

Research Article



Factors Associated with Declining Incidence of HIV-2 in West Africa: A Systematic Literature Review

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Abstract | The literature suggests that West Africa is the epicenter of human immunodeficiency virus type 2 (HIV-2), with only sporadic cases occurring in other parts of the world. However, surveillance has shown that both the incidence and prevalence of HIV-2 infection are declining in West Africa. This systematic literature review identifies the factors influencing this decline. We generated secondary data from three selected electronic databases: PUBMED, Google Scholar, and Science Direct, using a mix of keywords and MESH terms such as HIV-2, decline, incidence, and West Africa. Studies were selected if they reported data on the factors responsible for the decline in HIV-2 incidence in West Africa. This review identified eighteen (n=18) articles published between 1994 and 2021 that met this requirement. Among the identified factors are the high mortality rate and loss to follow-up of HIV-2 patients, the pathogenicity of the HIV-2 virus, and the clinical picture of the disease depending on the sex of individuals.

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Introduction

The impacts of HIV-1 infection are severe in West Africa [1]. The possibility of an increasing multi-type HIV burden in West Africa, and elsewhere is purportedly posed by HIV-2, which is said to be localized to the same area [2].

The history of HIV-2 revealed that West Africa was where the virus first appeared around 1966 or earlier

[3, 4]. However, serological evidence confirmed the first incidence of the infection in 1985 in Senegal [5]. The first HIV-2 viral isolate was reported in a patient from Cape Verde in 1986 [6]. Generally, trends in HIV infection remain inconsistent across countries in West Africa, but HIV-2 has reportedly maintained an endemic and declining pattern in the Region since 1987 [7-9].

Before the recorded history of HIV-2 infection in

humans, the virus was domiciled in Sooty mangabeys (*Cercocebus atys atys*) as a version known as the Simian Immunodeficiency Virus (SIV) [10]. Since the virus was detected in humans, it has spread to 1-2 million people worldwide [11]. Numerous researchers questioned this statistic because HIV-2 was handled casually and its data are muddled [11-13]. Mutually exclusive HIV data seem to intensify this debate [14, 15, 1].

HIV-2 and HIV-1 share certain characteristics, such as mode of transmission, cellular target, and outcomes. Despite this similarity, HIV-2 has been sidelined in terms of research and surveillance primarily because of its sluggish pathogenicity [16-18]. However, the nature of viruses is changing rapidly [19] and this retained HIV-2 as an important infectious agent [20, 21]. Therefore, inequality in HIV intervention programs and research would mean that we are still far from the hope of enjoying the good fortune that would be brought about by the HIV-free world.

Nonetheless, with the partial commitment to curtail the HIV-2 burden, surveillance has been able to reveal what appears to be a “dramatic decline” in the incidence of the disease among populations in West Africa, most notably in Guinea-Bissau and Senegal, where the disease is more prevalent than anywhere else in West Africa [1, 9, 12, 22-25]. The obvious question that may arise is why the incidence of HIV-2 is declining. Some studies suggest that factors that primarily fuel the spread of the disease might be reduced or are being eliminated [26-28]. In another study, it was suggested that more research is required to understand the reasons behind the decline in HIV-2 incidence, considering that there are mechanisms that allow HIV-2-infected patients to live longer and experience less AIDS-related symptoms than

those infected with HIV-1 [29]. The identification and understanding of these factors are crucial for reinforcing health security and mitigating HIV-2 threats in West Africa. To find the most relevant information that addresses this issue, we conducted systematic inquiries into the literature and our findings are presented in this report.

Materials and Methods

Eligibility criteria

Studies were eligible if they reported data on the factors responsible for the decline of HIV-2 incidence in West Africa. Additional eligibility criteria were only studies written and published in the English language and studies involving the human population. There was no restriction on age. We excluded HIV-1 studies, studies of HIV in animals, studies with incomplete data, and studies without full text. Other studies excluded were those that did not report the outcome of interest and studies not conducted in West Africa. We also checked off citations and patents.

Information sources and search strategy

We focused on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol in carrying out this review [30].

We used a blend of relevant keywords and MESH (Medical Subject Headings) terms integrated with Boolean operators and special characters (wildcards and truncations) to conduct searches within three selected electronic databases: PUBMED, Google Scholar, and Science Direct. The search strategy included terms for “HIV-2”, “decline”, “incidence” and “West Africa” (see Table 1 for a specific search query). The search was open-ended until September 26, 2022.

Table 1: Review search queries within selected databases.

Database	Search query
PubMed	("Incidence"[Mesh] OR Prevalence[tiab] OR Rate*[tiab] OR Trend*[tiab] OR Epidemiolo*[tiab] OR Declin*[tiab] OR decreas*[tiab] OR low[tiab]) AND ("HIV-2"[Mesh] OR "Human immunodeficiency virus 2"[tiab]) AND ("Africa, Western"[Mesh] OR "West Africa"[tiab]) AND ("Risk Factor"[Mesh] OR "risk determinant*[tiab] OR "related factor*[tiab] OR "associated factor*[tiab])
Google scholar	All in title: HIV-2 OR "human immunodeficiency virus 2" OR retrovirus AND incidence Lower transmission trends OR prevalence OR rates OR decline OR decrease OR "risk factor" OR "risk determinants" OR "related factor" OR "associated factor" OR "West Africa"
Science direct	("HIV-2" OR "human immunodeficiency virus type-2") AND (transmission OR prevalence OR incidence OR Rates OR decline OR trends) AND "West Africa"

Selection process and data collection

We properly sorted the articles found in the databases and imported them into two web systems for screening, namely Covidence and Rayyan [31]. Two reviewers separately examined the titles, abstracts and full texts of all the articles. Each time an exclusion occurred, the reviewers recorded the reason on a template within these systems using the predefined selection criteria, and they discussed and resolved any disagreements about their decisions. The selection of these tools was made for some reasons, including the fact they both support full blinding for screening and conflict resolution, offer deduping functionality, have user-friendly interfaces, and have standardized templates that ensure timeliness. The systems also reduce the risk of human error and alleviate reviewer fatigue while processing articles. One reviewer compiled the results information from each included article using a PRISMA extraction template.

Quality and certainty assessment

We used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach to assess the overall quality and confidence of the evidence taking into account factors that can either raise or decrease the evidence’s certainty, such as the possibility of bias, inconsistency, indirectness, imprecision, and publication bias [32]. GRADE employs four categories; high, moderate, low, and very low to describe certainty in the evidence. More than that, based on GRADE’s recommendations, we used a scale of 1 to 9 to determine the relevance of the research outcome in the final “GRADEing”. Ratings of 1-3 show that the study’s outcome is of limited significance, ratings of 4-6 show that the outcome is significant but not crucial for making decisions, and ratings of 7-9 show that the outcome is crucially important.

Results

We generated eight hundred and twenty-six (n=826) results from the different databases searched: Pubmed (n=67), Google Scholar (n=235), and Sciendirect (n=524), of which eighty-four (n=84) were duplicates and were removed by both the Covidence (n=79) and Rayyan (n=5) automation. After deduplication, seven hundred and forty-two (n=742) records were screened against titles and abstracts, of which we excluded six hundred and seventy-six (n=676). In the screening phase, sixty-six (n=66) studies were eligible for full-text assessment. During the full-text review, we

excluded forty-eight (n=48) studies due to incomplete data, different study locations, undesirable outcomes, and unsatisfactory outcomes. Eighteen (n=18) studies fully met the predefined inclusion criteria, and we included them for data extraction. Figure 1 shows a further explanation of the successive selection process. Summary characteristics of the eighteen (n=18) included studies are presented in Table 2.

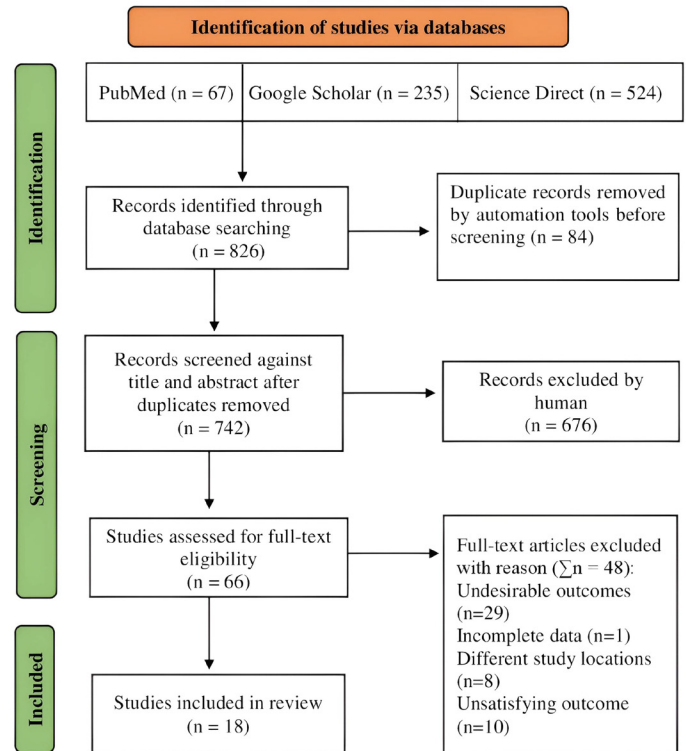


Figure 1: PRISMA flowchart of the articles selection process.

Results and Discussion

The results of our systematic review show that several factors were in play when the incidence of HIV-2 in West Africa started to decline.

Mortality or death and loss to follow-up (LTFU)

In this systematic literature review, we identified five studies (n=5) that cited mortality in HIV-2 patients, lack of therapy, and loss of follow-up (LTFU) as possible explanations for the declining incidence of HIV-2 in West Africa [33 -36, 19]. Likely causes of death include the fact that HIV-2 has an exceptionally long incubation period before it can become established in a host, which can discourage infected individuals from seeking early diagnosis and treatment, resulting in high morbidity and death [36]. Even in cases where diagnosis and treatment are promptly initiated, inadequate care can prevent suppression of the virus and high mortality can still occur [37].

Table 2: Summary characteristics of included studies.

Author names & Title & location of study publication year	Study design	Sample size	Population	Study quality	Specific findings	
Raugi et al., (2021) [12]	Long-term experience and outcomes of programmatic antiretroviral therapy for HIV-2 infection in Senegal, West Africa	Longitudinal observational cohort study	291	HIV-2-infected adults starting or receiving ART	High	Treatment for HIV-2 is Sub-optimal
Esbjornsson et al., (2018) [18]	Long-term follow-up of HIV-2-related AIDS and mortality in Guinea-Bissau: A prospective open cohort study (Guinea-Bissau)	Prospective open cohort study	2,984	Police officers	High	High probability of death and AIDS in HIV-1 and HIV-2 patients without therapy.
Poulsen et al., (1997) [33]	9-year HIV-2-associated mortality in an urban community in Bissau, west Africa	Prospective cohort study	1329	General population	Moderate	Adults with HIV-2 had mortality rates that were two times higher than those without the virus.
Togun et al., (2011) [34]	Pre-treatment mortality and loss-to-follow-up in HIV-1, HIV-2 and HIV-1/HIV-2 dually infected patients eligible for antiretroviral therapy in The Gambia, West Africa	Clinic-based cohort	HIV infected patients eligible for ART	Patients aged 15 years or older eligible for ART between June 2004 and September 2009	Moderate	Pre-treatment mortality rates among HIV-positive patients were found to be significant, and almost one-third of patients who were eligible for ART did not begin it.
Auld et al., (2014) [35]	Temporal Trends in Treatment Outcomes for HIV-1 and HIV-2-Infected Adults Enrolled in Côte d'Ivoire's National Antiretroviral Therapy Program	Retrospective chart review	3,682	Adults aged at least 15 years enrolled on ART	High	ART adherence and LTFU over time may explain increasing death.
Tchounga et al., (2016) [36]	Effect of sex and age on outcomes among hiv-2 infected patients starting antiretroviral therapy in west africa: A multicentre cohort study	Multicentre cohort study	1,825	HIV-2-infected individuals	Moderate	Men who are HIV-2 infected and on ART have greater mortality and LTFU rates than women.
Ghys et al., (1997) [40]	The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Côte d'Ivoire	Cross-sectional study with 1-week follow-up	1,201	Female sex workers (FSWs)	Moderate	Lower HIV-2 shedding from the cervicovaginal area.
Kanki et al., (1994) [41]	Slower heterosexual spread of HIV-2 than HIV-1 (Senegal)	Prospective cohort study	1452	Female sex workers	Moderate	HIV-2 heterosexual transmission spreads much more slowly than HIV-1.
Anderson et al., (2000) [43]	Plasma viral load in HIV-1 and HIV-2 singly and dually infected individuals in Guinea-Bissau West Africa	Experimental study	40	HIV-1 and HIV-2 positive patients	Moderate	lower plasma levels of HIV-2 RNA (low infectivity).
Adjorlolo-Johnson et al., (1994) [44]	Prospective comparison of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast	Prospective cohort study	18099	women giving birth between 1990 and 1992	High	Compared to the rate of prenatal transmission of HIV-1 (24.7%), the rate of perinatal transmission of HIV-2 (1.2%) was significantly lower.

Table continued on next page.....

Author names & publication year	Title & location of study	Study design	Sample size	Population	Study quality	Specific findings
O'Donovan et al., (2000) [45]	Maternal plasma viral RNA levels determine marked differences in mother-to-child transmission rates of HIV-1 and HIV-2 in The Gambia	Blinded, prospective cohort study	29,549	Pregnant women attending the eight largest antenatal clinics in The Gambia	High	Low levels of maternal HIV-2 RNA are a factor in the low MCT rate of HIV-2.
Tienen et al., (2010) [46]	Two Distinct Epidemics: The Rise of HIV-1 and Decline of HIV-2 Infection Between 1990 and 2007 in Rural Guinea-Bissau	cross-sectional community surveys	11,934 PYO	adult population 15 years and above	Moderate	The poor infectivity of HIV-2 and the significantly lower rates of vertical and sexual transmission compared to HIV-1 are contributing factors to the fall of HIV-2 incidence.
Chaillet et al., (2010) [47]	Evaluation of four rapid tests for diagnosis and differentiation of HIV-1 and HIV-2 infections in Guinea-Conakry, West Africa	Diagnostic study	445	Serum samples	Moderate	It may be preferable to utilize Immunoflow HIV1-HIV2 in place of SD Bioline HIV 1/2 3.0 as a discriminatory HIV test due to its poor performance.
Forbi et al., (2012) [48]	Absence of routine molecular testing and prevalence of HIV-2 infection in regions hardest-hit by HIV infection (Nasarawa, Nigeria)	Diagnostic study	900	Active female sex workers (FSWs)	High	Absence of molecular testing can lead to misclassified HIV-positive individuals.
Sousa, et al., (2016) [58]	Male Circumcision and the Epidemic Emergence of HIV-2 in West Africa	Literature review and Bayesian estimation	30 cities of all West African countries	Review of HIV-2 serosurveys	Moderate	Male circumcision (MC) rates have varied historically, which may explain the divergent HIV-2 distribution in West Africa.
Larsen et al., (1998) [69]	Declining HIV-2 prevalence and incidence among men in a community study from Guinea-Bissau	HIV serosurvey from 1987 to 1996	3747	Adult 15 years and above	Moderate	Incidence of HIV-2 overall was 0.54 per 100 person-years of observation (PYO), with men having a lower incidence (0.31 per 100 PYO) than women (0.72 per 100 PYO).
Da Silva et al., (2008) [70]	Changes in prevalence and incidence of HIV-1, HIV-2 and dual infections in urban areas of Bissau, Guinea-Bissau: is HIV-2 disappearing?	HIV serosurvey between May 2004 and January 2007	2,548	Adults aged at least 15 years	Moderate	HIV-2 decrease is influenced by age group and gender.
Gianelli et al., (2010) [27]	Prevalence and risk determinants of HIV-1 and HIV-2 infections in pregnant women in Bissau		23,869	Pregnant women attending the antenatal clinics of Bissau between January 2002 and June 2006	Moderate	Age of HIV testing, gender, ethnicity, and female circumcision affects HIV-2 spread.

In another study, a mortality rate of 5.8% was found in 551 HIV-2 patients on ART, while 10.2% went out of follow-up [38]. This coincides with another study showing that LTFU is associated with higher

mortality rates in ART recipients [39]. However, the age at which a patient is diagnosed has an impact on mortality and LTFU and is higher in males than in females [36, 38].

Slower transmission of HIV-2 or lower pathogenicity

Having sex with HIV-2-positive people without protection can spread the virus. However, in two studies (n=2) from our results, HIV-2 may spread more slowly between heterosexual partners. First, a cross-sectional study of female sex workers showed that individuals who tested positive for HIV-2 produced fewer cervicovaginal viral sheddings [40]. The second study found that the virus that infected female sex workers spread slowly between heterosexual partners [41]. This suggests that reduced HIV-2 incidence in West Africa may be associated with slower heterosexual transmission and lower virus concentrations in the genital tract. This is especially true since the results of these studies are consistent with those of other studies, such as a study conducted in Senegal, which observed that the presence and levels of HIV-2 RNA in the genital tract were lower in patients who were not treated compared to HIV-1 patients [42].

In addition, a study conducted in Guinea-Bissau shows that plasma from infected individuals contains less HIV-2 RNA [43]. This correlates with the results of studies in this review, in which four studies (n=4) from three African countries, namely Guinea-Bissau, Ivory Coast, and The Gambia, found that low levels of HIV-2 RNA reduced the risk of transmission from mother to child during pregnancy, childbirth or lactation [43-46]. These results suggest that a key factor in the decline in HIV-2 prevalence in West Africa was the low pathogenicity of the virus, caused by low levels of RNA in the plasma and genital tract of those infected.

Absence of molecular testing

The result of our review also shows that two studies (n=2) conducted among female sex workers showed that rapid serological HIV test kits have poor diagnostic performance, and the authors strongly recommended switching to molecular testing for diagnosis. First, in the study comparing four rapid serological HIV test kits, it was found that SD Biotec HIV 1/2 3.0, a popular discriminatory HIV test kit in Guinea-Conakry, performed poorly [47]. In the other study, conducted in Nigeria, 565 sex workers who underwent serological HIV testing tested negative for the virus. When the results were checked using a molecular approach (NucliSENS), 11 of the 565 HIV-negative samples tested positive for the virus [48]. Because of this, reliance on rapid HIV test kits

for diagnosis increases the likelihood of inconclusive or undifferentiated HIV status. Although tests based on nucleic acid is recommended for HIV diagnosis, a second-line assay has been developed to treat all possible HIV-2 sero-nonconclusive cases because some patients have an undetectable HIV-2 plasma RNA viral load [49]. However, performing this test requires compliance with appropriate laboratory quality control procedures and assistance from authorized personnel [50].

Circumcision

The role of circumcision in HIV prophylaxis has been the subject of considerable debate by many researchers [51]. However, studies have shown that arguments against male circumcision as HIV prophylaxis are unfounded and scientifically rejected without reasonable doubt [52-54], but safety concerns of circumcision related to its practice in underdeveloped countries remain worrisome [55,56]. Based on scientific evidence, the United Nations Joint Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) conducted an international expert consultation in 2007 endorsing male circumcision as a preventive strategy against HIV [57].

According to the results of a study (n = 1) in this review, male circumcision (MC) is another preventive measure specifically against the spread of HIV-2 in West Africa [58]. The researchers justified their findings by using Bayesian estimation to pull results from 30 West African countries. Initially, a study using dynamic simulation models suggested that MC could significantly reduce the prevalence of HIV in Africa, particularly in countries with low rates of male circumcision such as South Africa [59]. Cote d'Ivoire and Guinea-Bissau, following this pattern, now have high MC prevalence rates of 96.7% and 93.3%, respectively, with a drastic decline in HIV-2 incidence, indicating the authors' claim was correct [60]. Other West African nations with evidence of declining HIV-2 incidence also showed increased rates of male circumcision, such as Gambia (94.5%), Burkina Faso (83.3%), Guinea (84.2%), Senegal (93.5%), and Liberia (97.7%) [60].

Female circumcision (FC) (n=1) is believed to prevent HIV transmission, either by partner reduction, delaying first sexual activity, or promoting abstinence, particularly in young people, as the surgery should

resolve obsessive sex drives [61, 62]. However, evidence from research conducted in Mali shows that FC does not protect women from HIV infection [63]. Rather, the effectiveness of male circumcision might protect women from contracting HIV [64]. Since circumcision protects men from contracting HIV-2 [58], therefore, women are protected from contagion through the phenomenon of herd immunity.

Sub-optimal HIV-2 treatment

Based on our results, one study (n=1) suggests that the incidence of HIV-2 in West Africa may be declining due to sub-optimal HIV-2 therapy [12]. Participants in the study started treatment on time and responded to treatment. However, the authors noted that treatment for HIV-2 is still ineffective and there are significant barriers to better care [12]. Sub-optimal HIV-2 treatment is the result of several factors including antiviral resistance [65], poor adherence to therapy [36], low plasma viral load making diagnosis difficult [66], the lack of molecular testing in developing countries [50], and the challenge of selecting the best treatment option for the infection [38]. In general, treating HIV-2 is not the same as treating HIV-1. For example, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and several protease inhibitors used to treat HIV-1 are ineffective against HIV-2 [38, 14, 67]. Without antiretroviral therapy, the majority of HIV-2 carriers will eventually develop AIDS and mortality can increase [68].

Sex specific decline

The epidemiology of HIV-2 in West Africa shows that its prevalence and incidence in women have been consistently higher than in men, and older women bear the greatest burden [69]. From our results, three studies (n = 3) conducted in Guinea-Bissau show a more specific emphasis on disease patterns in relation to sex. The authors show in the studies that the incidence of HIV-2 in men is significantly lower than in women [27, 69, 70]. The decrease was in people no older than 45 years [27]. Research from West Africa confirmed these facts, and the explanation was based on differential mortality rates, loss of follow-up care [36], and an increase in male circumcision over time [58]. Underscoring factors that contribute to the high vulnerability of women to contracting the HIV-2 virus include socioeconomic vulnerabilities [71,72] and the fact that women are at higher risk due to the larger mucosal surface area exposed to infection and tissue injury [73].

Limitation

This systemic review detected the key factors responsible for the decline in HIV-2 incidence in West Africa. There may be other factors associated with the steady and rapid decline of this ailment in other parts of the world. Consequently, the suppositions of this study characterize the factors responsible for the decline in HIV-2 incidence in West Africa only. In addition, eligibility condition for English-only studies may have impacted our results, as studies published in other languages that might contain relevant information were excluded. Although the data from the studies included in this review may be helpful in understanding the overall trends in HIV-2 incidence in the region, they may not be applicable to individual countries. Finally, the lack of data on HIV-2 incidence in some countries means that the factors influencing the decline in incidence of the disease in West Africa remain largely unexplored.

Conclusions and Recommendations

Our review has classified the factors responsible for the steady decline of HIV-2 in West Africa. Prominent among these factors is the high mortality rate of HIV-2 patients, especially because the symptoms of the virus do not readily show up until the infection has progressed to fatal stages, leading to high morbidity and a decline in the number of active cases. We recommend that high-risk individuals living in West Africa should undergo regular screening for HIV-2. In addition, the absence of molecular testing to detect sub-patent levels of the virus has restricted the availability of data to determine the exact impact of HIV-2 in West Africa. Efforts should be made to improve the molecular diagnostic capacity of HIV-2 testing facilities. Furthermore, the sub-optimal HIV-2 treatment infrastructure that resulted in increased mortality of patients has paradoxically served to limit the spread of this infection. Finally, we found an interesting role of male circumcision in the decreased incidence of HIV-2 in West Africa. This finding should be further studied to determine the exact cellular, molecular, and immunological mechanisms of viral obstruction through male circumcision and its greater role in the limitation of other sexually transmitted diseases.

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Novelty Statement

Based on our systematic search, we're not aware of any systematic review available in the literature peculiar to the HIV-2 incidence decline in West Africa. Non-existent pool of data conveying this information could mire HIV intervention in the region. Our review congregates evidence to inform and recall authorities about the impact of HIV-2 in West Africa. The important concern, however, is whether the identified factors are sufficient to keep the virus in its nature and maintain the current pattern of the disease in West Africa.

Author's Contribution

LL conceptualized and designed the study plan, developed the search query and conducted the literature search, compiled the data, file uploads and submissions.

LL & OPN screened the articles, wrote and prepared the initial draft of the manuscript.

ICC & BBO manuscript writing and proofreading.

CTN review and approved the final manuscript draft prior to submission.

All authors revised and accepted the final version of the article for publication.

Conflict of interest

The authors have declared no conflict of interest.

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