroups of NoV, GI-GV. Based on amino acid differences in the major structural protein (VP1) (Zheng *et al.* 2006), these can be further subdivided into 35 genotypes with 8 genotypes in GI, 21 in GII, 3 in GIII, 2 in GIV and one in GV (CDC, 2011; Green 2007; Zheng *et al.* 2006). The strains that infect humans (referred to collectively as “human norovirus”) are found in GI, GII, GIV whereas strains infecting animals such as cows and mice fall within GII, GIII, GIV and GV (CDC, 2011; Patel *et al.* 2008). NoV cannot be cultivated *in vitro* (Duizer *et al.* 2004). The use of molecular assays for the detection of NoV is currently commonplace in diagnostic laboratories (Trujillo *et al.* 2006).

NoV is now the leading cause of medically attended acute gastroenteritis in USA children (Payne *et al.* 2013) and with the recent success of rotavirus vaccines, NoV will likely become the most common cause of childhood diarrhoea disease in many countries (Ramani *et al.* 2014; Bucardo *et al.* 2011; Karst 2010). In Africa, emerging Human NoV strains such as GII.4 2008 variant have been reported during an outbreak among South African hospitalised paediatric patients (Mans *et al.* 2010).

The symptoms associated with NoV infection, which manifest after an incubation period of between 1.2 days (95% CI 1.1-1.2 days) (Lee *et al.* 2013) are typically self-limiting, characterised by nausea, vomiting, abdominal pain and non-bloody diarrhoea (4-8 stools

per day). The duration of NoV illness is 12-72 hours (Patel *et al.* 2009), but the illness can be prolonged (and severe) in the very young or old, and immunocompromised persons (van Asten *et al.* 2011; Green 2007).

NoV epidemiology is influenced by many factors including population immunity, virus evolution, the environment and seasonality (Ramani *et al.* 2014). The host genotype is a prominent factor in the development of NoV infection since NoV infection depends on the presence of specific Histo-Blood Group antigens (HBGA) receptors in the gut of susceptible hosts (Lindesmith *et al.* 2003). Transmission occurs usually from person-to-person via the faecal-oral route or via aerosols generated by vomiting, but the importance of food and water in the spread of infection is also well-recognized (Daniels *et al.* 2000; Shieh *et al.* 2000; Kukkula *et al.* 1999). Several characteristics of NoVs facilitate their spread within the population (Hall *et al.* 2012; CDC, 2012; Atmar *et al.* 2008; Rockx *et al.* 2002). These include: Extremely low infectious dose (≥ 18 viral particles), coupled with copious viral shedding (10^5 - 10^{11} viral copies per gram of feces), even among asymptomatic infections; Environmentally stable, able to survive both freezing and heating, resistant to many common chemical disinfectants; Multiple ways in which NoVs may be transmitted; Genetically diverse group of viruses that rapidly evolve; Repeated infections throughout life with re-exposure, because lack of complete cross-protection against the diverse NoV strains and inadequate long-term immunity; Wide range of ages of susceptible persons as NoV can infect susceptible individuals of all ages from neonates to the elderly.

Despite the excessive burden of diarrheal disease in developing countries, the majority of Human NoV outbreaks have so far been reported in developed countries (UNICEF, 2012; WHO, 2011). Previous studies did generate pooled global estimates of Human NoV in developing and developed countries with small dataset from African countries where the effect of gastroenteritis probably has more severe consequences (Ahmed *et al.* 2014; Patel *et al.* 2009). This review provides a summation of studies that aim to assess the contribution of Human NoV to diarrheal diseases in Africa. In addition to the estimates of Human NoV in cases of gastroenteritis as previously calculated in other reviews (Ahmed *et al.* 2014; Patel *et al.* 2009), this review report on environmental

studies of Human NoV in Africa to ascertain the circulation and possible routes of transmission of Human NoV within the population (Iwai *et al.* 2003).

MATERIALS AND METHODS:

Search Strategy:

A review of selected studies that investigated Human NoV in Africa as listed by the National Institutes of Health PUBMED library and EMBASE (Excerpta Medica database) (Appendix A) was performed using the terms 'norovirus' AND 'Africa'. A second search was independently done for each of 54 sovereign states and 10 non-sovereign territories (www.nationsonline.org/org/oneworld/africa.htm) constituting the African continent using the following key words: Human Enteric virus, Human Calicivirus, Human NoV, Norwalk-virus, SRSV (small round structured virus) combined with each country name (Fig.1). After reviewing each article, studies were selected if they met the following inclusion criteria:

- Studies for the detection of Human NoV, Norwalk-virus, SRSV in patients with / or without diarrhea, in water, food and environment matrices. We included studies that tested for Calicivirus when NoV was differentiated from other viral agents. Diarrhea was defined as the passage of loose or watery stools, usually at least three times in a 24 hour period (WHO, 2003).
- Studies performed in Africa between 1990 and 2013.
- Studies using standardized laboratory techniques for detection and / or genotyping of NoV including EIA, RT-PCR, qRT-PCR and Sequencing.

Non-English articles, plus studies concerned with the detection of animal NoV were excluded, as were data on cases of sapovirus infection. If the authors repeated data in other studies, only 1 article was considered.

Data extraction:

The following information was extracted for each selected study when provided: first author, period and duration of study, country, clinical symptoms and settings (environment, outpatients and inpatients), study population, age group, diagnostic methods used, number of cases tested, number and percentage of positive for Human NoV (by genogroups and genotypes) in symptomatic and asymptomatic cases (Table 1, Table 2 and Appendix A).

Statistical analysis:

Data was imported to Stata Direct^{MT} (<http://www.statsdirect.co.uk/>) for the calculation of random effects pooled prevalence rates. This same package was used to calculate heterogeneity, estimate publication bias and generate forest plots. Heterogeneity was assessed by Cochran's Q test and by observing the forest plots for variation in results from the different studies. Publication bias was assessed by means of funnel plots and Harbord's bias index. In order to determine drivers of Human NoV heterogeneity and genotype prevalence we conducted random effects negative binomial regression with STATA version 13.0. A series of single predictor models were run.

RESULTS:

The initial broad searches identified 208 studies published during 1990-2013. After reviewing articles on the basis of the inclusion criteria, 55 studies from 19 countries of Africa were eligible (Fig.1; Table 1 and Appendix A).

Characteristics of selected studies

Of The 55 studies included in this analysis, 42 contained only human samples, 12 only environmental samples and one both human and environmental samples (Table 1). A The majority of studies (39/55) used one form of PCR or another as the sole detection method, 9 used EIA and 1 EM. The remaining six studies used a combination of methods. Fig.1 shows the locations of the 55 studies retained from the literature search, revealing the regional distribution: 14 (25.4%) Northern, 4 (7.3%) Central, 14 (25.4%) Eastern, 10 (18.2%) Western, 11 (20%) Southern and 2 (3.6%) from the horn of Africa.

Thirty seven (67.3%, 37/55) of the selected studies were from 7 countries, namely: South Africa, Tunisia, Ghana, Tanzania, Malawi, Egypt and Kenya.

Of the 43 studies that included human samples, 9 were from rural settings, 32 from urban settings and 2 from both urban and rural settings. Also 30 studies were only of outpatient samples, 7 from inpatient samples and the remaining 6 mixed inpatient and outpatient

The summary of selected studies on Human NoV in Africa (Table 1) reveals that 41 (74.5%) of the studies were carried out in urban settings, 11 (20%) from rural areas and 3 (5.4%) from both settings. 36 (65.4%) of studies were from non-hospitalised (outpatients) whereas 11 (20%) were from inpatients. Twenty two (40%) of the studies were carried out between 2006 and 2008. Out of 55 studies, 39 (70.9%) were from sporadic cases of gastroenteritis of which 32 (82.0%) were from children with diarrhea. Among children, the majority of cases (59.4%, 19/32) were from those under 5 years of age. Only 4 studies (Hassine-Zaafraane *et al.* 2013; Mans *et al.* 2010; Wolfaardt *et al.* 1995; Taylor *et al.* 1993) from Tunisia and South Africa reported on outbreak of Human NoV among the selected studies. There is a great absence of NoV outbreak reports in Africa, perhaps due to the lack of surveillance reporting.

Human NoV detection and Genotyping in Africa

For the meta-analysis of prevalence rates in human samples, 7 of the 43 human studies were excluded for the following reasons:

- 3 because they only included studies of outbreaks
- 3 because they were studies of sero-prevalence and not faecal carriage (Smith, 1999; Taylor, 1995 and Taylor, 1996)
- 1 because the study was exclusively of healthy people and was not within the study period (Rodriguez-Diaz *et al.* 2013):

Of the remaining 36 studies, 8 contained reported separately of symptomatic and asymptomatic participants. In these studies symptomatic and asymptomatic were

treated as separate study arms making 44 study arms. Figure 2 shows the forest plot of these 44 study arms. The random effects pooled prevalence is 11% (95% CI 8 – 14%). As can be seen in figure 2 with the dispersion in study prevalence there was high heterogeneity (Cochran $Q = 1,693$ (df = 43) $P < 0.0001$). From supplementary file 1 there does not appear to be any substantial publication bias.

Of the 44 study arms included in the meta-analysis, 24 had sufficient information to enable a estimates of the proportion of positive samples associated with GI (figure 3) and GII (figure 4). In these studies the pooled per percentage prevalence of GI was 18% (95%CI 12 – 24%) and GII 81% (95%CI 73 – 87%). Although again there substantial variation between studies. Clearly GII was the predominant genogroup in humans

Meta-regression analysis using Poisson regression of the drivers of prevalence of norovirus and of the proportion due to genotype GII is shown in supplementary file 2. Apart from a year on year increase in the prevalence of stool positives of about 9% per year, none of the other possible drivers (urban/rural, outpatient/inpatient, symptomatic/asymptomatic, children/adults, and detection method) achieved statistical significance

Of particular note is that 8 out of 43 human studies, reported detection of Human NoV in healthy controls and (participants without diarrhea) with rates ranging between 4.2% and 31%. The prevalence of Human NoV excretion in stools was similar in both symptomatic and asymptomatic participants and as already mentioned the meta-regression analysis found no significant difference (Fig. 2; Supplementary file 2 and 3). If anything prevalence in asymptomatic individuals was higher than in symptomatic individuals.

Only three studies of both age groups (children and adults) over a period of greater than 1 year have reported Human NoV detection showing that children aged ≤ 5 years

were associated with an increased risk of Human NoV infection (Ayukekbong *et al.* 2013; Hassine-Zafrane *et al.* 2013; Kamel *et al.* 2009).

Regardless of the method of Human NoV detection, the setting and the sub-regional climate conditions, the peak detection rate was variably reported (Supplementary file 5): 4 studies identified the rainy season (Trainor *et al.* 2013; Mans *et al.* 2010; Papaventsis *et al.* 2007; Dove *et al.* 2005) as the period with the highest prevalence while 4 studies found peak rates in the cool dry season (Nodgren *et al.* 2013; Abugalia *et al.* 2011; Sdiri-Loulizi *et al.* 2008; Armah *et al.* 2006). These data could not enable us to describe the seasonal distribution of NoV in Africa. In addition there was no statistical difference in prevalence of different genogroups and genotypes with successive seasons. We noticed the scarcity of GIV in the selected studies.

Out of twenty two studies which reported partial sequencing Human NoV, 13 (59.1%) were performed on capsid gene, 3 (13.6%) on polymerase gene, 5 (22.7%) on both ORF2 and ORF1 gene. Only one (4.5%) study was with sequence of junction region ORF1/ORF2. The capsid genotypes frequently reported were GII.4 (20/22, 90.9%), GII.6 (9/22, 40.9%), GII.3 (9/22, 40.9%) and GII.2 (9/22, 40.9%).

A markedly genetic diversity of Human NoV has been reported in 6 (46.1%) studies with children ≤ 5 years of age (Trainor *et al.* 2013; Nodgren *et al.* 2013; Mans *et al.* 2010; Papaventsis *et al.* 2007; Armah *et al.* 2006; Dove *et al.* 2005), showing up to 11 different genotypes of GII and 6 different genotypes of GI (Supplementary file 5). Two studies (Trainor *et al.* 2013; Mans *et al.* 2010) reported GII/GI coinfections with a median detection rate of 0.25% (range 0.1- 0.4). Recombinant NoV strains have been observed in one study from rural community of Ghana among children ≤ 5 years of age (Armah *et al.* 2006).

Human Norovirus distribution in the environment

Twelve of the selected studies (Table 2) reported on Human NoV detection in environmental samples, including eight water samples (from river, sewage, wastewater and drinking water), three shellfish samples and one soil sample. The median detection

rate of Human NoV in water samples was 62.2% (Range 3 - 80), with GI and GII at comparable frequencies.

Studies on shellfish samples observed Human NoV contamination with a median detection rate of 25.5% (Range 1.6 - 35).

In 3 selected studies, which employed molecular methods to detect NoV GIV, no positive environmental samples were found (Benabbes *et al.* 2013; Murray *et al.* 2013; Gibson *et al.* 2011).

A close relationship was found in two (16.6%, 2/12) of the environmental studies between Human NoV strains from both environmental and clinical samples (Kamel *et al.* 2010; Sdiri-Loulizi *et al.* 2010) meaning a correlation between the genogroups and genotypes seen in the environmental and clinical samples during the same period study. Phylogenetic analyses revealed that environmental Human NoV strains were similar to those found in children suffering from gastroenteritis during the same period study.

Out of seven studies which reported on the seasonality, six (85.7%) showed no pattern of seasonal distribution of Human NoV in the environment (Table 2).

DISCUSSION:

This review provides a summary of Human NoV detection studies in Africa, two decades after the introduction of molecular assays to detect NoVs. Only 55 studies fulfilled the inclusion criteria of this review highlighting the need for further work to assess the burden of Human NoV gastroenteritis in Africa. There are many areas of Africa where very little is known regarding the contribution of Human NoV to diarrhoeal disease, reflected in the fact that the majority of studies (37/55) came from only 7 countries (South Africa, Tunisia, Ghana, Tanzania, Malawi, Egypt and Kenya (Table 1). The data imply that NoV could be a common cause of moderate gastroenteritis among children under 5 years of age in Africa. The review showed that 70.9% (39/55) of selected studies were from sporadic gastroenteritis of which 48.7% (19/39) were among children with ≤ 5 years of age. This is consistent with the global increase of Human NoV in sporadic gastroenteritis in children under 5 years of age worldwide (Hoa Tran *et al.*

2013; Patel *et al.* 2008). However, the observation that the prevalence of Human NoV excretion in stools is similar in both symptomatic and asymptomatic participants raises questions about its pathogenic role and the immune status of the hosts. Indeed, in three of the four studies that compared samples for symptomatic and asymptomatic participants, the reported rates were lower in symptomatic patients than in asymptomatic controls (Huynen *et al.* 2013, Mattison *et al.* 2010, Trainor *et al.* 2013). The results of these studies indicate that the relationship between Human NoV infection and clinical disease is complex in Africa and requires further investigation. Nevertheless, the possibility of post-symptomatic shedding cannot be excluded considering the fact that the healthy children in the indicated reports were participants with no history of diarrhoea 2 weeks before sample collection (and in many cases, highly sensitive methods of detection were used). Previous studies have shown that Human NoV may be shed in faeces for over 3 weeks after symptoms (Milbrath *et al.* 2013; Atmar *et al.* 2008; Siebenga *et al.* 2008), although the infectivity of the virus after this time is not clear. Recently Moyo *et al.* (2014) who investigated in Tanzania on 705 hospitalized children with diarrhoea and 561 children without history of diarrhoea for one month prior to the study, found that prevalence of NoV was significantly higher in cases (18.3 %) than in controls (9.3 %).

Most of the studies (80%, 44/55) were carried out in urban settings, likely due to the lack of laboratory capacity for Human NoV detection in rural settings. The analyses revealed that 65.4% (36/55) of studies were of outpatients, indicating that Human NoV is a common viral agent of community acquired diarrhea in Africa.

In line with the predictions of some authors, the summary of studies confirms that GII is the predominant genogroup and GII.4 genotype followed by GII.3, GII.2 and GII.6 as the predominant genotypes circulating in communities worldwide (Hoa Tran *et al.* 2013; Siebenga *et al.* 2009; Patel *et al.* 2008). The GI strains (9.1%, 5/55) were mostly detected from environmental samples (El-Senousy *et al.* 2013; Mans *et al.* 2013; Kamel *et al.* 2010; Polo *et al.* 2010; Sdiri-Loulizi *et al.* 2010), which is in keeping with previous studies. It is possible that GI strains are more environmentally stable relative to GII strains (Mathews *et al.* 2012; Seitz *et al.* 2011; Atmar, 2010; Charles *et al.* 2009; Lysen *et al.* 2009).

Human NoV detection was found more frequently in children than in adults in 3 studies of both age groups over a period of greater than 1 year. Unfortunately the small numbers of these reports in the present review did not allow us to draw any conclusions about transmission patterns in different age groups.

The pooled prevalence rate of Human NoV was 11 % (95% CI 8-14%) (Fig. 2). Sporadic gastroenteritis due to Human NoV in childhood, in the developing world, remains poorly described. There is no reporting system of NoV infection in the primary healthcare system, meaning that sporadic cases of Human NoV are likely to be vastly underreported and the prevalence of the infections grossly underestimated.

Nevertheless, the combined prevalence of Human NoV among children under 5 years of age with diarrhoea, found in this review, is comparable to a previous global systematic review in which the pooled Human NoV detection rate was 12% in children under 5 (95% confidence interval 10%-15%) (Patel *et al.* 2008). The high frequency of Human NoV in sporadic infantile cases is a potential health risk as these children may act as reservoir for emerging epidemic Human NoV strains (Medici *et al.* 2006).

The limited number of studies that reported on the distribution of Human NoV in gastroenteritis cases throughout the year does not allow us to describe the seasonal distribution of Human NoV in Africa. Knowledge of the seasonality and influence of weather conditions on the transmission of the viruses in the community provides information needed to predict when a peak period is likely to occur, to instigate public health interventions. Therefore, more studies of at least 12 months duration are needed to determine the seasonal distribution of Human NoV in all regions of Africa. The majority (85.7%) of the studies on environmental samples (Table 2) showed no seasonal peaks or troughs of Human NoV throughout the year. Similar observations have been reported in previous studies (Lysen *et al.* 2009; Maunula *et al.* 2005). Human NoV has been shown to persist for long periods of time, which may go some way to explain their detection all year long (Lopman *et al.* 2012; Seitz *et al.* 2011; Le Guyader *et al.* 2000). Existing evidence suggests that Human NoV is environmentally stable and resistant to disinfection, and that environmental contamination with Human NoV is common both within and outside outbreak settings (Lopman *et al.* 2012; Seitz *et al.* 2011; CDC, 2008). Co-circulation of Human NoV in the environment and the population

has been reported in 16.6% of environmental surveys of this review. Phylogenetic analyses have revealed a close relationship between environmental Human NoV clinical cases within the same period of time (Kamel *et al.* 2010; Sdiri-Loulizi *et al.* 2010). This finding indicates that there are potential health risks associated with transmission of Human NoV via environmental routes.

A remarkably high genetic diversity of Human NoV in children under 5 years of age have been reported in this review, suggesting that NoV is likely to be common in Africa. However diversity of Human NoV has been previously reported worldwide (Zheng *et al.* 2011; Kremer *et al.* 2011; Ferreira *et al.* 2010; Reuter *et al.* 2005; Hanoman *et al.* 2004). Although the studies included in this review provide an indication of the circulating Human NoV strains across the African continent, they are not fully representative of all countries. Moreover, comparing the occurrence of Human NoV in Africa is difficult due to differing study/site conditions and the range of techniques used for sampling and detection. The lack of data may be attributed to the fact that Human NoV detection methods are costly and require specialised laboratories and expertise. Furthermore, due to the limited number of selected studies, we are unable to ascertain whether Human NoV diversity in children with gastroenteritis is related to the genetic ability of Human NoV itself to evolve rapidly (Hall *et al.* 2012; CDC, 2012; Bull *et al.* 2006) or to regional prevalence.

In conclusion, this review has found a high prevalence of Human NoV among children in Africa. The potential for environmental transmission routes of Human NoV has been highlighted. Joint environmental and clinical surveys, during the same period, are warranted (Iwai *et al.* 2009) and these can also be used to gauge the effectiveness of control measures that aim to reduce environmental transmission. The relationship between Human NoV infection and disease in Africa is complex. This review highlights the need for systematic surveillance of gastroenteritis caused by Human NoV in children in Africa, as they may provide an efficient way to monitor the emergence of variant strains and to assist with the development of Human NoV vaccines.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

Appendix A. Supplementary data

The following are the supplementary data to this review:

1. Supplementary file 1: Flow chart displaying the study profile.
2. Supplementary file 2: Funnel of standard errors for included studies. (A) Prevalence studies of Human NoV.
3. Supplementary file 3: Meta-regression analysis of factors affecting proportion positive and genotypes.
4. Supplementary file 4: Distribution of Human NoV infections in sporadic gastroenteritis from different countries of Africa, January 1990-December 2013.
5. Supplementary file 5: Distribution of Human NoV genogroups (genotypes) among Children ≤ 5 years of age from 10 selected studies in Africa, 1990-2013.

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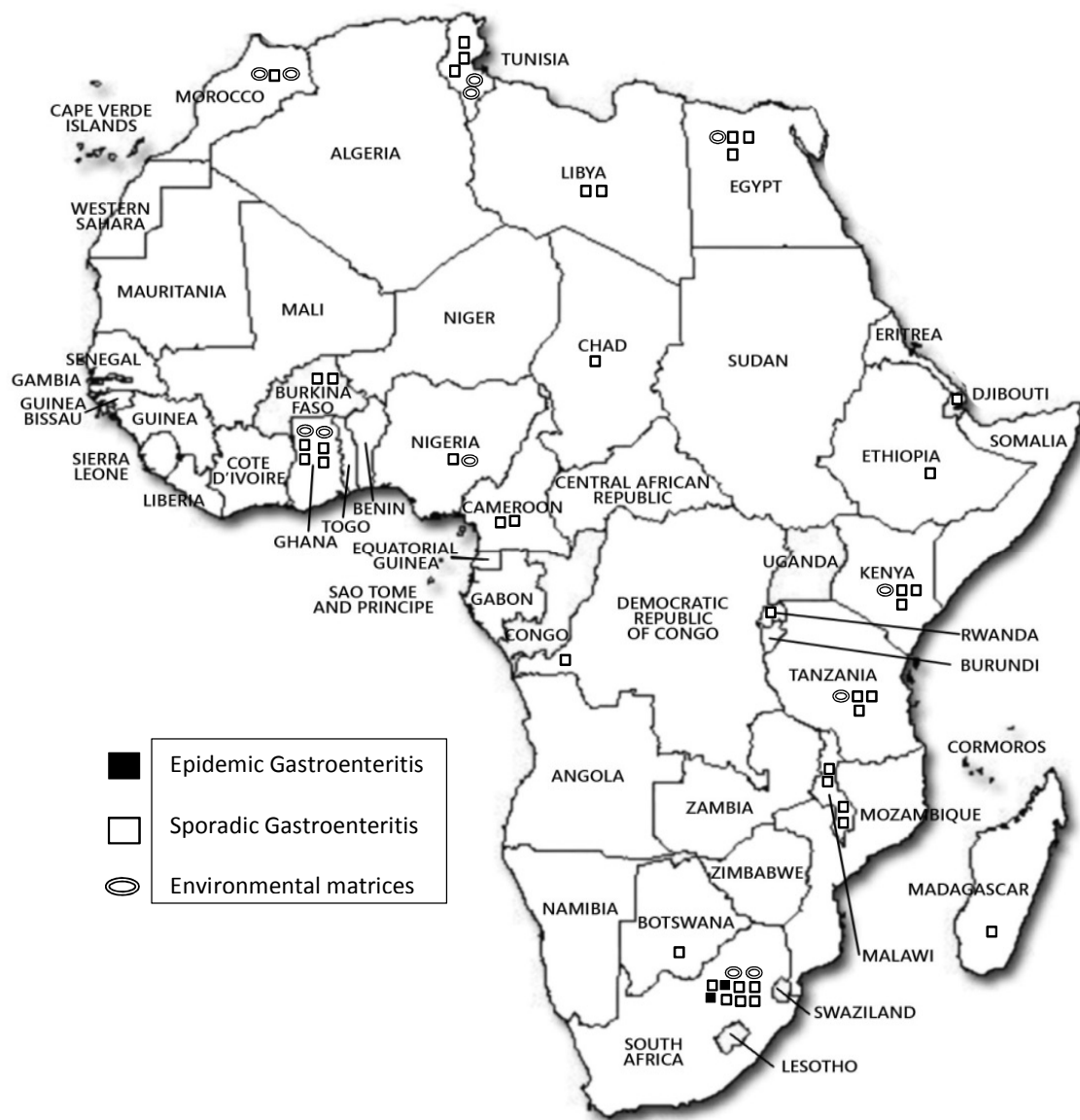


Figure 1: Distribution of selected studies for Human NoV in Africa. 55 selected studies where from 19 countries including: South Africa, Botswana, Malawi, Madagascar, Rwanda, Tanzania, Kenya, Ethiopia, Djibouti, Chad, Democratic Republic of Congo, Cameroon, Egypt, Morocco, Tunisia, Libya, Ghana, Nigeria and Burkina Faso. (Map of Africa obtained from www.kids.mongabay.com/elementary/Africa.html).

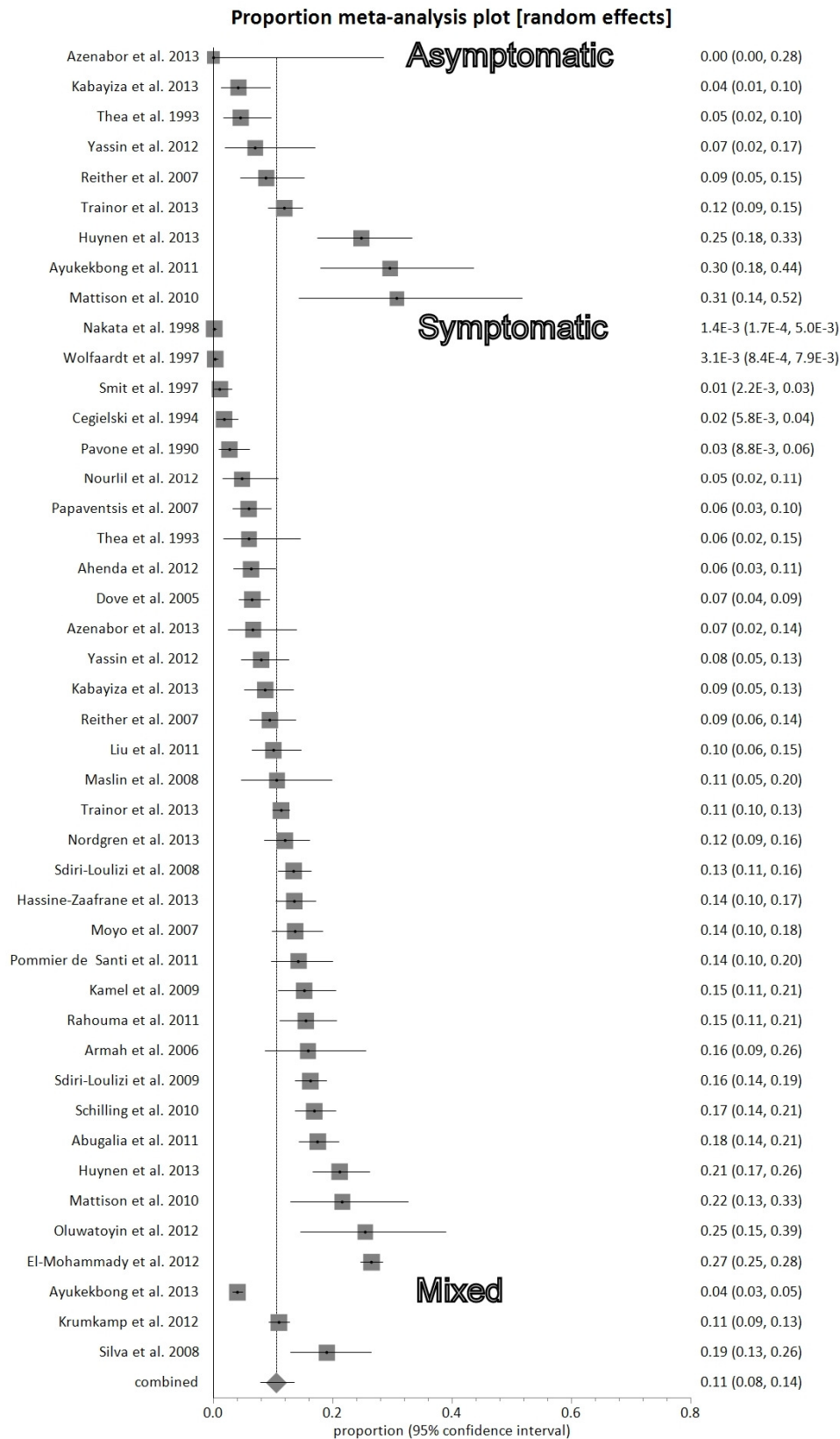


Figure 2

Figure 3

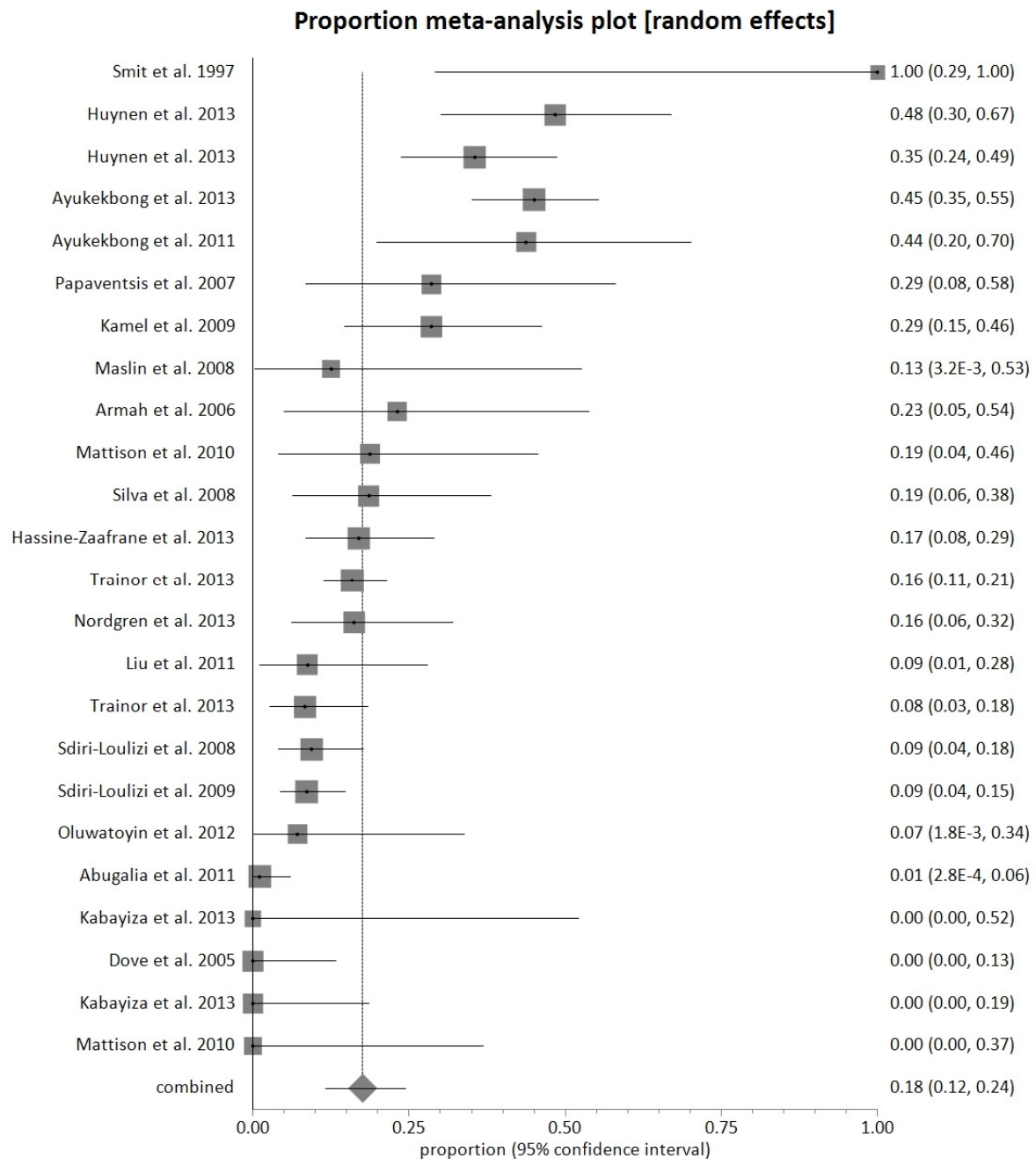


Figure 4

