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A narrative review on Rotavirus A in Mozambique

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ABSTRACT

Introduction: Rotavirus A (RVA) is a leading cause of acute infant gastroenteritis in Mozambique, responsible for approximately 13,000 annual infant deaths in peri-urban and other areas.

Aim: the present review aimed summarize the most relevant and recent literature regarding RVA infection in Mozambique.

Methods: the documents were obtained from electronic databases such as PubMed, Google Scholar, Scinapse, Scilit, and Microsoft Academic to find the leading scientific publications related to Mozambique's RVA.

Findings: The search allowed us to find 20 peer-reviewed journal articles, three official reports, eight abstracts from national conferences, one thesis, and other documents to supplement the information. Rotavirus frequency ranged between 24 to 42.4%, 34.8% attributable to Mozambique. Most data are hospital-based from Maputo, Sofala, Zambézia, and Nampula provinces. Nampula province shows the highest number of cases. Thus, there might be some bias on the geographical distribution of the virus. The prevalence is high in children less than one year. Regarding the control, the Expanded Program on Immunization (EPI) introduced a monovalent vaccine in September 2015 (Rotarix), which positively impacted the reduction of RVA cases. After vaccine introduction, a high diversity of RVA genotypes was observed, with the predominance of G1P[8] and the emergence of G9P[4], G9P[6], G3P[4]. However, only the whole genome sequence can confirm if it is due to the natural genotypes fluctuation. RVA infection was detected in swine, and a recent analysis reported an RVA strain from children clustered with different animal strains.

Conclusion: The scarce yet highly reliable research resources allowed scientists to detect RVA G1P[8] and other genotypes, potential animal reservoirs, and to find that RVA is more prevalent during the transition dry-rainy season, and the virus becomes more frequent when children approach the 11th month, to then decline as they age. It is essential to develop studies providing a broad view of RVA reservoirs as part of the strategy to control its dissemination.

Keywords: Rotavirus infections; Children; Diarrhea; Mozambique

INTRODUCTION

Diarrhea remains a tremendous public health problem globally and is associated with 446,000 deaths among children under five years old in 2016 [1]. In Mozambique, even with the strategies implemented to reduce diarrhea cases in the last two decades (improving hygiene, sanitation, and access to clean water) [2], diarrhea remains the leading cause of mortality of children under five years old, with 4383 deaths annually [1].

Rotavirus, particularly group A (RVA) [3], is among the significant causes of acute infant gastroenteritis globally [1,4]. Data from the global burden of annual RVA mortality shows that in 2016, about 128,500 children under five years old died, of which 104,733 in sub-Saharan Africa [1]. The World Health Organization [5] (WHO) recommended introducing the rotavirus vaccine in countries with high prevalence and countrywide continuous surveillance before and after the vaccine's introduction.

The global enteric multicenter study (GEMS) showed RVA as the leading cause of diarrheic diseases in Mozambique with an attributable factor of 34.8% and reported a prevalence ranging from 24 - 42.4% 6. Nevertheless, there is very little published literature on Mozambique's RVA and its impact on human or animal health, particularly in the northern and central regions of the country [2,7-10]. Thus, there is a need to expand

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surveillance and epidemiological studies to understand the impact of local strains and improve the current control measures [9-11]. It is also essential to identify the strains and compare them with others from different countries to understand the molecular epidemiology and design appropriate measures. Thus, this study reviews the most relevant information on RVA infection in Mozambique.

METHODS

We used Google Scholar, Scinapse, Scilit, PubMed, Scielo, and Microsoft Academic to find the leading scientific publications related to Mozambique's RVA to write this manuscript. The leading search keywords were "rotavirus" and "Mozambique." We selected scholarly documents with keywords or related in the title. In some cases, the titles presented Mozambique's districts or provinces' names, and some of the documents were about Rotavirus and other diarrheic diseases.

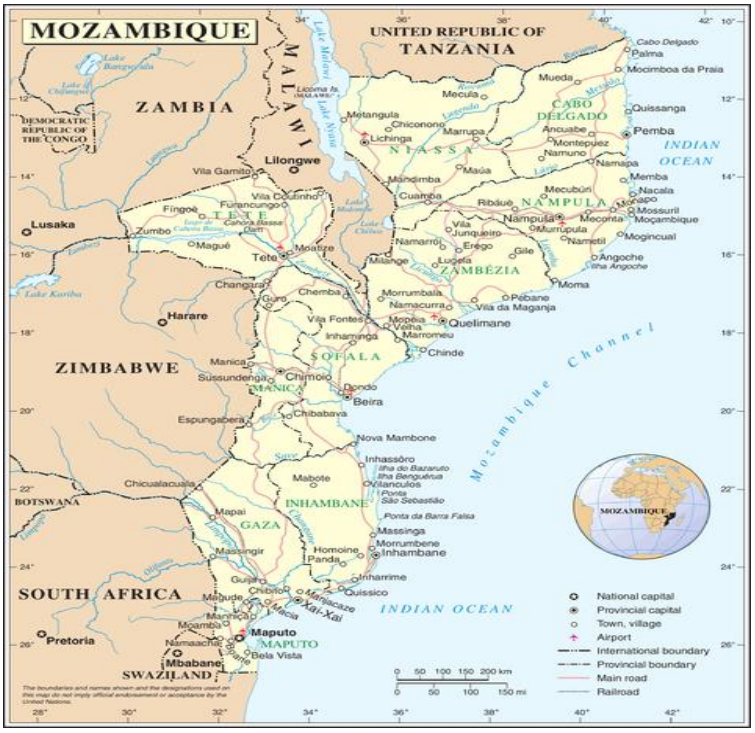
We found 20 peer-reviewed journal articles, three official reports, eight abstracts from national conferences, and one thesis through the search. We added other elements such as the map and figure as we reviewed the primary sources.

We analyzed the documents using the qualitative data analysis software Atlas.ti 9 (Atlas.ti Scientific Software Development GmbH, Berlin, 2020), using the codes "etiology," "transmission," "geographical distribution," "susceptible groups," "vaccination," "impact, surveillance, treatment," and "infrastructure." Then, we summarized the data into a coherent text, using other sources from the literature to provide more consistency to the text.

RESULTS AND DISCUSSION

Geographical distribution

First, it is essential to make a brief description of Mozambique (Map 1) so that anyone can easily understand how spread RVA is in Mozambique according to the current scholarly information. It is a tropical country with 801,590 km^2, located in Southeastern Africa, divided into eleven provinces, with an eastern coastline (Indian Ocean) from north to south. According to the last census (2017) [12], the population comprises 27,909,798 inhabitants, significantly below poverty. Diarrheic diseases are common and reported as the fourth major cause of mortality in children aged five years or less [2].



Map 1 - Mozambique, the country's regions, and cities. United Nations 16, under public domain

Rotavirus is highly prevalent among < 5-year old children in Mozambique [13]. Thus, non-surprisingly, there have been reports from different country areas. de Deus et al. [14] mentioned six surveillance sites from the National Surveillance of Diarrhea (ViNaDia): Hospital Geral José Macamo, Hospital Geral de Mavalane and Hospital Central de Maputo (Maputo City), Hospital Geral de Quelimane (Zambézia Province), Hospital Central da Beira (Sofala

Province), and Hospital Central de Nampula (Nampula Province). ViNaDia surveillance system produces most of the data on the epidemiology of RVA in Mozambique. INS is the leading institution studying RVA in Mozambique [10]. For the sake of research, the reference mentioned above virology laboratory of INS has the country's state-of-the-art equipment for RVA analysis [7,15], an integral component to achieve ViNaDia's goals. Manhiça Health Research Center (CISM) also develops studies on RVA[10]. Another laboratory with comparable equipment in the Directorate for Animal Sciences of the National Institute for Agricultural Research (IIAM) [8,9].

Nampula has registered the highest number of cases (see details in subsection 5.3) [7]. There are potential explanations for why this province presented most cases. For instance, (1) Nampula is the most populated province [12], and (2) there are serious hygiene issues in Nampula's urban areas impacting the spread of diarrheic diseases [17]. A recent analysis of the epidemiology of Rotavirus in Nampula observed that piped water was associated with rotavirus infection and suggested that this can be related to the water network that is old and damaged, while in the post-vaccine period age, year, and contact with different animals were associated with rotavirus infection [18]. It would be worthy of studying the epidemiology of RVA in the Novo Bairro area of Quelimane city, well-known as an urban area with very precarious sanitation and a history of cholera outbreak 30.

Mussa et al. [19] reported cases in the cities of Maputo and Matola, RVA infection was reported by de Deus et al. [14], in children less than five years old with diarrhea in Mavalane General Hospital (Maputo City) in 41.3% and Manhiça District Hospital (Maputo Province) in 44.3% [14]. On the other hand, Langa et al. [11] reported RVA infections in Chókwè District (Gaza Province) in 24.0% [11]. Based on the ViNaDiA platform, RVA infection was reported in four provinces of the country: Maputo city (southern region of the country), Sofala, Zambézia (Center region of the country), and Nampula (Northern region of the country), ranging from 12.2% - 40.2% regardless to the vaccine introduction period [14,20].

Vaccination

So far, there are four licensed vaccines for Rotavirus in the world: the pentavalent RotaTeq™, monovalent Rotatrix™ (GlaxoSmithKline Biologicals, Rixansart, Belgium), Rotavac® (Bharat Biotech, India), and Rotasiil® (Serum Institute of India Pvt. Ltd. India) [21]. Mozambique introduced Rotatrix™ in September 2015 as part of the National Immunization Program. The Instituto Nacional de Saúde and partner organizations have been assessing the vaccination outcomes. After vaccine introduction, there was a significant reduction in diarrhea hospitalization and rotavirus infection, from 40.2% in 2014 to 13.5% in 2017, and reduction cases occurred in undernourished children from 42.7% to 12.2% [18].

Susceptible groups

RVA is frequent in children up to 5 years old, with a slight majority in male patients [18,22]. A study reported the median age of hospitalization of 9 months in 2014 and 11 in 2015 during the pre-vaccine period than ten months in 2016 and 2017 in the post-vaccine period. In Chókwè, Langa et al. [11] found 94.1% of children positive for Rotavirus aged up to two years old. de Deus et al. [22] in Manhiça and Mavalane found 52.7% of RVA cases in children from 0 to 11 months. Similar results were found in a case-control study conducted in Manhiça, where children under one year had an attributable fraction of 34.8% of RVA infection [23]. Thus, these findings suggest that RVA infection is higher in children less than one year and decreases as they grow up.

Molecular characterization of RVA

Mozambique uses the WHO's algorithm for RVA detection and characterization [24]. Several studies on RVA uses ELISA through the commercial kits, mainly Prospect Oxoid with a specificity of 99.2% (96% - 100%) and sensitivity of 100% (95% - 100%). Reverse-transcriptase polymerase chain reaction (RT-PCR) performs the molecular characterization of RVA based on two significant proteins, VP7 and VP4, which gives the genotype combination G and P. The complete genome sequence is essential to perform the phylogenetic analysis and sequences comparison.

Globally the most common RVA genotypes are G1P[8], G2P[4], G3P[8], and G4P[8], being G1P[8] the most prevalent [25,26]. Studies conducted before the introduction of the vaccine in Mozambique (2015) reported G12P[8], G1P[8], and G12P[6] as the most common genotypes in Chokwé, a rural area in the Southern region of Mozambique [27]. João et al. [28], in a study conducted in rural (Manhiça) and urban (Maputo city) areas, found G2P[4] and G12P[6] as the most prevalent genotypes. However, after vaccine introduction, a high diversity of RVA genotypes was

observed, including the emergency of G9P[4], G9P[6], G3P[4], and G3P[8] in Mozambique [29]. Other authors also analyzed the most frequent genotypes in children with diarrhea but different areas [11]. The vaccine seems to

contribute to the increased diversity and uncommon strains circulating as G3P[4] and G3P[8], G4P[6]. However, only the complete genome sequences can confirm if it is due to the fluctuation of natural genotypes or the pressure of the vaccine.

RVA transmission pathways

RVA is a zoonotic virus able to be transmitted between different species. Swine is a significant reservoir [30], and P[6] strain has been reported in animals and children with diarrhea [11]. In Chòkwé, this strain was detected in children and clustered with three porcine prototype strains [11]. This finding shows the possible zoonotic RV transmission in Mozambique. There is a long way to build a concise body of knowledge on RVA in animals in Mozambique, but the currently known studies are a good starting point.

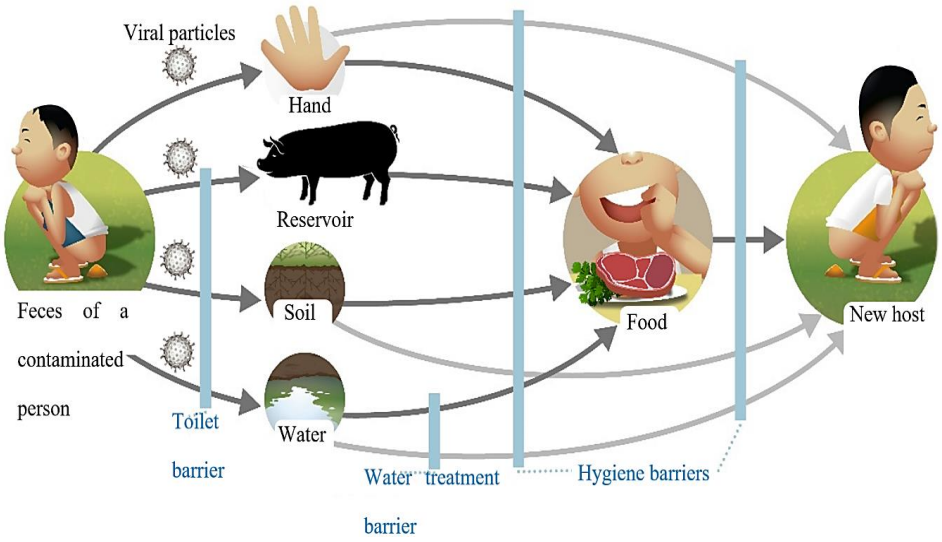


Figure 1 - Rotavirus transmission pathway. The vertical blue lines represent barriers to transmission. Adapted from the following sources: UNICEF Philippines et al. 34, licensed under the Creative Commons Attribution (CC-BY) 2.0 Generic; Beards 35, under CC-BY 3.0 Unported; Henderson 36, under Creative Commons 1.0 Universal Public Domain Dedication (CC0); and 37, licensed under Pixabay License (free for commercial use, no attribution required).

The reported data of Rotavirus in animals suggest the implantation of surveillance of Rotavirus in animals [31]. However, additional studies are needed to understand better the role of animals in the transmission of RVA in the country and the emergency of new strains.

RVA is a public health concern due to poor hygiene and environmental contamination (Fig. 1) [8]. Whole-genome sequencing of a mixed stool containing G12 and GXP[14] strains showed that the last one clustered with sequences from a diverse group of animal strains, highlighting the possible interspecies transmission of RVA in the country [32]. It was also observed that swine could carry the RVA without symptoms [9]. However, it is necessary to deepen the current knowledge on RVA reservoirs in Mozambique.

Most of the studies that analyzed the monthly distribution of RVA cases showed that the highest prevalence occurs during the cold/dry season [11,14,18]. The authors reported that RVA is more frequent during July, August, and September, with relatively low temperatures and low rainfall [11,14,18]. Furthermore, D'Souza et al. [33] performed a similar study in three Australian cities (Brisbane, Melbourne, and Canberra) and found similar results, suggesting that this trend is worldwide. However, since the vaccine was introduced, cases were shifted to the wet season (October and November) in Nampula province Northern of Mozambique [18]. It would be helpful to study how exactly weather affects the prevalence of RVA.

Health and commercial impact

In Mozambique, RVA is a significant cause of acute gastroenteritis and is associated with symptoms such as diarrhea [13,15], vomiting [38], resulting in dehydration [39], and undernutrition [22]. RVA and other diarrheic diseases often

demand high costs of medical assistance and hospitalization [7,15]. Swine presents similar symptoms as humans, varying in severity, resulting in significant losses in the commercial and familiar sectors [31].

CONCLUSION

Mozambique has data on RVA from surveillance and studies. Methods such as ELISA and RT-PCR provide highly reliable results, but they might be costly for routine analyzes. It would be valuable to promote more basic epidemiological and social research on RVA and build a more robust body of knowledge.

RVA affects Mozambique's infant health, particularly in children less than one-year-old. The prevalence has declined since the introduction of the vaccine.

The predominant genotypes change over time, and the most recent data point to the G1P[8] as the most common. The current epidemiological information might not reflect the country's current situation because most data came from Maputo City and province, Sofala, Zambézia, and Nampula provinces. There shall also be surveys in the community, rather than data only from people seeking medical care.

RVA also occurs in swine in Mozambique, but the virus is likely to occur in other carriers. It is essential to develop studies providing a broad view of RVA reservoirs as part of the strategy to control its dissemination.

Data confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Competing interests

The authors declare that there are no conflits of interest nor any form of support.

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