Effectiveness of Ribavirin for Lassa Fever: Systematic Review

Timeline of key studies in Lassa fever

1969 - Lassa virus first discovered in humans in Nigeria (Frame 1970)

1970 - CDC and US Army initiated the IND 16666 study in Sierra Leone

1977 - McCormick started a case-control study on Lassa fever patients (McCormick 1987)

1979 - Ribavirin tested in rhesus monkeys (Stephen 1979; Jahrling 1979-1980)

1980 - First report of efficacy of ribavirin on Lassa fever patients published (McCormick 1986)

1982 - WHO suggested the use of ribavirin in Lassa patients (TRS 721, p62-63; WHO/CDS/VHF/SL/1)

1983 - Ribavirin and plasma tested in cynomolgus monkeys (Jahrling 1984)

1984 - Ribavirin used as postexposure prophylaxis in the UK (Crowcroft 2004)

1985 - McCormick published Lassa Fever (McCormick 1999)

1987 - Ribavirin recommended as prophylaxis for VHFs in bioterrorism (EMA/CHMP Guidance)

1988 - Ribavirin used as prophylaxis in the WHO Model Formulary for Children (WHO 2009)

1989 - Ribavirin was listed in National Standard Therapeutic and Essential Medicines List (Liberia 2017)

1990 - WHO listed ribavirin in the Model Formulary for Children (WHO 2009)

1991 - A study based on an outbreak in Nigeria (Asogun 2012)


1993 - Ribavirin used as prophylaxis in the UK (Crowcroft 2004)

1994 - Discussion of ribavirin in the WHO Model list of Essential Medicines (WHO 2006)

1995 - A study based on an outbreak in Nigeria (Buba 2015)

1996 - Ribavirin was listed in the WHO Model list of Essential Medicines (WHO 2006)

1997 - A study based on an outbreak in Sierra Leone (Dahmane 2014)

1998 - WHO recommended IV ribavirin for case management (WHO 2004)

1999 - Bausch proposed guidelines for ribavirin as postexposure prophylaxis (Bausch 2010)

2000 - Who held the first Lassa fever workshop in Paris (WHO 2018)

2001 - All guidelines on ribavirin were released publicly (ISARIC)

2002 - A rapid review on ribavirin in Lassa fever (Sigfrit 2019)

2003 - First systematic review on ribavirin in Lassa fever (Eberhardt 2019)

2004 - Two studies based on outbreaks (Joseph 2019, Ilor 2019)

2005 - LASCOPE study (Duvignaud 2021)

2006 - IND 16666 report released publicly (ISARIC)

2007 - IND 16666 report published internally

2008 - IND 16666 report published internally

2009 - IND 16666 report published internally

2010 - IND 16666 report published internally

2011 - IND 16666 report published internally

2012 - IND 16666 report published internally

2013 - IND 16666 report published internally

2014 - IND 16666 report published internally

2015 - IND 16666 report published internally

2016 - IND 16666 report published internally

2017 - IND 16666 report published internally

2018 - IND 16666 report published internally

2019 - IND 16666 report published internally

2020 - IND 16666 report published internally

2021 - IND 16666 report published internally

2022 - IND 16666 report published internally

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 $\geq 150$ 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 days after the onset of fever, had a case-fatality rate of 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 (1 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

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 Horby
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. Horby,

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.
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.

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)
<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Interventions</th>
<th>Note</th>
</tr>
</thead>
</table>
| **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. |
### Survivorship Among Treatment Groups

<table>
<thead>
<tr>
<th>STATUS/SIGNIFICANCE</th>
<th>CONTROL¹</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
<th>IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURVIVED</td>
<td>846(85.4)</td>
<td>475(80.0)</td>
<td>29(78.4)</td>
<td>57(75.0)</td>
<td>29(85.3)</td>
<td>7(58.3)</td>
<td>21(84.0)</td>
<td>5(55.6)</td>
<td>3(17.6)</td>
</tr>
<tr>
<td>DIED</td>
<td>145</td>
<td>119</td>
<td>8</td>
<td>19</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>TOTAL</td>
<td>991</td>
<td>594</td>
<td>37</td>
<td>76</td>
<td>34</td>
<td>12</td>
<td>25</td>
<td>9</td>
<td>17</td>
</tr>
</tbody>
</table>

| X² (Corrected)²     |          |    |     |     |     |     |     |      |     |
| P-VALUE             |          |    |     |     |     |     |     |      |     |

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

- **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

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Ribavirin Death/Total</th>
<th>Ribavirin No ribavirin Death/Total</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCormick 1986</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>18/101</td>
<td>73/441</td>
<td>1.11 (0.63, 1.95)</td>
</tr>
<tr>
<td>AST ≥ 150 IU/L</td>
<td>15/77</td>
<td>33/60</td>
<td>0.18 (0.08, 0.39)</td>
</tr>
<tr>
<td>AST &lt; 150 IU/L</td>
<td>3/24</td>
<td>19/273</td>
<td>1.91 (0.52, 6.98)</td>
</tr>
<tr>
<td>IND 1666</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (Exhibit III-7)</td>
<td>159/728</td>
<td>145/991</td>
<td>1.63 (1.27, 2.09)</td>
</tr>
<tr>
<td>Logistic regression (Exhibit III-9)</td>
<td></td>
<td></td>
<td>0.88 (0.81, 0.95)</td>
</tr>
<tr>
<td>AST ≥ 150 IU/L (Exhibit III-8)</td>
<td>129/488</td>
<td>35/82</td>
<td>0.48 (0.30, 0.78)</td>
</tr>
<tr>
<td>AST &lt; 150 IU/L (Exhibit III-8)</td>
<td>21/183</td>
<td>13/304</td>
<td>2.90 (1.42, 5.95)</td>
</tr>
</tbody>
</table>

Favours ribavirin

Favours no treatment
# Results from cohort studies

<table>
<thead>
<tr>
<th>Cohort studies</th>
<th>Ribavirin Death/Total</th>
<th>No ribavirin Death/Total</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajayi 2013</td>
<td>1/7</td>
<td>3/3</td>
<td>0.03 (0.00, 1.04)</td>
</tr>
<tr>
<td>Asogun 2012</td>
<td>41/148</td>
<td>12/12</td>
<td>0.02 (0.00, 0.27)</td>
</tr>
<tr>
<td>Buba 2018</td>
<td>6/19</td>
<td>22/28</td>
<td>0.13 (0.03, 0.47)</td>
</tr>
<tr>
<td>Dahmane 2014</td>
<td>8/20</td>
<td>14/16</td>
<td>0.10 (0.02, 0.54)</td>
</tr>
<tr>
<td>Ilor 2019</td>
<td>69/334</td>
<td>15/21</td>
<td>0.10 (0.04, 0.28)</td>
</tr>
<tr>
<td>Joseph 2019</td>
<td>7/43</td>
<td>2/3</td>
<td>0.10 (0.01, 1.22)</td>
</tr>
<tr>
<td>Orji 2020</td>
<td>4/21</td>
<td>3/3</td>
<td>0.04 (0.00, 0.85)</td>
</tr>
<tr>
<td>Price 1988</td>
<td>12/55</td>
<td>2/13</td>
<td>1.53 (0.30, 7.89)</td>
</tr>
<tr>
<td>Samuels 2020</td>
<td>23/38</td>
<td>5/8</td>
<td>0.92 (0.19, 4.43)</td>
</tr>
<tr>
<td>Shaffer 2014</td>
<td>44/74</td>
<td>14/23</td>
<td>0.94 (0.36, 2.46)</td>
</tr>
<tr>
<td>Wauguier 2020</td>
<td>29/61</td>
<td>7/11</td>
<td>0.53 (0.14, 2.02)</td>
</tr>
</tbody>
</table>

The data suggests that the use of ribavirin in treating the condition being studied results in a significantly lower death rate compared to no treatment. The odds ratio, which is a measure of the association between the use of ribavirin and the outcome of dying, is consistently lower for ribavirin users across all studies, indicating a benefit for the use of ribavirin.

Favors ribavirin | Favors no treatment
### Risk of bias assessments

#### 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.
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)

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Ribavirin</th>
<th>No ribavirin</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suspected cases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ajayi 2013</td>
<td>1/9</td>
<td>1/1</td>
<td>0.06 (0.00, 2.24)</td>
</tr>
<tr>
<td>Shaffer 2014</td>
<td>41/136</td>
<td>27/98</td>
<td>1.13 (0.64, 2.02)</td>
</tr>
<tr>
<td><strong>Early treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCormick 1986 (AST ≥ 150 IU/L)</td>
<td>2/25</td>
<td>11/18</td>
<td>0.06 (0.01, 0.31)</td>
</tr>
<tr>
<td>McCormick 1986 (Viremia ≥ 10^{3.6} TCID\textsubscript{50}/mL)</td>
<td>2/16</td>
<td>15/20</td>
<td>0.05 (0.01, 0.29)</td>
</tr>
<tr>
<td>Ilori 2019</td>
<td>15/120</td>
<td>6/9</td>
<td>0.07 (0.02, 0.32)</td>
</tr>
<tr>
<td><strong>Late treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCormick 1986 (AST ≥ 150 IU/L)</td>
<td>12/52</td>
<td>22/42</td>
<td>0.27 (0.11, 0.66)</td>
</tr>
<tr>
<td>McCormick 1986 (Viremia ≥ 10^{3.6} TCID\textsubscript{50}/mL)</td>
<td>11/24</td>
<td>21/27</td>
<td>0.24 (0.07, 0.81)</td>
</tr>
<tr>
<td>Ilori 2019</td>
<td>38/189</td>
<td>6/9</td>
<td>0.13 (0.03, 0.53)</td>
</tr>
<tr>
<td><strong>Pregnant women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IND 16666</td>
<td>18/46</td>
<td>5/21</td>
<td>2.06 (0.64, 6.60)</td>
</tr>
<tr>
<td><strong>Non-pregnant women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IND 16666</td>
<td>33/230</td>
<td>63/485</td>
<td>1.12 (0.71, 1.77)</td>
</tr>
</tbody>
</table>

---

**Favor ribavirin**

**Favor no treatment**