Cheng, H-Y., French, C. E., Salam, A. P., Dawson, S., McAleenan, A., McGuinness, L. A., Savović, J., Horby, P. W., & Sterne, J. A. C. (2022). Lack of Evidence for Ribavirin Treatment of Lassa Fever in Systematic Review of Published and Unpublished Studies. *Emerging Infectious Diseases*, *28*(8), 1559-1568. https://doi.org/10.3201/eid2808.211787

Article Summary Line

Evidence from published and unpublished reports provides little support for ribavirin treatment in patients with confirmed Lassa fever.

Running title (46/50 characters)

Systematic review of ribavirin for Lassa fever

Keywords

Lassa fever, Ribavirin, Systematic Review; Bias; Observational study

Title

Evidence for ribavirin treatment of Lassa fever: systematic review of published and unpublished studies

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Abstract (149/150 words)

Ribavirin has been widely used 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 We conducted a systematic review of published and unpublished literature retrieved from electronic databases and grey literature from inception to 8 March 2022. We identified 13 studies of the comparative effectiveness of ribavirin and no ribavirin treatment on mortality, including unpublished data from a study in Sierra Leone provided via a Freedom of Information request. Although ribavirin was associated with decreased mortality, results of these studies were at critical or serious risk of bias when appraised using the ROBINS-I tool. Important risks of bias related 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.

Word count: 2834/3500

Introduction

Lassa virus infection, first described in 1962, is a viral haemorrhagic fever.(1) It is a significant public health burden, with an estimated 100,000 to 200,000 cases each year, mainly in West Africa.(2, 3) Many cases are mild or asymptomatic and are not formally diagnosed.(4) The non-specific clinical presentation makes Lassa fever difficult to recognize on clinical grounds alone, especially in the early phases. The case fatality rate is estimated to be 10% to 20% in hospitalised patients (5, 6) but increases sharply during outbreaks.(7) Currently, no vaccine is available but studies examining recombinant vaccinia virus in animals have entered the pre-clinical phase and a DNA vaccine has entered a phase I trial in humans.(8-10) Lassa virus is part of the Centres for Disease Control and Preventions list of category A Select Agents and is considered a priority pathogen by the World Health

Organization (WHO) due to its epidemic potential, its severity, a lack of available vaccines, and most importantly the 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 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 their results make it difficult to evaluate the effectiveness of ribavirin in clinical practice. Recent unpublished results obtained through the Freedom of Information Act, and secondary analysis of these, weaken the case for use of ribavirin.(18) Therefore, we undertook a systematic review of published and unpublished study results, appraised using a state-of-the-art risk of bias tool (19) to evaluate ribavirin for treatment of Lassa fever.

Methods

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (20) (see **Appendix 1**). A protocol is registered on the International Prospective Register of Systematic Reviews (PROSPERO CRD42019141818). We conducted a comprehensive search of multiple bibliographic databases from inception to 8 March 2022: Ovid Medline, Ovid Embase, Central Register of Controlled Trials (CENTRAL), BIOSIS, WHO Global Index Medicus, and Web of Science (including Science Citation Index Expanded (SCI-EXPANDED and Conference Proceedings Citation Index-Science (CPCI-S)). We also searched WHO International Clinical Trials Registry Platform (ITCRP), *ClinicalTrials.gov* and Pan African Clinical Trial Registry (PACTR) databases to

identify relevant reports. Keywords, "*Lassa*" and "*ribavirin*" were searched within *Google.com* and *WHO website* to retrieve grey literature on 8 March 2022. The search strings for each database can be found in **Appendix 2**. To identify further relevant studies, we checked reference lists of included studies and papers citing them using Web of Science database. We also contacted authors for clarification and supplementary information. There was no restriction in language, publication type, study design or date in the searches.

We also included unpublished results from a study including the data reported by McCormick et al.(21) which were requested by PWH through the U.S. Freedom of Information Act.(22) We refer to this study as IND 16666, its FDA Investigational New Drug application number.

Study selection

We included randomised controlled trials (RCT), controlled trials, cohort and case-control studies comparing ribavirin treatment with no ribavirin (e.g. supportive treatment), in patients with confirmed and/or suspected Lassa fever, which reported mortality (number of deaths or case fatality rate). No study reported pre-specified secondary outcomes, adverse events, except McCormick et al.(11) Therefore, we only focused on mortality in this review.

Titles and abstracts of retrieved records were screened by two authors independently using Rayyan.(23) All records were screened twice, once by the first author (HC) and by one of the co-authors (CEF, SD, AM, and APS), independently. For records that were potentially eligible, the full-text articles were retrieved and screened, using Microsoft Excel to record inclusion decisions and manage the workflow. Full-text articles were reviewed independently (HC paired with CEF or APS) to assess the eligibility. Any discrepancies between authors were resolved by discussion between the paired assessors. Data were extracted by two

authors (HC paired with CEF or APS) independently using a pre-piloted data extraction form in a Microsoft Excel spreadsheet.

Risk of bias assessment

Three authors (CEF, LAM and HC) independently assessed risk of bias for each study using the ROBINS-I tool.(19) The tool consists of seven domains with a series of signalling questions to judge risk of bias as low, moderate, serious, and critical. For the first domain, bias due to confounding, potential confounding factors were determined through a literature review and expert opinion (APS and PWH). We identified three 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.(24) Support for judgements in individual results are summarised in **Appendix 3.**

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 (21) to derive aggregated datasets containing the number of deaths according to treatment groups and individual characteristics. Based on these, we estimated mortality odds ratios comparing ribavirin with no treatment, overall and within subgroups defined by patient characteristics (aminotransferase (AST) level (21) and whether pregnant (21 p41). We also extracted results from a logistic regression (21 p44) in which the effect of ribavirin compared with no treatment was adjusted for patient characteristics (age, gender, time to admission, time to treatment, length of stay and log(AST)).

Different criteria and diagnostic tests were used to define their confirmed Lassa fever cases. Only one study, Shaffer et al.(12, 15), provided raw data reporting confirmed Lassa fever according to different case definitions: based on antigen (Ag), immunoglobulin M (IgM), and immunoglobulin G (IgG). In this study, we used positive Ag solely as the criteria

for the confirmed case as it was consistently reported in the dataset.(15) We also conducted a sensitivity analyses estimating odds ratios based on other case definitions.

We estimated overall odds ratios and, when available, odds ratios in subgroups defined by timing of treatment (starting ≤ and > 6 days after disease onset). We did not conduct meta-analyses because most results were rated as at critical overall risk of bias.(19) We displayed odds ratios and 95% confidence intervals (CIs) for the association of ribavirin with no treatment in in forest plots, using Stata 15 MP.(25)

Results

We retrieved 2232 unique records, of which 2162 were excluded based on titles and abstracts. Full-text articles for the remaining 70 records were retrieved for eligibility assessment, following which 55 further records were excluded (**Figure 1)**. One study met the inclusion criteria but was excluded because it reported aggregated outcome data that included unknown treatment status.(26) Other studies did not report outcome data according to treatment status.(27-31) We contacted the authors for further information, but no responses were received. Results were extracted from 13 eligible studies described in 15 published and unpublished reports, and the risk of bias in these results was assessed.

Study characteristics

The characteristics of the included studies are summarised in **Table 1**. All were from West Africa (6 Nigeria and 7 Sierra Leone).(11, 12, 14, 15, 17, 21, 32-40) McCormick et al. (11) and its additional data reported in IND 16666 (21) were 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 between 1986 and 2020. The length of follow up was between 1 month and 15 years.

The studies ranged in size from 10 to 1850 confirmed cases. Most included both children and adults, though two did not report the characteristics of patients comprehensively.(11, 38) Price et al. included pregnant women only (38). Dahmane et al. recruited children and women with obstetric conditions.(14) Samuels et al.(39) and Orji et al. (37) 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 (**Table 1**). Real-time polymerase chain reaction (RT-PCR) was the most common diagnostic test used, followed by virus isolation and Lassa IgM antibody. In IND 16666 (21), the criterion for the no treatment group was febrile and/or positive Lassa immunoglobulin G (IgG) antibody while to receive ribavirin participants had to meet one of the three specified diagnostic criteria (**Table 1**).

Only four studies reported details of ribavirin treatment regimens (11, 14, 21, 39) (**Table 2**). McCormick et al. reported three ribavirin regimens: one oral and two intravenous (11). Dahmane et al. reported one intravenous ribavirin regimen according to an international guideline (14). Although seven ribavirin regimens were reported in IND 16666 (21), the treatment durations and administration routes were not clear. In all studies except Samuels et al.(39), there was lack of detailed information regarding the supportive treatment used. Three studies reported malaria screening and the use of anti-malarial drugs and antibiotics prior to Lassa fever confirmation (14, 38, 40).

We assessed risk of bias in 14 results from 13 studies comparing the effects of ribavirin treatment with no ribavirin treatment on overall mortality outcomes, including two results with and without logistic regression adjustment from IND 16666 (**Figure 2**). The overall risk of 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 (21), ribavirin treatment was associated with higher overall mortality 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 (OR 0.88 [95% CI 0.81-0.95]). We noted that the confidence interval for this logistic regression result appeared too narrow when compared with the unadjusted result derived from the reported numbers of patients and deaths. This was most likely due to an error in the statistical analysis, but could not be checked further.

When results of these studies were stratified by AST levels, ribavirin treatment was associated with lower mortality in patients with AST ≥150 IU/L (OR 0.18 [0.08-0.39] in McCormick et al. (11) and OR 0.48 [0.30-0.78] in IND 16666 (21)). By contrast, in patients with AST <150 IU/L, ribavirin was associated with higher mortality (OR 1.91 [0.52-6.98]) in McCormick et al. (11) and OR 2.90 [1.42-5.95] in IND 16666 study (21)). In patients with measurable viremia, ribavirin was associated with lower mortality rates. However, these results should be interpreted with cautions as 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 compared with no ribavirin treatment (**Figure 4**). However, most of these results were rated as at critical risk of bias due to lack of adjustment for confounding and/or immortal time bias (14, 17, 32, 37), which arose because some patients did not receive their intended ribavirin treatment because they died before treatment could be started, and were then analysed in the no treatment group.

Figure 5 shows estimated associations of ribavirin treatment with mortality within patient subgroups reported in the included studies. Many studies included suspected Lassa fever cases but only two studies provided usable data for estimating associations of ribavirin treatment with mortality 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) Case fatality rates and odds ratios from Shaffer et al. (12, 15), based on different case definitions, are reported in **Appendix 4** Table 1.

Two studies investigated the effects of early versus late ribavirin treatment after disease onset (11, 35). McCormick et al. (11) found that in the subgroups AST ≥150 IU/L and viremia $\geq 10^{3.6}$ $TCID_{50}$/mL, the association of ribavirin treatment with lower mortality was more pronounced for treatment within 6 days (early) than at ≥7 days (late) after disease onset (11). Similar results were noted in Ilori 2019 (35): the ORs were 0.07 [95% CI 0.02-0.32] for early treatment (within 7 days of disease onset) and 0.13 [0.03-0.53] for late treatment (>7 days after disease onset).

The IND 16666 study reported separate results for pregnant women (OR 2.06 [95% CI 0.64-6.60]) and non-pregnant women (OR 1.12 [0.71-1.77]).(21 p41)

Discussion

This systematic review summarises associations of ribavirin treatment, compared with no ribavirin treatment, with overall mortality in confirmed Lassa fever, using both published and unpublished study results. Although ribavirin treatment was generally associated with lower mortality, almost all results were rated as at critical risk of bias. In the single adjusted result from IND 16666, ribavirin was associated with modestly lower mortality. However, this result was assessed as at serious risk of bias, and the confidence interval appeared too narrow when compared with the confidence interval derived from the numbers of patients

and deaths. Although ribavirin was reported to be associated with lower mortality 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 from 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 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 sub-groups (e.g. patients with AST <150 IU/L) where benefit has not been demonstrated and, in fact, there may be hazard from using ribavirin.(41, 42) As ribavirin causes side-effects and is expensive (up to €5000 per patient) (14, 41), it is important to justify its use in treating Lassa fever, especially in low- and middle-income countries where healthcare resources are limited. Whilst 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 randomised controlled clinical trials. For example, WHO has identified the need for a multicentre Phase 2b/3 RCT with two possible designs: 1) a four-arm factorial design with ribavirin and best supportive care; and 2) a three-arm RCT with ribavirin, best supportive care and another drug.(43) In line with this, a combination of ribavirin and favipiravir treatment has been proposed by Raabe et al.(44)

Our findings agree with those of a previous systematic review.(45) Both reviews identified a need to re-evaluate the safety and efficacy of ribavirin for Lassa fever. In comparison with the prior review (which included studies published up to March 2019), we include six 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 grey literature, without date, language, or study design restrictions. We used the ROBINS-I tool for risk of bias assessments: this is the most comprehensive and widely-used tool for assessing risk of bias in the results of non-randomized studies of interventions. Our review incorporated recent changes to ROBINS-I that address immortal time bias: evidence of such bias was identified in a number of the included studies.

We conducted secondary analyses of the related McCormick (11) and IND 16666 (21) studies. To estimate overall associations of ribavirin treatment with mortality, 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 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, this 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 ethical and resource issues to fund and conduct such trials in West Africa.

Acknowledgements

The authors thank the study authors and experts who took time to reply to our requests and provided suggestions.

Disclaimers

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.

Funding

This review was supported by the WHO (Ref: 2019/890244-1). HC, SD, JS, and JACS received financial support. The funder played no role in the conduct of this review. LAM is supported by an NIHR Doctoral Research Fellowship (DRF-2018-11-ST2-048). CEF is supported by the NIHR Health Protection Research Unit (HPRU) in Behavioural Science and Evaluation at the University of Bristol in partnership with the UK Health Security Agency. JS is partly supported by the National Institute for Health Research Applied Research Collaboration West (NIHR ARC West). APS is funded by UK aid from the Department of Health and Social Care via the UK Public Health Rapid Support Team Research Programme. PWH is supported by the Wellcome Trust (215091/Z/18/Z), the Bill & Melinda Gates

Foundation (OPP1209135), and the EDCTP2 programme supported by the European Union (ALERRT: RIA2016E-1612). JACS is supported by the NIHR Bristol Biomedical Research Centre and by Health Data Research UK South West.

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 grey 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.

Biographical Sketch

Dr Cheng is a research fellow in the Bristol Medical School, University of Bristol, and a practicing pharmacist. His research interests include high consequence infectious disease and clinical pharmacology and pharmacotherapy in infectious diseases.

Footnote

[1] Preliminary results from this study were presented at the WHO emergency programme on 21st Dec 2019.

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Figures

Figure 1. Study selection flowchart

Figure 2. Summary of risk of bias assessment

Figure 3. Estimated effects of ribavirin compared with no treatment on mortality, from the McCormick and IND 16666 studies

Figure 4. Estimated effects of ribavirin compared with no treatment on mortality, from studies other than McCormick and IND 16666

Figure 5. Estimated effects of ribavirin compared with no treatment on mortality, within patient subgroups

Tables

Table 1. Characteristics of studies

Table 2. Summary of treatment regimens

Appendix

S1. PRISMA checklist

S2. Search strategies

S3. Summary of judgements on risk of bias assessment

S4. Secondary analysis of Shaffer et al.

Figure 1. Study selection flowchart

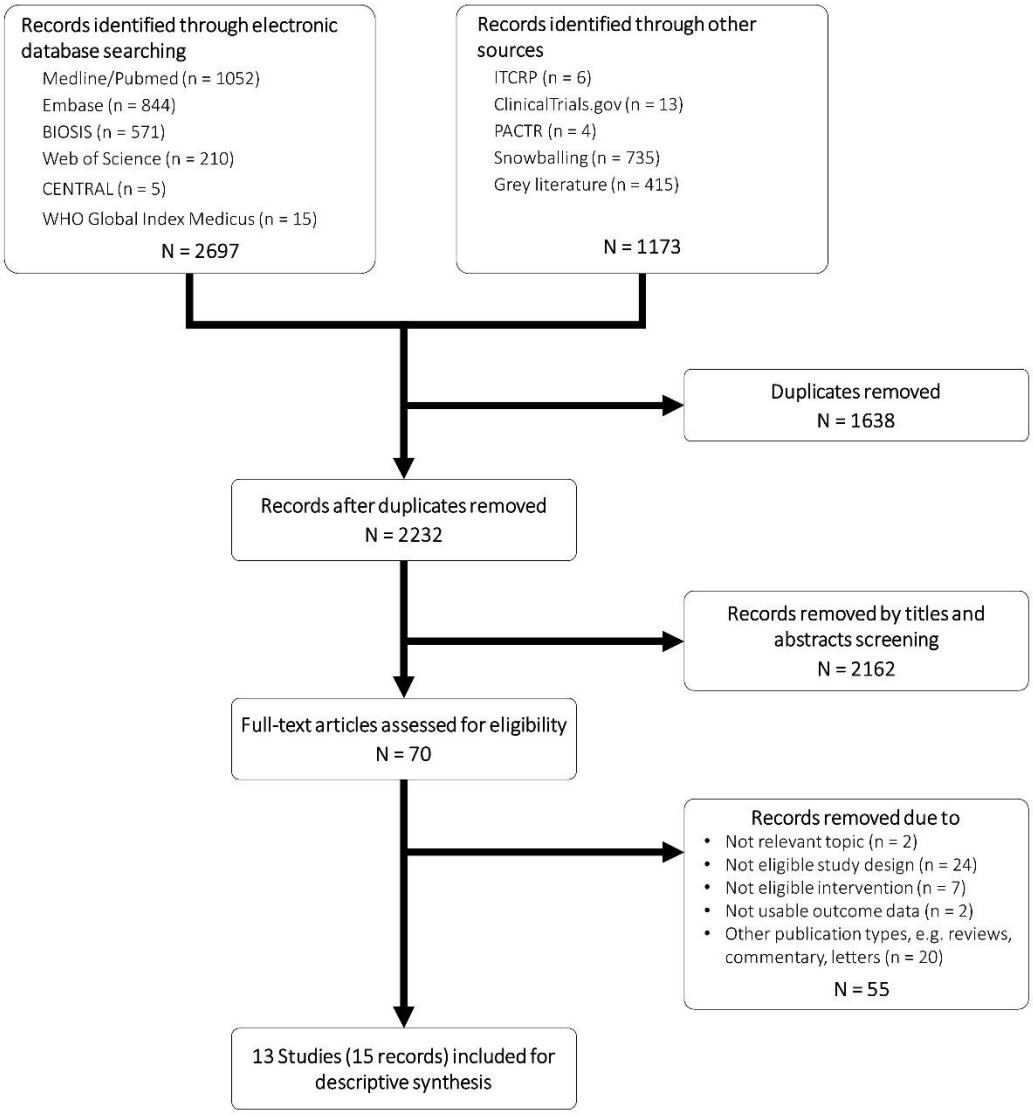


Figure 2. Summary of risk of bias assessments

Study	Overall	D1	D2	D3	D4	D5	D6	D7	Main reason
McCormick 1986	!	−	!	▲	+	−	+	!	Selectively used historical controls in the analysis and selectively reported subset results
IND 16666 (Overall, Exhibit III-7)	!	!	+	!	+	−	+	▲	No adjustment for confounding factors
IND 16666 (Logistic regression, Exhibit III-9)	−	−	+	+	+	−	+	▲	Did not control for all the important confounding factors
Ajayi 2013	!	!	+	!	+	+	+	▲	No adjustment for confounding factors and evidence of immortal time bias leading to misclassification of interventions
Asogun 2012	!	!	+	!	+	▲	+	▲	No adjustment for confounding factors and evidence of immortal time bias leading to misclassification of interventions
Buba 2018	!	!	+	−	+	+	+	▲	No adjustment for confounding factors
Dahmane 2014	!	!	+	!	+	+	+	▲	No adjustment for confounding factors and evidence of immortal time bias leading to misclassification of interventions
Ilor 2019	!	!	+	−	+	−	+	▲	No adjustment for confounding factors
Joseph 2019	!	!	+	−	+	−	+	▲	No adjustment for confounding factors
Orji 2020	!	!	+	!	+	+	+	▲	No adjustment for confounding factors and evidence of immortal time bias leading to misclassification of interventions
Price 1988	!	!	+	−	+	+	+	▲	No adjustment for confounding factors
Samuels 2020	!	!	+	▲	+	−	+	▲	No adjustment for confounding factors
Shaffer 2014	!	!	+	▲	+	+	+	▲	Unable to adjust for confounding factors in the secondary analysis
Wauguier 2020	!	!	+	+	+	−	+	▲	No adjustment for confounding factors

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

+ Low risk
▲ Moderate risk
− Serious risk
! Critical risk

Figure 3. Estimated effects of ribavirin compared with no treatment on mortality, from the McCormick and IND 16666 studies.

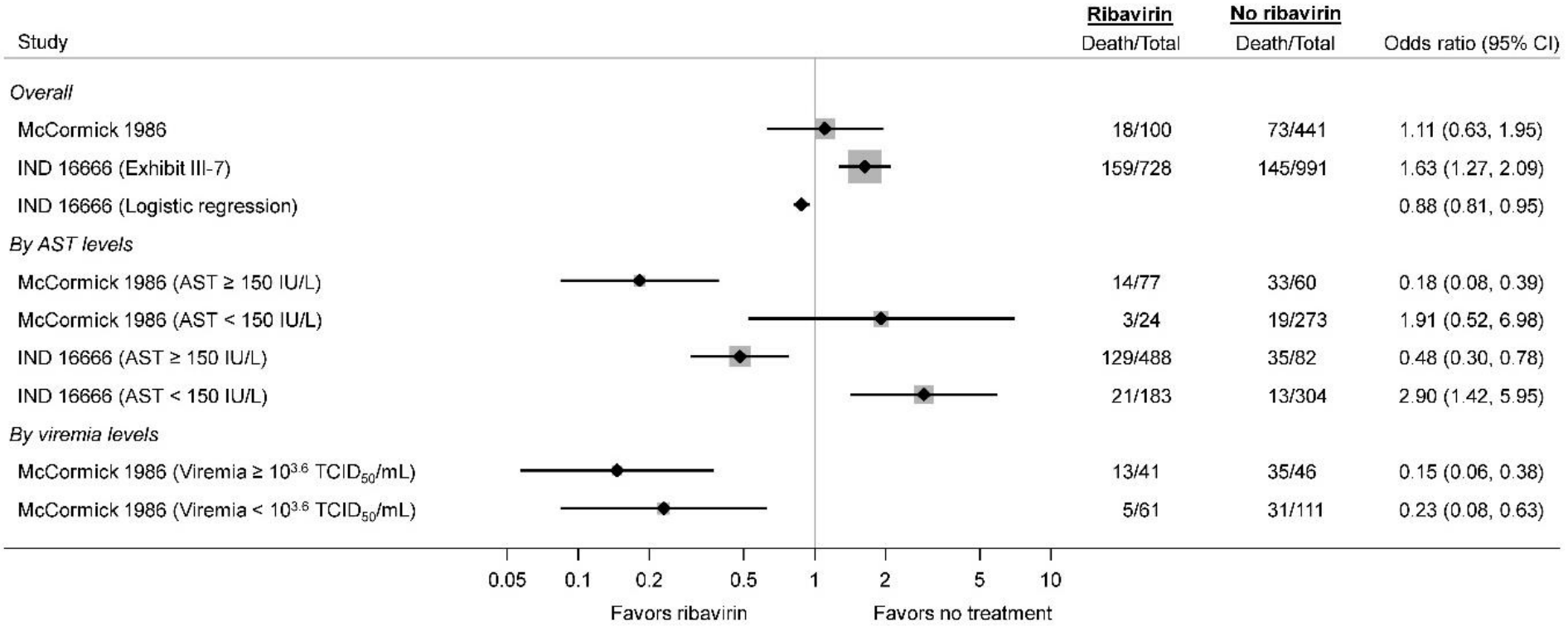


Figure 4. Estimated effects of ribavirin compared with no treatment on mortality, from studies other than McCormick and IND 16666.

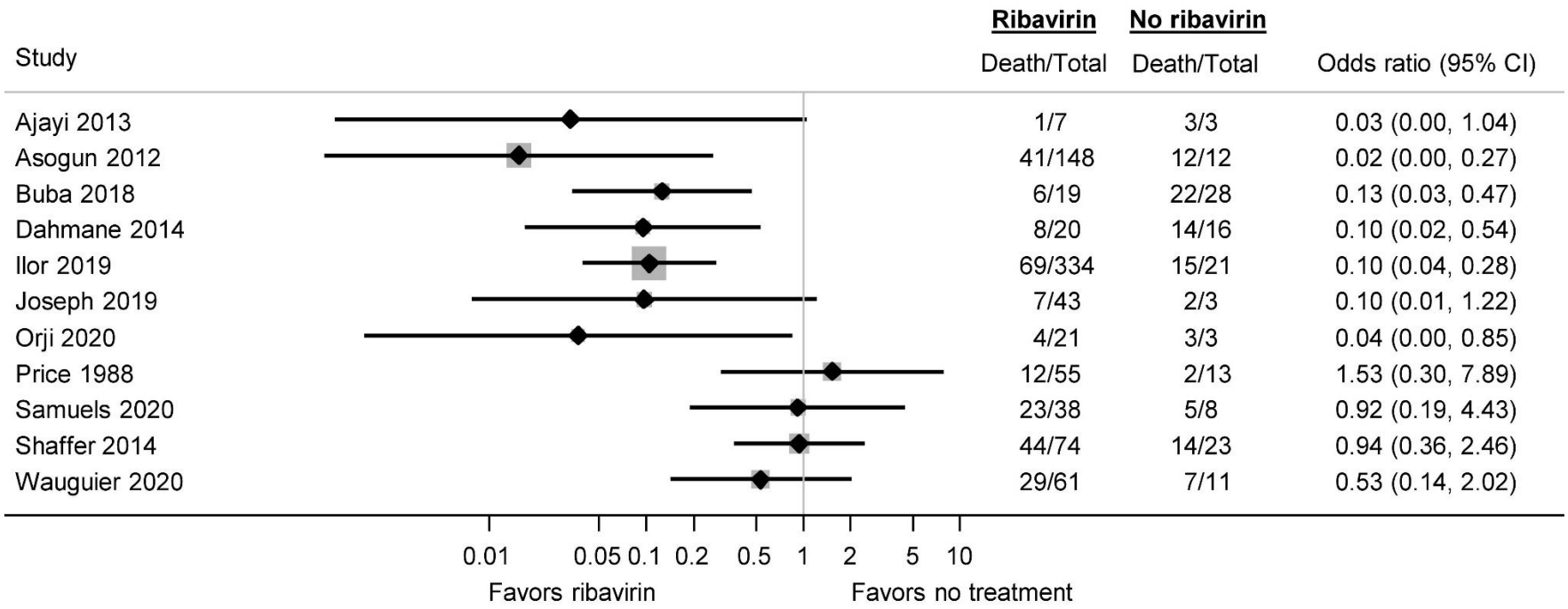
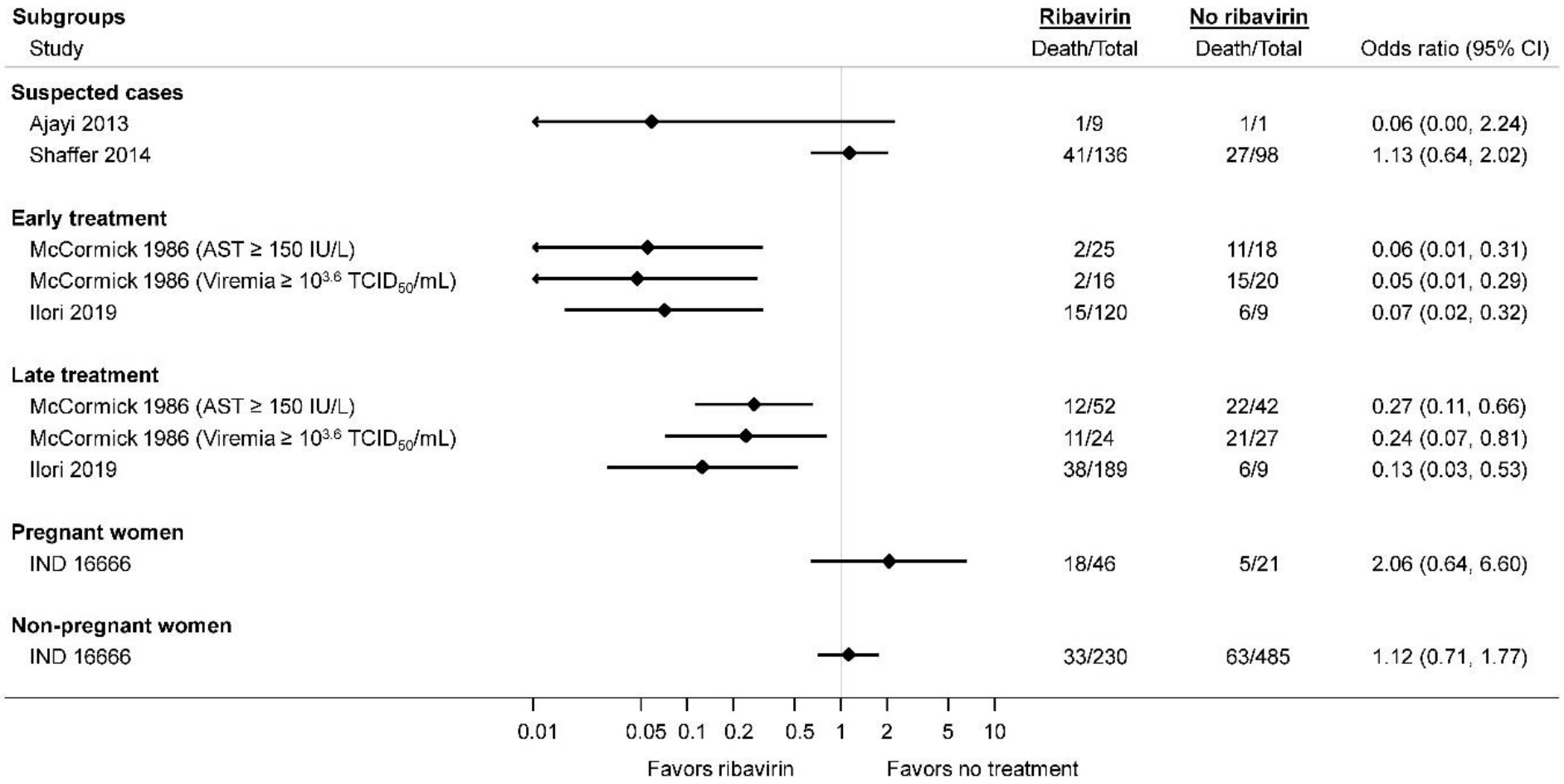


Figure 5. Estimated effects of ribavirin compared with no treatment on mortality, within patient subgroups.



13 **Table 1. Characteristics of studies**

Study	Country	Study period	Design	No. of patients (% male)	Population; Age (year)	Criteria for confirming Lassa fever cases	Funding
Ajayi 2013 (17)	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 (32)	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 (34)	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 (14, 33)	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 (35)	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 (21)	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 (36)	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 (37)	Nigeria	Jan 2019 – Jan 2020	Cohort	24* (37.5%)	Children; Age <12 yrs: 70.8%	RT-PCR	NR
Price 1988 (38)	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 (39)	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 In stitute of Allergy and Infectious Diseases, and U.S. Agency for International Development (USAID)
Shaffer 2014 (12, 15)	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 (40)	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; IgG: immunoglobulin G; IgM: immunoglobulin M; IQR: interquartile range; NR: not reported; PCR: polymerase chain reaction; RT-PCR: reverse transcription polymerase chain reaction; yrs: years

* Confirmed cases only

18 **Table 2. Summary of treatment regimens**

Study	Ribavirin treatment regimen	No ribavirin treatment	Other case management
Ajayi 2013 (17)	NR	Supportive therapy	NR
Asogun 2012 (32)	NR	NR	NR
Buba 2018 (34)	NR	NR	NR
Dahmane 2014 (14, 33)	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 (35)	NR	NR	NR
IND 16666 (21)	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 (36)	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 (37)	NR	NR	NR
Price 1988 (38)	NR	NR	Chloroquine and broad-spectrum antibiotics until Lassa fever was confirmed
Samuels 2020 (39)	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 (46, 47), 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 (12, 15)	NR	NR	NR
Wauquier 2020 (40)	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

20