

Systematic Review

Marburg Virus Disease Outbreaks – A Systematic Review

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Conflict of Interest: None.

Jamali YA., et al. (2023). 3(2): DOI: <https://doi.org/10.61919/jhrr.v3i2.541>

ABSTRACT

Background: Marburg virus disease (MARV) is a highly virulent disease that presents a significant threat to public health. First identified in 1967, MARV has since manifested sporadically across various regions, with varying consequences. This systematic review aims to collate and analyze epidemiological data to understand the impact of MARV globally.

Objective: The primary objective of this study was to synthesize data from past outbreaks to evaluate the epidemiological characteristics of MARV, understand its transmission dynamics, and assess the effectiveness of response strategies.

Methods: We conducted a systematic search across several academic databases including MEDLINE, Google Scholar, and Web of Science, up until August 2023. Studies were included if they reported the total number of cases and fatalities during MARV outbreaks. The meta-analysis focused on case fatality rates (CFRs) and seroprevalence measurements. Data from health ministries, the World Health Organization, and the Centers for Disease Control and Prevention were used to verify the findings.

Results: The review identified 16 studies for inclusion. The reported case fatality rates varied significantly across different outbreaks, with Angola (2006) reporting the highest number of cases (252) and deaths (227). The recent outbreak in Ghana (2023) indicated an uptick in both case numbers (40) and CFR (87.3%). The containment of an outbreak in Equatorial Guinea by June 2023 highlights the effectiveness of international cooperation and robust health systems.

Conclusion: The study concludes that the Marburg virus remains a critical concern for global health, particularly in regions with previous outbreaks. The data underscore the necessity for improved public health preparedness and response strategies in high-risk areas to mitigate future outbreaks.

Keywords: Marburg Virus Disease, Epidemiology, Outbreaks, Public Health, Case Fatality Rate, Seroprevalence, Systematic Review, Viral Haemorrhagic Fever, Global Health, Infection Control.

INTRODUCTION

The Marburg virus disease (MARV), closely related to the Ebola virus disease (EBOV), is a viral haemorrhagic fever of significant concern within the realm of infectious diseases. Both MARV and EBOV belong to the Filoviridae family, notorious for their severe manifestations and high mortality rates. The initial identification of the Marburg virus occurred in the German cities of Marburg and Frankfurt, leading to a protracted debate regarding its origins. Current evidence strongly suggests Uganda as the primary locus of the virus's emergence. The transmission dynamics of MARV are complex, involving direct contact with bats or other animal reservoirs, although the precise physiological mechanisms remain elusive. Human-to-human transmission is facilitated through unprotected exposure to infected bodily fluids, typically in household or healthcare settings, with an incubation period ranging from 3 to 21 days. The clinical presentation post-incubation is characterized by acute, non-specific symptoms including fever, chills, vomiting, diarrhoea, headache, and myalgia (1).

Despite multiple outbreaks across the African continent, MARV has historically received less public and scientific scrutiny compared to EBOV. Significant outbreaks in Uganda in 2012, 2014, and 2017 resulted in 15, 1, and 4 cases, respectively (3), highlighting the sporadic nature of MARV epidemics. The broader impact of such diseases extends well beyond Uganda, with central and southern African regions also experiencing outbreaks. Notably, the World Health Organization (WHO) confirmed the first case of MARV in

West Africa, specifically in Guinea, prior to last year, marking a significant geographical expansion of the disease which had been predominantly confined to other regions of Africa (4). This occurrence is particularly significant given the history of Ebola and other viral haemorrhagic fever epidemics in West Africa (5).

The reporting of the first MARV cases in Ghana to the WHO on July 19, 2022, marked a critical point in the understanding and response to the disease within the region (6). The identification of two infected individuals triggered a comprehensive contact tracing effort, monitoring 90 individuals to prevent further spread. This proactive response is reflective of the expected measures, considering the region's recent history with EBOV outbreaks. Furthermore, the situation in Ghana not only tests the resilience of the local healthcare system but also underscores the potential for MARV to affect global health security, beyond the African continent. The ongoing efforts to contain the Marburg virus disease underscore the importance of international collaboration and vigilance in the face of emerging infectious diseases, reflecting a commitment to safeguarding public health worldwide.

MATERIAL AND METHODS

We conducted a systematic review by meticulously searching various academic databases. These included MEDLINE, Google Scholar, Web of Science, African Journals Online, and Embase, alongside specialized publications within public health and infectious diseases disciplines. The search strategy was meticulously designed to encompass specific terms within the subject headings, such as "Marburg virus," "Marburg virus disease," "Marburg virus disease outbreaks," "human Marburg outbreaks," and "Human Marburg disease." Our focus was on articles published in English up until August 2023, ensuring a comprehensive and up-to-date review of the literature.

For inclusion in our meta-analysis, we selected studies that reported both the overall number of fatalities and the total number of cases resulting from MVD outbreaks. Additionally, studies providing case fatality rates (CFRs) and seroprevalence measurements in percentages were considered. Conversely, we excluded any studies or publications that lacked complete counts of fatalities or cases, as well as those failing to publish primary data. Specifically, research focusing on Ebola species not harmful to humans or those not resulting in human fatalities were also omitted from our analysis. Given the abundance of publications available, preference was given to those offering the most comprehensive data or the latest information.

To reconcile any discrepancies in the reported number of cases and fatalities, it was imperative to cross-reference the collected data with the databases from various health ministries, the World Health Organization (WHO), and the Centers for Disease Control and Prevention (CDC). This step ensured the accuracy and reliability of our findings. Inclusion criteria for seroprevalence studies were stringent, considering only population-based research involving individuals in optimal health. Studies documenting antibody prevalence during outbreaks or in ill populations were excluded, as they did not align with our research focus.

Data extraction was conducted using a standardized form, enabling the systematic collection of relevant information from each eligible study and epidemic report. Required data elements included the author's name, the country of origin, the total number of diagnosed cases, the total number of deaths, the publication year, and the specific month and year of the epidemic. For population-based seroprevalence studies, additional data on the sample size and the proportion of seropositive samples were collected. This rigorous methodological approach facilitated a comprehensive synthesis of available evidence on MVD outbreaks, contributing valuable insights into the disease's epidemiology and impact.

RESULTS

The PRISMA flow chart presents the process of identification, screening, eligibility, and inclusion of studies in a systematic review. Initially, 186 records were identified from databases (107) and registers (79). Prior to screening, 77 records were removed due to duplication (35), being marked as ineligible by automation tools (25), or for other reasons (17). Consequently, 109 records were screened, which led to the exclusion of 30 records. Efforts to retrieve 79 reports were made, but 14 could not be retrieved. Out of the 65 reports assessed for eligibility, 49 were excluded for various reasons: 16 for reason 1, 18 for reason 2, and 15 for reason 3. Ultimately, 16 studies met the criteria and were included in the review.

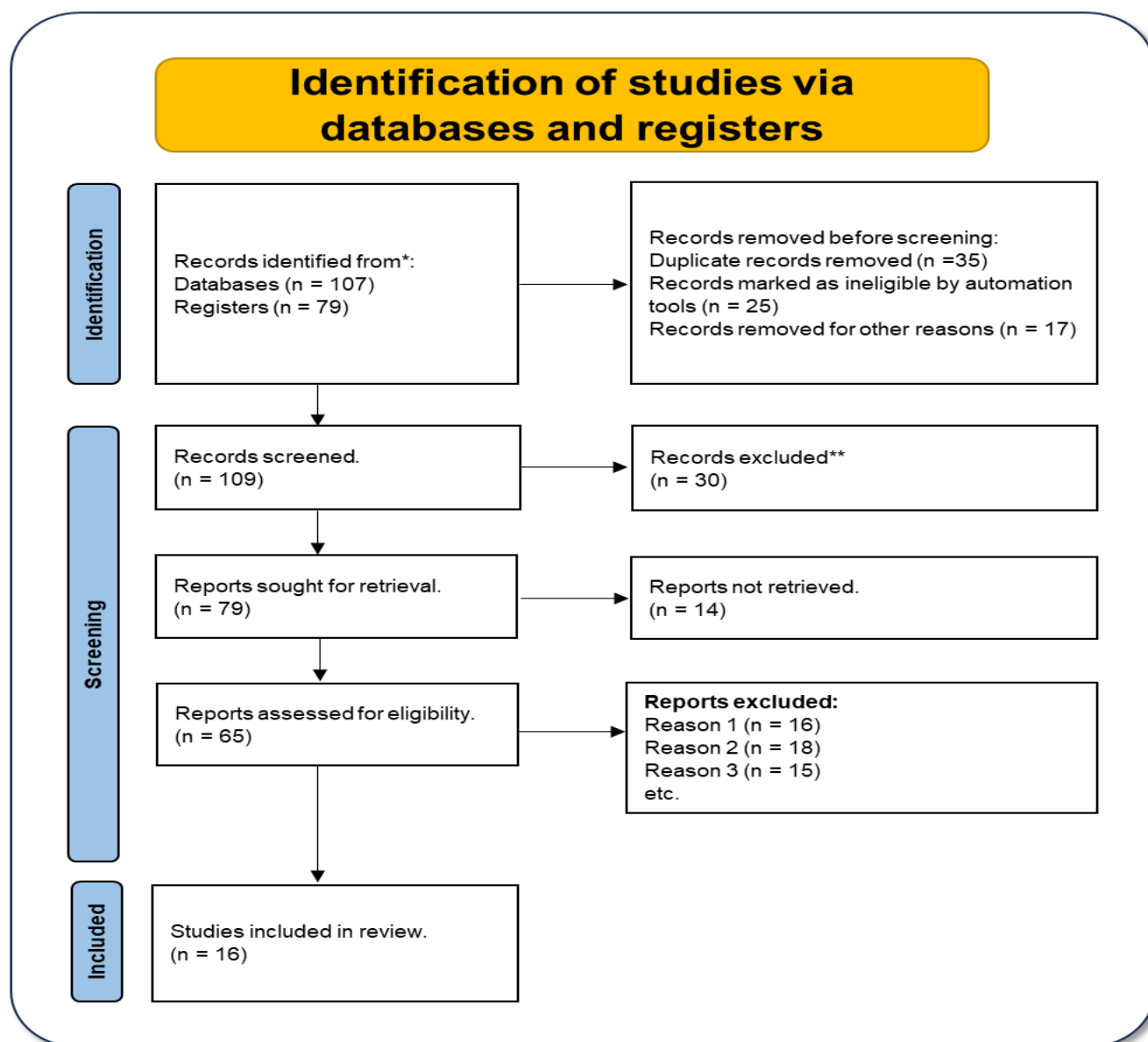


Figure 1 PRISMA Flowchart

Table 1 Study Characteristics

| First Author and Year of Publication | Country of Outbreak | Suspected Origin | Number of Cases | Deaths (Case Fatality Rate) |
|--------------------------------------|------------------------------|---|-----------------|-----------------------------|
| Felfmann et al., 1996 (13) | Germany, Yugoslavia | Uganda | 31 | 7 (23%) |
| Conrad et al., 1978 (14) | Johannesburg, South Africa | Zimbabwe | 3 | 1 (33%) |
| Smith et al., 1982 (15) | Kenya | Kenya | 2 | 1 (50%) |
| Johnson et al., (16) | Kenya | Kenya | 1 | 1 (100%) |
| Nikiforov VV et al., (17) | Russia | Russia | 1 | 1 (100%) |
| Bausch et al., 2006 (8) | Democratic Republic of Congo | Durba, DRC | 154 | 128 (83%) |
| Towner et al., 2006 (18) | Angola | Uige Province, Angola | 252 | 227 (90%) |
| Adjemian et al., 2011 (19) | Uganda | Lead and Gold mine in Kamwenge District, Uganda | 4 | 1 (25%) |

| First Author and Year of Publication | Country of Outbreak | Suspected Origin | Number of Cases | Deaths (Case Fatality Rate) |
|---|-----------------------|--|-----------------|-----------------------------|
| Fujita et al., (20) | USA ex Uganda | Cave in Maramagambo forest, Uganda | 1 | 0 (0%) |
| Timen et al., WHO 2008 (21,22) | Netherlands ex Uganda | Cave in Maramagambo forest, Uganda | 1 | 1 (100%) |
| Albarino et al., 2013 (23) | Uganda | Kabale | 15 | 4 (27%) |
| Uganda Ministry of Health 2014 (24) | Uganda | Kampala | 1 | 1 (100%) |
| Nyakarahuka et al., 2019 (25) | Uganda | Kween | 4 | 3 (75%) |
| Center for Disease Control and Prevention 2021 (26) | Guinea | Gueckedou | 1 | 1 (100%) |
| Center for Disease Control and Prevention 2022 (27) | Ghana | Ashanti Region | 3 | 2 (66.7%) |
| WHO 2023 (12) | Ghana | Bata, Evinayong, Nsork, Nsok Nsomo, Ebibiyin | 40 | 35 (87.3%) |

The data presented in the table delineates the global incidence of Marburg virus disease (MVD) outbreaks across various geographical locations and years, alongside the corresponding case fatality rates (CFRs). Notably, the earliest recorded outbreak in the table occurred in Germany and Yugoslavia in 1996, with 31 cases and a CFR of 23%, and the origin of the virus was suspected to be Uganda (13). In Johannesburg, South Africa, an outbreak in 1978 resulting from a suspected Zimbabwean origin reported a CFR of 33% with 3 cases (14). Kenya experienced outbreaks in 1982 and another year with a total of 3 cases, each with a high CFR of 50% and 100%, respectively, indicating the virus's lethality when it occurs (15, 16).

Russia reported an outbreak with a single case that resulted in death, marking a 100% CFR, which emphasizes the severity of the disease irrespective of the geographic location (17). The Democratic Republic of Congo faced a substantial outbreak in 2006 with 154 cases and an 83% CFR, one of the highest numbers of cases reported (8). Angola had the largest outbreak represented in the table with 252 cases in 2006 and an alarming CFR of 90%, highlighting the virus's devastating impact in Uige Province (18).

Uganda, a recurring location for MVD outbreaks, had several incidents over the years with varying CFRs. An outbreak in 2011 originating from a lead and gold mine in Kamwenge District reported 4 cases with a CFR of 25% (19). Additional outbreaks in Uganda with origins ranging from Kabale to Kampala and Kween were documented between 2013 and 2019, with case numbers ranging from 1 to 15 and CFRs between 25% to 100% (23, 24, 25).

The United States reported an imported case from Uganda in an individual who had visited a cave in Maramagambo forest, but fortunately, there were no deaths (0% CFR) (20). The Netherlands also reported an imported case from the same Ugandan forest in 2008, which resulted in a fatality (100% CFR) (21, 22).

More recently, the table includes data from Guinea and Ghana, marking the spread of MVD to West Africa. Guinea reported a single case with a fatality in 2021 (100% CFR) (26). Ghana experienced an outbreak with 3 cases and a 66.7% CFR in 2022 and a more significant outbreak in 2023 with 40 cases and an 87.3% CFR, indicating a concerning increase in both the number of cases and the CFR (27, 12).

In summary, the table encapsulates the grim reality of MVD's impact, with case fatality rates often exceeding 50%, underlining the critical need for effective control and preventive measures against this deadly virus. The spread across continents and the persistence of outbreaks over the years reflect the ongoing challenge that MVD poses to global health.

DISCUSSION

The epidemiological profile of Marburg virus disease (MARV) as elucidated by this study underscores the heterogeneity of the virus's impact across different geographical regions. Since the initial recognition of MARV in 1967 following simultaneous outbreaks in Serbia, Belgrade, Frankfurt, and Marburg, the virus has intermittently surfaced, leading to sporadic yet severe outbreaks in nations such as the Democratic Republic of the Congo, Kenya, and South Africa (7,8). The foundational work conducted during these early outbreaks was pivotal in defining the clinical landscape of MARV and establishing a protocol for subsequent research and intervention strategies.

The zoonotic nature of MARV was highlighted by an incident in Uganda in 2008 involving tourists visiting a cave inhabited by Rousettus bats, prompting a deeper inquiry into potential risky behaviors and vectors of transmission (9). The recent outbreak in

Ghana has further complicated the understanding of transmission dynamics. The fatalities in this outbreak, believed to be the result of human-to-human transmission, add complexity to the epidemiological characteristics of the virus and hint at possible unidentified vectors or transmission mechanisms, considering the absence of direct links to dead animals (10,11).

The successful mitigation of the outbreak in Equatorial Guinea by June 2023, as reported by the World Health Organization (2023), was achieved through stringent quarantine measures and the completion of a 42-day observation period with no new cases (12). This scenario exemplifies the crucial role robust health systems and international cooperation play in the effective management of MARV outbreaks.

This comprehensive review has identified Angola as having experienced the most substantial MARV outbreaks, both in case numbers and fatality rates. Such insights necessitate a targeted approach to public health interventions in areas at elevated risk for MARV emergence. The observed variation in case fatality rates among different outbreaks suggests that diverse factors, including the genetic variation of MARV strains, healthcare infrastructure robustness, and the timeliness of the public health response, may influence outbreak severity.

CONCLUSION

In conclusion, given the substantial mortality rates associated with MARV, particularly highlighted by the outbreaks in Angola, it is crucial for public health preparedness to focus on regions prone to MARV emergence. The strategies should encompass enhancing surveillance systems, strengthening health infrastructure, and fostering international collaboration for rapid response to potential outbreaks. This study's strength lies in its extensive data collection and analysis across multiple outbreaks, providing a comprehensive overview of the global MARV landscape. However, it also encounters limitations, such as the variability in data quality and the potential underreporting in some regions, which could skew the true incidence and severity of the disease. Future research should aim to decipher the transmission dynamics further, explore the genetic diversity of MARV strains, and evaluate the efficacy of intervention strategies to refine the public health approach to managing MARV outbreaks.

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