Lack of Evidence for Ribavirin Treatment of Lassa Fever in Systematic Review of Published and Unpublished Studies[1]

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the overall effectiveness of ribavirin for treatment of Lassa fever, according to a systematic review of published literature and unpublished study results
- Determine the effectiveness of ribavirin for treatment of Lassa fever in subgroups, according to a systematic review of published literature and unpublished study results
- Identify clinical implications of the effectiveness of ribavirin for treatment of Lassa fever, according to a systematic review of published literature and unpublished study results

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[1]Preliminary results from this study were presented at the World Health Organization Emergency Program on December 21, 2019.

Ribavirin has been used widely to treat Lassa fever in West Africa since the 1980s. However, few studies have systematically appraised the evidence for its use. We conducted a systematic review of published and unpublished literature retrieved from electronic databases and gray literature from inception to March 8, 2022. We identified 13 studies of the comparative effectiveness of ribavirin versus no ribavirin treatment on mortality outcomes, including unpublished data from a study in Sierra Leone provided through a US Freedom of Information Act request. Although ribavirin was associated with decreased mortality rates, results of these studies were at critical or serious risk for bias when appraised using the ROBINS-I tool. Important risks for bias related to lack of control for confounders, immortal time bias, and missing outcome data. Robust evidence supporting the use of ribavirin in Lassa fever is lacking. Well-conducted clinical trials to elucidate the effectiveness of ribavirin for Lassa fever are needed.

Lassa virus infection, first described in 1962, is a viral hemorrhagic fever (*1*). It is a substantial public health burden, causing an estimated 100,000–200,000 cases each year, mainly in West Africa (*2*,*3*). Many cases are mild or asymptomatic and are not formally diagnosed (*4*). The nonspecific clinical manifestation makes Lassa fever difficult to recognize on clinical grounds alone, especially in the early phases. The case-fatality rate is estimated to be 10%–20% in hospitalized patients (*5*,*6*) but increases sharply during outbreaks (*7*). No vaccine is available, but studies examining recombinant vaccinia virus in animals have entered the preclinical phase, and a DNA vaccine has entered a phase I trial in humans (*8*–*10*). Lassa virus is part of the US Centers for Disease Control and Prevention's list of category A Select Agents and is considered a priority pathogen by the World Health Organization (WHO) because of its epidemic potential, its severity, lack of available vaccines, and, most important, limited therapeutic options.

The most influential study of the efficacy of ribavirin in treatment of Lassa fever, published in 1986, reported that administration of intravenous ribavirin within the first 6 days of illness decreased mortality rates from severe Lassa fever from 55% to 5% (*11*). These findings have underpinned the widespread use of, and unequivocal recommendations for, ribavirin for treatment of Lassa fever. Several retrospective observational studies document the use of ribavirin and describe lower case-fatality rates in patients treated with ribavirin (*12*–*17*). However, potential biases in those results make it difficult to evaluate the effectiveness of ribavirin in clinical practice. Recent unpublished results obtained through the US Freedom of Information Act, and secondary analysis of these results, weaken the case for use of ribavirin (*18*). Therefore, we undertook a systematic review of published and unpublished study results, which we appraised by using a state-of-the-art risk for bias tool (*19*), to evaluate ribavirin for treating Lassa fever.

Methods

This review follows the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (*20*) (Appendix Table 1, https://wwwnc.cdc.gov/EID/article/28/8/21-1787-App1.pdf). A protocol is registered on the International Prospective Register of Systematic Reviews (PROSPERO 2019 CRD42019141818) (https://www.crd.york.ac.uk/prospero).

We conducted a comprehensive search of multiple bibliographic databases from inception to March 8, 2022: Ovid Medline, Ovid Embase, Central Register of Controlled Trials, BIOSIS, WHO Global Index Medicus, and Web of Science (including Science Citation Index Expanded and Conference Proceedings Citation Index-Science). We also searched the WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, and Pan African Clinical Trial Registry databases to identify relevant reports. We searched the keywords "Lassa" and "ribavirin" within Google.com and the WHO website to retrieve gray literature on March 8, 2022. We developed search strings for each database (Appendix). To identify further relevant studies, we checked reference lists of included studies and papers, citing them using the Web of Science database. We also contacted authors for clarification and supplementary information. We applied no restriction in language, publication type, study design, or date in the searches.

We also included unpublished results from a study that included the data reported by McCormick et al. (*11*). The unpublished results (Birch & Davis Associates and Sherikon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf; G.V. Ludwig, pers. comm., 2019 March 4, https://media.tghn.org/medialibrary/2019/03/Dr._Ludwig_memo.pdf) were requested by P.W.H. through the US Freedom of Information Act. We refer to this study as IND 16666, its Food and Drug Administration Investigational New Drug application number.

Study Selection

We included randomized controlled trials (RCTs), controlled trials, cohort and case–control studies

comparing ribavirin treatment with no ribavirin (e.g., supportive treatment) in patients having either or both confirmed and suspected Lassa fever that reported mortality (number of deaths or case-fatality rate). No study reported prespecified secondary outcomes or adverse events, except McCormick et al. (*11*). Therefore, we focused only on mortality in this review.

Two authors independently screened titles and abstracts of retrieved records by using Rayyan (*21*). All records were screened twice, once by the first author (H.C.) and then by 1 of the co-authors (C.E.F., S.D., A.M., and A.P.S.). For records that were potentially eligible, we retrieved and screened the full-text articles, using Excel (Microsoft, https://www.microsoft.com) to record inclusion decisions and manage the workflow. Full-text articles were reviewed independently (H.C. paired with C.E.F. or A.P.S.) to assess the eligibility. We resolved any discrepancies between authors by discussion between the paired assessors. Two authors independently extracted data compitled by 2 authors (H.C. paired with C.E.F. or A.P.S.) by using a prepiloted data extraction form in an Excel spreadsheet.

Risk for Bias Assessment

Three authors (C.E.F., L.A.M., and H.C.) independently assessed risk for bias for each study by using the ROBINS-I tool (*19*). The tool consists of 7 domains containing a series of signaling questions to judge risk for bias as low, moderate, serious, or critical. For the first domain, we determined bias attributable to confounding or potential confounding factors through a literature review and expert opinion (A.P.S. and P.W.H.). We identified 3 key confounding factors: age, pregnancy status, and indicators of disease severity. For the third domain, bias in classification of interventions, we included assessment of immortal time bias (*22*). We provide support for judgments in individual results (Appendix Table 2).

Data Analysis and Presentation

As described by Salam et al. (*18*), we used data reported in tables and an appendix within the IND 16666 report to derive aggregated datasets containing the number of deaths according to treatment groups and individual characteristics. On the basis of these datasets, we estimated mortality odds ratios (ORs) comparing ribavirin with no treatment, overall and within subgroups defined by patient characteristics (aminotransferase [AST] level and whether pregnant) in the IND 16666 report. We also extracted results from a logistic regression analysis in the IND 16666 report in which the effect of ribavirin compared with no treatment was adjusted for patient characteristics (age, sex, time to admission, time to treatment, length of stay, and log transformed AST level).

The various reports used different criteria and diagnostic tests to define confirmed Lassa fever cases. Only 1 study, Shaffer et al. (*12*,*15*), provided raw data reporting confirmed Lassa fever according to different case definitions: based on antigen, IgM, and IgG. In this study, we used positive antigen solely as the criteria for the confirmed case because it was consistently reported in the dataset (*15*). We also conducted a sensitivity analyses estimating ORs on the basis of other case definitions.

We estimated overall ORs and, when available, ORs in subgroups defined by timing of treatment (starting <7 and ≥ 7 days after disease onset). We did not conduct meta-analyses because most results were rated as at critical overall risk for bias (*19*). We displayed ORs and 95% CIs for the association of ribavirin with no treatment in forest plots by using Stata 15 MP (StataCorp LLC, https://www.stata.com).

Results

We retrieved 2,232 unique records, of which we excluded 2,162 on the basis of titles and abstracts. We retrieved full-text articles for the remaining 70 records for eligibility assessment, after which we excluded 55 further records (Figure 1). One study met the inclusion criteria but was excluded because it reported aggregated outcome data that included unknown treatment status (*23*). Other studies did not report outcome data according to treatment status (*24*–*28*). We contacted the authors for further information but received no responses. We extracted results from 13 eligible studies described in 15 published and unpublished reports and assessed the risk for bias in these results.

Study Characteristics

We summarized the characteristics of the included studies (Appendix Table 3). All studies were from West Africa (6 from Nigeria and 7 from Sierra Leone) (*11*,*12*,*14*,*15*,*17*,*29*–*36*; Birch & Davis Associates and Sherikon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf; G.V. Ludwig, pers. comm., 2019 March 4, https://media.tghn.org/medialibrary/2019/03/Dr._Ludwig_memo.pdf; M.-L. Orji et al., unpub. data, https://doi.org/10.20944/preprints202005.0269.v1). McCormick et al. (*11*) and its additional data reported in IND 16666 were

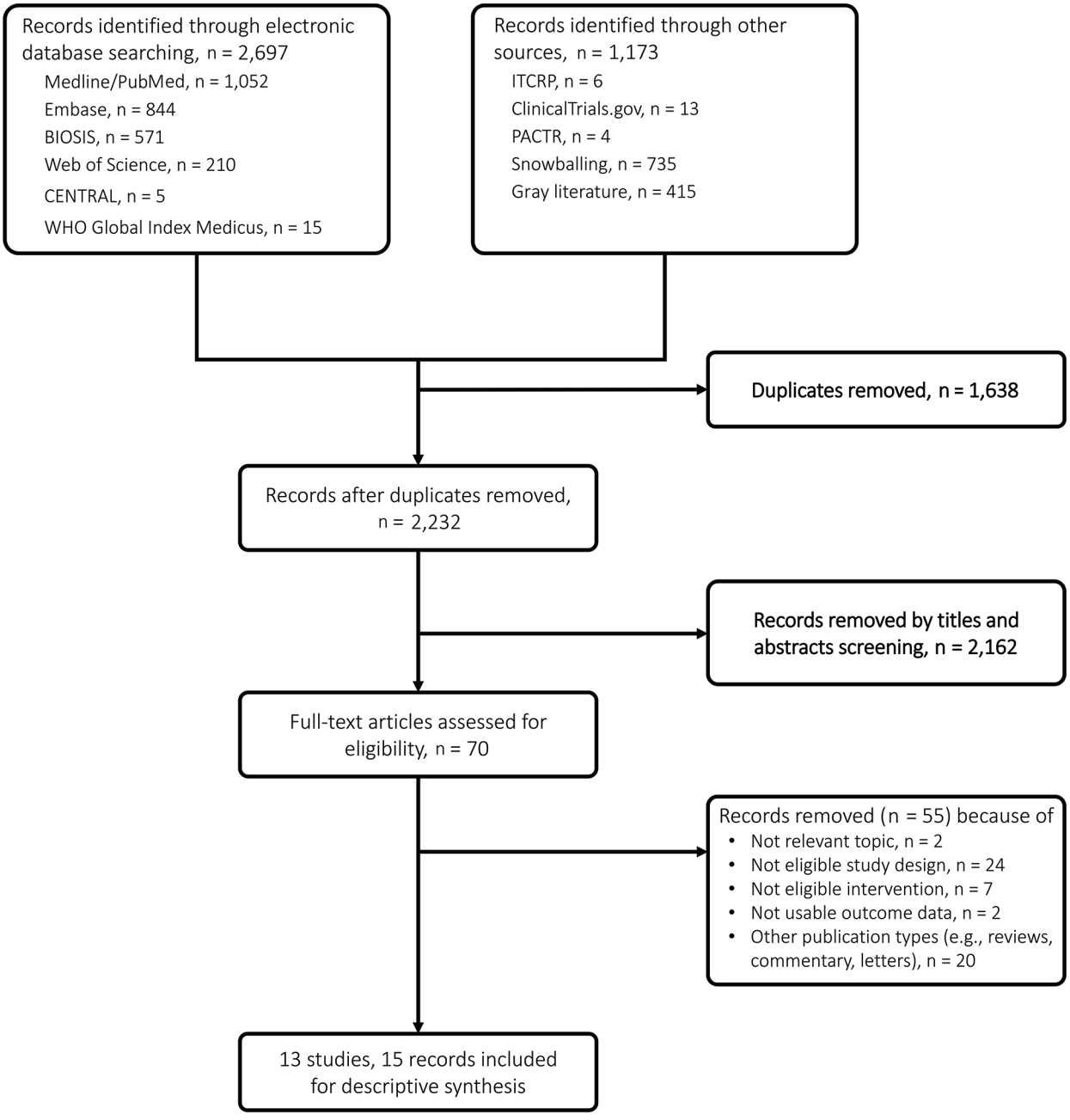

Figure 1. Study selection flowchart for a systematic review of published and unpublished studies for evidence for ribavirin treatment of Lassa fever. ITCRP, World Health Organization International Clinical Trials Registry Platform; PACTR, Pan African Clinical Trial Registry.

described as clinical trials, but we concluded that all studies were observational cohorts, because they did not compare treatment groups that were assigned using randomization. The year of publication ranged from 1986 to 2020. The length of follow up ranged from 1 month to 15 years.

The studies ranged in size from 10 to 1,850 confirmed cases. Most included both child and adult patients, although 2 did not report the characteristics of patients comprehensively (*11*,*34*). Price et al. (*34*) included pregnant women only. Dahmane et al. (*14*) recruited children and women with obstetric conditions. Samuels et al. (*35*) and Orji et al. (M.-L. Orji et al., unpub. data) included children only. Nine of 13 studies were funded by internal or not-for-profit research funders.

Criteria for confirming Lassa fever varied between studies (Appendix Table 4). Real-time PCR

was the most common diagnostic test used, followed by virus isolation and Lassa IgM. In IND 16666, the criterion for the no treatment group was either or both bring febrile and having positive Lassa IgG whereas to receive ribavirin participants had to meet 1 of 3 specified diagnostic criteria (Appendix Table 3).

Only 4 studies reported details of ribavirin treatment regimens (*11*,*14*,*38*; Birch & Davis Associates and Sherikon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf; G.V. Ludwig, pers. comm., 2019 March 4, https://media.tghn.org/medialibrary/2019/03/Dr._Ludwig_memo.pdf) (Appendix Table 4). McCormick et al. (*11*) reported 3 ribavirin regimens: 1 oral and 2 intravenous. Dahmane et al. (*14*) reported 1 intravenous ribavirin regimen according to an international guideline. Although 7 ribavirin regimens were reported in IND 16666, the treatment durations and administration routes were not clear. In all studies except Samuels et al. (*35*), detailed information regarding the supportive treatment used was lacking.Three studies reported malaria screening and the use of antimalarial drugs and antibiotics before Lassa fever confirmation (*14*,*34*,*36*).

We assessed risk for bias in 14 results from 13 studies comparing the effects of ribavirin treatment with no ribavirin treatment on overall mortality outcomes, including 2 results with and without logistic regression adjustment from IND 16666 (Figure 2). The overall risk for bias was rated critical for all results, except for the logistic regression result from IND 16666, which was rated serious.

Estimated Effects of Ribavirin Treatment on Mortality, Overall and in Subgroups

In the McCormick et al. (*11*) study, for which additional data was reported by IND 16666, ribavirin treatment was associated with higher overall mortality rates in confirmed Lassa fever patients, compared with no ribavirin treatment (Figure 3). However, the IND 16666 study found that, after adjusting for confounding factors using logistic regression, ribavirin was associated with lower overall mortality rates (OR 0.88 [95% CI 0.81–0.95]). We noted that the CI for this logistic regression result appeared too narrow when compared with the unadjusted result derived from the reported numbers of patients and deaths, which was most likely caused by an error in the statistical analysis but could not be checked further.

When results of those studies were stratified by AST levels, ribavirin treatment was associated with lower mortality rates in patients with AST ≥150 IU/L (OR 0.18 [0.08–0.39] in McCormick et al. [*11*] and OR

Figure 2. Summary of risk for bias assessment for a systematic review of published and unpublished studies for evidence for ribavirin treatment of Lassa fever. Bias categories: D1, bias due to confounding; D2, bias in selection of participants into the study; D3, bias in classification of interventions; D4, bias due to deviations from intended interventions; D5, bias due to missing data; D6, bias in measurement of outcomes; D7, bias in selection of the reported result. *IND 16666, unpublished study requested by P.W.H. through the US Freedom of Information Act (Birch & Davis Associates and Sherikon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf; G.V. Ludwig, pers. comm., 2019 March 4, https://media.tghn.org/medialibrary/2019/03/Dr._Ludwig_memo.pdf). †M.-L. Orji et al., unpub. data, https://doi.org/10.20944/preprints202005.0269.v1.

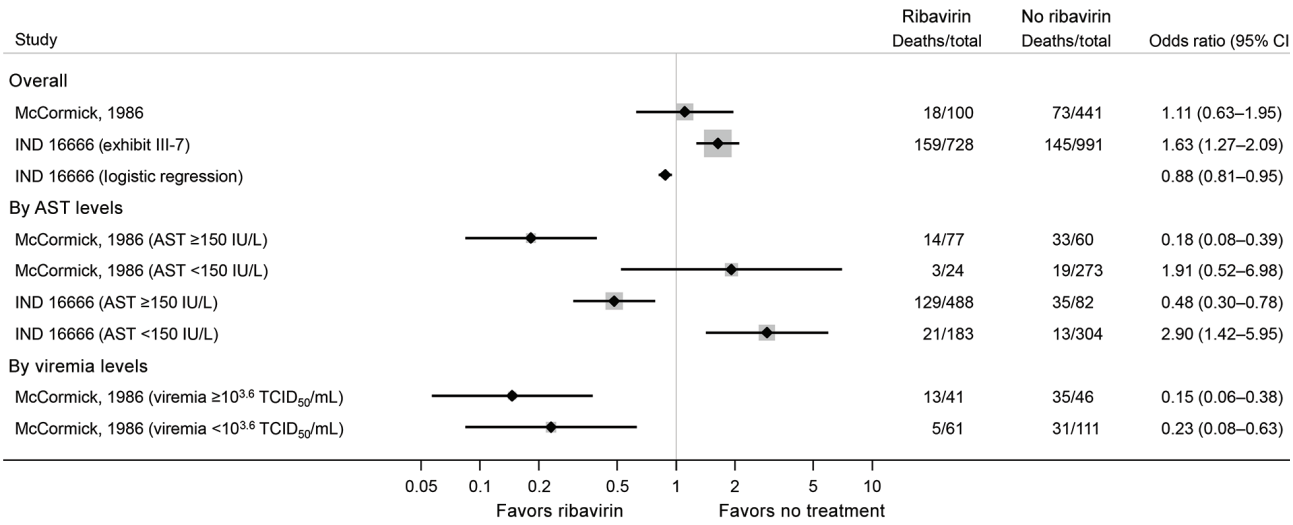

Figure 3. Estimated effects of ribavirin compared with no treatment on mortality outcomes from the McCormick (11) and IND 16666 (Birch & Davis Associates and Sherikon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf; G.V. Ludwig, pers. comm., 2019 March 4, https://media.tghn.org/medialibrary/2019/03/Dr._Ludwig_memo.pdf) studies in a systematic review of published and unpublished studies for evidence for ribavirin treatment of Lassa fever. A horizontal line represents the 95% CI of a study result, with each end of the line representing the boundaries. A point estimate of the study result is represented by a black diamond. A gray box gives a representation of the size of a study compared with all studies in the figure.

0.48 [0.30–0.78] in IND 16666). By contrast, in patients with AST <150 IU/L, ribavirin was associated with higher mortality rates (OR 1.91 [0.52–6.98] in McCormick et al. [*11*] and OR 2.90 [1.42–5.95] in IND 16666 study). In patients with measurable viremia, ribavirin use was associated with lower mortality rates. However, those results should be interpreted with caution because AST or viremia levels were reported to be missing or not measurable in 20%–40% of patients in each study.

The other studies mostly found that ribavirin was associated with lower overall mortality rates compared with no ribavirin treatment (Figure 4). However, most of these results were rated as being at critical risk for bias because of lack of adjustment for confounding, immortal time bias, or both (*14*,*17*,*32*; M.-L. Orji et el.,

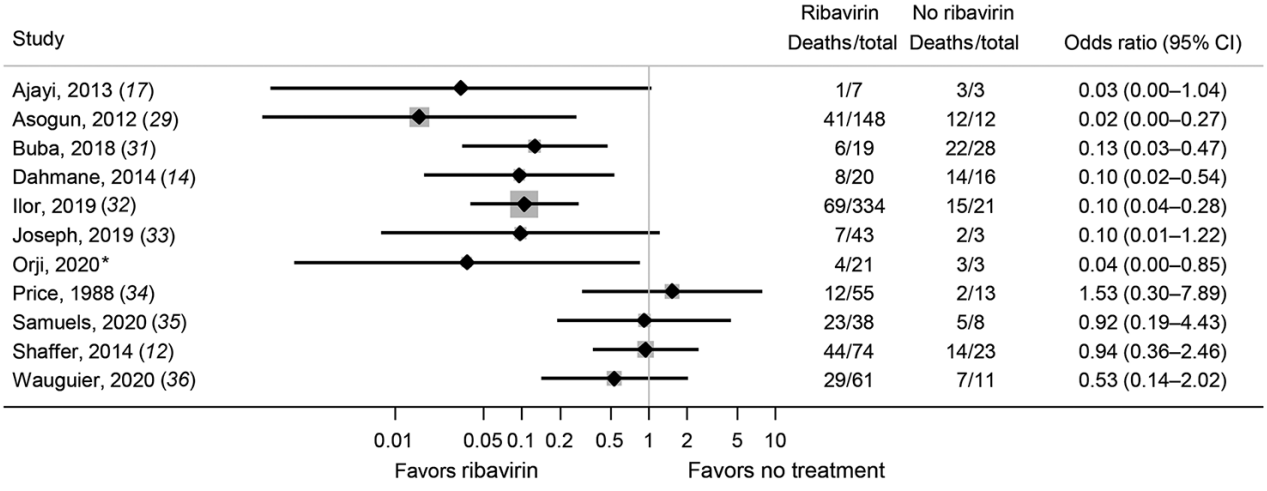

Figure 4. Estimated effects of ribavirin compared with no treatment on mortality outcomes from studies other than McCormick (*11*) and IND 16666 (Birch & Davis Associates and Sherikon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf; G.V. Ludwig, pers. comm., 2019 March 4, https://media.tghn.org/medialibrary/2019/03/Dr._Ludwig_memo.pdf) studies in a systematic review of published and unpublished studies for evidence for ribavirin treatment of Lassa fever. *M.-L. Orji et al., unpub. data, https://doi.org/10.20944/preprints202005.0269.v1. A horizontal line represents the 95% CI of a study result, with each end of the line representing the boundaries. A point estimate of the study result is represented by a black diamond. A gray box gives a representation of the size of a study compared with all studies in the figure.

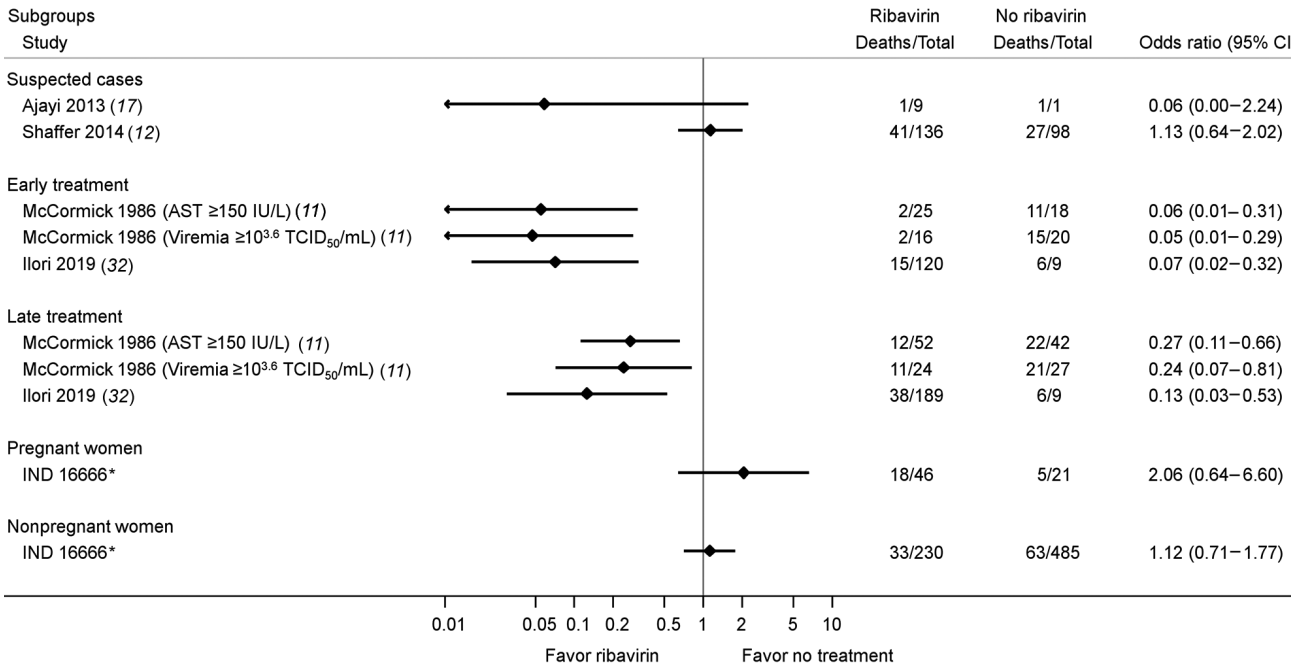

Figure 5. Estimated effects of ribavirin compared with no treatment on mortality outcomes within patient subgroups in a systematic review of published and unpublished studies for evidence for ribavirin treatment of Lassa fever. *IND 16666, unpublished study requested by P.W.H. through the US Freedom of Information Act (Birch & Davis Associates and Sherikon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf; G.V. Ludwig, pers. comm., 2019 March 4, https://media.tghn.org/medialibrary/2019/03/Dr._Ludwig_memo.pdf).

unpub. data), which arose because some patients did not receive their intended ribavirin treatment because they died before treatment could be started and were then analyzed in the no treatment group.

Estimated associations of ribavirin treatment with mortality rates within patient subgroups are reported in the included studies (Figure 5). Many studies included suspected Lassa fever cases, but only 2 studies provided usable data for estimating associations of ribavirin treatment with deaths in suspected cases. Results were discordant; the estimated ORs were 0.06 (95% CI 0.00–2.24) in Ajayi et al. (*17*) and 1.13 (0.64–2.02) in Shaffer et al. (*12*,*15*). We calculated case-fatality rates and ORs from Shaffer et al. (*12*,*15*) on the basis of different case definitions (Appendix Table 5).

Two studies investigated the effects of early versus late ribavirin treatment after disease onset (*11*,*32*). McCormick et al. (*11*) found that in the subgroups AST ≥150 IU/L and viremia $\geq 10^{3.6}$ median tissue culture infectious dose/mL, the association of ribavirin treatment with a lower mortality rate was more pronounced for treatment within 7 days (early) than at ≥7 days (late) after disease onset (*11*). Similar results were noted in Ilori et al. (*32*); the ORs were 0.07 (95% CI 0.02–0.32) for early treatment (within 7 days of disease onset) and 0.13 (95% CI 0.03–0.53)] for late treatment (≥7 days after disease onset).

Only 1 study provided a result of subgroup analysis to compare pregnant women with nonpregnant women. The IND 16666 study reported separate results for pregnant women (OR 2.06 [95% CI 0.64–6.60]) and nonpregnant women (OR 1.12 [95% CI 0.71–1.77]).

Discussion

This systematic review summarizes associations of ribavirin treatment, compared with no ribavirin treatment, with overall mortality outcomes in confirmed Lassa fever, using both published and unpublished study results. Although ribavirin treatment was generally associated with lower mortality rates, almost all results were rated as being at critical risk for bias. In the single adjusted result from the IND 16666 study, ribavirin was associated with modestly lower mortality rates. However, that result was assessed as being at serious risk for bias, and the CI appeared too narrow compared with the CI derived from the numbers of patients and deaths. Although ribavirin was reported to be associated with lower mortality rates in certain subgroups, including patients with AST ≥150 IU/L and measurable viremia, missing data and the post-hoc nature of the analyses limit the credibility of these findings. By contrast, ribavirin was reported to be associated with higher mortality rates than

ribavirin treatment in other subgroups, such as patients with AST <150 IU/L. In summary, it is uncertain based on the available literature whether ribavirin reduces mortality rates in Lassa fever patients.

For decades, ribavirin has been used to treat Lassa fever, supported in particular by the results of the McCormick study (*11*). However, treatment guidelines generally do not highlight the weakness of the primary evidence, nor do they distinguish patient subgroups (e.g., patients with AST <150 IU/L) where benefit has not been demonstrated and, in fact, there may be hazard from using ribavirin (*37*,*38*). Because ribavirin causes adverse events and is expensive (up to 5,000€/patient) (*14*,*37*), it is important to justify its use in treating Lassa fever, especially in low- and middle-income countries where healthcare resources are limited. Although such uncertainty exists in the efficacy and safety of ribavirin, we believe that it is important to firmly establish evidence of efficacy and safety by conducting randomized controlled clinical trials. For example, WHO has identified the need for a multicenter phase 2b/3 RCT with 2 possible designs: a 4-arm factorial design with ribavirin and best supportive care and a 3-arm RCT with ribavirin, best supportive care, and another drug (*39*). In line with this approach, a combination of ribavirin and favipiravir treatment has been proposed by Raabe et al. (*40*)

Our findings agree with those of a previous systematic review (*41*). Both reviews identified a need to reevaluate the safety and efficacy of ribavirin for Lassa fever. In comparison with the prior review (which included studies published up to March 2019), our study included 6 additional studies, presented more detailed results (including secondary analyses), and provided a more detailed evaluation of the potential biases in study results.

Our review was conducted using state-of-the-art systematic review methodology. We conducted comprehensive literature searches, including a range of electronic databases and gray literature, without date, language, or study design restrictions. We used the ROBINS-I tool (*19*) for risk for bias assessments; this tool is the most comprehensive and widely used tool for assessing risk for bias in the results of nonrandomized studies of interventions. Our review incorporated recent changes to ROBINS-I that address immortal time bias; evidence of such bias was identified in several of the included studies.

We conducted secondary analyses of the related McCormick (*11*) and IND 16666 studies. To estimate overall associations of ribavirin treatment with mortality outcomes, we grouped different ribavirin treatment regimens and routes of administration. Treatment efficacies might differ between these regimens, but it was challenging to distinguish the ribavirin regimens used in these studies because their details were not fully described. There may have been differences in the care given to the no ribavirin treatment groups across studies; such care could be no medical support, minimal medical support, or supportive treatment, and the type of care is likely to have varied over time, by country and by setting. We did not perform subgroup analyses, investigating the implications of different criteria used to define Lassa fever, because except for Shaffer et al. (*12*,*15*), no studies provided data that could be used for subgroup analyses. We only identified studies conducted in Nigeria and Sierra Leone, but Lassa fever is endemic in several other countries in West Africa.

These findings have important implications for both clinical practice and research. The serious limitations of the available evidence means that although the studies we reviewed suggest an association of ribavirin treatment for Lassa fever with decreased mortality rates, this conclusion must be viewed with limited confidence. Evidence from high-quality randomized trials is urgently required, and clinical and research communities should work collaboratively to address and overcome ethics and resource issues to fund and conduct such trials in West Africa.

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Author contributions: H.C., S.D., C.E.F., A.M., A.P.S., and J.S. preformed screening for the review. SD designed, managed, and conducted electronic database searches. H.C. conducted gray literature searches. H.C., C.E.F., and A.P.S. conducted data extraction. H.C., C.E.F., J.S., and J.A.C. conceived the risk of bias assessment tool while A.S. and P.W.H. acted as field experts, providing clinical inputs. H.C., C.E.F., A.M., L.A.M. and A.S. assessed risk of bias in the included studies. H.C. drafted the manuscript, designed screening, data collection tools, performed data analysis, and manage the review. P.H. initiated the collaboration with J.S. and J.A.C.S. to conceptualize the review and oversee the review project together. All authors revised the draft paper and provided comments and declarations. All authors read and approved the final manuscript. All authors declare that there is no conflict of interest regarding the publication of this manuscript. Data and materials are available from the corresponding author upon request. The views expressed in this article are those of the authors and do not necessarily reflect the opinions of the National Health Service, the National Institute for Health Research, or the Department of Health and Social Care.

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Lack of Evidence for Ribavirin Treatment of Lassa Fever in a Systematic Review of Published and Unpublished Studies

Appendix

Search Strategies

Ovid MEDLINE(R) ALL <1946 to March 8 2022>

1. Lassa Fever/
2. Lassa virus/
3. (lassa adj3 (infect* or fever or virus* or viral or arenavir* or outbreak?)).ti,ab,kf.
4. lassa.ti,ot.
5. (LASV or Lassa mammarenavirus).mp.
6. or/1-5
7. Ribavirin/
8. (ribavirin* or tribavirin* or viramidin* or ribamidin* or Copegus or Ibavyr or Moderiba or Rebetol).mp.
9. Disease Management/ or Drug Evaluation/ or Infection Control/ or Treatment Outcome/
10. (drug therapy or prevention & control or therapy).fs.
11. (death? or disease outbreak? or mortalit* or survival or survivor?).kf,hw.
12. case fatalit*.mp.
13. or/7-12
14. 6 and 13

PubMed NOT MEDLINE (All years to 8 Mar 2022)

#1 Search ("LASSA FEVER"[Mesh:NoExp]) OR "LASSA VIRUS"[Mesh:NoExp]

#2 “lassa fever” OR “lassa hemorrhagic fever” OR “lassa haemorrhagic fever” OR “lassa virus” or LASV OR “Lassa mammarenavirus”

#3 (#1 OR #2)

#4 pubmednotmedline[sb]

#5 publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook

#6 (#4 OR #5)

#7 (#3 AND #6)

Ovid Embase <1980 to 2022 March 08>

1 Lassa fever/

2 Lassa virus/

3 (lassa adj3 (infect* or fever or virus* or viral or arenavir* or outbreak?)).ti,ab,kw.

4 lassa.ti,ot.

5 (LASV or Lassa mammarenavirus).ti,ab,kw.

6 Arenavirus Infection/

7 old world arenavirus/ or mammarenavirus/

8 or/1-7

9 ribavirin/

10 (ribavirin* or tribavirin* or viramidin* or ribamidin* or Copegus or Ibavyr or Moderiba or Rebetol).mp.

11 drug therapy.dy,fs,kw,ox,xw.

12 (drug adj (administration or comparison or efficacy or therapy)).hw.

13 antivirus agent/

14 INFECTION CONTROL/ or TREATMENT OUTCOME/

15 or/9-14

16 8 and 15

Web of Science (All years to 8 Mar 2022)

• Science Citation Index Expanded (SCI-EXPANDED) --1900-present

• Conference Proceedings Citation Index- Science (CPCI-S) --1990-present

#1 TITLE: (lassa) OR TOPIC: ((lassa SAME (infect* or fever or virus* or viral or arenavir* or outbreak*))) OR TOPIC: (LASV)

#2 (ribavirin* or tribavirin* or viramidin* or ribamidin* or Copegus or Ibavyr or Moderiba or Rebetol)

#3 (#1 and #2)

BIOSIS Citation Index (BCI) (2020 to 8 March 2022)

#1 TOPIC: ((lassa SAME (infect* or fever or virus* or viral or arenavir* or outbreak*))) AND TOPIC: (ribavirin* or tribavirin* or viramidin* or ribamidin* or Copegus or Ibavyr or Moderiba or Rebetol)

#2 TITLE: (lassa or LASV)

#3 TAXONOMIC DATA: (Hominidae [86215])

#4 (#2 AND #3)

#5 (#1 OR #4)

Central Register of Controlled Trials (CENTRAL) on the Cochrane Library, Issue 3 of 12, 2022

(lassa or LASV) AND (ribavirin* OR tribavirin* OR viramidin* OR ribamidin* OR Copegus OR Ibavyr OR Moderiba OR Rebetol) [all fields]

WHO Global Index Medicus

S1 (lassa or LASV)

S2 (ribavirin* OR tribavirin* OR viramidin* OR ribamidin* OR Copegus OR Ibavyr OR Moderiba OR Rebetol)

S3 (S1 or S2)

WHO International Clinical Trials Registry Platform (ICTRP)

(lassa and ribavirin* or lassa and tribavirin* or lassa and viramidin* or lassa and ribamidin* or lassa and Copegus or lassa and ibavyr or lassa and moderiba or lassa and rebetol or LASV and ribavirin* or LASV and tribavirin* or LASV and viramidin* or LASV and ribamidin* or LASV and copegus or LASV and ibavyr or LASV and moderiba or LASV and rebetol)

ClinicalTrials.gov

(lassa OR LASV)

Pan African Clinical Trials Registry (PACTR) (https://pactr.samrc.ac.za)

S1 Lassa

S2 LASV

S3 Ribavirin

S4 Arenavirus

OR/S1-S4

Note: Additional scoping searches were conducted on *LILACS*, but no relevant records were retrieved.

Summary of Judgments on Risk of Bias Assessment

Protocol stage

- Participants: Patients, regardless of age, with confirmed (e.g. PCR, Lassa Ag + or IgM positive) or suspected Lassa fever
- Experimental intervention: Any treatment regimen or administration routes (e.g. intravenous or oral) of ribavirin for treating or preventing Lassa fever
- Comparator: Placebo, supportive care, no treatment or other intervention. Supportive care includes any supportive interventions for treating or relieving symptoms of Lassa fever, such as respiratory distress, hemorrhaging and organ failure.
- Outcome: Mortality

List of the confounding factors relevant to all or most studies

- Age
- Pregnancy status
- Biomarkers/signs/symptoms of disease severity

Aim for each study

- To assess the effect of assignment to intervention

Secondary Analyses

The full data set includes 1740 observations. The details of eligibility criteria for the data set can be found in Shafer et al (*1*,*2*). In this review, we were concerned with effect of ribavirin compared with no treatment, on survival. Thus, only 373 of 1740 patients were eligible (because they had both treatment status and survival recorded). Among these 373 patients, all those with admission status 'Not admitted' died (n = 42), providing no efficacy comparison, so we excluded them. This left 331 patients (suspected and confirmed cases) with treatment status, survival outcome, and 'admitted' status for the secondary analysis.

Shaffer et al. reported three types of serostatus according to antigen (Ag), immunoglobulin M (IgM), and immunoglobulin G (IgG) ELISA tests for determining Lassa fever. In our main results we use positive Ag (Ag+) as the criterion for Lassa fever confirmation, after discussion with clinical experts.

In sensitivity analyses, we explored the following criteria for confirmed Lassa fever cases. There were discrepancies in IgM serostatus between serostatus 1 and serostatus 2. Thus, we presented two results for IgM serostatus:

1. IgM+ only (IgM+ in serostatus 1 or 2)
2. IgM+ only (IgM+ in serostatus 1 and 2)
3. IgG+ only
4. Ag+ or IgM+ (IgM+ in serostatus 1 or 2)
5. Ag+ or IgM+ (IgM+ in serostatus 1 and 2)
6. Ag+ or IgG+

7. IgM+ or IgG+ positive (IgM+ in serostatus 1 or 2)

8. IgM+ or IgG+ positive (IgM+ in serostatus 1 and 2)

9. Ag+, IgM+ or IgG+

Next, we explored suspected cases in the following criteria:

1. Ag- only

2. IgM- only (IgM- in serostatus 1 and 2)

3. IgM- only (IgM- in serostatus 1 or 2)

4. IgG- only

5. Ag- or IgM- (IgM- in serostatus 1 and 2)

6. Ag- or IgM- (IgM- in serostatus 1 or 2)

7. Ag- or IgG-

8. IgM- or IgG- positive (IgM+ in serostatus 1 and 2)

9. IgM- or IgG- positive (IgM+ in serostatus 1 or 2)

10. Ag-, IgM- or IgG-

Last, we conducted an all-case analysis (regardless of ELISA test results) (Appendix Table 5).

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Appendix Table 1. PRISMA 2009 Checklist (*3*)

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2-3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tab 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 3, 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig 3, 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tab 1, Tab 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Fig 4-5
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

Appendix Table 2. Summary of risk of bias assessment

Domain	Study: McCormick 1986	IND 16666 (Overall)	IND 16666 (Logistic regression)	Ajayi 2013	Asogun 2012	Buba 2018	Dahmane 2014	Ilori 2019	Joseph 2019	Price 1988	Shaffer 2014	Wauguier 2020	Orji 2020	Samuels 2020
Overall bias	Critical	Critical	Serious	Critical	Critical	Critical	Critical	Critical	Critical	Critical	Critical	Critical	Critical	Critical
Bias due to confounding	Serious Authors explored effects of some confounding factors on the outcome but did not control for all the important confounding domains. (Q1.4)	Critical No adjustments for confounding factors.	Serious Authors explored effects of some confounding factors on the outcome but did not control for all the important confounding domains. (Q1.4)	Critical No adjustments for confounding factors.	Critical No adjustments for confounding factors.	Critical No adjustments for confounding factors.	Critical No adjustments for confounding factors.	Critical No adjustments for confounding factors.	Critical No adjustments for confounding factors.	Critical No adjustments for confounding factors.	Critical Unable to adjust for confounding factors in the secondary analysis.	Critical No adjustments for confounding factors on ribavirin and controls.	Critical No adjustments for confounding factors.	Critical No adjustments for confounding factors.
Bias in selection of participants into the study	Critical The authors used historical controls in the analysis without providing further information nor justification. (Q 2.1 & 2.4)	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.	Low Participants were not selected nor analyzed based participant characteristics observed after the start of intervention. Start of follow-up and start of intervention coincide for most participants.
Bias in classification of interventions	Moderate The authors combined certain groups in the later analysis, "*We observed a case-fatality rate of 29 percent (9 of 31) in patients*	Critical "*The treated group were more severely ill and, thus, they would be at a disadvantage in terms of survival*." – suggesting	Low Immortal time bias in classification of interventions was adjusted by logistic regression.	Critical "*Four of the patients who died during the outbreak did not receive ribavirin therapy. The index case was not*	Critical "*…23% of Lassa fever patients with fatal outcome did not receive ribavirin because they died the day of*	Serious *"We defined ribavirin commencement as early if it was started within 7 days of symptom onset and as delayed if it was not."* –	Critical "*Of 16 patients who did not receive ribavirin, 14 (87%) died before ribavirin treatment could be*	Serious *"Patients in severe conditions might have not received ribavirin because they died before reaching healthcare*	Serious "Although there is an improved case detection and access to ribavirin, some patients still presented late to the hospital.	Serious "*Women less than 20 weeks pregnant suspected of having Lassa fever were admitted to hospital and treated on the general*	Moderate Classification of interventions was derived from clinical records (administration of ribavirin therapy observed	Low No evidence of bias in classification of interventions nor immortal time bias.	Critical "A total of 12.5% of the children that tested positive to Lassa virus PCR and were unable to receive ribavirin	Moderate Classification of interventions was derived from clinical records (administration of ribavirin therapy observed

	Study													
Domain	McCormick 1986	IND 16666 (Overall)	IND 16666 (Logistic regression)	Ajayi 2013	Asogun 2012	Buba 2018	Dahmane 2014	Ilori 2019	Joseph 2019	Price 1988	Shaffer 2014	Wauguier 2020	Orji 2020	Samuels 2020
	treated with 1 unit of Lassa-convalescent plasma; this rate did not differ significantly from the rate in patients treated with 2 units of plasma (36 percent, 8 of 22). Hence, we combined both these patient groups for analysis as the plasma-treated group (53 patients)." (Q 3.2)	immortal time bias in classification of interventions (Q 3.3)		*treated because the confirmatory diagnosis did not return until her death. The other three patients died within a few hours of presentation*." – suggesting immortal time bias on classification of interventions (Q 3.3)	*presentation or the next day*." – suggesting immortal time bias on classification of interventions (Q 3.3)	suggesting a possibility of immortal time bias (Q 3.3)	*commenced."* – suggesting immortal time bias in classification of interventions (Q 3.3)	*facilities where treatment was available…"* – authors recognized the situation in the discussion, implying potential immortal time bias in classification of interventions (Q 3.3)	Majority of the fatalities occurred among health workers." – suggesting immortal time bias in classification of interventions (Q 3.3)	*female ward. If the clinical diagnosis was strongly suspected or had been confirmed by serologic testing, the patient was transferred to an isolation room."* – suggesting some aspects of treatment status depending on pregnancy (Q 3.3)	during hospitalization).		medication died." – authors recognized the situation in the discussion, implying potential immortal time bias in classification of interventions (Q 3.3)	during hospitalization). And "It is not clear why only 66% (38/57) of our cohort with LF antigen received ribavirin" – suggesting a chance of intervention given by patient's status.
Bias due to deviations from intended interventions	Low No or few deviations from the intended intervention.	Low No or little deviations from the intended intervention due to a retrospective study design.	Low No or little deviations from the intended intervention due to a retrospective study design.	Low None or little deviations from the intended intervention due to retrospective study design.	Low None or little deviations from the intended intervention due to retrospective study design.	Low None or little deviations from the intended intervention due to retrospective study design.	Low No or little deviations from the intended intervention due to a retrospective study design.	Low No or little deviations from the intended intervention due to a retrospective study design.	Low No or little deviations from the intended intervention due to a retrospective study design.	Low No or few deviations from the intended intervention.	Low No or few deviations from the intended intervention.	Low No or few deviations from the intended intervention.	Low No or few deviations from the intended intervention.	Low No or few deviations from the intended intervention.
Bias due to missing data	Serious Complete data were not available for all participants due to the use of historical controls.	Serious There were only 1795/2154 (83.3%) cases reported with survivorship in Table Exhibit III-7. (Q 5.1)	Serious There were missing data on survivorship and SGOT levels.	Low No evidence of missing data was found.	Moderate There were missing data (161/183) and no reasons were given. However, the proportion of missing in both groups is similar, 21/169 (ribavirin) vs	Low No evidence of missing data was found.	Low No evidence of missing data was found.	Serious There were only 355/414 (85.7%) cases reported with treatment status. (Q 5.1)	Serious 62 confirmed cases but only 46 cases with unknown treatment status (Q 5.1)	Low No evidence of missing data was found.	Low No evidence of missing data was found.	Serious 79 confirmed cases but only 72 cases with unknown treatment status.	Low No evidence of missing data was found.	Serious Intervention status was missing for 11/57 patients (19%) who were excluded (6 in the 'survived' group (21%) and 13 (36%) in the 'died' group).

	Study													
Domain	McCormick 1986	IND 16666 (Overall)	IND 16666 (Logistic regression)	Ajayi 2013	Asogun 2012	Buba 2018	Dahmane 2014	Ilori 2019	Joseph 2019	Price 1988	Shaffer 2014	Wauguier 2020	Orji 2020	Samuels 2020
					2/14 (no ribavirin). (Q 5.1)									
Bias in measurement of outcomes	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.	Low The outcome measure, death, was unlikely to be influenced by knowledge of the intervention or present systematic errors.
Bias in selection of the reported result	Critical Lack of protocol. The authors did post-hoc decisions on their analysis and emphasized on subgroup results.	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result	Moderate Lack of protocol but no evidence of bias in selection of the reported result

Appendix Table 3. Characteristics of studies

Study	Country	Study period	Design	No. of patients (% male)	Population; Age (year)	Criteria for confirming Lassa fever cases	Funding
Ajayi 2013 (*4*)	Nigeria	Jan 2012 - Mar 2012	Cohort	10* (70%)	Children and adults; Median: 36 (range 12-47)	Positive Lassa IgM antibody, PCR, or virus isolation	German Research Foundation and WHO
Asogun 2012 (*5*)	Nigeria	Jan 2009 - Dec 2010	Cohort	198* (51.3%)	Adults; Median: 32 (IQR 23-46)	RT-PCR	Volkswagen Foundation, German Research Foundation, European Community and Harvard University
Buba 2018 (*6*)	Nigeria	Oct 2015 - Feb 2016	Cohort	47 (63.8%)	Children and Adults; Mean: 31.4 (SD 18.4)	RT-PCR or ELISA	NR
Dahmane 2014 (*7*,*8*)	Sierra Leone	Apr 2011 - Feb 2012	Cohort	36* (55.6%)	Children and women with obstetric conditions; Age<15 yrs: 80%	Positive Lassa virus Ag or Lassa IgM antibody	An anonymous donor, Department for International Development, UK and Medecins Sans Frontieres
Ilori 2019 (*9*)	Nigeria	Jan – May 2018	Cohort	423 (62.1%)	Children and adults; Age 0-20 yrs: 26.2%	Positive IgM, RT-PCR, or virus isolation	NR
IND 16666†	Sierra Leone	1977 – 1991	Cohort	1850* (45.6%)	Children and adults; Age<15 yrs: 7.1%	Confirmed by the CDC; or an IFA reading of 30 or more; or had a positive viremia, IgG, IgM; or had a positive liver touch prep (21 p16)	Ministry of Health of Sierra Leone and Centers for Disease Control (CDC) and the U.S. Army Medical Research and Development Command
Joseph 2019 (*10*)	Nigeria	March 2018	Cohort	62 (36.2%)	Children and adults; Age 0-19 yrs: 18.8%	RT-PCR	NR
McCormick 1986 (*11*)	Sierra Leone	Feb 1977 – Jan 1979	Controlled study	596 (NR)	Children and adults; NR	Virus isolation from serum or other body fluids/organs, IFA titers <1:4 to ≥1:16, or Lassa antibody titer ≥1:256 and Lassa IgM antibody titer ≥1:16	Ministry of Health of Sierra Leone and Centers for Disease Control (CDC)
Orji 2020‡	Nigeria	Jan 2019 – Jan 2020	Cohort	24* (37.5%)	Children; Age <12 yrs: 70.8%	RT-PCR	NR
Price 1988 (*12*)	Sierra Leone	1981-1985	Cohort	68 (NR)	Pregnant women; NR	Lassa IgG antibody titer ≥ 1:4 to ≥1:16, Lassa IgG antibody titer ≥1:256 and Lassa IgM antibody, or virus isolation	United States Army Medical Research and Development Command
Samuels 2020 (*13*)	Sierra Leone	Jan 2012 – Dec 2018	Cohort	57* (63.2%)	Children; Age<15yrs: 82%	ELISA for Lassa Ag, IgM and IgG	Fogarty International Center of the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases, and U.S. Agency for International Development (USAID)
Shaffer 2014 (*1*,*2*)	Sierra Leone	2008-2012	Cohort	97* (37.1%)	Children and adults; Age<15 yrs: 70.1%	Positive Lassa virus Ag ELISA, IgM ELISA, or IgG ELISA	National Institute of Allergy and Infectious Diseases and Burroughs Wellcome Fund
Wauquier 2020 (*14*)	Sierra Leone	NR	Cohort	79 (39.2%)	Children and adults; Median: 22 (IQR: 14-30)	RT-PCR	French National Agency of Research (ANR-13-BSV-0004)

Abbreviations: Ag: antigen; ELISA: enzyme-linked immunosorbent assay; IFA: immunofluorescent-antibody assay; IQR: interquartile range; NR: not reported; RT-PCR: reverse transcription PCR.
*Confirmed cases only.
†Birch & Davis Associates and Sherikon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf
‡M.-L. Orji et al., unpub. data, https://doi.org/10.20944/preprints202005.0269.v1.

Appendix Table 4. Summary of treatment regimens

Study	Ribavirin treatment regimen	No ribavirin treatment	Other case management
Ajayi 2013 (*4*)	NR	Supportive therapy	NR
Asogun 2012 (*5*)	NR	NR	NR
Buba 2018 (*6*)	NR	NR	NR
Dahmane 2014 (*7*,*8*)	Loading dose of 30 mg/kg, followed by 15 mg/kg QID from day 1 to 4 and 7.5 mg/kg TID from day 5 to 10	NR	Patients with malaria positive on testing received anti-malarial drugs, and antibiotics if clinically indicated
Ilori 2019 (*9*)	NR	NR	NR
IND 16666*	Regimen 2: IV Ribavirin followed by oral dose Regimen 3: Ribavirin + plasma Regimen 5: Ribavirin 25-30mg loading dose Regimen 6: Ribavirin 34mg loading dose Regimen 7: Ribavirin 33mg loading dose followed by 1/4 dose Regimen 8: Ribavirin 33mg loading dose followed by 1/8 dose Regimen 9: Ribavirin + prostacyclin	Regimen 1: No treatment Regimen 10: no drugs were available	NR
Joseph 2019 (*10*)	NR	NR	Antipyretics
McCormick 1986 (*11*)	IV ribavirin (1): 2-g loading dose and 1 g QID for 4 days, reduced to 0.5 g TID for another 6 days IV ribavirin (2): 2-g loading dose and 1 g QID for 4 days, reduced to 0.5 g TID for another 6 days with 1 unit (300ml) of convalescent plasma Oral ribavirin: 2-g loading dose followed by 1 g QID for 10 days	NR	NR
Orji 2020†	NR	NR	NR
Price 1988 (*12*)	NR	NR	Chloroquine and broad-spectrum antibiotics until Lassa fever was confirmed
Samuels 2020 (*13*)	Loading dose of IV ribavirin 30 mg/kg with 24 hours of admission, and then maintenance dose as follow: 15 mg/kg every 6 hours for 4 days followed by 7.5 mg/kg every 8 hours for 5 days to complete 10 total days of therapy	Supportive care provided according to the WHO Integrated Management of Childhood Illnesses guidelines (prior 2017) or the WHO Emergency Triage Assessment and Treatment guidelines (*15*,*16*), which involved IV fluids, use of oxygen, nasogastric feeding, and catheterization, and treatment of comorbidities when necessary and available.	Broad spectrum antibiotics with either intravenous ceftriaxone or cefotaxime, depending on age; intravenous antimalarial medications if a rapid malaria test was positive; and blood transfusions for patients with anemia
Shaffer 2014 (*1*,*2*)	NR	NR	NR
Wauquier 2020 (*14*)	NR	NR	Antibiotics, antimalarials and other medicines (not specified)

Abbreviations: IV: intravenous; NR: not reported; QID: four times a day; TID: three times a day
*Birch & Davis Associates and Sherikon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf
†M.-L. Orji et al., unpub. data, https://doi.org/10.20944/preprints202005.0269.v1.

Appendix Table 5. Case fatality rates and odd ratios for the effect of ribavirin compared with no ribavirin from mean and sensitivity analyses

Test	%Case fatality rate (death/total)		Odds ratio (95% CI)
	Ribavirin	No ribavirin	
Ag+ only (main analysis)	59.5% (44/74)	60.9% (14/23)	0.94 (0.36-2.46)
IgM+ only (IgM+ in serostatus 1 or 2)	44.8% (64/143)	41.9% (18/43)	1.13 (0.57-2.24)
IgM+ only (IgM+ in serostatus 1 and 2)	37.4% (34/91)	17.4% (4/23)	2.83 (0.89-9.03)
IgG+ only	21.4% (3/14)	100.0% (2/2)	*
Ag+ or IgM+ (IgM+ in serostatus 1 or 2)	44.8% (64/143)	41.9% (18/43)	1.13 (0.57-2.24)
Ag+ or IgM+ (IgM+ in serostatus 1 and 2)	44.8% (64/143)	41.9% (18/43)	1.13 (0.57-2.24)
Ag+ or IgG+	55.4% (46/83)	62.5% (15/24)	0.75 (0.29-1.90)
IgM+ or IgG+ positive (IgM+ in serostatus 1 or 2)	44.8% 64/143)	41.9% (18/43)	1.13 (0.57-2.24)
IgM+ or IgG+ positive (IgM+ in serostatus 1 and 2)	36.8% (35/95)	20.8% (5/24)	2.22 (0.76-6.46)
Ag+, IgM+ or IgG+	44.8% (64/143)	41.9% (18/43)	1.13 (0.57-2.24)
Ag- only (suspected cases)	30.1% (41/136)	27.6% (27/98)	1.13 (0.64-2.02)
IgM- only (IgM- in serostatus 1 and 2)	31.3% (21/67)	29.5% (23/78)	1.09 (0.54-2.22)
IgM- only (IgM- in serostatus 1 or 2)	42.9% (51/119)	37.8% (37/98)	1.24 (0.72-2.14)
IgG- only	41.8% (82/196)	32.8% (39/119)	1.48 (0.92-2.38)
Ag- or IgM- (IgM- in serostatus 1 and 2)	31.3% (21/67)	29.5% (23/78)	1.09 (0.54-2.22)
Ag- or IgM- (IgM- in serostatus 1 or 2)	31.3% (21/67)	29.5% (23/78)	1.09 (0.54-2.22)
Ag- or IgG-	30.7% (39/127)	26.8% (26/97)	1.21 (0.67-2.18)
IgM- or IgG- positive (IgM+ in serostatus 1 and 2	31.3% (21/67)	29.5% (23/78)	1.09 (0.54-2.22)
IgM- or IgG- positive (IgM+ in serostatus 1 or 2)	43.5% (60/115)	37.1% (36/97)	1.3 (0.75-2.27)
Ag-, IgM- or IgG-	31.3% (21/67)	29.5% (23/78)	1.09 (0.54-2.22)
All cases	40.5% (85/210)	33.9% (41/121)	1.33 (0.83-2.12)

* Not estimable