DEPARTMENT OF THE ARMY
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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.

I have provided below, background information from one of the primary investigators (now retired) responsible for sponsoring the report:

a. During 1991/1992, the U.S. Army Medical Materiel Development Activity (USAMMDA), and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) commissioned Sherikon, Inc. to perform a Meta-analysis of data collected during a Centers for Disease Control and Prevention (CDC) Sierra Leone Lassa fever/Ribavirin study. This analysis hoped to expand upon initial study results to include examination of additional study variables that might better predict treatment outcomes.

b. On examination of accessible data available from CDC Atlanta revealed that information critical to the analysis was missing, so a data collection team consisting of a member from CDC Special Pathogens Branch, USAMMDA and USAMRIID went to the Sierra Leone study site. They collected both missing information in existing records and created new records on over 1000 additional patients. During the data collection, the Charles Taylor Gorillas from Liberia attacked the hospital study site and several villagers were killed, so the entire team evacuated the area. Due to the continuing civil

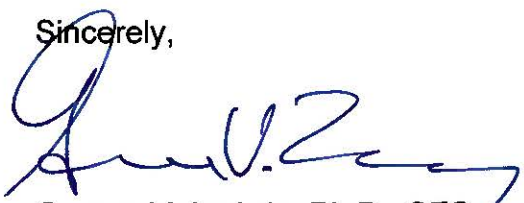
conflict, lasting several years, the site was abandoned and it was not possible to retrieve all study records.

c. Consequently, the database had a very large number of missing values and critical variables. In addition, a flaw in the study execution was identified that provided higher doses of ribavirin to the sickest patients, when supplies of the drug were limited, resulting in a significant imbalance between treatment groups. The only way to correct this imbalance was to separate patient groups based on SGOT liver function test of greater than 150. To obtain any type of statistically meaningful analysis it was necessary to collapse all Ribavirin treatment groups into a single group.

d. The numbers of Lassa positive individuals presented in the report is also suspect. A confirmed diagnosis required serum immunofluorescence assay testing on paired sera, demonstrating a 4-fold or greater rise in titer. In this study, patients without paired acute and convalescent serum samples were miscoded to indicate a serum immunofluorescence titer of 1:30 when the test was actually conducted on undiluted sera. In malaria endemic areas such as Sierra Leone, false IFA positive responses in undiluted sera are common. Additionally, later studies showed that newer, more sensitive tests could detect infection much earlier so the non-disease group may actually contain some Lassa infected patients making study conclusions using reported case numbers difficult to interpret. Another set of confounding factors is the impact of missing values that did not allow for correction of risk factors in unbalanced treatment groups and the impact of pooling Ribavirin groups that did not receive a loading dose with those that did. Lastly, there was significant inconsistency in the total Ribavirin dose administered to patients in the treatment group. It is not possible to determine if a complete dataset would have yielded the same results.

Thank you for your interest in USAMRMC research. Although we have provided the report itself, and an explanation of the potential limitations of the report and our inability access to the historical raw data, I would be happy to attempt to answer any additional questions that you may have.

Sincerely,



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