of PCV dose schedule on carriage in observational studies, studies must be carried out with a very large sample size or a high prevalence of PCV13 serotype carriage. Meta-analyses of this and other carriage studies should be considered to enhance the power to evaluate this question [8, 9].

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.

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References


Clinical Laboratory Values in Human Ebola Virus Disease Support the Relevance of the Intramuscular Ebola-Kikwit Rhesus Model

To the Editor—We read with interest the recent article in Clinical Infectious Diseases by Lanini et al, which focused on the relationship between human Ebola virus (EBOV) RNA and clinical chemistry values obtained during the West African outbreak in Goderich, Sierra Leone [1]. While many investigators have demonstrated that EBOV viremia is associated with survival [2–6], Lanini et al found that multilevel mixed-effects regression models demonstrated a significant correlation between EBOV viremia and aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), international normalized ratio (INR), and adjusted partial thromboplastin time (aPTT). This is important because these findings further support the possibility of using human clinical laboratory values as surrogate markers of EBOV viral load as Janvier et al suggested with regard to AST [7]. Moreover, we recently published that in a linear regression model at 5 days postinfection (dpi) in rhesus macaques exposed to 1000 plaque-forming units (PFU) of EBOV-Kikwit intramuscularly (IM), that platelet counts, prothrombin time (PT), AST, ALT, LDH, and CPK correlated significantly with time to death and with log_{10} viral RNA [8]. Similarly, we found in a linear regression model that at 7 dpi, LDH and CPK correlated significantly with time to death and with log_{10} viral RNA. These findings are not surprising given that Warren et al [9] showed that in the 1000 PFU IM EBOV-Kikwit rhesus macaque model, the course of EBOV viral load is mirrored by the clinical chemistry results in the setting of successful Ebola virus disease (EVD) treatment using GS-5734.

In the absence of another large-scale human EBOV outbreak, the path to licensure of an antiviral in the United States would most likely need to be via the US Food and Drug Administration (FDA) Animal Rule [10], with human data supplementing the animal data. We found that laboratory values in humans and in the IM EBOV-Kikwit rhesus model are strikingly similar, exhibiting changes consistent with systemic inflammatory response syndrome and multiorgan injury. Humans and rhesus nonhuman primates (NHPs) both exhibit thrombocytopenia, and alterations of serum AST, ALT, blood urea nitrogen, creatinine, albumin, C-reactive protein, LDH, PT, aPTT, and CPK. Both humans and rhesus NHPs exhibit high systemic viral load at the peak of disease and in the time leading to death.

We are encouraged that the laboratory values we observed in the IM EBOV-Kikwit NHP model recapitulate what has been reported by Lanini et al in human EVD. We plan to continue further characterizing this model at the US Army Medical Research Institute of Infectious Diseases. We believe that the model is a useful animal model for predicting response in human EVD and is well suited to be utilized to evaluate medical countermeasures under the FDA Animal Rule.

Notes

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**Ethics statement.** Animal research at the USAMRIID was conducted under an Institutional Animal Care and Use Committee–approved protocol in compliance with the Animal Welfare Act, Public Health Service Policy, and other federal statutes and regulations relating to animals and experiments involving animals. The facility where this research was conducted is accredited by the Association for the Care and Use of Laboratory Animals, National Research Council, 2011.

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No reported conflicts of interest. All authors use of Laboratory Animals, National Research principles stated in the Guide for the Care and Use of Laboratory Animals, National Research Council, 2011.

The authors are employees of the US government. Their views do not represent the official policy or position of the US government.

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**Reply to Reisler et al**

To the Editor—We were delighted to read the letter by Reisler et al [1] published in response to our article on the potential relationship between Ebola virus (EBOV) viremia and alteration of biomarkers associated with damage to specific organs in humans [2].

Reisler et al report striking similarities between the values of biomarkers our group estimated in the analysis of real clinical dataset (predictive models) and the alterations of biomarkers that they observed using an experimental model of infection in nonhuman primates. Both models seem consistent in providing evidence that (1) Ebola virus disease (EVD) is characterized by a systemic inflammatory response syndrome (SIRS) that may be followed by multiorgan injury and (2) the degree of the damage that EBOV can produce in the host correlates directly with the viral load intensity.

Concordant and reproducible results independently obtained through radically different research methodologies [3] are reassuring and within the logic of scientific discovery [4]. The complementarity of our results obtained using routine clinical data with those observed in experimental animal models has direct implications for future development of translational research.

First, these new biological insights should guide future clinical studies aimed to assess efficacy of new interventions for clinical management of patients with EVD such as (1) development of new drugs (or biologics) directed against the virus either for hampering viral replication or for containing the spread of the infection in early phase of the disease; (2) development of innovative approaches for management of SIRS; (3) development of a solid framework for intensive care to manage multiorgan injury in resource-limited settings [5].

Second, as the clinical presentation and severity of EVD ranges from moderate to lethal systemic infections (both in humans and animals), it is urgent that the new knowledge about EBOV pathogenesis are promptly used to define those clinical signs and symptoms associated with most severe consequences and poor prognosis. In particular, a clinical score, which combines symptoms and patterns of standard clinical biomarkers, would be exceptionally useful to optimize the access to innovative intervention(s) and intensive care during outbreaks by stratifying patients according to immediate needs [6] and prognosis in the long term [7].

Finally, we strongly agree with the observation of Reisler et al, who point out the complementarity between the scientific approach based on observational clinical studies in humans (predictive models) and those based on applied research in animals (animal model). In fact both approaches can provide, and cross-validate, evidence to exploring new pathways of pathogenesis and define new interventions to solve topical clinical problems, such as the improvement of treatment of patients with EVD.

**Notes**

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