Lassa fever outbreaks, mathematical models, and disease parameters: a systematic review and meta-analysis

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Summary

Background Understanding the epidemiological parameters and transmission dynamics of Lassa fever, a significant public health threat in west Africa caused by the rodent-borne Lassa virus, is crucial for informing evidence-based interventions and outbreak response strategies. Therefore, our study aimed to collate and enhance understanding of the key epidemiological parameters of Lassa fever.

Methods We conducted a systematic review, searching PubMed and Web of Science for peer-reviewed studies published from database inception up to June 13, 2024, to compile and analyse key epidemiological parameters, mathematical models, and outbreaks of Lassa fever. English-language, peer-reviewed, original research articles were included if they reported on Lassa fever outbreak sizes, transmission models, viral evolution, transmission, natural history, severity, seroprevalence, or risk factors. Non-peer-reviewed literature was excluded. Data were extracted by two independent individuals from published literature, focusing on seroprevalence, transmissibility, epidemiological delays, and disease severity. We performed a meta-analysis to calculate pooled estimates of case-fatality ratios (CFRs) and the delay from symptom onset to hospital admission. This study is registered with PROSPERO (identifier number CRD42023393345).

Findings The database search returned 5614 potentially relevant studies, and a further 16 studies were identified from backward citation chaining. After de-duplication and exclusion, 193 publications met our inclusion criteria and provided 440 relevant parameter estimates in total. Although Lassa virus is endemic in west Africa, the spatiotemporal coverage of general-population seroprevalence estimates (ranging from 2·6% [6/232] to 58·2% [103/177]) was poor, highlighting the spatial uncertainty in Lassa fever risk. Similarly, only four basic reproduction number estimates (ranging from 1·13 to 1·40) were available. We estimated a pooled total random effect CFR of 33·5% (95% CI 25·8–42·2, I^2=95%) and found potential variation in severity by geographical regions typically associated with specific Lassa virus lineages. We estimated a pooled total random effect mean symptom-onset-to-hospital-admission delay of 8·19 days (95% CI 7·31–9·06, I^2=93%), but other epidemiological delays were poorly characterised in the existing literature.

Interpretation Our findings highlight the absence of empirical Lassa fever parameter estimates despite its high burden in west Africa. Improved surveillance approaches to capture mild cases in humans and to further cover rodent populations are needed to better understand Lassa fever transmission dynamics. Addressing these gaps is essential for developing accurate mathematical models and informing evidence-based interventions to mitigate the effect of Lassa fever on public health in endemic regions.

Funding UK Medical Research Council, National Institute for Health and Care Research, Academy of Medical Sciences, Wellcome, UK Department for Business, Energy, and Industrial Strategy, British Heart Foundation, Diabetes UK, Schmidt Foundation, Community Jameel, Royal Society, and Imperial College London.

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Lancet Glob Health 2024; 12: e1962–72

For the French translation of the abstract see Online for appendix 1

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Introduction

Exemplified by the COVID-19 pandemic, the emergence and spread of high-consequence infectious diseases continue to pose a global public health threat. Since 2018, the WHO research and development blueprint[1] has defined a priority list of pathogens likely to cause future epidemics, but for which medical countermeasures are few or not available. Lassa virus, a rodent-borne arenavirus, is the causative agent of the acute viral haemorrhagic illness Lassa fever. Lassa virus has the second highest spillover risk among viral pathogens and is on both the WHO and the Coalition for Epidemic Preparedness Innovations (CEPI) priority lists.[2] Currently, two of the four Lassa virus vaccine candidates under development are in phase 1 trials, and although the antiviral ribavirin is commonly administered in Lassa endemic regions, its role in the effective treatment of Lassa fever is unclear.[3–5]

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See Online for appendix 2

Research in context

Evidence before this study

We searched PubMed and Web of Science from database inception up to June 13, 2024, using the search terms: ((lassa fever) or (lassa virus)) and (epidemiology or outbreak or (models not image) or transmissibility or severity or delays or (risk factors) or (mutation rate) or seroprevalence), with no language restrictions. We found eight systematic reviews relating to Lassa fever between 2019 and 2024: one on historical importations of cases from west Africa to non-endemic countries, one on mathematical models, one on the basic reproduction number estimates (which ranged from 1·08 to 1·84 for human-to-human transmission and 1·54 to 1·74 for rodent-to-rodent transmission), one focused on prevalence (8·7% [95% CI 6·8–10·8] in humans, 3·2% [1·9–4·6] in rodents, and 0·7% [0·0–2·3] in other mammals) and case fatality ratios (29·7% [22·3–37·5] in humans), one on Lassa fever outcomes in pregnancy, and one each on clinical characteristics for protocol development, case treatment and outcomes, and ribavirin as a treatment.

Added value of this study

We provided a comprehensive overview of published outbreaks, transmission models, and epidemiological parameters for Lassa fever and made these data available in the epireview R package, which hosts standardised data for the WHO research and development blueprint priority pathogens. We highlighted the sparsity and challenges of quantifying key epidemiological parameter estimates for Lassa fever, such as the serial interval or generation time. Our study is a useful basis to inform future Lassa fever transmission models, which are useful tools for the real-time analysis of outbreaks, and assessing epidemic trajectories and the effect of interventions.

Implications of all the available evidence

Many knowledge gaps need to be filled in to understand Lassa fever spatial extent, transmission, and natural history. The discrepancy between the high overall severity and the high seroprevalence in the general population suggests a high proportion of infections are asymptomatic or only result in mild disease. Current surveillance systems might need refining to better characterise Lassa fever transmission dynamics, and future Lassa fever studies will benefit from integrating human and rodent reservoir surveillance.

Lassa fever was first recorded in humans in the 1950s, with the virus later identified in 1969.[6] It is endemic in Guinea, Liberia, Sierra Leone, and Nigeria, and transmission is probable in other west African countries where *Mastomys natalensis* rodent reservoir hosts are present.[7] Seven distinct lineages with substantial genetic divergence are typically present in specific geographical regions across west Africa, separated by environmental barriers such as rivers, which limit the movement of rodent reservoirs.[8–10] Transmission to humans occurs through contact with infected animals or direct contact, inhalation, or ingestion of their excreta. Outbreaks due to human-to-human transmission can occur through direct contact with bodily fluids, contaminated medical equipment, or rarely via sexual contact. In endemic regions, outbreaks of Lassa fever can occur seasonally, because climate affects food availability and therefore rodent population sizes.[11]

Although approximately 80% of infections are thought to be asymptomatic or mild, with symptoms including fever, headache, nausea, and vomiting, a small proportion of patients develop severe disease that can be fatal or lead to long-term sequelae such as deafness.[12] Pregnant women in their third trimester are particularly at risk, with maternal death or adverse birth outcomes, or both, occurring in more than 80% of cases.[12] Despite the reportedly low infection-fatality ratio, Lassa fever is one of the diseases with the highest burden among the WHO research and development priority pathogens. Estimates of the disease burden in west Africa, dating back to 1988, vary from 100 000 to 300 000 cases and 5000 deaths annually,[13] to more recent estimates in 2021 of 897 700 infections and up to 233 400 cases requiring hospitalisation per year.[14] Furthermore, the Nigeria Centre for Disease Control and Prevention reports increasing Lassa fever cases since 2015, with outbreaks occurring in both dry and rainy seasons.[15] Thus, Lassa fever continues to be a significant public health burden in west Africa, and understanding the changing transmission dynamics will be key to designing and implementing effective control measures.

Epidemiological models of disease transmission during outbreaks are used to understand the epidemic trajectory and severity, and quantify the potential effect of interventions. These outputs support policy makers to respond to outbreaks in real time by informing the allocation of resources and public policies. Despite robust epidemiological parameter estimates being crucial for making reliable projections, at the beginning of an outbreak, parameters are often inferred from similar pathogens or drawn from the literature until enough data are collected to make estimates about the current outbreak. Previous systematic reviews have focused on synthesising specific aspects of Lassa fever, such as clinical presentation or management, infection prevalence, and case fatality ratio (CFR) estimates, or reproduction numbers.[16–19] Furthermore, previous transmission models have predominantly been theoretical, with an absence of empirical data to support their assumptions and predictions.[20] Therefore, we

conducted a systematic review of published studies to provide a comprehensive resource that synthesises key epidemiological information for Lassa fever transmission models. Furthermore, with phase 2 studies underway on the Lassa virus vaccine candidate rVSVΔG-LASV-GPC, a robust compendium of Lassa fever parameters for models that can inform optimal Lassa virus vaccine trials and subsequent targeting is crucial.[21] This review sits within a wider effort to create a central, dynamic, and easily accessible resource to facilitate the design and parameterisation of mathematical models for multiple infectious pathogens with epidemic potential (appendix 2 p 37).

Methods

Search strategy and study selection

We conducted a systematic review and meta-analysis. We followed the PRISMA guidelines, and we registered our study protocol with PROSPERO under the identifier CRD42023393345. Preliminary, conceptual work on this project was started in 2019 but paused due to the COVID-19 pandemic. The work on Lassa fever commenced in July, 2023, after PROSPERO registration.

We searched PubMed and Web of Science for studies published from database inception up to March 8, 2019, and the search was then repeated to include publications up to Aug 2, 2023, and again to June 13, 2024, with no language restrictions. The search terms we used were: lassa AND ((transmissi* OR epidemiolog*) OR (model* NOT imag*) OR (severity OR "case fatality ratio*" OR CFR OR "case fatality rate*" OR "mortality rate*" OR "attack rate*") OR ("infectious period*" OR "serial interval*" OR incubation period*" OR "generation time*" OR "generation interval*" OR "latent period*" OR latency) OR (heterogeneit* OR superspread* OR "super spread*" OR super-spread* OR overdispersion OR overdispersed OR over-dispersion OR over-dispersed OR "over dispersion" OR "over dispersed") OR (infectivity OR infectiousness OR "growth rate*" OR "reproduction number*" OR "reproductive number*" OR R0 OR "reproduction ratio*" OR "reproductive rate*") OR ("pre-existing immunity" OR serological OR serology OR serosurvey*) OR (evolution* OR mutation* OR substitution*) OR (outbreak* OR cluster* OR epidemic*) OR ("risk factor*")). Results were imported into Covidence (2023) and de-duplicated.[22] Titles and abstracts, and then full texts were independently screened by two reviewers (PD, DJ, TMN, KM, RM, KC, GC-D, AH, HJTU, CM, and NI-E) and conflicts were resolved by consensus among the two individuals reviewing the title, abstract, and full texts. Studies reporting on Lassa fever outbreak size, transmission models, viral evolution, transmission, natural history, severity, or seroprevalence in human populations were included. Non-English language studies, non-peer-reviewed literature, and non-original research (such as other reviews) were excluded, but backward citation chaining from other systematic reviews was conducted to expand the search (appendix 2 p 41). Further details on study selection and full inclusion and exclusion criteria are presented in appendix 2 (p 2), as are PRISMA checklists (appendix 2 p 38).

Data extraction

10% of the studies that met the inclusion criteria were randomly selected and double extracted to validate the extraction process. For double extraction, two individuals independently extracted data from a paper and their extractions were reconciled. Further information is available in appendix 2 (p 3). A consensus on discordant results was established, after which ten reviewers (PD, TMN, KM, JTH, RM, GC-D, DN, TR, RJS, and CM)

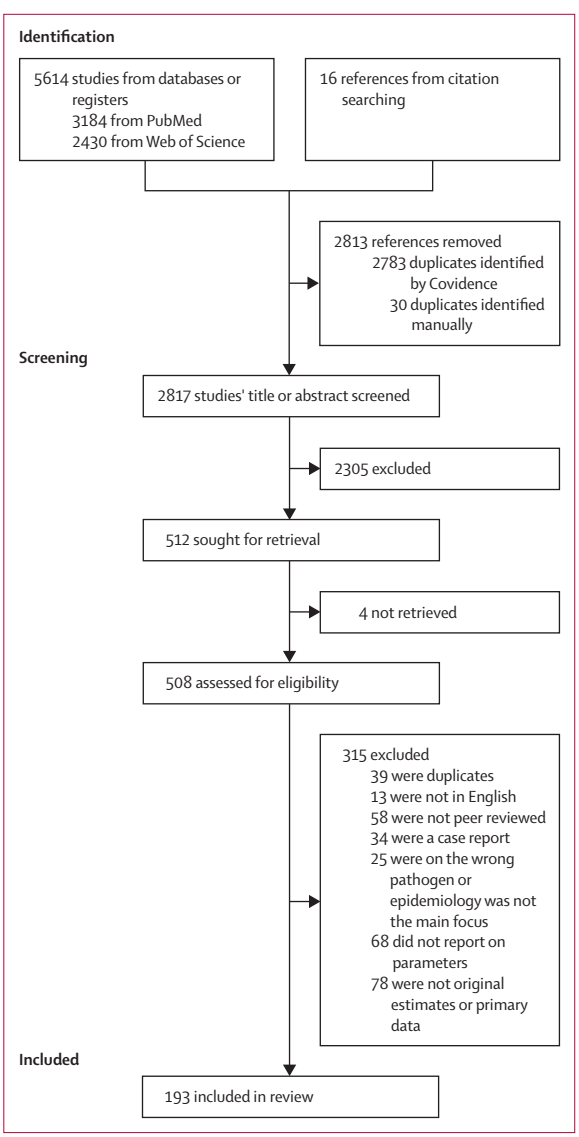


Figure 1: **Study selection flowchart**
According to PRISMA guidelines and criteria described in appendix 2 (p 2). The reasons for title or abstract exclusion were not provided by the Covidence software.

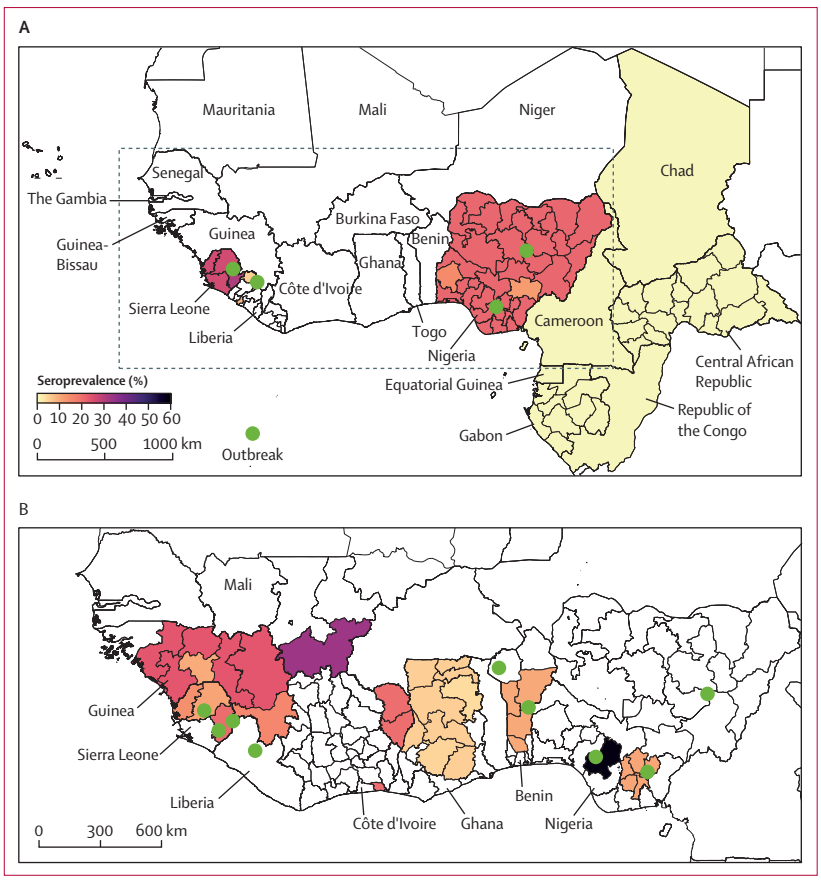


Figure 2: **Lassa virus seroprevalence in population and community settings (general population) of west Africa**

(A) Mean Lassa virus seroprevalence from studies conducted between 1965 and 1987 (target antibodies not reported in the articles). (B) Mean Lassa virus seroprevalence using IgG assays from studies conducted between 1990 and 2018. Where subnational estimates were available, these are shown at administrative level 1. Green circles show reported Lassa fever outbreak locations and white areas show the absence of estimates. The dashed grey box in panel A shows the corresponding area depicted in panel B.

conducted single extraction on all other studies. Data were extracted on publication details, risk of bias, outbreak locations, dates, case numbers, and deaths (as reported by the articles; appendix 2 p 4), transmission model characteristics, basic and effective reproduction numbers, epidemiological delays (such as the incubation period, symptom-onset-to-hospital-admission delay, or outcome delays), CFRs, seroprevalence, and risk factors, using a Microsoft Access database (version 2406). The linage was identified on the basis of the geographical area reported in each article, because phylogenetic analyses were not available in all cases. Because Lassa fever outbreaks are difficult to demarcate due to frequent rodent-to-human transmission in endemic areas, we only extracted outbreaks or epidemics as described by the study authors. For risk factors, only statistical significance or adjustment, or both, were extracted, because differences in reference groups and stratification made it challenging to compare other measures (eg, odds ratios) across studies. Full details of the data extraction process, database structure, and extracted data are provided in appendix 2 (pp 3–7, 9–24). Curated data on outbreaks, models, and epidemiological parameters were added to the epireview R package version 1.3.1 (appendix 2 p 37).[23]

Data analysis

Meta-analyses of parameter estimates were conducted using the meta R package[24] for the CFR and the mean symptom-onset-to-hospital-admission delay. Random and common effects models were used to calculate pooled CFR and delay estimates with 95% CIs and I^2 estimates of heterogeneity (appendix 2 p 8). The random effects model results were the main result of interest, and we provided the common effects model results as a sensitivity analysis.[25,26] All meta-analyses used maximum likelihood to estimate the between-study variance, which is the preferred method.[27] For the CFR meta-analysis, a generalised logistic mixed effects model was used to estimate the pooled effect, in which the individual CFR estimates were transformed using the logit transformation to ensure that the distribution was approximately normal. We considered lineage region, country, reported case numbers, and subpopulation affected (eg, children or pregnant women) as potential drivers of differences in CFR. We did not perform meta-analyses for other epidemiological delays, such as the incubation period, due to insufficient numbers of estimates of central tendency paired with sample variability. In the maps, administrative level 0 boundaries referred to national boundaries, and administrative level 1 boundaries were boundaries that were inferior to the first sub-national level but superior to national units as defined by each country.

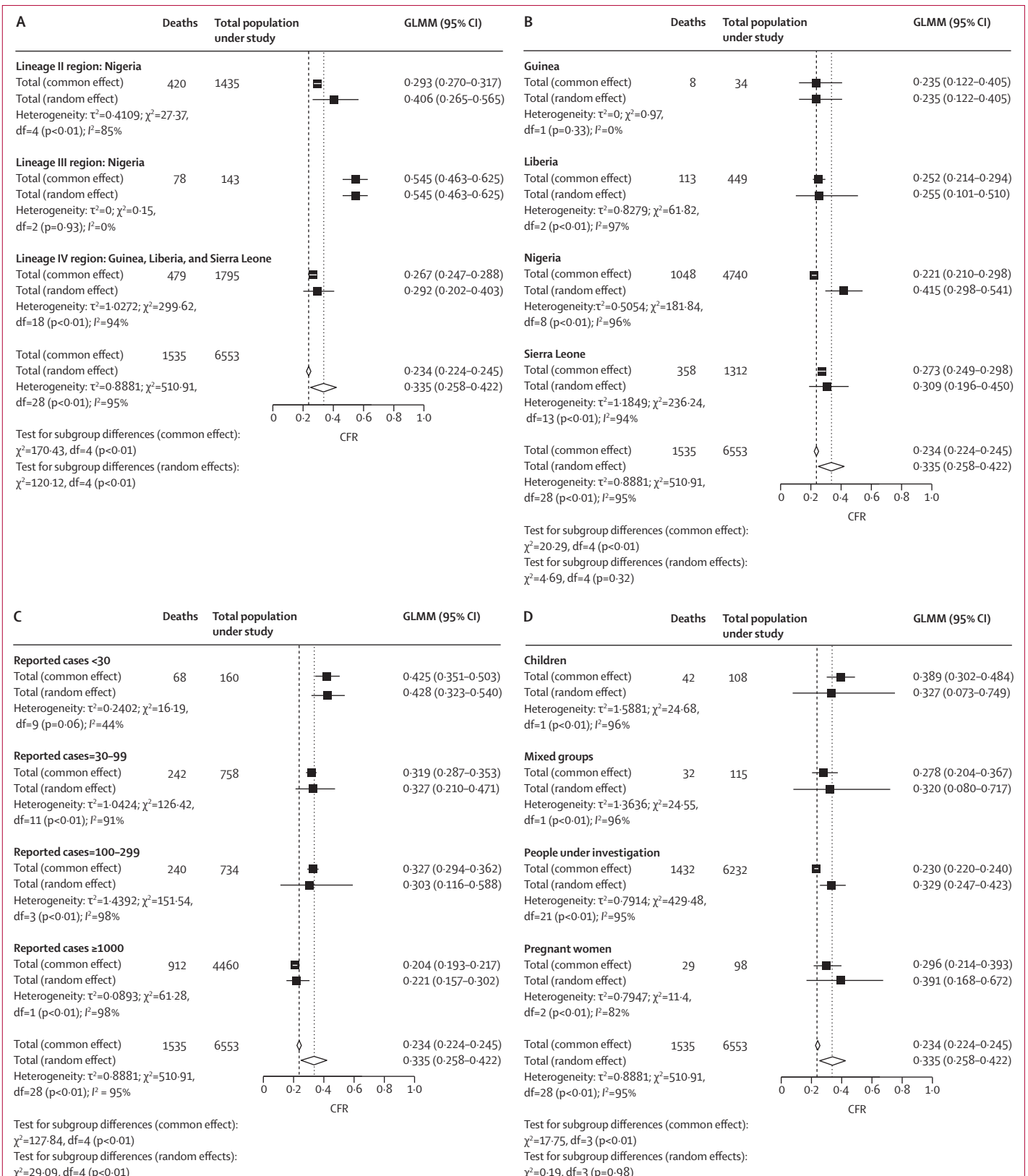
Risk of bias was assessed using a custom-designed quality assessment questionnaire answered by the reviewers (appendix 2 p 7) and quality assessment scores were defined as the mean number of yes responses to the seven questions (excluding not applicable responses). A local polynomial regression fit was used to analyse trends in quality assessment scores by publication year (appendix 2 p 25). All analyses were conducted in R (version 4.2.2) and the code to reproduce our results is available online.[28]

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The database search returned 5614 potentially relevant studies, and a further 16 studies were identified from backward citation chaining. After de-duplication, 2817 studies were screened, with 2305 excluded at the title or abstract stage. 512 studies were retained for full text screening, with four studies with no full text



(Figure 3 continues on next page)

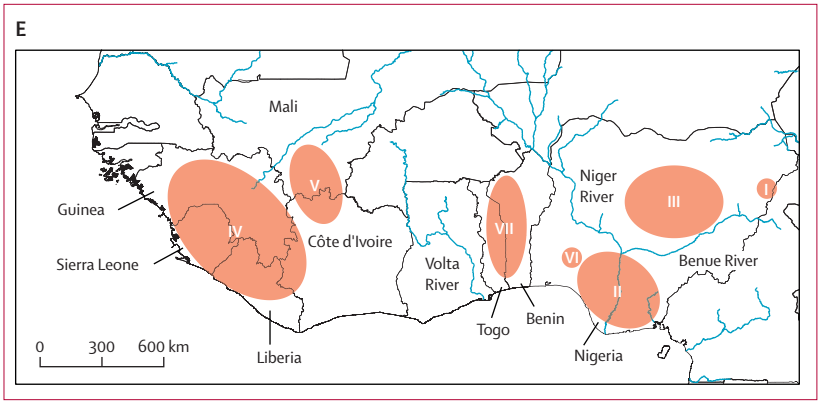


Figure 3: **CFR estimates from meta-analyses**
(A) CFR estimates by Lassa virus lineage region, inferred from the location reported in each study. (B) CFR estimates by country. (C) CFR estimates by total number of reported cases. (D) CFR estimates by population group under study. (E) Reported geographical distribution of Lassa virus lineages. The circles show the region where different lineages are present, which tend to be seperated by geographical features such as rivers. Two studies reported on children, one with an age range of 0–14 years and one with an age range of 0–18 years. People under investigation was the term used for cases of Lassa fever, but where a specific demographic was not specified, whereas total is the total across all studies. Mixed groups is where there are specified, mixed demographic groups (eg health-care workers and patients). Individual study estimates and further subgroup decompositions are shown in appendix 2 (pp 29–33). Both the fixed and random GLMM are shown. The 300–999 cases group was not included because no study reported 300–999 cases. CFR=case fatality ratio. df=degrees of freedom. GLMM=generalised linear mixed model.

available excluded, and a further 315 excluded for other reasons. 193 studies met the criteria for final inclusion (figure 1).

26 studies reported 18 distinct Lassa fever outbreaks between 1969 and 2019, with the highest number of outbreaks reported in Nigeria (n=9), Sierra Leone (n=4), Liberia (n=3), and Benin (n=2; appendix 2 pp 9–10). Confirmed case numbers reported in studies ranged from two cases in Benin in 2014[29] to 1463 cases in Nigeria during a multi-year outbreak in 2018–19.[30] 52 studies used Lassa fever transmission models, the majority of which were compartmental models and accounted for both rodent-to-human and human-to-human transmission pathways (appendix 2 pp 9, 11–12, 26). We extracted 440 epidemiological parameter estimates in total, including seroprevalence estimates (n=139) from 30 countries, risk factors (n=128), and severity or CFR estimates (n=85; appendix 2 pp 9, 13–24, 27).

Figure 2A shows that for population-based and community-based studies between 1965 and 1987, aggregated seroprevalence estimates ranged from 0·0% (Haut-Ogooue, Gabon) to 30·5% (Eastern Province, Sierra Leone). The underlying data range from 0·0% (Kenya [0/1899],[31] not plotted, and Gabon [0/253][32]) to 52·0% (Sierra Leone).[33] Seroprevalence estimates using IgG assays from more recent studies (1990–2018) were only available from seven countries where the reported seroprevalence was generally higher (figure 2B), ranging from 2·6% (Pita, Guinea [6/232])[34] to 58·2% (Edo State, Nigeria [103/177]).[35]

No recent population-based or community-based seroprevalence estimates were available from Chad, Cameroon, Central African Republic, Republic of the Congo, Gabon, Equatorial Guinea, Liberia, or Kenya, where serosurveys were conducted before 1990 (figure 2A). Due to differences in assays and exact geographical locations of studies, temporal trends in population seroprevalence cannot be inferred. Figure 2B shows evidence of past infection in areas of known outbreaks, but also highlights high seroprevalence in Bougouni district in Mali, and Abidjan and the northeastern region of Côte d'Ivoire, despite few reported cases or outbreaks, indicating the underreporting of Lassa fever cases or transmission.

85 CFR estimates were reported across 69 studies between 1970 and 2021 in Nigeria (n=41), Sierra Leone (n=26), Liberia (n=13), Guinea (n=2), and Benin (n=1), and then two studies reported on Guinea, Liberia, and Sierra Leone together in the Lassa virus lineage IV region (figure 3E). Using de-duplicated CFR estimates (appendix 2 p 8), we estimated a pooled CFR of 33·5% (95% CI 25·8–42·2, I^2=95%) for total random effect models and 23·4% (22·4–24·5, I^2=95%) for total common effect. Notably, CFR estimates differed by lineage region (geographical areas associated with the transmission of different genetic lineages of Lassa virus; figure 3A, E), with the highest CFR in the lineage III region at 54·5% (95% CI 46·3–62·5%, I^2=0%). Lineage regions II and IV reported broadly consistent CFRs. There was a single study reporting a CFR of 44% (8/18) within lineage region VII.[29] CFR estimates did not differ significantly when comparing random effects across countries, but the CFR in Sierra Leone was significantly higher than in Nigeria using the common effects model (figure 3C). CFR estimates for studies reporting more than 1000 cases were based on large retrospective studies conducted by the Nigeria Centre for Disease Control and Prevention, which reported cases and deaths over multiple years (between 2008 and 2018, and 2018 and 2021). The common effect model on CFR for 1000 or more reported cases was significantly lower than estimates from studies with smaller case numbers (less than 1000). Sensitivity analyses performed without de-duplicating the CFR estimates produced similar results (appendix 2 pp 34–35).

We extracted 56 estimates of epidemiological delays from 29 studies (figure 4), including five incubation period estimates, 21 symptom-onset-to-hospital-admission delays, ten admission-to-clinical-outcomes delays, and ten symptom-onset-to-clinical-outcome delays. These estimates were a mixture of means, medians, and ranges, with one unspecified incubation period estimate. The five incubation periods were broadly consistent across the studies, with central estimates ranging between 7·0 and 12·8 days. Hospital-admission-to-death delays were consistent across the four estimates and were shorter than admission-to-recovery delays (four estimates) or admission-to-unspecified-outcome delays (two estimates; figure 4C). Mean symptom-onset-to-admission delays included in the meta-analysis ranged from 6 days to

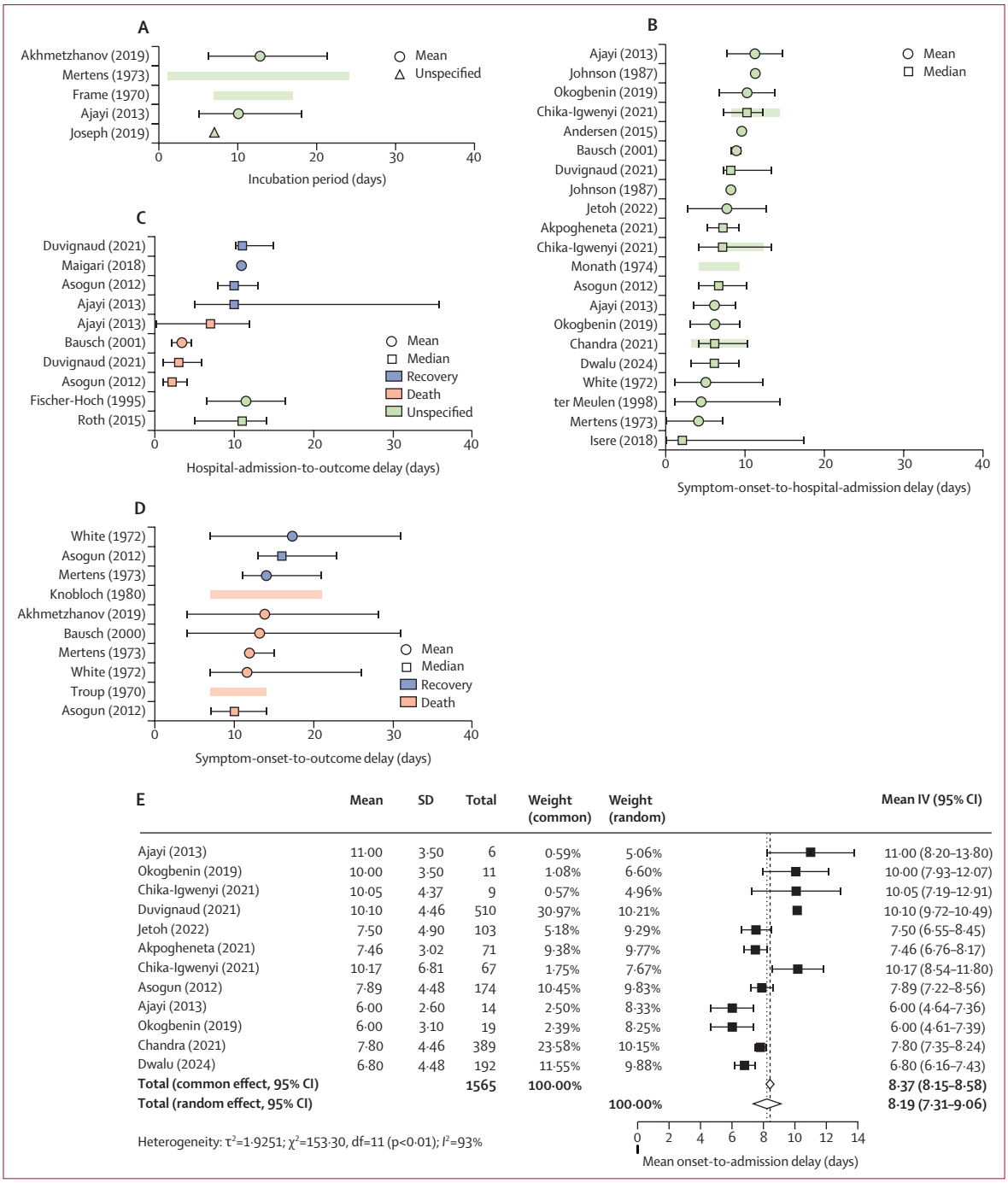


Figure 4: **Overview of Lassa fever epidemiological delays and mean symptom-onset-to-hospital-admission delay meta-analysis**
(A) Estimates of the incubation period, by study. (B) Estimates of the symptom-onset-to-hospital-admission delay. (C) Estimates of hospital-admission-to-recovery, hospital-admission-to-death, or hospital-admission-to-unspecified-outcome delay. (D) Estimates of symptom-onset-to-recovery or symptom-onset-to-death delay time. Circles, squares, and triangles represent mean, median, and unspecified estimates, respectively. Thin solid lines represent uncertainty intervals, and thick shaded lines represent the range across central estimates of disaggregated parameters (eg, region, time, age, and sex). (E) Meta-analysis of mean symptom-onset-to-hospital-admission delay. Both fixed and random effects models are shown. The references to the studies listed in this figure are included in appendix 2.

11 days (figure 4E). Pooled mean symptom-onset-to-admission estimates were 8·19 days (95% CI 7·31–9·06, I^2=93%) for total random effects and 8·37 days (8·15–8·58, I^2=93%) for total common effects models.[36]

We extracted information on a range of Lassa fever transmission parameters (figure 5), including seven studies reporting Lassa fever reproduction numbers, one study reporting on growth rates, three studies on attack rates,

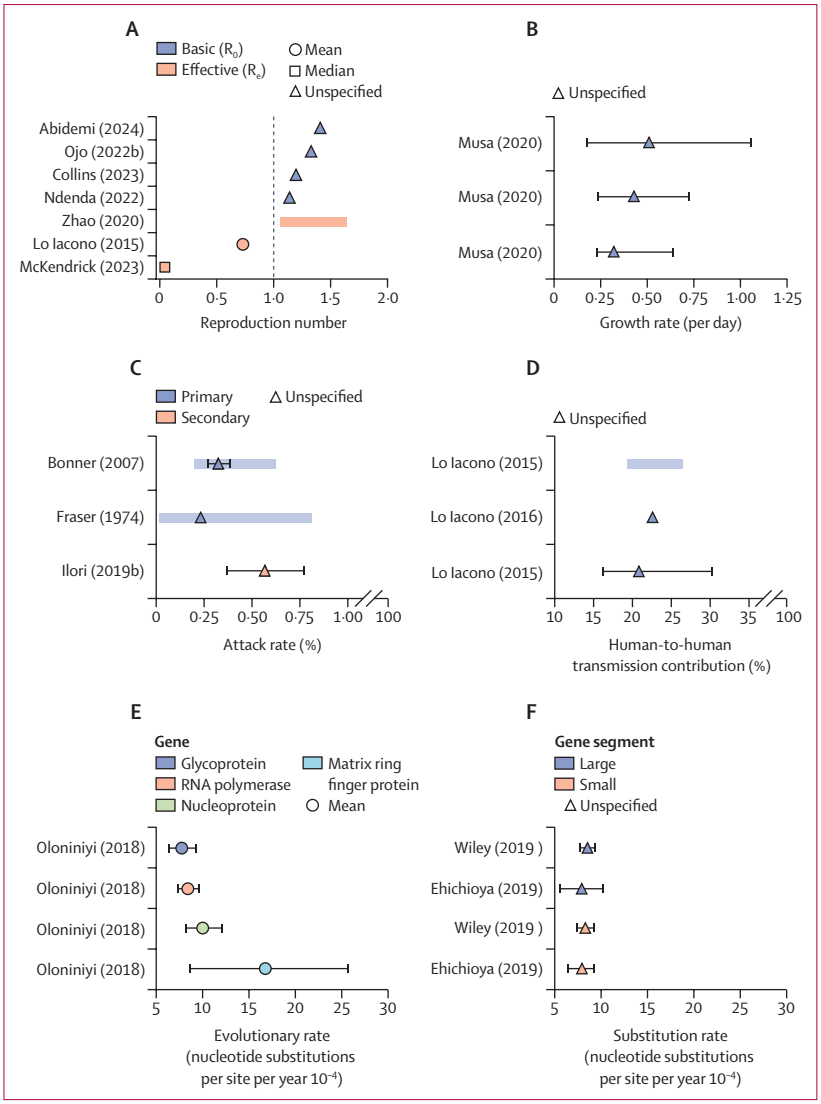


Figure 5: **Overview of the transmission and genetic characteristics of Lassa fever**
(A) Reproduction numbers. (B) Growth rates. (C) Attack rates. Primary attack rates indicate an entire population at risk, whereas secondary attack rates indicate risk among contacts of cases. (D) Human-to-human transmission contribution percentage. (E) Evolutionary rates for each protein-encoding gene. (F) Substitution rates for Lassa virus genome segments. Parameters in panels E and F are measured in nucleotide substitutions per site per year. Circles, squares, and triangles represent mean (panels A and E), median (panel A), and unspecified (panels A–F) estimates respectively. Thin solid lines are uncertainty intervals and thick shaded lines are the range across central estimates of disaggregated parameters (eg, regions, time, age, and sex). R_0=basic reproduction number. R_e=effective reproduction number. The references to the studies listed in this figure are included in appendix 2.

and two estimating the percentage contribution of human-to-human (as opposed to the rodent-to-human) transmission. Three studies (one on genes and two on segments) reporting Lassa virus evolutionary and substitution rates were largely consistent (figure 5E,F). Four basic reproduction number (R_0) estimates were available from four studies, with similar results ranging from 1·13 to 1·40.[37,38] Three other studies reported effective reproduction numbers ranging from 0·02 to 0·73 for human-to-human-only transmission,[39,40] and from 1·05 to 1·62 for overall transmission.[41] However, due to consistent spillover from the rodent population, it is difficult to interpret the reproduction number estimates as the actual risk of sustained human transmission, as highlighted by the two mathematical modelling studies estimating that human-to-human transmission contributed to less than a third of transmission overall.[39,42] Furthermore, the few available attack rate estimates were also low at between 2·2 and 3·1 per 1000 for primary[43,44] and 0·56% (28/5001) for secondary attack rates.[45] We also extracted reported risk factors for seropositivity, infection, severe disease or hospitalisation, deaths, and other outcomes (appendix 2 pp 22–24).

In assessing risk of bias, descriptive studies (eg, seroprevalence studies or studies not using a mathematical model) accounted for most non-applicable responses, as per the design of the quality assessment questionnaire. We found that the local polynomial regression fitted to the quality assessment score, excluding mathematical modelling studies, monotonically increased since 1970 (appendix 2 p 25). In general, we found that data extractors (the same ten reviewers) assigned lower quality scores to modelling studies, potentially because most of these studies presented transmission models that were not fitted to data (appendix 2 p 26).

The risk of publication bias was assessed as low (appendix 2 pp 8, 28, 36) because meta-analyses were performed on the severity and the mean onset-to-admission delay. These are observed disease parameters rather than study results, which might have selective reporting for positive results.

Discussion

In this systematic review, we compiled and analysed key epidemiological parameters, mathematical models, and past outbreaks of Lassa fever to inform future Lassa fever transmission models. Despite the wide distribution of environmental suitability for Lassa fever transmission across west Africa,[46,47] there are few empirical data on Lassa fever outbreaks or seroprevalence. Only 18 distinct outbreaks were described between 1969 and 2019, and it has been suggested that this is due to diagnostic limitations and a bias towards areas with established Lassa fever treatment units.[47,48] Furthermore, the spatial distribution of Lassa virus is poorly characterised in the existing literature (because the estimates are sparse and not sufficiently granular, and there are many regions with missing data), with a paucity of advanced serosurveys since 1990. The identification of potential new reservoirs other than *M natalensis*, including domestic animals, farm animals, and reptiles, and other rodent species,[49–51] adds to this uncertainty in the true distribution. Spatiotemporal modelling studies have combined predictions of rodent reservoir range with human Lassa virus seroprevalence data to estimate geographical patterns of spillover risk.[14] Some statistical models suggest that Lassa virus risk extends into central African countries, but there are no recent seroprevalence

estimates from this region.[14,46,52,53] The highly heterogeneous spatial distribution of Lassa virus might be due to differences in human–rodent interactions, which are difficult to capture. This poses challenges for surveillance and highlights the need for improved One Health approaches, such as integrating human and peridomestic rodent surveillance, particularly in the light of increasing Lassa fever cases and deaths in Nigeria.[54,55] Climate and land-use change and their effect on the rodent reservoir are anticipated to influence the future spatial spread and extent of Lassa fever transmission.[11] Spatial and environmental modelling suggests an expanding endemic area and increased population at risk,[53] but the change in Lassa virus spillover risk will not be uniform.[56] Therefore, gaining a better understanding of how individual reservoir hosts respond to environmental stressors is crucial for accurately predicting future changes in transmission risk.

Our overall pooled CFR estimates align with previous reviews of Lassa fever and CFR estimates for other rodent-borne arenaviruses causing haemorrhagic fevers, such as Machupo virus[57] and Guanarito virus,[58] with slightly lower CFRs observed in Junín virus.[59] However, there is a contradiction between high Lassa fever CFR estimates and the high seroprevalence in general populations, suggesting a high proportion of infections might be asymptomatic or result in mild disease.[33] The high CFR estimates are probably biased because they are based on patients seeking health care, who by definition have a more severe disease. Due to the endemic nature of Lassa virus in Nigeria, these CFR estimates likely represented different circumstances to more acute and smaller outbreaks typical of other settings with a higher CFR. One study by Simons[60] has also shown systematic underreporting of Lassa fever burden and cases in countries with (Nigeria) and without (Ghana, Guinea, and Togo) routine Lassa fever surveillance. Characterising asymptomatic or mild cases is crucial for refining severity estimates and developing robust models of Lassa fever transmission, which will inform the design of Lassa virus vaccine trials.[61] Understanding the evolutionary dynamics of Lassa virus, including the emergence of distinct Lassa virus lineages, is also important for understanding variation in disease severity. Our results suggest that CFRs might differ by lineage region, with the highest estimates observed in outbreaks in the lineage III region in Nigeria. However, it is important to note that these lineage regions were established on the basis of geographical location rather than specific phylogenetic analyses of the outbreaks. Additionally, it has been suggested that differences in apparent severity by lineage region might also be attributable to health-seeking behaviours.[15] Furthermore, published estimates of Lassa virus evolutionary rates are low, and it has been shown that Lassa virus circulation occurs at a slow pace, with a weighted lineage dispersal velocity of 0·8–1·0 km per year.[53]

We only found five estimates of the incubation period, which reflects the challenges in attributing probable exposure times due to the complex transmission dynamics and the multiple potential routes of infection. More delay distributions were available for hospital admissions and treatment-related delays. Although the observed delays from symptom onset or hospital admission to outcome (recovery or death) were broadly consistent across studies, these observed delays are conditional on patients having severe disease and these delay distributions will probably differ for mild infections.

Few mathematical models were fitted to empirical data, because most studies focused on theoretical models of transmission. This reflects the challenges in parameterising complex reservoir–human meta-population models and makes it difficult to robustly project the potential effect of interventions such as ribavirin or targeted vaccination campaigns.[62] Modelling frameworks developed to assess vaccine demand for CEPI priority pathogens have identified gaps in surveillance and data regarding the true geographical distribution of Lassa virus, the key routes of rodent-to-human spillover, and the role of human-to-human transmission outside healthcare settings.[63] Although R_0 estimates are greater than 1, indicating the potential for sustained Lassa fever transmission from reservoirs to human populations, human-to-human transmission risk varies greatly. The three available estimates suggests that human-to-human transmission contributes to less than a third of overall transmission, with spillover from the rodent population being the primary cause of human infections.[39] The low human-to-human transmission risk and challenges in quantifying this might explain the absence of generation time or serial interval estimates. *M natalensis*, the primary reservoir host for Lassa virus, plays a crucial role in the virus transmission dynamics and integrating rodent seroprevalence studies with human seroprevalence data will be important in developing mathematical models of transmission. To improve epidemiological estimates, future mathematical models should also ensure that new empirical Lassa fever data, such as from the CEPI-funded Enable study, are integrated.[64]

Our findings are limited by the exclusion of non-English language publications, preprints, and grey literature. This language limitation is particularly relevant in the Lassa virus endemic region, which includes non-English speaking countries. Furthermore, this review focused solely on human hosts and excluded seroprevalence studies in rodents. For practical reasons, we extracted overall results when studies provided disaggregated data based on factors such as region, time, or sex. Information on studies reporting such data is annotated in our database in the epireview R package to make them easier to find. We focused on extracting results presented in the tables or text, and did not extract data presented in figures, although this probably represents a small proportion of parameters. Finally,

although we validated the data extraction process, minor discrepancies between individual reviewers might exist.

We have provided a comprehensive overview of key epidemiological parameters, mathematical models, and past outbreaks of Lassa fever to enhance our understanding of the disease dynamics. However, there are still several significant gaps and uncertainties in our understanding of Lassa fever, particularly regarding the spatial distribution and burden of Lassa virus and its reservoirs. This research gap underscores the need for improved surveillance methods and integrated One Health approaches, especially in endemic regions where the burden is increasing. The anticipated effect of climate and land-use change on Lassa fever transmission further emphasises the importance of understanding how environmental factors influence disease dynamics. Addressing these limitations and incorporating a broader range of data sources in policy making, modelling, and public health and epidemiological studies is crucial for advancing our knowledge and mitigating the effect of Lassa fever on public health.

Contributors

SB, SvE, AC, and NI-E conceptualised this systematic review. PD, DJ, KC, AH, CM, and NI-E searched the literature and screened the titles and abstracts. PD, DJ, TMN, KM, RM, KC, GC-D, HJTU, CM, and NI-E reviewed all full-text articles. PD, TMN, KM, JTH, RM, GC-D, DN, TR, RJS, and CM extracted the data. PD, DJ, CM, and NI-E did formal analysis of, visualised, and validated the data. PD, SB, and RKN were responsible for software infrastructure. AC acquired funding. GC-D, SB, SvE, AC, CM, and NI-E were responsible for project administration. PD, GC-D, RKN, DN, HJTU, and SvE were responsible for training individuals on and accessing Covidence and designing the Access system. CM and NI-E supervised the systematic review. PD, DJ, CM, and NI-E wrote the original draft of the manuscript. All authors were responsible for the methods and review and editing of the manuscript. All authors debated, discussed, edited, and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. PD and CM accessed and verified the data.

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. HJTU reports payment from the Moderna Charitable Foundation (paid directly to institution for an unrelated project). 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-E is currently employed by Wellcome. However, Wellcome 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

Data are available from: https://github.com/mrc-ide/epireview/ and https://github.com/mrc-ide/priority-pathogens.

Acknowledgments

This study was funded by the Medical Research Council (MRC) Centre for Global Infectious Disease Analysis (MR/X020258/1) funded by the UK MRC and carried out in the frame of the Global Health EDCTP3 Joint Undertaking supported by the EU; and the NIHR for support for the Health Research Protection Unit in Modelling and Health Economics, a partnership between the UK Health Security Agency (UKHSA), Imperial College London, and London School of Hygiene & Tropical Medicine (grant code NIHR200908). AC was supported by the Academy of Medical Sciences Springboard scheme, funded by the Academy of Medical Sciences, the Wellcome Trust, the UK Department for Business, Energy, and Industrial Strategy, the British Heart Foundation, and Diabetes UK (reference SBF005\1044). CM acknowledges the Schmidt Foundation for research funding (grant code 6–22–63345). PD and TMN acknowledge funding from Community Jameel. GC-D acknowledges funding from the Royal Society. RM acknowledges the NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, a partnership between UKHSA, the University of Oxford, the University of Liverpool, and the Liverpool School of Tropical Medicine (grant code NIHR200907). DJ acknowledges funding from the Wellcome Trust and Royal Society (216427/Z/19/Z). RKN acknowledges research funding from the MRC Doctoral Training Partnership (grant MR/N014103/1). KM acknowledges research funding from the Imperial College President's PhD Scholarship.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

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