University of BRISTOL

Effectiveness of Ribavirin for Lassa Fever: Systematic Review

Hung-Yuan Cheng, Clare French, Alex Salam, Sarah Dawson, Alexandra McAleenan, Luke McGuinness, Jelena Savovic, Julian P.T. Higgins, Peter Horby and Jonathan A.C. Sterne

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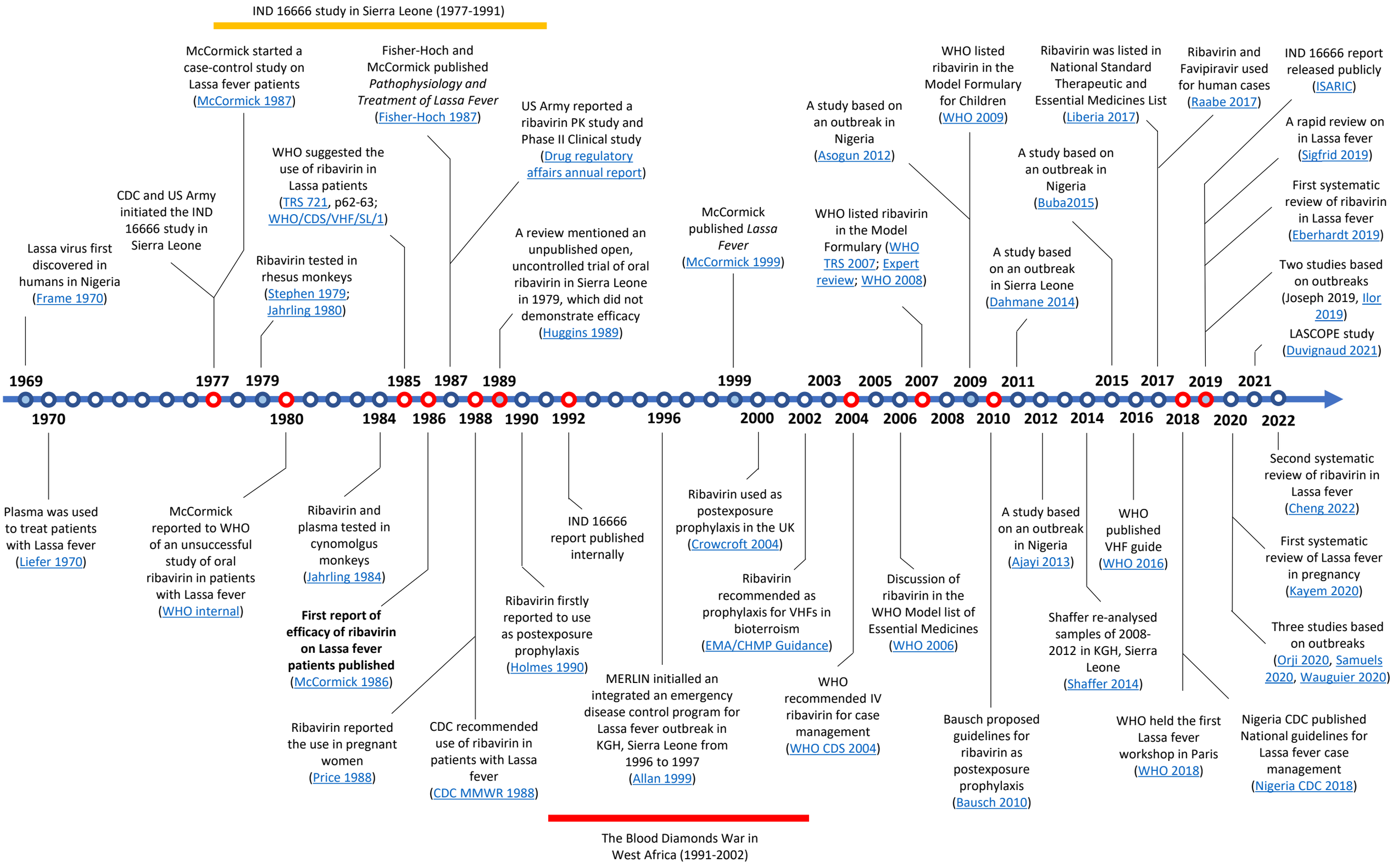
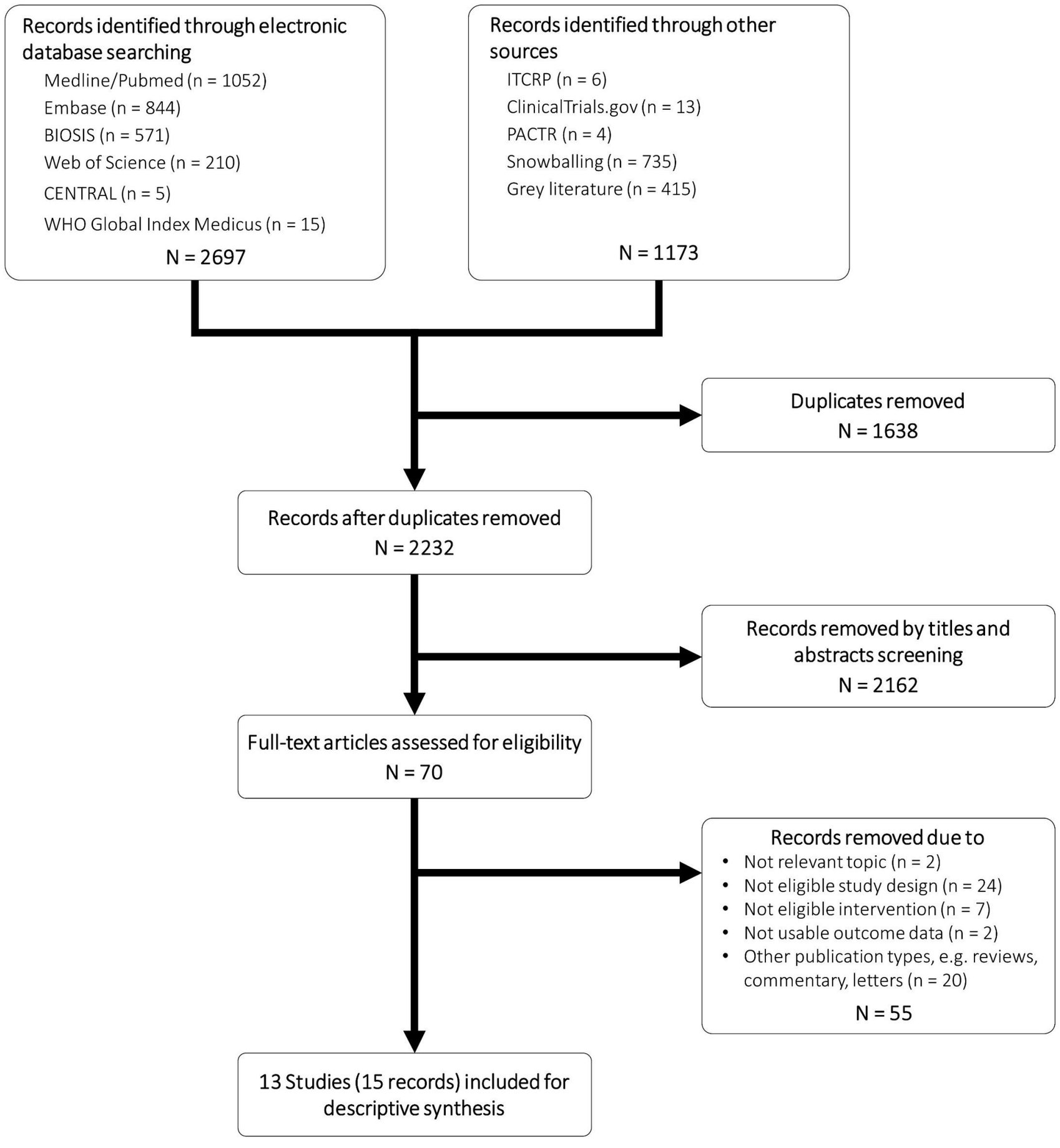
Timeline of key studies in Lassa fever



Methods

- Eligibility:
  - Randomized trials, 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
- Searches (up to 8 March 2022):
  - Ovid Medline (including PubMed subset), Embase, Web of Science, BIOSIS, WHO International Clinical Trials Registry Platform (ITCRP), ClinicalTrials.gov, Pan African Clinical Trial Registry (PACTR)
  - Keywords "*Lassa*" and "*ribavirin*" were searched within Google.com and WHO website to retrieve grey literature
  - Reference lists of included studies and systematic reviews
- Study Selection:
  - Two-stage screening (titles/abstracts and full-text articles) by two reviewers independently, discrepancies resolved by discussion
- Data were extracted by two reviewers independently. Data on subgroups were extracted if reported
- Risk of bias was assessed using the ROBINS-I tool (Sterne et al. *BMJ* 2016)


Records identified through electronic database searching
Medline/Pubmed (n = 1052)
Embase (n = 844)
BIOSIS (n = 571)
Web of Science (n = 210)
CENTRAL (n = 5)
WHO Global Index Medicus (n = 15)
N = 2697
Records identified through other sources
ITCRP (n = 6)
ClinicalTrials.gov (n = 13)
PACTR (n = 4)
Snowballing (n = 735)
Grey literature (n = 415)
N = 1173
Duplicates removed
N = 1638
Records after duplicates removed
N = 2232
Records removed by titles and abstracts screening
N = 2162
Full-text articles assessed for eligibility
N = 70
Records removed due to
Not relevant topic (n = 2)
Not eligible study design (n = 24)
Not eligible intervention (n = 7)
Not usable outcome data (n = 2)
Other publication types, e.g. reviews, commentary, letters (n = 20)
N = 55
13 Studies (15 records) included for descriptive synthesis

LASSA FEVER

Effective Therapy with Ribavirin

JOSEPH B. MCCORMICK, M.D., ISABEL J. KING, M.D., PATRICIA A. WEBB, M.D., CURTIS L. SCRIBNER, M.D., ROBERT B. CRAVEN, M.D., KARL M. JOHNSON, M.D., LUANNE H. ELLIOTT, M.S., AND ROSE BELMONT-WILLIAMS, M.D.

Abstract In a study of Lassa fever in Sierra Leone, West Africa, we identified two variables associated with a high risk of death, and we evaluated the efficacy of ribavirin and Lassa virus–convalescent plasma for the treatment of Lassa fever. A serum aspartate aminotransferase level ≥150 IU per liter at the time of hospital admission was associated with a case-fatality rate of 55 percent (33 of 60). Patients with the same risk factor who were treated for 10 days with intravenous ribavirin, begun within the first six days after the onset of fever, had a case-fatality rate of 9 percent (1 of 20) ($P = 0.0002$ by Fisher's exact test). Patients whose treatment began seven or more days after the onset of fever had a case-fatality rate of 26 percent (11 of 43) ($P = 0.01$). Viremia with levels $\geq 10^{3.6}$ $TCID_{50}$ per milliliter on admission was associated with a case-fatality rate of 76 percent (35 of 46). Patients with this risk factor who were treated with intravenous ribavirin within the first

LASSA FEVER was first reported as a severe, often fatal disease occurring in Africa and resulting from infection by an arenavirus.[1-6] The virus was isc

DEPARTMENT OF THE ARMY
HEADQUARTERS, U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
810 SCHREIDER STREET
FORT DETRICK, MARYLAND 21702-5000

4 March 2019

Office of the Principal Assistant
for Acquisition

Dr. Peter William Hornby
Professor of Emerging Infectious Diseases and Global Health
Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine,
University of Oxford, Roosevelt Drive, Oxford, OX3 7BN, United Kingdom

Dear Dr. Hornby,

On behalf of Major General Holcomb, I am pleased to fulfill your request, under the U.S. Freedom of Information Act, for the "Final Report Analysis of a Clinical Trial Ribavirin and the Treatment of Lassa Fever", dated 7 February 1992.

I must offer, however, that any results, conclusions, or recommendations provided in the report be interpreted with extreme caution. The original data used in the analysis resulting in the report no longer exist. Therefore, substantiation or validation of the results/conclusions is impossible. Furthermore, the data collected from the study were incomplete from the beginning and sampling bias that may impact the final conclusions is highly likely.

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO
ATTENTION OF

June 8, 1992

Human Use Review and
Regulatory Affairs Office

SUBJECT: IND 16666 - Ribavirin (Virazole)
(Serial No. 011)

Director
Division of Anti-Infective Drug Products (HFD-815)
Center for Drug Evaluation and Research
Office of Drug Review II
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

Enclosed in triplicate is a report entitled "Final Report Analysis of a Clinical Trial Ribavirin and the Treatment of Lassa Fever." The data were collected by the Centers for Disease Control under their IND 17186, however, since the U.S. Army Medical Research and Development Command provided funding for the study, we felt it appropriate to submit the report to our IND 16666.

FINAL REPORT
ANALYSIS OF A CLINICAL TRIAL
RIBAVIRIN AND THE TREATMENT OF LASSA FEVER

Submitted To

Sherikon, Inc.
92 Thomas Jefferson Drive
Suite 130
Frederick, MD 21702

Under Contract No. DAMD17-89-C-9160

This document was prepared for Birch & Davis Associates, Inc., by David Bodycombe, Task Manager, and Hillard Davis, Analyst.

February 7, 1992

McCormick (1986) and IND 16666

- Study *IND 16666* (the FDA Investigational New Drug application number) is a retrospective audit of clinical studies conducted between 1977 and 1991, in Sierra Leone, West Africa.
- The study dataset includes the data reported by McCormick *et al.* (*NEJM* 1986). It is not possible to separate data that were and were not included in the McCormick study.
- We digitised data reported in IND 16666 main tables and Appendix D, which shows characteristics of patients who died. Some discrepancies could not be resolved.
- We derived estimates of the effect of ribavirin compared with no treatment (overall and according to AST)

McCormick et al. (NEJM 1986)

	Patient characteristics	Interventions	Note
Phase I	Confirmed Lassa fever cases recruited from a case-control study and a study of oral ribavirin and Lassa-convalescent plasma	Case-control study: 1. No therapy (untreated patient from the case-control study; N = 441) Randomised study: 1. Oral ribavirin (2g loading dose and 1g in divided eight hours for 10 days (N = 39)) 2. Lassa-convalescent plasma (~ 4mL/kg; 1 unit) with an immunofluorescent-antibody titer ≥ 1:128 within 24 hours of admission (N = 31))	Pregnant patients were not included in the study and treated with plasma only
Phase II	Confirmed Lassa fever cases with AST ≥150 IU/L	Patients were randomly assigned to: 1. IV ribavirin (2g loading dose and 1g every 6 hours for 4 days. Then reduced to 0.5g every 8 hours for another 6 days (N = 29)) 2. IV ribavirin (same regimen as 1) + convalescent plasma (1 unit; 300 ml) (N = 33)	Pregnant patients with AST ≥ 150 IU/L were not included in the study and treated with plasma only.

Deriving estimates from IND 16666

SIT III-7

SURVIVORSHIP AMONG TREATMENT GROUPS

STATUS/ SIGNIFICANCE	TREATMENT GROUP								
	CONTROL[1]	II	III	IV	V	VI	VII	VIII	IX
SURVIVED	846(85.4)	475(80.0)	29(78.4)	57(75.0)	29(85.3)	7(58.3)	21(84.0)	5(55.6)	3(17.6)
DIED	145	119	8	19	5	5	4	4	14
TOTAL	991	594	37	76	34	12	25	9	17
X^2 (Corrected)[2]		7.4	0.9	5.1	NC	NC	NC	NC	NC
P-VALUE		.0064	.3484	.0244	NC	NC	NC	NC	NC

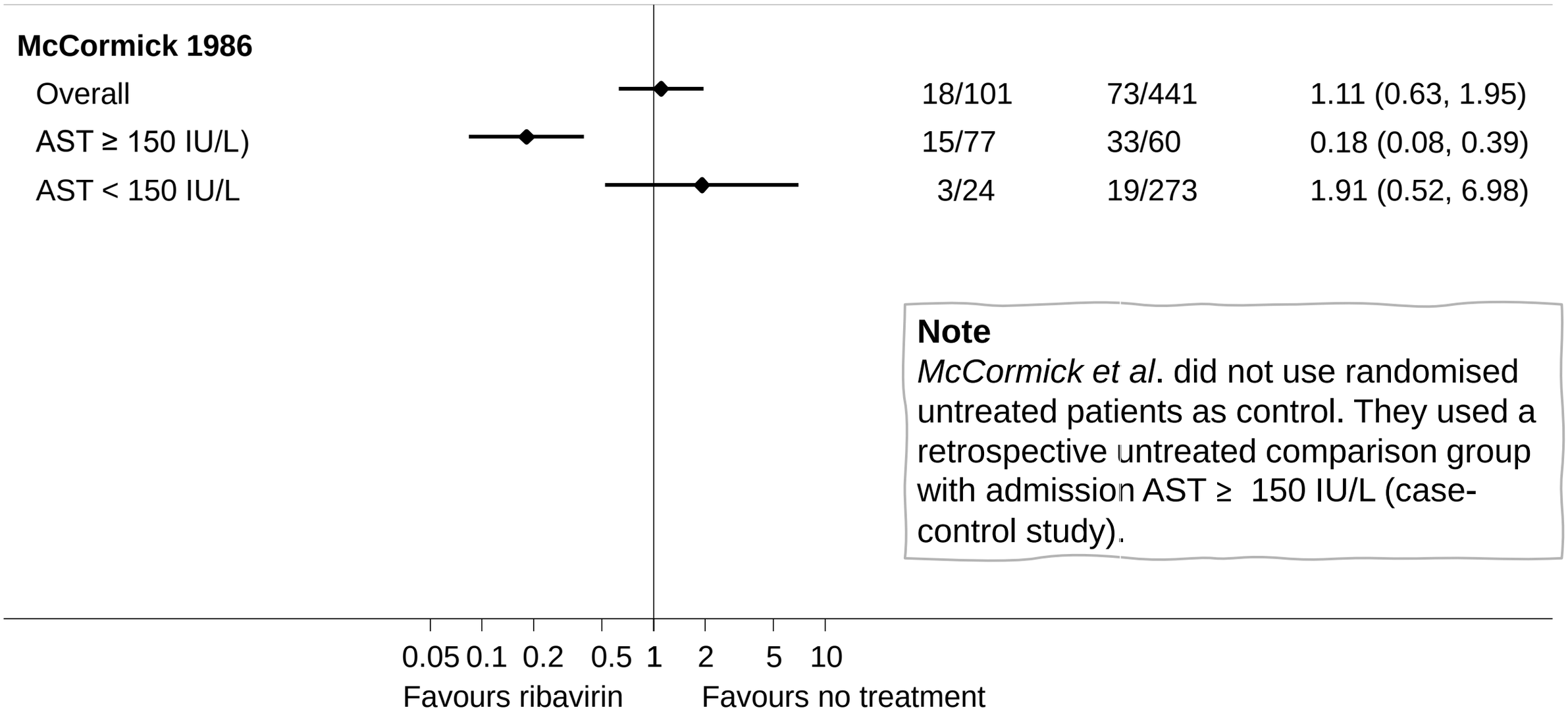
	Treatment group								
	Control (I and X)	II	III	IV	V	VI	VII	VIII	IX
Survived	846	475	29	57	29	7	21	5	3
Died	145	119	8	19	5	5	4	4	14
Total	991	594	37	76	34	12	25	9	17

- Treatment groups:

(I) No treatment; (II) IV Ribavirin followed by oral dose; (III) Ribavirin + plasma; (IV) Plasma alone; (V) Ribavirin 25-30mg loading dose; (VI) Ribavirin 34mg loading dose; (VII) Ribavirin 33mg loading dose followed by ¼ dose; (VIII) Ribavirin 17mg loading dose followed by ⅛ dose; (IX) Ribavirin + prostacyclin; (X) Patients for whom no drugs were available.

Results from McCormick (1986) and IND 1666

Controlled Studies	Ribavirin Death/Total	No ribavirin Death/Total	Odds ratio (95% CI)
McCormick 1986			
Overall	18/101	73/441	1.11 (0.63, 1.95)
AST ≥ 150 IU/L)	15/77	33/60	0.18 (0.08, 0.39)
AST < 150 IU/L	3/24	19/273	1.91 (0.52, 6.98)



Note
McCormick et al. did not use randomised untreated patients as control. They used a retrospective untreated comparison group with admission AST ≥ 150 IU/L (case-control study).

Results from McCormick (1986) and IND 1666

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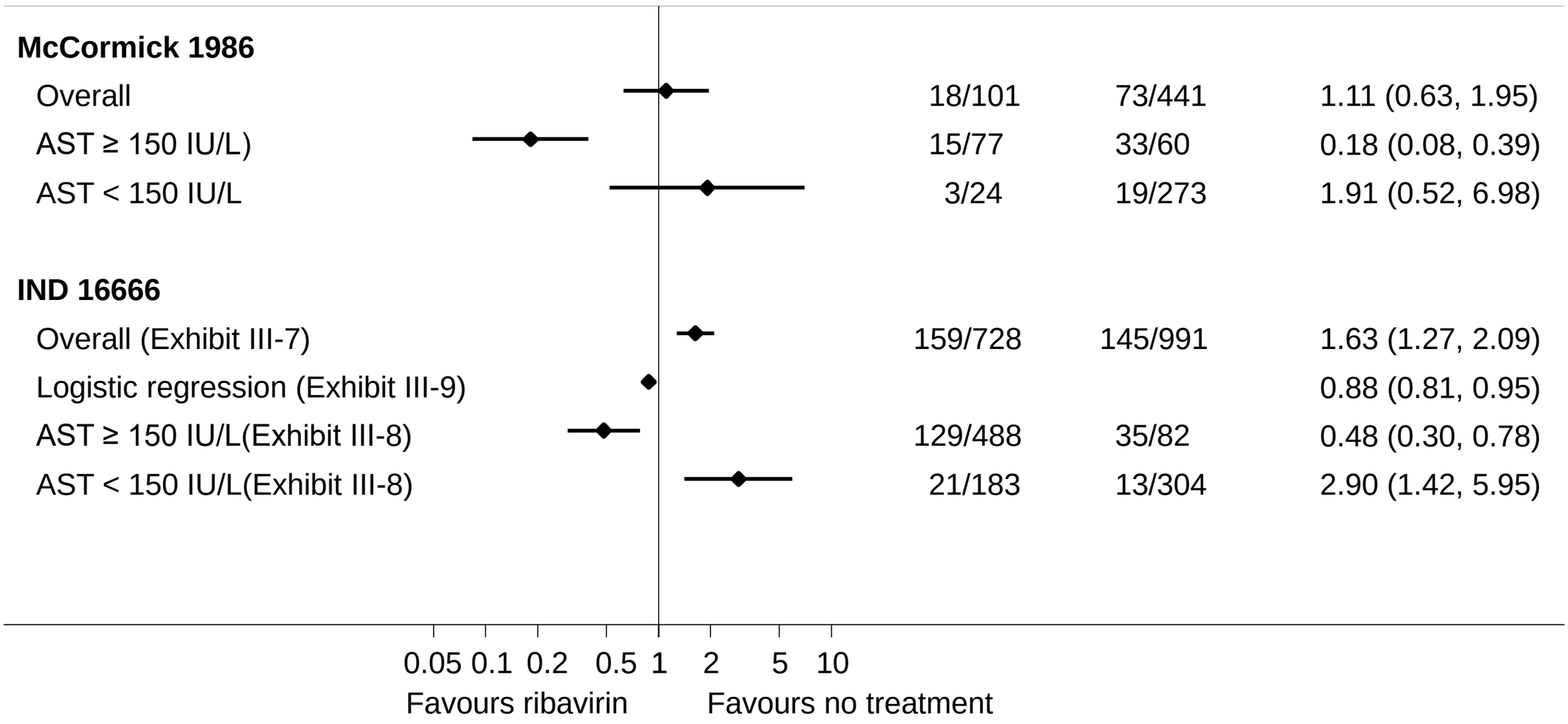
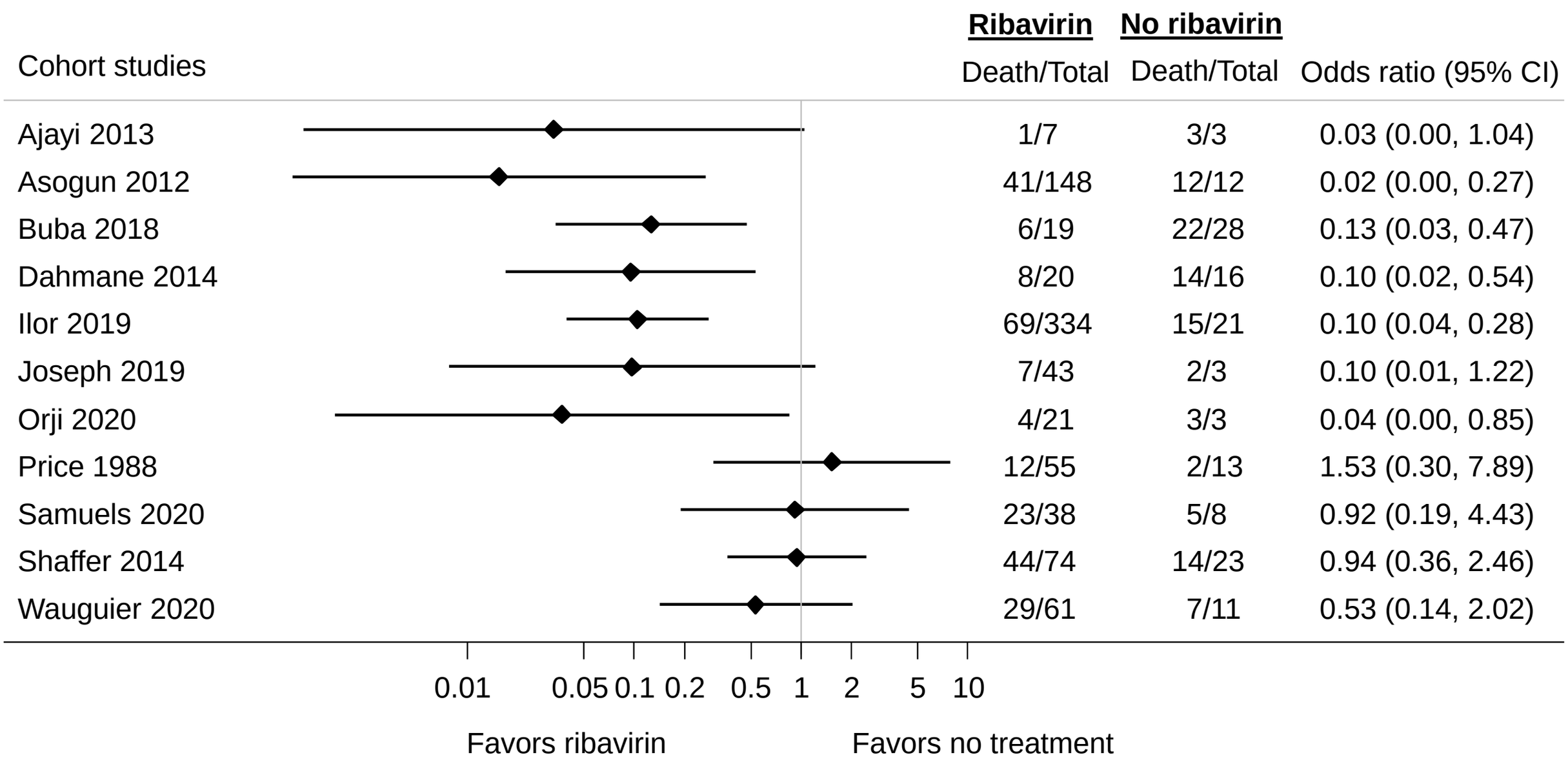
AST < 150 IU/L	3/24	19/273	1.91 (0.52, 6.98)
IND 16666			
Overall (Exhibit III-7)	159/728	145/991	1.63 (1.27, 2.09)
Logistic regression (Exhibit III-9)			0.88 (0.81, 0.95)
AST ≥ 150 IU/L(Exhibit III-8)	129/488	35/82	0.48 (0.30, 0.78)
AST < 150 IU/L(Exhibit III-8)	21/183	13/304	2.90 (1.42, 5.95)



Results from cohort studies



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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									of immortal time bias leading to
Buba 2018									
Dahmane 2014									of immortal time bias leading to
Ilor 2019									
Joseph 2019									
Orji 2020									of immortal time bias leading to
Price 1988									
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

Major issues:

1. Lack of, or limited, control for confounding.
2. Potential for immortal time bias, because some individuals may have died before they could be treated with ribavirin

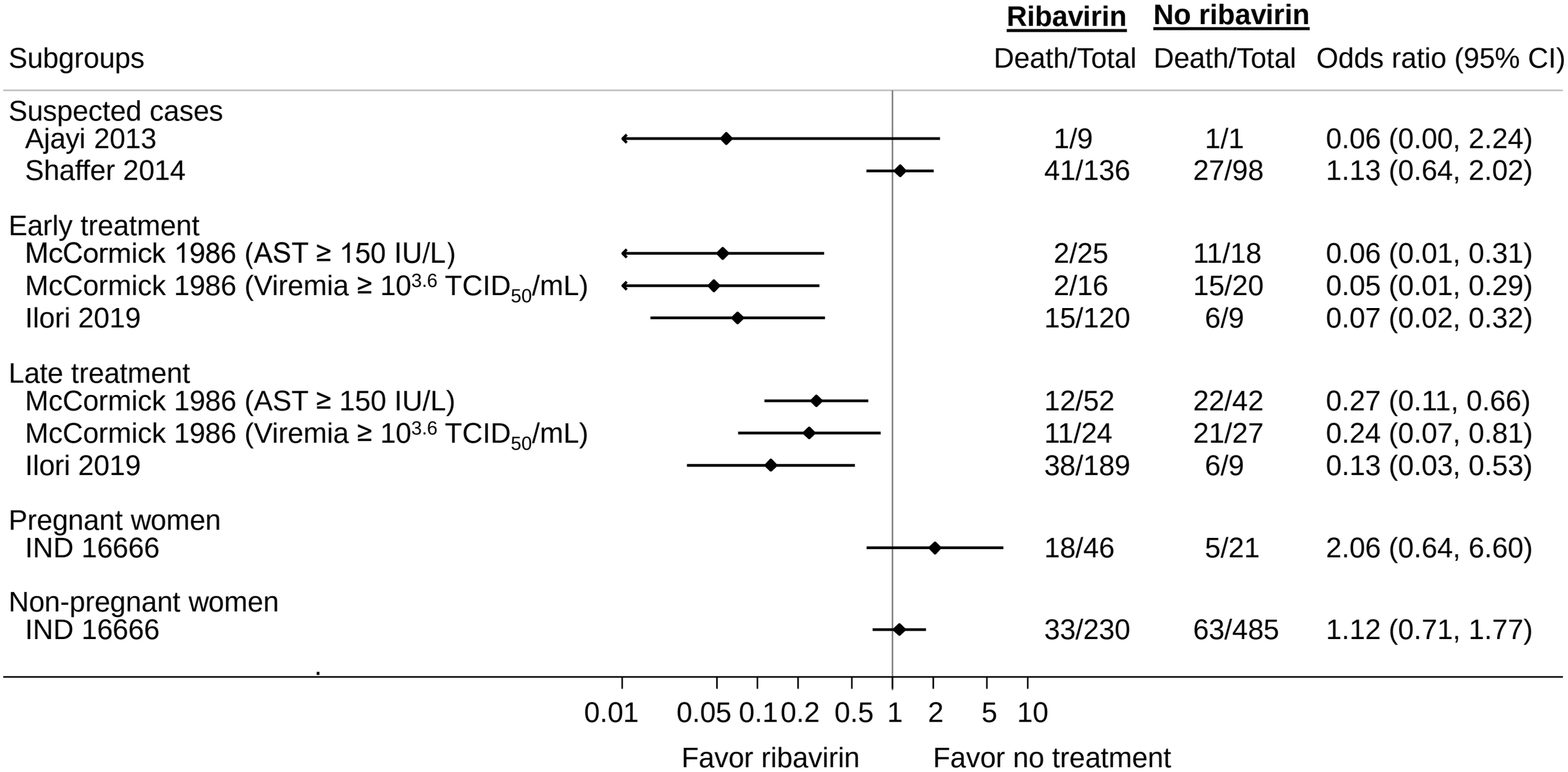
D1: Bias due to confounding
D2: Bias in selection of participants into the study
D3: Bias in classification of interventions
D4: Bias due to deviations from intended interventions
D5: Bias due to missing data
D6: Bias in measurement of outcomes
D7: Bias in selection of the reported result

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

Conclusions

- It is uncertain whether ribavirin reduces mortality in Lassa fever patients.
- Among the 13 included studies, 11 were rated as at critical and one at serious risk of bias.
  - Most of the included studies were not designed to assess the effectiveness of ribavirin for Lassa fever, and did not attempt comparative analyses adjusting for confounding factors.
- Although ribavirin was associated with lower mortality in specific subgroups, including patients with AST ≥150 IU/L and measurable viremia, the risk of bias in these studies and the post-hoc nature of the analyses limit the credibility of the findings.
  - Albeit equally weak, evidence of harm from ribavirin treatment was observed in other patient subgroups, such as patients with AST
- Full results, including other subgroup analyses, are in Cheng HY. *Emerg Infect Dis. 2022*. doi: 10.3201/eid2808.211787.

Results (4)


Ribavirin
No ribavirin
Subgroups
Death/Total
Death/Total
Odds ratio (95% CI)
Suspected cases
Ajayi 2013 1/9 1/1 0.06 (0.00, 2.24)
Shaffer 2014 41/136 27/98 1.13 (0.64, 2.02)
Early treatment
McCormick 1986 (AST ≥ 150 IU/L) 2/25 11/18 0.06 (0.01, 0.31)
McCormick 1986 (Viremia ≥ 10^3.6 TCID50/mL) 2/16 15/20 0.05 (0.01, 0.29)
Ilori 2019 15/120 6/9 0.07 (0.02, 0.32)
Late treatment
McCormick 1986 (AST ≥ 150 IU/L) 12/52 22/42 0.27 (0.11, 0.66)
McCormick 1986 (Viremia ≥ 10^3.6 TCID50/mL) 11/24 21/27 0.24 (0.07, 0.81)
Ilori 2019 38/189 6/9 0.13 (0.03, 0.53)
Pregnant women
IND 16666 18/46 5/21 2.06 (0.64, 6.60)
Non-pregnant women
IND 16666 33/230 63/485 1.12 (0.71, 1.77)
0.01
0.05
0.1
0.2
0.5
1
2
5
10
Favor ribavirin
Favor no treatment