Cross-species transmission of bat coronaviruses in the Americas: contrasting patterns between alphacoronavirus and betacoronavirus.

Diego Caraballo

Corresponding Author(s): Diego Caraballo, Instituto de Ecología, Genética y Evolución de Buenos Aires

**Review Timeline:**

- Submission Date: April 22, 2022
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*Editor: Biao He*

*Reviewer(s): The reviewers have opted to remain anonymous.*

**Transaction Report:**

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. The original formatting of letters and referee reports may not be reflected in this compilation.)

DOI: [https://doi.org/10.1128/spectrum.01411-22](https://doi.org/10.1128/spectrum.01411-22)
May 9, 2022

Dr. Diego A. Caraballo
Instituto de Ecología, Genética y Evolución de Buenos Aires
Universidad de Buenos Aires, CONICET
Intendente Guiraldes 2160
Ciudad Universitaria, Pabellón 2, 4to piso
Buenos Aires 1428
Argentina

Re: Spectrum01411-22 (Cross-species transmission of bat coronaviruses in the Americas: contrasting patterns between alphacoronavirus and betacoronavirus.)

Dear Dr. Diego A. Caraballo:

Thank you for submitting your manuscript to Microbiology Spectrum. Generally, the topic is interesting, but the sequence dataset is very limited, leading to the conclusions are not well supported. I would like to expect a significant improvement of this study.

When submitting the revised version of your paper, please provide (1) point-by-point responses to the issues raised by the reviewers as file type "Response to Reviewers," not in your cover letter, and (2) a PDF file that indicates the changes from the original submission (by highlighting or underlining the changes) as file type "Marked Up Manuscript - For Review Only". Please use this link to submit your revised manuscript - we strongly recommend that you submit your paper within the next 60 days or reach out to me. Detailed instructions on submitting your revised paper are below.

Sincerely,

Biao He
Editor, Microbiology Spectrum
Journals Department
American Society for Microbiology
1752 N St., NW
Washington, DC 20036
E-mail: spectrum@asmusa.org

Reviewer comments:

Reviewer #1 (Comments for the Author):

In this manuscript, the authors proposed a routine phylogenetic analysis on less than 200 RdRp protein sequences of coronaviruses, trying to identify the cross-species transmissions of the virus among bats. Overall, the limited dataset and the rough data processing cannot support the conclusions in the MS.

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events of coronaviruses, which was not a good choice. My suggestion would be using the genome data to analyze the recombinations of coronaviruses in the Americas, which would be more interesting.

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Staff Comments:

Preparing Revision Guidelines
To submit your modified manuscript, log onto the eJP submission site at https://spectrum.msubmit.net/cgi-bin/main.plex. Go to Author Tasks and click the appropriate manuscript title to begin the revision process. The information that you entered when you first submitted the paper will be displayed. Please update the information as necessary. Here are a few examples of required updates that authors must address:

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• Figures: Editable, high-resolution, individual figure files are required at revision, TIFF or EPS files are preferred

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Please return the manuscript within 60 days; if you cannot complete the modification within this time period, please contact me. If you do not wish to modify the manuscript and prefer to submit it to another journal, please notify me of your decision immediately so that the manuscript may be formally withdrawn from consideration by Microbiology Spectrum.

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Corresponding authors may join or renew ASM membership to obtain discounts on publication fees. Need to upgrade your membership level? Please contact Customer Service at Service@asmusa.org.

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To illustrate the enormous disparity between full genomes and partial batCoV sequences, I would like to share with you the following figure, which summarizes the number of available batCoV sequences in the Americas.
The vast majority of available sequences are short (<1000 bp). There are only 2 full genomes which are insufficient for any host-shift analysis. To exemplify this situation, all the sequences from Brazil, the most probable hotspot for the diversification of bat-CoVs, are all shorter than 816 bp, and restricting the analysis to full genomes or multi-loci approaches would leave out the sequences of the most diverse region.

For the same reason, recombination tests cannot be performed with the actual dataset (I am convinced that recombination should be tested whenever it is possible. I underlined this necessity in a recent contribution on rabies virus: https://dx.doi.org/10.3390/v13010023). However, as I state in the manuscript, the RdRp gene is less prone to recombination than other regions of the CoV genome. In addition, even if they are the product of recombination, the finding of sequences that commonly circulate in one host species in a novel species, means that there was coinfection (and hence, cross-species transmission).

I agree that this dataset has inherent limitations, and as such, the conclusions that follow this analysis must be with precaution (and this is reflected in the Discussion section). But if a strict criterion of sequence length is applied, the analysis cannot be done, and the opportunity to start gaining insight into batCoVs at a continental scale for the Americas would be lost. I am sure there will be more batCoV sequences available in the next few years (I am personally working on generating full genome sequences in Argentina), but I am also convinced that these results could serve as good working hypotheses to guide future research and to point out precisely how important it would be to count with genomic analyses of virus and hosts diversity in the Americas.

2. Some sentences need rephrasing. For example, it is courageous to assert that "the evolution and diversification of these coronaviruses remains poorly studied".

Response: This sentence is referred specifically to bat-CoVs in the Americas, which indeed remain poorly studied, as reflected by the limited number of complete genomes as well as by the fact that most countries have no reported sequences. It was modified to better reflect this situation:

“However, due to the limited number of complete genomes and the lack of reported sequences in most of the Americas’ countries, the evolution and diversification of these CoVs is poorly understood”.

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In this manuscript, Caraballo assembled a large dataset of bat coronaviruses, employed phylogenetic approaches to analyze the evolution of alpha coronaviruses and beta coronaviruses in bats of the Americas, and identified hosts and regions with high spillover risk. The author reached several conclusions: (1) Cross species transmission were frequently identified in alpha coronaviruses; (2) Brazil appears to be the center of alpha and beta coronavirus diversification; (3) Phyllipstomidae has the highest host transition rates. In my
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(3) Recombination analyses should be performed before phylogenetic and molecular clock analyses.

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Response: Thank you for your suggestion, it was taken into consideration and the manuscript was changed accordingly. Although I still indicated a distinction between deep and terminal CSTs, because in many cases the former represent long-term establishment in novel hosts, while the latter generally are dead ends in the transmission chain.

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polyphyletic alphaCoVs, and on the other hand, because it did not contribute to enriching the CST analysis, which is the main focus of the study. Clade-specific ancestral location reconstructions were performed instead, and discussed in the manuscript (Supplementary Figure 1).

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Response: The temporal analysis was removed, for the same reasons explained for the spatial diffusion analysis.
June 5, 2022

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Instituto de Ecología, Genética y Evolución de Buenos Aires
Universidad de Buenos Aires, CONICET
Intendente Guiraldes 2160
Ciudad Universitaria, Pabellón 2, 4to piso
Buenos Aires 1428
Argentina

Re: Spectrum01411-22R1 (Cross-species transmission of bat coronaviruses in the Americas: contrasting patterns between alphacoronavirus and betacoronavirus.)

Dear Dr. Diego A. Caraballo:

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Sincerely,

Biao He

Editor, Microbiology Spectrum

Journals Department
American Society for Microbiology
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Corresponding authors may join or renew ASM membership to obtain discounts on publication fees. Need to upgrade your membership level? Please contact Customer Service at Service@asmusa.org.

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Response: Thank you for the suggestion. The Discussion and Abstract were modified to reflect the fragmentary nature of the available dataset and to underscore the importance of CoV surveillance and typing in those countries with no reported sequences.

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Intendente Guiraldes 2160  
Ciudad Universitaria, Pabellón 2, 4to piso  
Buenos Aires 1428  
Argentina

Re: Spectrum01411-22R2 (Cross-species transmission of bat coronaviruses in the Americas: contrasting patterns between alphacoronavirus and betacoronavirus.)

Dear Dr. Diego A. Caraballo:

I am glad to inform you that your manuscript has been accepted, and I am forwarding it to the ASM Journals Department for publication. You will be notified when your proofs are ready to be viewed.

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ASM policy requires that data be available to the public upon online posting of the article, so please verify all links to sequence records, if present, and make sure that each number retrieves the full record of the data. If a new accession number is not linked or a link is broken, provide production staff with the correct URL for the record. If the accession numbers for new data are not publicly accessible before the expected online posting of the article, publication of your article may be delayed; please contact the ASM production staff immediately with the expected release date.

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