Marburg virus disease outbreaks, mathematical models, and disease parameters: a systematic review

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The 2023 Marburg virus disease outbreaks in Equatorial Guinea and Tanzania highlighted the importance of better understanding this lethal pathogen. We did a systematic review (PROSPERO CRD42023393345) of peer-reviewed articles reporting historical outbreaks, modelling studies, and epidemiological parameters focused on Marburg virus disease. We searched PubMed and Web of Science from database inception to March 31, 2023. Two reviewers evaluated all titles and abstracts with consensus-based decision making. To ensure agreement, 13 (31%) of 42 studies were double-extracted and a custom-designed quality assessment questionnaire was used for risk of bias assessment. We present detailed information on 478 reported cases and 385 deaths from Marburg virus disease. Analysis of historical outbreaks and seroprevalence estimates suggests the possibility of undetected Marburg virus disease outbreaks, asymptomatic transmission, or cross-reactivity with other pathogens, or a combination of these. Only one study presented a mathematical model of Marburg virus transmission. We estimate an unadjusted, pooled total random effect case fatality ratio of 61·9% (95% CI 38·8–80·6; I^2=93%). We identify epidemiological parameters relating to transmission and natural history, for which there are few estimates. This systematic review and the accompanying database provide a comprehensive overview of Marburg virus disease epidemiology and identify key knowledge gaps, contributing crucial information for mathematical models to support future Marburg virus disease epidemic responses.

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See Online for appendix

Introduction

Infectious disease outbreaks pose a substantial threat to health and wellbeing globally.[1–3] Since the emergence of SARS-CoV-2 at the end of 2019, there have been several other outbreaks of emerging or re-emerging pathogens, including mpox (formerly known as monkeypox),[4] novel hepatitis in children,[5] Ebola virus disease,[6] and Marburg virus disease.[7,8] These examples show that the world remains susceptible to infectious disease outbreaks and underscore the importance of developing a better understanding of pathogens that are more likely to cause epidemics in the future.

In 2018, WHO published a list of nine known infectious diseases for research and development prioritisation due to their epidemic and pandemic potential and the absence of licensed vaccines or therapeutics.[9,10] This list was updated in 2023 to include COVID-19.[9] Among the listed pathogens is Marburg virus, a lethal infectious Filoviridae single-stranded RNA virus of the *Marburgvirus* genus, first described in Germany and Serbia (formerly Yugoslavia) in 1967.[11] Subsequent outbreaks of Marburg virus disease have primarily occurred in sub-Saharan Africa, including outbreaks in Equatorial Guinea and Tanzania in 2023.[7,8]

The host of Marburg virus is the fruit bat (*Rousettus aegyptiacus*), with transmission to humans occurring via direct contact with an infected animal host.[12,13] Human-to-human transmission has also been observed, primarily occurring in household or health-care settings with insufficient infection protection and control measures—for example, via contact with bodily fluids from a patient with Marburg virus disease.[14,15] Phylogenetic analyses have confirmed multiple spillovers from bats to humans,[16] but the first known human outbreak was associated with African green monkeys (*Cercopithecus aethiops*).[17] The *Marburgvirus* genus contains two viruses—Marburg virus and Ravn virus—that have a genetic divergence of approximately 20%, with Marburg virus having six variants with fewer genomic differences than Ravn virus.[11] Both viruses are indistinguishable in their clinical presentation, with symptoms including fever, severe headaches, and malaise, which can progressively develop into severe haemorrhagic fever, including spontaneous bleeding from one or more orifices.[11,17] Although there is a high risk of serious illness on infection,[16] supportive care has been shown to increase

Key messages

- We provide an overview of all outbreaks of Marburg virus disease from PubMed and Web of Science from database inception to March 31, 2023, consisting of 478 reported cases and 385 deaths.
- We estimate an unadjusted, pooled total random effect case-fatality ratio for Marburg virus disease of 61·9% (95% CI 38·8–80·6; I^2=93%).
- We identify important epidemiological parameters relating to Marburg virus disease transmission and natural history that are poorly characterised in the literature.
- The extensive collection of knowledge gathered here will be crucial in developing mathematical models for use in the early stages of future outbreaks of Marburg virus disease.
- All data are published alongside this article in the R package epireview, with functionality to easily update the database as new data become available.

the chance of survival in the absence of Marburg virus disease-specific treatments.[17] However, previously published overviews have shown that, to date, the majority of reported patients with Marburg virus disease have died.[11,17]

Mathematical models of disease transmission and control can be deployed in response to infectious disease outbreaks and are used to guide policy, for example by projecting plausible epidemic trajectories and expected health-care demand and assessing the potential effects of interventions.[18,19] Epidemiological parameters are key inputs to such models, for example governing the rates at which individuals move through disease states. However, gathering information on model structures and appropriate parameter values can be time-consuming and impede real-time modelling.

To address these issues, we have systematically reviewed the literature relevant to rapid design of dynamic transmission models for pathogens with high epidemic potential, focusing on Marburg virus disease. We have collated available information on outbreaks, modelling studies, and epidemiological parameters related to transmissibility, disease severity, delays, risk factors, mutation rates, and seroprevalence. We highlight knowledge gaps and provide a key resource for modelling future outbreaks of Marburg virus disease or similar (known or unknown) pathogens.

Methods

PRISMA checklists for this systematic review have been included in the appendix (pp 13–15).

Search strategy and study selection

We searched PubMed and Web of Science for published mathematical transmission models and articles reporting on Marburg virus disease transmission, evolution, natural history, severity, seroprevalence, and size of previous outbreaks published from database inception to March 31, 2023 (appendix p 2). Inclusion and exclusion criteria were applied (appendix p 4). In Covidence, two independent reviewers (from GC-D, HJTU, PD, KC, BL, JS, and CM) screened each title and abstract and then each full text to assess eligibility for data extraction. Covidence does not record reasons for abstract exclusion. Disagreements were resolved by consensus between reviewers.

For more on **Covidence** see https://get.covidence.org/systematic-review

Data extraction

13 reviewers (GC-D, KM, RM, HJTU, PD, RKN, JTH, CG, DN, JW, SvE, AC, and CM) extracted data on article information (publication details and risk of bias), estimated parameters (value, uncertainty intervals, distribution, context, and risk factors), outbreaks (dates, locations, and case and death numbers), and models (model type and structure, interventions modelled, transmission routes, and assumptions) from the included studies into a Microsoft Access database (version 2305), with one reviewer per full-text article. Risk of bias was assessed by use of a seven-question form addressing the quality and reliability of the methods, assumptions, and data. For each of the randomly selected 13 (31%) of 42 full-text articles, extraction was done by two independent reviewers from the previously mentioned 13 reviewers. Consensus on discordant results was established before each reviewer extracted data from their assigned articles (appendix p 2). We collated information only from outbreaks that were reported to be complete.

We extracted parameter values, units, uncertainty intervals, and ranges (capturing heterogeneity in estimates across different population groups, time, or location) for all parameters except risk factors. Study context was also recorded, when reported. We extracted risk factors investigated in the studies and if they were statistically significant or adjusted, or both. We chose not to extract odds ratio estimates because varying stratifications and reference groups complicate comparison across studies. Information extracted about previous outbreaks, namely the number of cases and deaths, was further used to generate estimates of the case-fatality ratio (CFR). Full details on data extraction, including descriptions of variables and predefined options for categorical variables, are in the appendix (pp 4–7).

R package

We designed an R package, epireview, in which all curated data on epidemiological parameters, models, and outbreaks are publicly available.[20] A dedicated vignette explains how independent contributors can add information to the package, so that it provides a live view of the latest knowledge on Marburg virus disease (appendix p 12).

Data analysis

Unless otherwise specified, uncertainty intervals in tables and figures (eg, 95% CI or 95% credible intervals) were extracted from the full-text articles or computed from reported central estimates and standard errors (appendix p 3). In the following, an unadjusted CFR estimate is an estimate in which the raw number of deaths is divided by the raw number of cases, with no weighting or controlling for other variables or cases with unknown outcomes.

We did two meta-analyses for the CFR, one with CFR estimates extracted from the studies and the second with unadjusted CFRs computed from extracted outbreak data. Comparison between the two sets of estimates enabled assessment of any bias due to outbreaks for which there were no CFR estimates or multiple reported CFR estimates in the literature. For this analysis, we defined an outbreak as one or more cases identified in the same country within the same date range. These outbreaks included single cases—often related to zoonotic spillover or importation events—and large

outbreaks. We ensured that each case was counted only once: if multiple studies reported the same outbreak, we chose the study covering the longest period. We estimated exact 95% binomial CIs on individual outbreak estimates.

Meta-analyses were done by use of the meta R package,[21] providing a total common effect and a total random effect pooled CFR estimate with 95% CI and statistics on heterogeneity in CFR across studies (appendix p 3). Overall quality assessment scores were calculated as a mean of the responses to the seven questions, excluding non-applicable questions (ie, if the quality assessment question was not applicable to a study it did not contribute to the score). A local polynomial regression fit using the R function loess was used to analyse trends in quality assessment scores by publication year. Although we excluded systematic reviews from our search, we used those listed in the appendix (p 16) to ensure that no outbreaks were missed and that parameter estimates were within the previously reported ranges. Analyses were done with R (version 4.2.2).

Results

The search returned 4410 studies from which we removed 1256 duplicates (figure 1). We screened the abstracts of the remaining 3154 studies and 221 were kept for full-text review. 177 studies were further excluded, leaving 42 studies included for data extraction.

We collated evidence from 13 studies reporting 23 observed Marburg virus disease outbreaks. On the basis of the reported dates and locations, we identified seven distinct outbreaks (table 1). These outbreaks included the first identified one in Marburg, Germany, and Serbia (formerly Yugoslavia), from which Marburg virus disease was identified and named; an outbreak in DR Congo from 1998 to 2000; a series of cases from Johannesburg, South Africa, in early 1975 (linked to previous travel from Zimbabwe); three outbreaks in Uganda; and an outbreak in Angola in 2004–05. In addition, we noted the reporting of individual cases of Marburg virus disease in Kenya in 1980 and 1987 (probably caused by animal exposure); in Russian Federation in 1988 and 1990 (both linked to a laboratory worker in a research facility); and in the Netherlands and the USA in 2008, both linked to the 2007 Ugandan outbreak. At the time of the literature search, there were no peer-reviewed studies on the 2023 outbreaks in Equatorial Guinea and Tanzania. We include both outbreaks in table 1 on the basis of WHO-reported numbers[34,35] after the end of the outbreak was declared. These numbers are not included in the epireview database, which could be updated in the future as and when peer-reviewed articles are available.

The only transmission modelling study of Marburg virus disease was by Ajelli and Merler.[36] The authors used a stochastic, individual-based, Susceptible-Exposed-Infectious-Removed model to examine the effects of behaviour change interventions on the number of

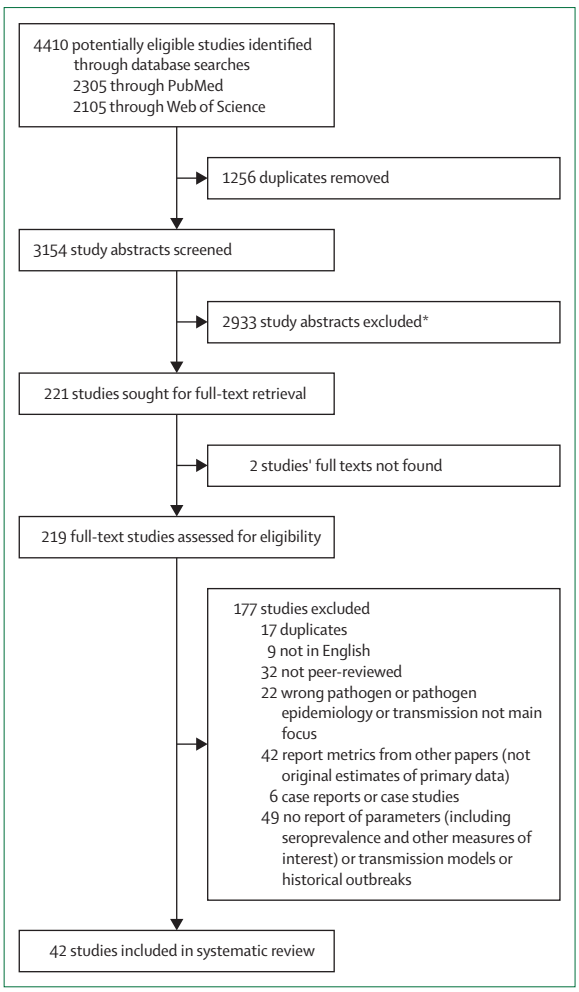

Figure 1: **Study selection**
*Reasons for abstract exclusion not provided by Covidence.

Marburg virus disease cases and deaths.[36] Transmission in the model occurred via direct, non-sexual human contact, assuming homogeneous mixing; transmission rates were heterogeneous over time with temporal changes in viral load and hence transmissibility; susceptibility was assumed to be age-dependent; and the latent and incubation periods were assumed to coincide.[36] The potential effects of quarantine were simulated, although they were not explicitly based on real-world data. As detailed later, the authors provided estimates of the mean generation time and the basic reproduction number (R_0).[36]

Overall, we extracted 71 epidemiological parameter estimates. The parameter definitions and details of the extraction process in the accompanying R package epireview[20] are given in the appendix (pp 4–7). Seroprevalence estimates were the most frequently reported in the literature, followed by epidemiological delays (eg, incubation period) and disease severity. Two studies reported on transmission parameters

	Study	Start	End	Deaths (n)	Confirmed cases (n)	Confirmation method
Germany and Serbia (formerly known as Yugoslavia), 1968						
Marburg and Frankfurt	Albariño et al (2013)[22]	Aug 18, 1968	Nov 13, 1968	5	23 confirmed, 1 asymptomatic	Symptoms
Marburg, Frankfurt, and Belgrade	Martini et al (1973)[23]*	August, 1968	November, 1968	7	31 confirmed, 1 asymptomatic	Symptoms
Unspecified location	Pavlin et al (2014)[24]	1967	NA	7	31 confirmed	NA
South Africa and Zimbabwe, 1975						
Johannesburg	Conrad et al (1978)[25]*	Feb 12, 1975	NA	1	3 confirmed, 1 severe or hospitalised	Molecular
Kenya, 1980						
Unspecified location	Pavlin et al (2014)[24]*	1980	NA	1	2 confirmed	NA
Kenya, 1987						
Unspecified location	Pavlin et al (2014)[24]*	1987	NA	1	1 confirmed	NA
Russian Federation, 1988						
Unspecified location	Pavlin et al (2014)[24]*	1988	NA	1	1 confirmed	NA
Russian Federation, 1990						
Unspecified location	Pavlin et al (2014)[24]*	1990	NA	0	1 confirmed	NA
DR Congo, 1998						
Durba and Watsa	Borchert et al (2002)[26]	October, 1998	May, 1999	61	73 confirmed, 0 severe or hospitalised	Symptoms
Durba and Watsa	Bausch et al (2006)[16]	October, 1998	September, 2000	125	48 confirmed, 106 suspected, 0 severe or hospitalised	Molecular
Durba and Watsa	Borchert et al (2006)[27]	October, 1998	August, 2000	NA	76 confirmed, 33 suspected, 0 asymptomatic	Molecular
Unspecified location	Pavlin et al (2014)[24]*	1998	2000	128	154 confirmed	NA
Angola, 2005						
Unspecified location	Carroll et al (2013)[28]	2005	2005	227	252 confirmed, 0 severe or hospitalised	NA
Unspecified location	Pavlin et al (2014)[24]*	2004	2005	227	252 confirmed	NA
Uige Province	Towner et al (2006)[29]	October, 2004	July, 2005	227	252 confirmed, 0 severe or hospitalised	NA
Uganda, 2007						
Kamwenge and Ibanda	Adjemian et al (2011)[30]	June 10, 2007	Sept 14, 2007	1	4 confirmed, 0 severe or hospitalised	Molecular
Unspecified location	Pavlin et al (2014)[24]*	2007	NA	2	4 confirmed	NA
Netherlands, 2008						
Unspecified location	Pavlin et al (2014)[24]*	2008	NA	1	1 confirmed	NA
USA, 2008						
Colorado	Pavlin et al (2014)[24]*	2008	NA	0	1 confirmed	NA
Uganda, 2012						
Kabale, Ibanda, Mbarara, and Kampala	Albariño et al (2013)[22]	Oct 18, 2012	Nov 7, 2012	4	15 confirmed	Molecular
Ibanda, Kabale, and Kamwenge districts	Knust et al (2015)[31]*	July, 2012	Nov 10, 2012	15	15 confirmed, 11 suspected	Molecular
Ibanda and Kabale	Mbonye et al (2012)[32]	September, 2012	Nov 13, 2012	7	9 confirmed, 5 suspected	Molecular
Uganda, 2014						
Kampala	Nyakarahuka et al (2017)[33]*	Sept 17, 2014	Sept 28, 2014	1	1 confirmed, 1 severe or hospitalised	Molecular
Equatorial Guinea, 2023†						
Unspecified location	WHO (2023)[34]	Feb 13, 2023	June 8, 2023	35	17 confirmed, 23 suspected	Molecular
Tanzania, 2023†						
Bukoba district and Kagera region	WHO (2023)[35]	March 21, 2023	June 2, 2023	6	8 confirmed, 1 suspected	Molecular

We report the country and outbreak year; the location refers to the place of the actual outbreak in the country if known. NA=not available—ie, information unable to be found in or extracted from the literature. *Unique outbreaks (478 reported cases [confirmed and suspected] and 385 deaths). †The 2023 outbreaks in Equatorial Guinea and Tanzania are captured from WHO announcements after the end of the outbreaks was declared. These data are not from peer-reviewed articles and not captured in the epireview database.

Table 1: **Overview of Marburg virus diseases outbreaks in countries and locations as reported in the studies included in this systematic review**

(eg, attack rates and reproduction numbers),[27,36] and three provided estimates of evolutionary mutation rates.[28,37,38] We also extracted reported risk factors for different outcomes, namely, infection, severe disease, seropositivity, recovery, and death.

Reproduction number estimates were reported in two studies.[27,36] Ajelli and colleagues used a mathematical model to estimate R_0 for the 2005 Angola outbreak. They estimated that R_0 was 1·59 (95% CI 1·53–1·66),[36] suggesting that in the absence of mitigation efforts, the virus would be expected to propagate in a similar population. They also provided the only estimate of doubling time, at 12·4 days (11·3–13·6).[36] Borchert and colleagues[27] estimated the effective reproduction number

(R_e) based on secondary attack rates derived from seroprevalence in contacts of confirmed cases in DR Congo in 2002. This study also provided the only estimate of attack rate, at 21%.[27]

Six CFR estimates were reported, corresponding to the outbreaks in Angola in 2005,[36] DR Congo in 1999,[16] the original 1968 outbreak in Germany and Serbia (formerly Yugoslavia),[23] and three estimates from the 2012 Uganda outbreak (figure 2, appendix p 10).[31,32] Pooling these estimates gave a total common effect CFR of 80·6% (95% CI 77·3–83·6; I^2=93%) and a total random effect CFR of 61·9% (38·8–80·6; I^2=93%). Additionally, we estimated an unadjusted, pooled CFR with the extracted historical outbreak data (appendix p 10), combining data from 467 confirmed cases and 11 suspected cases across 13 distinct outbreaks with 385 reported deaths.[16,22–30,33–35] The pooled common effect CFR estimate from the extracted outbreak data was 80·5% (76·7–83·8; I^2=82%) and the pooled random effect CFR was 63·8% (41·6–81·3; I^2=82%), which are both consistent with the previously published estimates.[39]

We collated estimates of the generation time, incubation period, time in care, and time from symptom onset to care seeking, death, or other outcomes (figure 3; appendix p 8). The two mean generation time estimates were based on viral load data from non-human primates under two distinct assumptions—namely, that infectiousness is directly proportional to viral load, and probability of death is directly proportional to viral load.[36,41] This study also estimated the time from symptom onset to death by use of additional assumptions about these relationships.[36] The sole estimate of time in care was a median of 14·3 days (range 4–22) based on the time six survivors of the 2012 Uganda outbreak spent in care, with a median duration in isolation of 22 days (range 16–30).[31] The two incubation period estimates came from studies from the 1970s that only reported ranges with little overlap (figure 3).[23,40] Central estimates of time from symptom onset to care seeking across the 1975 South Africa, 1998 DR Congo, and 2012 Uganda outbreaks were consistently less than 5 days, although Bausch and colleagues[16] showed a large range of delays from symptom onset to seeking medical care[31,40] for the 1998 DR Congo outbreak.

We extracted 13 risk factors for Marburg virus infection and seropositivity from four studies (appendix p 9).[12,16,31,42] Having contact with someone with confirmed Marburg virus disease, including through working in funeral and burial services, was a statistically significant risk factor for infection. The classification of other encompassed a wide range of factors, such as prevalence of infection in the host reservoir, subsistence activities, and previous invasive medical treatment, and as such is not directly comparable, although some constituted statistically significant risk factors.[12,31,42] Sex was not significantly associated with Marburg virus infection.[31] Although similar risk factors were explored to assess effects on seropositivity, the only statistically significant risk identified for this outcome was known admission to hospital with Marburg virus disease.

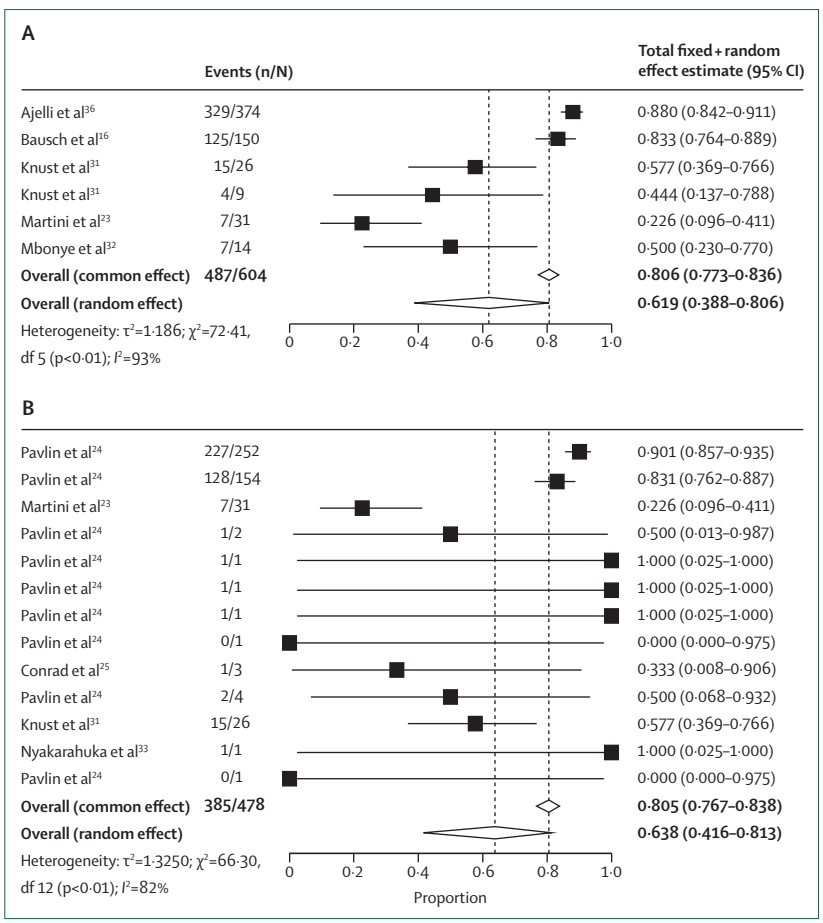

Figure 2: **CFR meta-analyses by use of logit-transformed proportions and a GLMM**
Black squares indicate study estimates. White diamonds represent overall common effect estimates, in which all data are effectively pooled and assumed to come from a single data-generating process with one common CFR, and overall random effect estimates that allow the CFR to vary by study and accordingly give different weights to each study when determining an overall estimate (appendix p 3).[23] The number of events indicates the number of deaths. Multiple listings of the same study indicate separate outbreaks (table 1). (A) CFR estimates reported in the included studies. (B) CFR estimated from extracted outbreak data, including only one observation per outbreak in the study with the longest duration of outbreak reported, ensuring no case is counted twice. CFR=case-fatality ratio. GLMM=generalised linear mixed-effects model (appendix p 3).

Three studies reported molecular evolutionary rates of Marburg virus; two estimated evolutionary rates by use of whole-genome sequencing[28,37] and one study estimated them based on individual genes.[38] The three evolutionary rate estimates from whole genomes are largely consistent with one another, but those based on individual genes tended to be lower (figure 3).

21 studies contained seroprevalence estimates across a 38-year period—from 1980 to 2018—in 15 countries, predominantly in sub-Saharan Africa (table 2).[23,27,42–44,46–61] The presence of antibodies was assessed by a range of assays: indirect fluorescent antibody (IFA; six studies[42,44,48,53,55,62]) assay, haemagglutination inhibition assay (HAI; one study[59]), IgG (seven studies[27,43,45–47,49,58]),

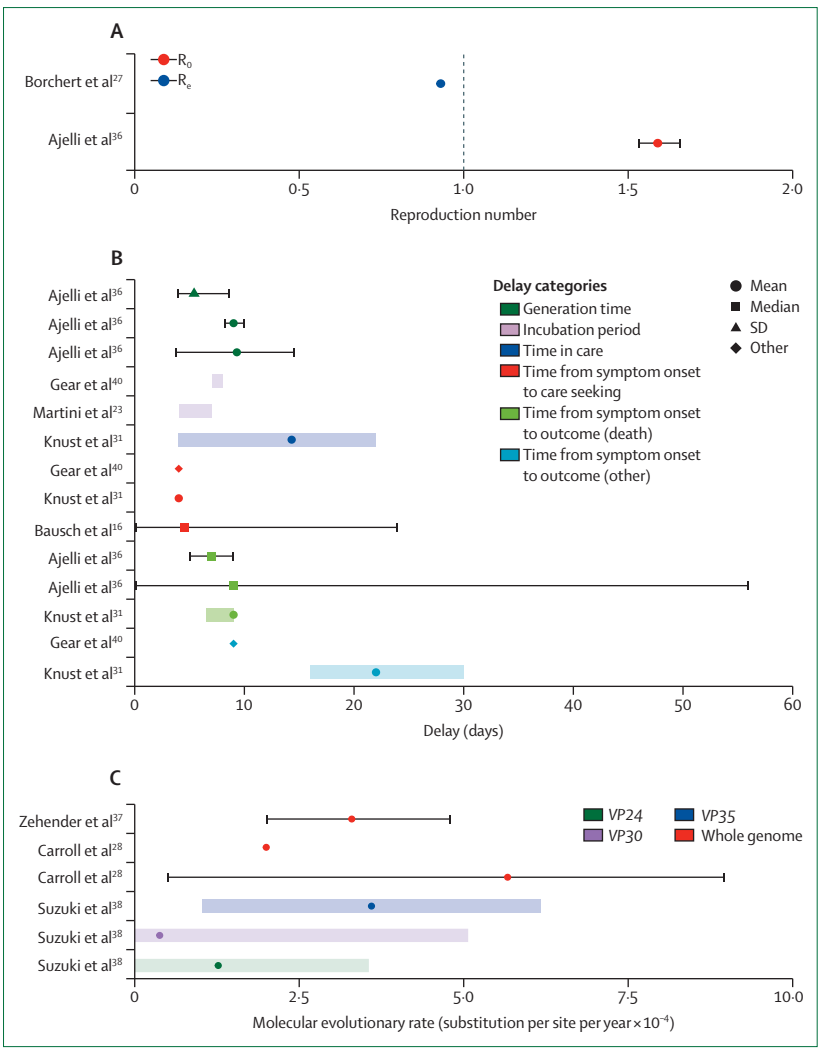

Figure 3: **Overview of the reproduction numbers, epidemiological delays, and evolutionary rate estimates**
Solid lines represent uncertainty intervals and shaded lines indicate a parameter range (eg, across different populations or over time). (A) Estimates of the reproduction number. The dashed vertical line is the threshold for epidemic growth. (B) Delay parameters, stratified into five categories. Diamond other category type is anything that did not fit into other categories—eg, the estimate type was not recorded. (C) Evolutionary rates of different genes stratified into four categories; points represent central estimates. R_0=basic reproduction number. R_e=effective reproduction number.

and IgM (two studies[56,57]). The remaining studies did not specify the assay used.[20,43,54] IgG and IgM were used for all studies from 1995 onwards, highlighting developments in serology and the retirement of assays testing for IFA and HAI. The studies included in this systematic review showed low prevalence of antibodies in surveyed populations, with approximately a third of studies reporting a seroprevalence of 0%.[23,47,48,52,54,58,61] Among studies with estimates above zero, seroprevalence ranged from 0·5% in the Republic of the Congo in 2011,[45] to 2·1% in health-care workers in DR Congo in 2001–02,[47] to 4·5% in Uganda in 1984.[59] Overall, the evidence gathered here indicates high susceptibility to Marburg virus disease among populations in the surveyed regions, including Tanzania, where one of the 2023 outbreaks occurred.[57] However, these seroprevalence estimates must be interpreted in the context of the very small sample sizes of most of the studies.

The results of the quality assessment are summarised in the appendix (p 10). The number of non-applicable answers are driven by more descriptive studies, such as seroprevalence studies that did not use a model or statistical analysis. Articles on transmission parameters had, on average, the highest quality assessment scores (reproduction number article score 0·80; other transmission parameters article score 0·87—we note the small number of articles in this category) and articles on seroprevalence had the lowest score of 0·48. Scores improved over time (appendix p 10), which could also explain the differences in quality assessment score between parameters, as seroprevalence articles tended to be published earlier than other study types.

Discussion

This systematic review presents a comprehensive set of mathematical models, outbreaks, and epidemiological parameters of Marburg virus disease. Historical outbreaks and case reports in the peer-reviewed literature were rare, with only seven outbreaks reported, and small in size compared with other pathogens, including other viral haemorrhagic fevers, such as Ebola virus disease. Only two outbreaks had over 100 confirmed cases (154 cases in DR Congo in 1998 and 254 cases in Angola in 2005), with the remainder reporting 31 cases or fewer. For most parameters, we were only able to obtain a small number of estimates, many of which were only reported as point estimates with no quantification of uncertainty. Seroprevalence of Marburg virus disease was the metric most widely reported across many locations in sub-Saharan Africa and indicates that seroprevalence is generally low. However, serosurveys suggest that some past outbreaks might have gone undetected. Reported seroprevalence in the Central African Republic is high (3·2%, range among subgroups 1·0–7·4) despite having no recorded Marburg virus disease outbreaks, although these results might stem from cross-reactivity or low assay specificity. Seroprevalence estimates of Marburg virus disease are consistently lower than for Ebola virus disease, although estimates are often reported together.[43,45,48,57]

An R_0 of 1·59 (95% CI 1·53–1·66) was estimated for the largest known outbreak to date in Angola.[36] However, Borchert and colleagues[27] estimated an R_e of 0·93 for the 1998 DR Congo outbreak after the introduction of public health and social measures, suggesting that such interventions can effectively mitigate Marburg virus transmission.

The pooled CFR estimates provide several key insights. The pooled random effect CFR of 61·9% (95% CI 38·8–80·6; I^2=93%) highlights the heterogeneity in CFR across outbreaks. By comparison, the pooled common

	Survey year	Parameter type*	Seroprevalence (uncertainty)	Seropositive people (n)	Sample size (n)	Population group	Timing of survey	Disaggregated data available
Central African Republic								
Gonzalez et al (2000)[43]	November, 1995	IgG	2·40% (range 0–5·6)	33	1340	..	..	..
Johnson et al (1993)[44]	..	IFA	..	3	427	Outdoor workers	..	..
Johnson et al (1993)[44]	..	IFA	3·20% (range 1·0–7·4)	137	4295	General population	..	Age, region, and sex
Republic of the Congo								
Moyen et al (2015)[45]	March 3–July 7, 2011	IgG	0·50%	..	..	..	Pre outbreak	..
DR Congo								
Bausch et al (2003)[46]	May, 1999	IgG	2·00%	15	912	..	Mid outbreak	..
Borchert et al (2005)[42]	..	IFA	0·00% (range 0–1·2)	0	300	..	Post outbreak	..
Borchert et al (2006)[27]	..	IgG	1·65% (95% CI 0·2–5·8)	..	..	Household contacts of survivors	Post outbreak	..
Borchert et al (2007)[47]	2001–02	IgG	2·10%	..	..	Health-care workers	Post outbreak	..
Gabon								
Ivanoff et al (1982)[48]	February–March, 1980	IFA	0·00%	0	197	..	..	..
Ivanoff et al (1982)[48]	February–March, 1980	IFA	0·00%	0	28	Pregnant women	..	..
Germany								
Becker et al (1992)[49]	..	IgG	2·60%	..	..	Other	..	..
Guinea, Liberia, and Sierra Leone								
O'Hearn et al (2016)[50]	2007–14	IgG	10·70%	71	663	Other	..	..
Kenya								
Johnson et al (1993a)[51]	1980–81	IFA	..	8	1899	..	..	Region
Johnson et al (1993b)[44]	..	IFA	0·00%	0	741	General population	Post outbreak	..
Martini (1973)[23]	..	Unspecified	..	0	79	Other	Post outbreak	..
Smith et al (1982)[52]	..	Unspecified	..	2	186	People under investigation	Post outbreak	..
Smith et al (1982)[52]	..	Unspecified	..	3	100	Health-care workers	Post outbreak	..
Smith et al (1982)[52]	..	Unspecified	..	0	224	General population	Post outbreak	..
Smith et al (1982)[52]	..	Unspecified	..	0	63	Other	Post outbreak	..
Smith et al (1982)[52]	..	Unspecified	..	0	79	Other	Post outbreak	..
Smith et al (1982)[52]	..	Unspecified	..	0	44	Outdoor workers	Post outbreak	..
Liberia								
Van der Waals et al (1986)[53]	1981–82	IFA	1·30%	3	225	Other	Other	Other, region
Madagascar								
Mathiot et al (1989)[54]	..	Unspecified	0·00%	0	381	..	Other	Region
Nigeria								
Tomori et al (1988)[55]	..	IFA	1·70%	29	1677	General population	..	..
Sierra Leone								
Schoepp et al (2014)[56]	2006–08	IgM	3·60%	..	..	People under investigation	Other	..
Tanzania								
Rugarabamu et al (2022)[57]	June–November, 2018	IgM	0·30%	1	308	..	Other	Region
Uganda								
Smiley Evans et al (2018)[58]	March–July, 2013	IgG	..	0	331	Other	..	..
Rodhain et al (1989)[59]	May, 1984	HAI	4·50%	6	132	..	..	..
Cameroon, Central African Republic, Chad, Republic of the Congo, Equatorial Guinea, and Gabon								
Gonzalez et al (1989)[60]	1985–87	Unspecified	0·39%	20	5070	General population	..	Region

Estimates were primarily reported as percentages. Associated uncertainty and sample sizes are provided where these were reported. Where available, additional information regarding the location and timing of the estimates, the antibody being tested for, the target population, the timing in relation to any ongoing outbreak, and the availability of disaggregated data is also summarised. IFA=indirect fluorescent antibody assay. Unspecified= unspecified assay. *HAI=hemagglutination inhibition assay.

Table 2: **Overview of seroprevalence estimates for Marburg virus disease as reported in the included studies**

effect CFR of 80·6% (77·3–83·6; I^2=93%) is skewed towards the two large outbreaks in Angola and DR Congo, which had very high CFRs. These data present a possibly misleadingly narrow uncertainty interval, but highlight that Marburg virus disease outbreaks with higher transmissibility might also be associated with higher severity. The results from the meta-analyses of reported CFR parameters and computed, unadjusted CFR from outbreak data are consistent, and our estimates are in line with a previous systematic review.[39] All CFR estimates—irrespective of the method—are extremely high, implying very high costs of human life in the affected countries that are, to date, all located in sub-Saharan Africa. Low seroprevalence estimates in these regions, combined with high fatality ratios and an R_0 above 1, show the pandemic potential of Marburg virus disease.

Our gaps in knowledge are substantial. Although we found some epidemiological estimates, several are from the previous century and based on poor-quality data; for example, most estimates of the CFR for Marburg virus disease reported in the literature are unadjusted estimates.[16,31,32,36] Crucial model inputs, such as the generation time, were estimated from primate studies and would benefit from confirmation from human outbreak data. Marburg virus evolutionary rates were also imperfectly characterised across only a few, sometimes dated, studies with small sample sizes and some methodological issues, including not accounting for synonymous mutations.[28,37,38] The reported substitution rates are also substantially lower than those reported for Ebola virus.[63] Although such comparison should be interpreted with the caveats above in mind, this points to Marburg virus evolving approximately 3 times more slowly than Ebola virus.[28,37,64] With a shorter mean generation time of 9·15 days (appendix p 3; approximately half that of Ebola; 15·3 days[65]), these results suggest that very little pathogen genetic diversity between Marburg virus disease cases is to be expected, and hence genomic data might be of little value in inferring transmission trends in future epidemics.[63] However, better characterisation of Marburg virus disease evolution should be prioritised on the research agenda.

The 2023 outbreaks of Marburg virus disease in Equatorial Guinea and Tanzania were controlled through basic measures, such as infection prevention and control and risk communication and community engagement.[66] WHO declared the end of the Equatorial Guinea outbreak on June 8, 2023 (17 laboratory-confirmed cases, 12 deaths, and a further 23 probable cases, all of whom died),[34] and the Ministry of Health of Tanzania confirmed the end of the first outbreak on June 2, 2023 (eight laboratory-confirmed cases, one probable case, and six deaths).[35] These are severe and traumatic events for the communities affected, but are also opportunities to gather higher-quality data. Careful collection of patient information, documentation of disease progression, and regular follow-ups post-infection would enable the research community to better characterise epidemiological delays and risk factors for infection and death.

The collection of parameters presented here, a synthesis of peer-reviewed information up to March 31, 2023, will enable researchers to construct and parameterise simple epidemiological models for Marburg virus disease. Our accompanying R package epireview[20] will facilitate this process and ensure that information from studies beyond March, 2023, can be added to the package, offering a continuously updated repository of parameter estimates. The importance of this work is underlined by the scarcity of published Marburg virus disease mathematical models, which contrasts with the abundance of published models describing Ebola virus disease.[67] Improved knowledge of parameters will enable more modelling analyses to explore the potential effects of interventions, such as public health and social measures, as has been done for Ebola virus disease.[68] Although there is no vaccine approved for Marburg virus disease, phase 1 clinical trials have shown promising results,[69] and mathematical models could support the design of vaccination strategies, as they did for Ebola virus disease.[70]

This systematic review was challenging, as it contained a wide variety of studies and parameters for which we could not find a unique pre-existing, validated quality assessment tool. We therefore constructed a scoring system tailored specifically to the broad range of information we collated to assess the validity of the methods, assumptions, and data. We observed an improvement in article quality over time, which we attribute to increasing transparency in models, assumptions, and data (including publication of data and code), enabling reproducibility of research.

We acknowledge our findings are constrained by our restriction to peer-reviewed articles in English, especially as many of the countries reported to have had Marburg virus disease outbreaks are not English speaking. Extending this work to include non-English language articles and non-peer-reviewed work, to avoid language bias and provide a more comprehensive and generalisable picture, would be valuable but challenging.

Removing barriers to mathematical epidemic model design is important to enable timely generation of evidence that can support epidemic responses to future outbreaks. Here, we provide a comprehensive summary of published mathematical models, outbreaks, and epidemiological parameters of Marburg virus disease. Future research should review the available evidence on past outbreaks, mathematical models, and epidemiological parameters for other high-threat pathogens, such as those on the WHO blueprint priority list.[9] Alongside this systematic review, we publish the database of extracted Marburg virus disease models,

parameters, and outbreaks (appendix p 12), thus enabling future additions as more information becomes available from future studies on Marburg virus disease or other pathogens. The epireview package[20] includes functionalities to visualise the latest information, thereby providing a continuously up-to-date picture of Marburg virus disease epidemiological knowledge. This tool should further enhance global epidemic modelling preparedness.

Contributors

AC, SvE, SB, and NI conceptualised this systematic review. GC-D, HJTU, KC, BL, JS, and CM searched the literature and screened the titles and abstracts. GC-D, PD, KC, JS, and CM reviewed all full-text articles. GC-D, KM, RM, HJTU, PD, RKN, JTH, KC, CG, BL, DN, JS, JW, SvE, AC, and CM extracted the data. GC-D, KM, RM, PD, RKN, and CM did formal analysis of, visualised, and validated the data. AC acquired funding. GC-D, MK, SB, NI, SvE, AC, and CM were responsible for project administration. GC-D, RM, HJTU, PD, DN, MK, and SvE were responsible for training individuals on and accessing Covidence and designing the Access system. AC and CM supervised the systematic review. GC-D, KM, RM, HJTU, KC, BL, AC, and CM wrote the original draft of the manuscript. All authors were responsible for the methodology and review and editing of the manuscript. All authors debated, discussed, edited, and approved the final version of the manuscript. All authors had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

AC reports payment from Pfizer for teaching mathematical modelling of infectious diseases. PD reports payment from WHO for consulting on integrated modelling. All other authors declare no competing interests. The views expressed are those of the authors and not necessarily those of the National Institute for Health and Care Research (NIHR), UK Health Security Agency, or the Department of Health and Social Care. NI is currently employed by the Wellcome Trust. However, the Wellcome Trust had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data sharing

The data and materials, and the code used is available at GitHub. This systematic review is registered with PROSPERO: CRD42023393345 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID&RecordID=393345).

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