Response to Comment on “Mutation rate and genotype variation of Ebola virus from Mali case sequences”

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Rambaut et al. show that the erratum to our report on Ebola virus Makona evolution not only corrected sample dates modified by others in GenBank but also corrected an additional transcriptional error in our original analysis. We agree with their observation that both factors contributed to our revised evolutionary rate estimate but continue to stand by our revised estimate and conclusions.

In March of 2015, we reported several new sequences from the recent West African Ebola virus (EBOV) Makona epidemic, along with a phylogenetic analysis of these and all other sequences available in GenBank at that time (1). Upon request, we immediately shared our data (including detailed analysis files) with Rambaut and colleagues, who had coauthored an earlier study, which had reported that EBOV in the West African epidemic was mutating roughly twice as fast as historically observed (2). However, at the same time, we also noticed that the sampling dates for 15 samples in GenBank had been changed. Given that this represented 14% of the data set, and because almost all of the samples in this data set were collected during a very short time frame of 26 days, we were concerned that these changes of up to 6 days might alter the outcome of our analysis. This prompted us to redo our whole analysis. We published the results of this second analysis in an erratum in May 2015 (3).

The rigorous analysis presented here by Rambaut et al. (4) using the data set we shared with them, and which was used to generate our original evolutionary rate estimate, has now, as is clearly shown in their Technical Comment, uncovered a further error in this original data set. Unfortunately, and unbeknownst to us, when transcribing the sampling dates of the genome sequences for phylogenetic analysis, a mistake occurred—specifically, one block of sampling dates was inadvertently shifted relative to the sample names. As a consequence of repeating our analysis using a data set completely reassembled from scratch for the erratum, this additional transcription error was also corrected at the same time. The analysis by Rambaut et al., although clearly supporting our revised evolutionary rate estimate (3), now shows that the correction of this transcription error during our reanalysis of the data was primarily responsible for the difference between our original and revised estimates.

Rambaut et al. are indeed correct in their analyses: A mistake was made when transcribing some of the original data for the analysis software, which of course we deeply regret. However, both this mistake and the revisions to the primary data in GenBank have already been corrected in our erratum last year. Importantly, the revised evolutionary rate estimate derived from that analysis, and reported in our erratum, remains correct and has now been confirmed by several other more recent studies that benefited from more diversified data sets based on longer-term sampling efforts (5–7). Further, in their Comment, Rambaut et al. now also point out that the value of 1.9 × 10−3 that they originally reported was based on erroneous data and that a revised analysis by them using corrected data gives a rate estimate coinciding with our revised rate estimate, as well as more recent estimates from other groups, so that there is now a general consensus in the field as to this rate.

Regarding the main conclusions of our study, we also believe that these remain correct. We are not aware of any epidemiological evidence of changes in transmission (something that remains true even considering recently demonstrated rare late sexual transmissions from survivors). Overall, case fatality rates in this epidemic appear to have been somewhat lower than during previous outbreaks, even though confounding factors (particularly the extent of diagnostics performed) complicate such a comparison. This also seems supported by initial infection studies in macaques, which did not result in increased virulence of the West African EBOV Makona strain (8), as well as by the first experiments in humanized mice, where infection with a wild-type EBOV Makona isolate resulted in a longer mean-time-to-death than infection with the prototype EBOV Mayinga strain from 1976 (9). Similarly, a vaccine that was developed against the EBOV Kikwit strain from 1995 remains protective against the West African EBOV Makona strain from 20 years later in the macaque model (10) and has shown promising results in a human ring vaccination trial (11). Also, a first experimental study addressing sequence changes occurring early in the epidemic did not reveal evidence for altered virus biology between different EBOV Makona variants or between EBOV Makona and EBOV Mayinga (12), and comparative studies of virus entry also revealed no differences between EBOV Makona and EBOV Mayinga (13). Lastly, so far as we are aware, laboratory diagnostics have not been affected by sequence changes over the period of the epidemic, which is of course one of the biggest concerns in outbreak response, and systematic in vitro evaluation of available diagnostic reverse transcription polymerase chain reaction assays showed that they perform virtually identically for the EBOV Makona and the EBOV Kikwit strains, which were isolated 20 years apart (14). Overall, we believe that our study has directly helped to balance some misconceptions in the media and public about this emerging EBOV virus strain and thus supported proper public health intervention.

In summary, Rambaut and colleagues have indeed identified a technical error in our analysis, which had already been corrected in our erratum last year; and we certainly appreciate their efforts to further correct the scientific record by identifying this error. However, we continue to stand by our revised evolutionary rate estimate, and believe that the major conclusions drawn from it have also been well supported by the experiences made during this epidemic.

REFERENCES AND NOTES

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