From:	Su, Lishan
To:	Liu, Shan-Lu; apc@tandf.co.uk
Cc:	Shan Lu
Subject:	Re: Your Open Access article publishing charge invoice [ref:_00D0Y35Iji._5002X2h5qN4:ref]
Date:	Wednesday, February 26, 2020 7:52:15 AM

Yes, it was waived at the beginning. Thanks

-Lishan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Wednesday, February 26, 2020 4:11:35 AM
To: apc@tandf.co.uk <apc@tandf.co.uk>
Cc: Shan Lu <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Your Open Access article publishing charge invoice [ref:_00D0Y35Iji._5002X2h5qN4:ref]

Thank you, but my understanding is that the publication fee is waived for this commentary, the fee waive code is: TEMI-2020-C3865. See below email for EMI editor in chief Dr. Shan Lu on Feb 12.

Thank you.

> **From:** "Lu, Shan" <Shan.Lu@umassmed.edu>
> **Date:** February 12, 2020 at 9:08:04 PM EST
> **To:** "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
> **Cc:** "min.yang@emi2012.org" <min.yang@emi2012.org>
> **Subject: RE: EMI commentary**
>
> Ok, then please submit asap.
>
> Since this is a special invited commentary, I will waive your fee although the price is quite low.
>
> Please use this code when you submit: TEMI-2020-C3865. Only use once.
>
> I am copying Min Yang from EMI office to assist you.
>
> Let her know by email if you have any questions.
>
> Shan
>
> On Feb 26, 2020, at 3:54 AM, "apc@tandf.co.uk" <apc@tandf.co.uk> wrote:

Dear Mr Shan-Lu Liu,

Ref : No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2
DOI: 10.1080/22221751.2020.1733440

Congratulations on the acceptance of your paper.

Publication in the journal is subject to payment of an APC (article publishing charge). Thank you for accepting responsibility for payment of this charge when you submitted your paper.Please find attached your APC invoice. Should you have any queries about this document, please don't hesitate to contact us

To pay by credit card online please click here.

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For more information around our Open programme, please visit http://authorservices.taylorandfrancis.com/publishing-open-access which contains a wealth of information and resources, including information on how to promote your paper and optimise citations once it is published online.

Kind regards,
Evelyn Wong
Customer Service Executive

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ref:_00D0Y35Iji._5002X2h5qN4:ref
<Invoice 952282459.pdf>

From: Su, Lishan
To: Weiss, Susan; Liu, Shan-Lu
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)
Date: Friday, February 21, 2020 4:58:56 PM
Attachments: image001.png

Thanks, Susan!
I will do a minor revision of the sentence in the proof. Please let me know if you have other suggestions to the proof. I will upload it after hearing from all of you.
Best,

-Lishan

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Friday, February 21, 2020 at 3:57 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

I think old sentence is more correct

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 2:53 PM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

I agree with you on these points, but NIH/government at the time put it as a gof study relative to the original S antigen…

-Lishan

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Friday, February 21, 2020 at 2:51 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Is the adaptation of MA15 to mice considered “gain of function”- that selected virus is more virulent than SHC014-MA15 chimeric virus? Seems to me like more loss of function relative to MA15 when inserting the bat derived spike. MA15 with the urbani spike is like de- adapting the virus to mice.

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 1:40 PM

To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

I have noticed that too, probably happened when we tried to simplify the chimeric virus paragraph, and I think Ralph had added the attenuation sentence relative to M15 in mice…

What was reported in the NM paper was that the SHC014-rMA15 chimeric virus was less pathogenic than M15, but more so than the chimeric M15 virus with the original Urbani Spike-gene in M15, probably due to one of the 6 mutations in the M15 S gene.

See old sentence:
Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the original human Urbani S-MA15 chimeric virus in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies…

I will try to fix this.
Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 12:14 PM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Cc: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Lishan: see below comments from Susan.

Susan: thank you. I had the same question before – Lishan, could you explain this?

Shan-Lu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Friday, February 21, 2020 at 9:06 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Please list me as Susan R Weiss (with the "R"). there are too many other Susan Weiss'

I noticed what looks like a contradictory statement in the paper- sorry I missed it before- I

highlighted in yellow lines 124-133. The first part says chimeric virus is attenuated producing less antigen than MA15 but the next part says it has elevated activity- this seems contradictory

I remain concerned about the insertion of the furin site

Susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 10:05 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: [External] Re: Your article proofs for review (ID# TEMI 1733440)

We agreed to add this link to the proof to the third paragraph regarding RaTG13.

The Proximal Origin of SARS-CoV-2
http://virological.org/t/the-proximal-origin-of-sars-cov-2/398

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: Shan-Lu Liu <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 4:46 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, Susan Weiss <weisssr@pennmedicine.upenn.edu>
Subject: FW: Your article proofs for review (ID# TEMI 1733440)

All,

See message below and also the attached proof.

Please mark your changes in the attached PDF file, and Lishan and I will incorporate to finalize.

Thanks.

Shan-Lu

From: "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
Reply-To: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Date: Friday, February 21, 2020 at 4:13 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Your article proofs for review (ID# TEMI 1733440)

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear Shan-Lu Liu,

Your article proofs are now available for review through the Central Article Tracking System (CATS) at: https://cats.informa.com/PTS/in?ut=B2AB6692AA414D96905B59E6C51FA240 .

PLEASE NOTE: The CATS system only supports Internet Explorer 6 (and later), or Firefox 3 (and later) browser software. Popup blockers should be disabled. If you have any difficulty using CATS, please contact me.

• Your User Name is: [redacted]

• If you do not know your password, you may reset it here: http://cats.informa.com/PTS/forgottenPassword.do

1. Click on 'Review Proofs'.

2. Select 'Download PDF'.

3. Follow the guidance on the proof cover sheet to return your corrections. Please limit changes to answering any author queries and to correcting errors. We would not expect to receive more than 30 corrections.

Please check your proofs thoroughly before submitting your corrections as once they have been submitted we are unable to accept further corrections. If you have any queries, please email me.

To avoid delaying publication of your article, please approve these proofs or return any corrections by 26 Feb 2020.

Reprint and issue orders may be placed by logging in to your CATS account and accessing the order form on the "Additional Actions" menu. If you have any questions on this process, please contact me or visit our author services site https://authorservices.taylorandfrancis.com/ordering-print-copies-of-your-article/

• The DOI of your paper is: 10.1080/22221751.2020.1733440. Once your article has published online, it will be available at the following permanent link: https://doi.org/10.1080/22221751.2020.1733440 .

Thank you,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

From: Weiss, Susan
To: Liu, Shan-Lu
Subject: Re: [External] FW: Your article proofs for review (ID# TEMI 1733440)
Date: Friday, February 21, 2020 10:13:18 AM

Henry and I have been speculating- how can that site have appeared at S1/S2 border- I hate to think to was engineered- among the MHV strains, the cleavage site does not increaser pathogenicity while it does effect entry route (surface vs endosome) . so for me the only significance of this furin site is as a marker for where the virus came from- frightening to think it may have been engineered

---

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 9:50 AM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Cc: Lishan Su <lishan_su@med.unc.edu>
Subject: Re: [External] FW: Your article proofs for review (ID# TEMI 1733440)

Susan, I completely agree with you, but rumor says that furin site may be engineered. Importantly, the virus RNA sequence around the furin site (288 nt), before and after, has 6.6 % differences, but with no amino acid changes at all.

Shan-Lu Liu sent from iPhone

> On Feb 21, 2020, at 5:42 AM, Weiss, Susan <weisssr@pennmedicine.upenn.edu> wrote:
>
> Shan-Lu
>
> Maybe too late to add to the paper, but I think the fact that the RaTG13 spike does not include a furin sequence makes it unlikely that it is the precursor to SARS-CoV-2.
> I find it hard to imagine how that sequence got into the spike of a lineage b betacoronavirus- not seen in SARS or any of the bat viruses.
>
> The BioRx preprint on Pangolin sequence is very weak- says the RBD from the pangolin virus is closer to SARS-CoV-2 than RaTG13 is. But again pangolin sequence lacks the furin site.
> The furin site to me is a good marker for ancestral virus
>
> Any thoughts on this?

susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 7:47 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: [External] FW: Your article proofs for review (ID# TEMI 1733440)

All,

See message below and also the attached proof.

Please mark your changes in the attached PDF file, and Lishan and I will incorporate to finalize.

Thanks.

Shan-Lu

From: "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
Reply-To: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Date: Friday, February 21, 2020 at 4:13 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Your article proofs for review (ID# TEMI 1733440)

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

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• The DOI of your paper is: 10.1080/22221751.2020.1733440. Once your article has published online, it will be available at the following permanent link: https://doi.org/10.1080/22221751.2020.1733440 .

Thank you,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

From: Su, Lishan
To: Liu, Shan-Lu
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)
Date: Friday, February 21, 2020 7:19:10 PM

Uploaded and you should have received a message.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 5:44 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Looks good, let's submit. Linda should be fine with it.
Thanks.

Shan-Lu Liu sent from iPhone

> On Feb 21, 2020, at 2:35 PM, Su, Lishan <lishan_su@med.unc.edu> wrote:
>
> Done, and waiting to be submitted after hearing from Linda.
>
> -Lishan
>
> ---
>
> **From:** "Liu, Shan-Lu" <liu.6244@osu.edu>
> **Date:** Friday, February 21, 2020 at 3:07 PM
> **To:** "Su, Lishan" <lishan_su@med.unc.edu>
> **Subject:** Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)
>
> Lishan,
>
> Do you have the corrected proof? Thanks for doing this. I am almost done with the meeting.
>
> SL
>
> ---
>
> **From:** "Su, Lishan" <lishan_su@med.unc.edu>
> **Date:** Friday, February 21, 2020 at 11:52 AM
> **To:** "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>, Shan-Lu Liu <liu.6244@osu.edu>
> **Subject:** Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

I agree with you on these points, but NIH/government at the time put it as a gof study relative to the original S antigen…

-Lishan

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Friday, February 21, 2020 at 2:51 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Is the adaptation of MA15 to mice considered "gain of function"- that selected virus is more virulent than SHC014-MA15 chimeric virus? Seems to me like more loss of function relative to MA15 when inserting the bat derived spike. MA15 with the urbani spike is like de- adapting the virus to mice.

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 1:40 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

I have noticed that too, probably happened when we tried to simplify the chimeric virus paragraph, and I think Ralph had added the attenuation sentence relative to M15 in mice…

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See old sentence:
Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the original human Urbani S-MA15 chimeric virus in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies…

I will try to fix this.
Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 12:14 PM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Cc: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Lishan: see below comments from Susan.

Susan: thank you. I had the same question before – Lishan, could you explain this?

Shan-Lu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Friday, February 21, 2020 at 9:06 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

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I remain concerned about the insertion of the furin site

Susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 10:05 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: [External] Re: Your article proofs for review (ID# TEMI 1733440)

We agreed to add this link to the proof to the third paragraph regarding RaTG13.

<image001.png>
Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: Shan-Lu Liu <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 4:46 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, Susan Weiss <weisssr@pennmedicine.upenn.edu>
Subject: FW: Your article proofs for review (ID# TEMI 1733440)

All,

See message below and also the attached proof.

Please mark your changes in the attached PDF file, and Lishan and I will incorporate to finalize.

Thanks.

Shan-Lu

From: "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
Reply-To: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Date: Friday, February 21, 2020 at 4:13 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Your article proofs for review (ID# TEMI 1733440)

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear Shan-Lu Liu,

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PLEASE NOTE: The CATS system only supports Internet Explorer 6 (and later), or Firefox 3 (and later) browser software. Popup blockers should be disabled. If you have any difficulty using CATS, please contact me.

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1. Click on 'Review Proofs'.

2. Select 'Download PDF'.

3. Follow the guidance on the proof cover sheet to return your corrections. Please limit changes to answering any author queries and to correcting errors. We would not expect to receive more than 30 corrections.

Please check your proofs thoroughly before submitting your corrections as once they have been submitted we are unable to accept further corrections. If you have any queries, please email me.

To avoid delaying publication of your article, please approve these proofs or return any corrections by 26 Feb 2020.

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• The DOI of your paper is: 10.1080/22221751.2020.1733440. Once your article has published online, it will be available at the following permanent link: https://doi.org/10.1080/22221751.2020.1733440 .

Thank you,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

<TEMI_A_1733440 Proof-Su.pdf>

From:	Su, Lishan
To:	Liu, Shan-Lu; Lu, Shan
Subject:	Re: 2019-nCoV-EMI_commentary
Date:	Wednesday, February 12, 2020 10:08:24 AM
Attachments:	image001.png image002.png 2019 CoV Copy.enl EMI-2019-nCoV_Commentary LJS_SLL_Refs.docx

---

See minor revisions and new endnote file. My new MS office word is refusing endnote?!
I don't know how to add website into the Endnote file.
Thanks!

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>

Date: Wednesday, February 12, 2020 at 9:08 AM

To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>

Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Once you complete and send me your revision along with the updated Endonote, I will quickly finish it and send it to Stanley Perlman and Susan Weiss and copy you of course.

Thank you.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>

Date: Wednesday, February 12, 2020 at 8:32 AM

To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>

Subject: Re: 2019-nCoV-EMI_commentary

Got it. Thanks

-Lishan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Wednesday, February 12, 2020 7:19:41 AM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Please use the latest updates, with minor changes.

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Wednesday, February 12, 2020 at 1:13 AM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

See the endnote file. Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 7:44 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Sounds good, thank you. I still like “however” over “In contrast” – it just reads better

Shan: Are you sure that you prefer not to be included in the coauthorship? Before I send, I think we should have the authorship listed, along with affiliations. Lishan should be the first author, unless he prefers otherwise. Agreed?

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 7:34 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

I made some minor change for the following:

In summary, there is no credible evidence at this point to support the claims that the 2019-nCoV was

originated from a laboratory-engineered CoV. In contrast, we cannot rule out the possibility that 2019-nCoV is a recombinant generated in nature between a bat CoV and another coronavirus in an intermediate host. More studies are needed to explore this possibility and resolve the origin of 2019-nCoV.

Maybe now SLL can send the next version to other CoV experts?

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 5:47 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

See the new version with all incorporated.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 4:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I have made additional changes to the Lishan's version, see attached.

Lishan: I share your concern, and that is one reason that Shan, the editor, decides to have a short version.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 4:16 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

The new title is good if we will cover the RaTG13 and HIV insertion issues.
I am still worried if we can shed any light on the major claim of RaTG13 lab escape/evolution in other hosts/humans over the years…?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 3:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Perhaps Lishan can take a look at the latest version, which has the new title I suggested, and modify it as needed.
The last paragraph is also crucial, but I did not have time to work on it because of a meeting this morning.
Once we have almost a final draft, I will contact Linda Saif, Stanley Perlman, Thomas Gallgaher etc. to see if they are willing to join, but this may delay the publishing time.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 1:52 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I agree that it should be simple and clear. I have included some details in the 1st draft for your information. There is not intention to defend Baric, but to clarify the facts.

Regarding all three, are you combining Goa Feng's piece with this one? For the RaTG13, it involves complicated viral evolution kinetics and maybe hard to simply clarify…
Best,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 1:44 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Sorry here is the attachment with tracking

From: Lu, Shan
Sent: Tuesday, February 11, 2020 1:44 PM
To: 'Su, Lishan' <lishan_su@med.unc.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Hi, I am adding Shuying from my group. She just read the last draft from Lishan and identified a few errors (with tracking).

Also I just had a phone call with SSL and we agreed on the following:

1. We need to make this commentary very simple and short;
2. It is better not going to too much science/tech details as it can only confuse people and

provide more room for people to raise more questions;
3. We don't want to appear that we are defending Ralph even though he did nothing wrong.
4. We feel it is best to cover 3 issues in this commentary (for the above reason, plus it is more powerful to cover multiple issues in one summary)
5. ??

SLL: please add anything I missed.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 12:52 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Looking at Shanlu's version, we may need a separate for the RaTG13 vs lab accident theory...

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 12:44 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

Thanks.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

SARVS-CoV-2: no evidence of a laboratory origin

Lishan Su[1], and Linda J. Saif [2,3], XXX, XXX, and Shan-Lu Liu[3, 4,5.6]

[1] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[3] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[4] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[5] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[6] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

Dr. Lishan Su, lsu@med.unc.edu

Dr Linda J. Saif, Saif.2@osu.edu

XXX, XXX

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A novel human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (WHO website link ref).

According to what has been reported [1-3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4,5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding DNA sequences (CDSs), and among the 128 nonsynonymous mutations, 89 led to a predicted radical amino-acid changes (Song, H.D. et al. Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci U S A 102, 2430-2435 (2005)). Given that there are greater than 1000 nt differences between the human

SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern and follow the evolution characteristics typical of CoVs, including the S gene as the most variable region, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might have CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (website link ref).

Another claim points to a Nature Medicine paper published in 2015 [6], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [7]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2.

The recombinant mouse-adapted SARS virus (MA15) (Roberts, A. et al. A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. PLoS Pathog 3, e5 (2007)) was generated by serial passage of an infectious SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding

genetic mutations associated with mouse adaptation. It is also likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [8,9]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans (need to find refs). However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [7]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [10], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-SHC014 was used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-MA15 can replicate efficiently in the mouse lung, leading to severe pathogenesis [6].

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus were restricted as gain of function (GOF) studies under the US government-mandated pause policy (from Oct. 2014 to Dec. 2017: https://www.nih.gov/about-nih/who-we-

are/nih-director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5,11], the SARS-CoV-2 is undoubtedly distinct from SHC014- MA15, with >5000 nt differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SHC014-MA15 virus.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv, (a manuscript sharing site prior to any peer review ~~and not yet peer reviewed for accuracy~~) claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. A rebuttal paper led by an HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of randomly occurring mutations.---And should not be present? in naturally isolated viruses such as RaTG13. Currently, there is no credible evidence to support the claim that SARS-CoV-2 was originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a

bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

1. Wang, D.*, et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* (2020).
2. Chang*, et al.* Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. *JAMA* (2020).
3. Chen, N.*, et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* (2020).
4. Zhou, P.*, et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* (2020).
5. Zhu, N.*, et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* (2020).
6. Menachery, V.D.*, et al.* A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med* **21**, 1508-1513 (2015).
7. Ge, X.Y.*, et al.* Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature* **503**, 535-538 (2013).
8. Li, F., Li, W., Farzan, M. & Harrison, S.C. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* **309**, 1864-1868 (2005).
9. Li, W.*, et al.* Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* **426**, 450-454 (2003).
10. Demogines, A., Farzan, M. & Sawyer, S.L. Evidence for ACE2-utilizing coronaviruses (CoVs) related to severe acute respiratory syndrome CoV in bats. *J Virol* **86**, 6350-6353 (2012).
11. Wu, F.*, et al.* A new coronavirus associated with human respiratory disease in China. *Nature* (2020).

From:	Su, Lishan
To:	Liu, Shan-Lu
Subject:	Re: Submitted Corrections for article TEMI 1733440
Date:	Friday, February 21, 2020 7:39:02 PM
Attachments:	image001.png image002.png TEMI_A_1733440 Proof-Su copy.pdf

---

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>

Date: Friday, February 21, 2020 at 7:33 PM

To: "Su, Lishan" <lishan_su@med.unc.edu>

Subject: Re: Submitted Corrections for article TEMI 1733440

I just went online to see if we replace with a new one.
Could you send me the PDF of the corrected one?

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>

Date: Friday, February 21, 2020 at 4:32 PM

To: Shan-Lu Liu <liu.6244@osu.edu>

Subject: Re: Submitted Corrections for article TEMI 1733440

My bad. How do we fix it? send her a message?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>

Date: Friday, February 21, 2020 at 7:29 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

Lishan:

I just saw that you deleted nt for 1,100 – “nt” should be kept. Could you correct that?

Thanks.

SL

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 4:28 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

Thanks!

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 7:22 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, Susan Weiss <weisssr@pennmedicine.upenn.edu>
Subject: Fwd: Submitted Corrections for article TEMI 1733440

Shan-Lu Liu sent from iPhone

Begin forwarded message:

From: "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
Date: February 21, 2020 at 4:04:41 PM PST
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Subject: Submitted Corrections for article TEMI 1733440
Reply-To: TEMI-production@journals.tandf.co.uk

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

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This email confirms that you have submitted your corrections to your article proofs.

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Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

TEMI1733440 VOL 0, ISS 0

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Shan-Lu Liu, Linda J. Saif, Susan Weiss, and Lishan Su

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Emerging Microbes & Infections
https://doi.org/10.1080/22221751.2020.1733440

COMMENTARY

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No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Q1 Shan-Lu Liu[a,b,c,d], Linda J. Saif[d,e], Susan Weiss [f] and Lishan Su[g]

[a]Center for Retrovirus Research, The Ohio State University, Columbus, OH, USA; [b]Department of Veterinary Biosciences, The Ohio State University, Columbus, OH, USA; [c]Department of Microbial Infection and Immunity, The Ohio State University, Columbus, OH, USA; [d]Viruses and Emerging Pathogens Program, Infectious Diseases Institute, The Ohio State University, Columbus, OH, USA; [e]Food Animal Health Research Program, Ohio Agricultural Research and Development Center, CFAES, Department of Veterinary Preventive Medicine, The Ohio State University, Wooster, OH, USA; [f]Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [g]Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

ARTICLE HISTORY Received 13 February 2020; Accepted 13 February 2020

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1–3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4,5].

Currently, there are speculations, rumours and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10,11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6,12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe

CONTACT Shan Lu Liu lsu@med.unc.edu; Lishan Su Liu.6244@osu.edu

bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titres as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5,14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus.

There are also rumours that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 virologist Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random [15]. Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2. We should emphasize that, although SARS-CoV-2 shows no evidence of laboratory origin, viruses with such great public health threats must be handled properly in the laboratory and also properly regulated by the scientific community and governments.

Disclosure statement

No potential conflict of interest was reported by the author(s). Q2

ORCID

Susan Weiss http://orcid.org/0000 0002 8155 4528

References Q3

[1] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus infected pneumonia in Wuhan, China. JAMA. 2020 Feb 7. Q4

[2] Chang LM, Wei L, et al. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. JAMA. 2020 Feb 7. Q5

[3] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Jan 30. Q6

[4] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Feb 3. Q7

[5] Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020 Jan 24. Q8

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SARS coronavirus. Nature. 2003 Nov 27;426 (6965):450 454.
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[15] Xiao C, Li X, Liu S, et al. HIV 1 did not contribute to the 2019 nCoV genome. Emerg Microbes Infect. 2020 Dec;9(1):378 381.

Q9

From: Su, Lishan
To: Liu, Shan-Lu
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)
Date: Friday, February 21, 2020 4:57:07 PM
Attachments: image001.png

I am doing the proof, and waiting to get anything from Linda. You and Susan seem to have responded already.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 3:07 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Lishan,

Do you have the corrected proof? Thanks for doing this. I am almost done with the meeting.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 11:52 AM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

I agree with you on these points, but NIH/government at the time put it as a gof study relative to the original S antigen…

-Lishan

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Friday, February 21, 2020 at 2:51 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Is the adaptation of MA15 to mice considered “gain of function”- that selected virus is more virulent than SHC014-MA15 chimeric virus? Seems to me like more loss of function relative to MA15 when inserting the bat derived spike. MA15 with the urbani spike is like de- adapting the virus to mice.

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 1:40 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

I have noticed that too, probably happened when we tried to simplify the chimeric virus paragraph, and I think Ralph had added the attenuation sentence relative to M15 in mice…

What was reported in the NM paper was that the SHC014-rMA15 chimeric virus was less pathogenic than M15, but more so than the chimeric M15 virus with the original Urbani Spike-gene in M15, probably due to one of the 6 mutations in the M15 S gene.

See old sentence:
Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the original human Urbani S-MA15 chimeric virus in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies…

I will try to fix this.
Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 12:14 PM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Cc: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Lishan: see below comments from Susan.

Susan: thank you. I had the same question before – Lishan, could you explain this?

Shan-Lu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Friday, February 21, 2020 at 9:06 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Please list me as Susan R Weiss (with the “R”). there are too many other Susan Weiss’

I noticed what looks like a contradictory statement in the paper- sorry I missed it before- I highlighted in yellow lines 124-133. The first part says chimeric virus is attenuated producing less antigen than MA15 but the next part says it has elevated activity- this seems contradictory

I remain concerned about the insertion of the furin site

Susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 10:05 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: [External] Re: Your article proofs for review (ID# TEMI 1733440)

We agreed to add this link to the proof to the third paragraph regarding RaTG13.

The Proximal Origin of SARS-CoV-2
http://virological.org/t/the-proximal-origin-of-sars-cov-2/398

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: Shan-Lu Liu <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 4:46 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, Susan Weiss <weisssr@pennmedicine.upenn.edu>
Subject: FW: Your article proofs for review (ID# TEMI 1733440)

All,

See message below and also the attached proof.

Please mark your changes in the attached PDF file, and Lishan and I will incorporate to finalize.

Thanks.

Shan-Lu

From: "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
Reply-To: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Date: Friday, February 21, 2020 at 4:13 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Your article proofs for review (ID# TEMI 1733440)

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear Shan-Lu Liu,

Your article proofs are now available for review through the Central Article Tracking System (CATS) at: https://cats.informa.com/PTS/in?ut=B2AB6692AA414D96905B59E6C51FA240 .

PLEASE NOTE: The CATS system only supports Internet Explorer 6 (and later), or Firefox 3 (and later) browser software. Popup blockers should be disabled. If you have any difficulty using CATS, please contact me.

• Your User Name is: [redacted]

• If you do not know your password, you may reset it here:
http://cats.informa.com/PTS/forgottenPassword.do

1. Click on 'Review Proofs'.

2. Select 'Download PDF'.

3. Follow the guidance on the proof cover sheet to return your corrections. Please limit changes to answering any author queries and to correcting errors. We would not expect to receive more than 30 corrections.

Please check your proofs thoroughly before submitting your corrections as once they have been submitted we are unable to accept further corrections. If you have any queries, please email me.

To avoid delaying publication of your article, please approve these proofs or return any corrections by 26 Feb 2020.

Reprint and issue orders may be placed by logging in to your CATS account and accessing the order form on the "Additional Actions" menu. If you have any questions on this process, please contact me or visit our author services site
https://authorservices.taylorandfrancis.com/ordering-print-copies-of-your-article/

• The DOI of your paper is: 10.1080/22221751.2020.1733440. Once your article has published online, it will be available at the following permanent link:
https://doi.org/10.1080/22221751.2020.1733440 .

Thank you,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

F om Su, Shan
To [illegible]
Subje t Re Eme g ng Mic obes & Infect ons - TEMS-20 0-0121 - changes qui ed o ou subm s ion
Date sday eb ua y 4 2020 1 17 7 M

Very good point about working wi h the new irus. I was referr ng to ra g13 and the chimeric iruses in the lab.

-Lishan

F om Liu, Shan-Lu l u 6244@osu.edu>
Sent F iday, Feb ua y 14, 2020 12 47 18 PM
To Su, L shan l shan_su@med.unc.edu> Lu, Shan shan.lu@umassmed.edu>
Subject Re Eme g ng Mic obes & Infect ons - TEMI-2020 0121 - changes equi ed to you submiss on

Lishan

I get you point – maybe below one eads bet e ?

'We should emphas ze that, although SARS-CoV-2 shows no evidence of labo ato y o sign, such a vi us, and clo sely elated, do pose g eat public health th eats and must be handled p ope ly n the labo a o y and also p ope ly egulated by gove nments and scientific commun ty'

Thoughts?

Shan-Lu Liu, M.D., Ph D.
P ofesso
Co-Di ecto , Vi uses and Eme ging Pathogens P og am
Infectious Diseases Inst tu e
Cente fo Ret ovi us Resea ch
Depa rments of Ve e na y Biosciences, Mic obial Infection and Immunity, and M c ob ology
The Oh o State Un ve s ty
1900 Co fey Rd, Room 480 VMAB
Columbu , Oh o 43210
Phone (614) 292-8690
Fax (614) 292-6473
Ema l l u 6244@osu.edu shan l.u l u@osumc.edu

On 2/14/20, 11 08 AM, Su, Lishan l shan_su@med.unc edu> w ote

How about adding the last sentence n the p oof?

Evolution s stepwise and acc ues mutations g adually ove t me, whe eas synthet c consl uc s would typica ly use a known backbone and nt oduce logical o ta geted changes instead of the andomly occu ing mutations that a e p esent in natu ally i ola ed vi uses such as bat CoV RaTG13. In ou view, the e is cu ently no c ed ble evidence to uppo t the cla m that SARS CoV 2 o iginated f om a labo ato y-eng nee ed CoV. It is mo e l kely that SARS-CoV-2 is a ecomb nant CoV gene ated in natu e beween a bat CoV and anothe co onavi us in an nte mediate animal hos . Mo e studies a e needed to explo e th s possibility and esolve the natu al o g n of SARS CoV-2. Although the SARS2 CoV has shown no evidence of labo ato y o igin, it is impo tant to point out that such vi uses in the labo ato y as d scussed he e do pose public health conce ns and should be ca efu ly moni o ed and egulated.

-Lishan

--- O ig nal Message- ---
F om Liu, Shan-Lu l u 6244@osu.edu>
Date Thu sday, Feb ua y 13, 2020 at 10 04 AM
To Lu, Shan shan.lu@umassmed.edu>
Cc Su, Lishan l shan_su@med.unc edu>
Subject Re Eme g ng Mic obes & Infect ons - TEMI-2020 0121 - changes equi ed to you submiss on

Thanks, Shan fo you e fic ent ac ion!

On 2/13/20, 9 56 AM, Lu, Shan Shan.Lu@umassmed.edu> w ote

You pape is now accepted. Hope you have eceived the dec sion let e .

Best.

Shan

--- O ginal Message----
F om L u, Shan-Lu liu.6244@osu.edu>
Sent Thu sday, Feb ua y 13, 2020 8 57 AM
To temi-pee eview@jou nals.tandf.co.uk
Cc Lu, Shan Shan.Lu@umassmed.edu> Su, Lishan l shan_su@med unc.edu>
Subject Re Eme ging Mic obes & Infections - TEMI-2020-0121 - changes equi ed to you subm ssion
Impo tance H gh

Hi Jo gie

I have modif ed as inst ucted and at ached the new one to this ema l. Please help upload and p oceed.

Thank you.

Shan-Lu

Shan-Lu Liu, M.D., Ph D.
P ofesso
Co-Di ecto , Vi uses and Eme ging Pathogens P og am Infectious Diseases Inst tute Cente fo Ret ovi us Resea ch Depa tments of Vete ina y Biosc ences, M c ob al Infect on and Immun ty, and Mic obiology The Ohio State Unive sity
1900 Co fey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone (614) 292 8690
Fax (614) 292 6473
Ema l l u.6244@osu.edu shan lu.liu@osumc.edu

On 2/13/20, 8 43 AM, Eme ging Mic obes and Infec ions onbehalfo @manusc iptcent al.com> w ote

13-Feb 2020

Dea P ofesso Liu,

You above efe enced manusc ipt, entitled SARS-CoV-2 no evidence of a labo ato y o ig n equi es some fu the changes befo e it is eady fo eviewing n Eme g ng Mic obes & Infec ions. You submiss on has been etu ned to you and is located in you Autho Cen e as a d aft, so that you due to these easons

1. No line numbe ng

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u l=h tps*3A*2F*2Fu ldefense com*2Fv2*2F__http*3A*2F*2Fmc manusc iptcent al.com*2Fsociety mages*2Fstandf_pd*2FCon inue rq*2Da*2D5uSm ssion_sc eenshot pdf__*3BSU IKGKeukYlnGv1RgRI1P-OGXuZ8Bz2hKGjXoDFOmBwDONuR_njCdwERJF1HkBIV4Sggg 9 e62BfA*24&amp data=02*7C01*7CShan.Lu*40umassmed edu*7Cde7fc6818f7047e0d7900d8d7b08c97ea*7Cee9155fe2da34578a6c44405faf57b2e*7C0*7C0*7C637171990355158902&amp sdata=JDlO3OLwBEOX pTKWpzb2Ar5*2FIlUA32FF5n1KHtVyB*3D&amp ese ved=0__ JSU JSU JSU JSUqKUJ JSU JSU JSU JQJIIKGKeukYlmmUOKG7xwWhIjHcQpOeGIvzwUGqZ XE JwJPoFzezoh3pwjO9XD9bST-kC1 d8CF7I5

You may contact the Edito ial O fice if you have fu the quest ons.

S nce ely,

Jo g e Lyn Luna
Eme ging M c obes & Infect ons Edi o al Off ce
temi-pee ev ew@jou nals tandf co uk

From: Su, Lishan
To: Liu, Shan-Lu; Lu, Shan
Subject: Re: Welcome to Taylor & Francis Production: Emerging Microbes & Infections 1733440 #TrackingId:5682455
Date: Thursday, February 20, 2020 1:39:16 AM
Attachments: Liu et al_EMI Commentary_Revision_中文-sls.docx

See attached file. Feel free to further revise.
Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Thursday, February 20, 2020 at 12:29 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Welcome to Taylor & Francis Production: Emerging Microbes & Infections 1733440 #TrackingId:5682455

Great! Share when done.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Wednesday, February 19, 2020 at 9:28 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Welcome to Taylor & Francis Production: Emerging Microbes & Infections 1733440 #TrackingId:5682455

All is well。我快把中文翻译修改完了。

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Thursday, February 20, 2020 at 12:15 AM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Welcome to Taylor & Francis Production: Emerging Microbes & Infections 1733440 #TrackingId:5682455

Better make sure 100%.

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Thursday, February 20, 2020 12:14 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Welcome to Taylor & Francis Production: Emerging Microbes & Infections 1733440 #TrackingId:5682455

I think so

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Wednesday, February 19, 2020 at 9:13 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: RE: Welcome to Taylor & Francis Production: Emerging Microbes & Infections 1733440 #TrackingId:5682455

Thanks. You submitted it online, right?

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Thursday, February 20, 2020 12:12 AM
To: Liu, Shan-Lu <liu.6244@osu.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Welcome to Taylor & Francis Production: Emerging Microbes & Infections 1733440 #TrackingId:5682455

Fyi。See title and author names.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Thursday, February 20, 2020 at 12:11 AM
To: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Cc: "shan.lu@umassmed.edu" <shan.lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Welcome to Taylor & Francis Production: Emerging Microbes & Infections 1733440 #TrackingId:5682455

We are fixing it right now and will submit very shortly.

Thank you.

Shan-Lu

From: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Date: Wednesday, February 19, 2020 at 9:07 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: "shan.lu@umassmed.edu" <shan.lu@umassmed.edu>, "lishan_su@med.unc.edu" <lishan_su@med.unc.edu>
Subject: Re: Re: Welcome to Taylor & Francis Production: Emerging Microbes & Infections

1733440 #TrackingId:5682455

Hi Shan,

Your copyright form was rejected as there were no article title and author names filled in the form. Please fill and resubmit the form.

Regarding publication time, normally this would publish articles in 18 days. If editor asks us to prioritise, we will do. I will discuss with editor and get back to you on this.

Regards,

Malathi
Emerging Microbes & Infections

From:liu.6244@osu.edu
Sent:
To:liu.6244@osu.edu
Cc:lishan_su@med.unc.edu,Shan.Lu@umassmed.edu
Subject: Re: Re: Welcome to Taylor & Francis Production: Emerging Microbes & Infections 1733440

I am currently out of town, but may I ask my co-corresponding author Dr, Lishan Su, who is copied, to sign on the agreement on behalf of us.

Another piece of note, because this commentary is extremely time-sensitive, is it possible to process it with an accelerated speed? Last few days, similar comments have been published by other journals.

Thank you.

Shan-Lu Liu sent from iPhone

> On Feb 19, 2020, at 3:51 PM, TEMI-production@journals.tandf.co.uk <cats@taylorandfrancis.com> wrote:
>
> Article: SARS-CoV-2: no evidence of a laboratory origin
>
> Journal: *Emerging Microbes & Infections* TEMI
>
> Article ID: TEMI 1733440
>
> Dear Shan-Lu Liu,

We are delighted that you have chosen to publish your article in *Emerging Microbes & Infections*. I will be your Production Editor and will work with you to oversee the production of your article through to publication. My contact details are given at the end of this email.

• Please print and sign the attached Author Publishing Agreement. Then return the completed agreement to Taylor & Francis, by uploading to CATS (see below), or post it to the address below.

Proofs will be ready for you to check in approximately 7 working days and we would like you to return your corrections within 3 days. Please let me know if there will be any difficulty in meeting this schedule.

We will be sending proofs to you through our workflow system, CATS (Central Article Tracking System).

• You can check the status of your paper online through the CATS system at: https://cats.informa.com/PTS/in?ut=B2AB6692AA414D96905B59E6C51FA240

• Your User Name is: [redacted]

• Your Password is: [redacted] (You will be required to change this first time you log in)

• The DOI of your paper is: 10.1080/22221751.2020.1733440. Once your article has published online, it will be available at the following permanent link: https://doi.org/10.1080/22221751.2020.1733440 .

Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

<Copyright_Form.pdf>

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

没有可信的证据支持 SARS-CoV-2 来自实验室工程的说法

Shan-Lu Liu [1, 2,3,4], Linda J. Saif [4,5], Susan Weiss [6], and Lishan Su [7]

[1] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[2] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[3] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

[4] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[5] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[6] Department of Microbiology, Perelman School of Medicine,

University of Pennsylvania, Philadelphia, Pennsylvania, USA

[7] Lineberger Comprehensive Cancer Center, Department of Microbiology and

Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

截止 2020 年 2 月 10 日，在中国武汉出现和爆发的急性呼吸疾病已波及 4 万多人，导致 1000 多人死亡。研究人员很快~~确定~~找到了~~这~~一种新型人体内的冠状病毒，称之为 2019 nCoV 或 SARS-CoV-2，而相应的疾病称之为 COVID-19，意为 2019 年发生的冠状病毒疾病 (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/)。

According to what has been reported [1-3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4,5].

据现有的报道[1-3]，COVID-2019 似乎与 SARS-CoV 导致的 SARS 有相似的临床表现。SARS-CoV-2 基因组序列也和 SARS-CoV 有 80%~~一致~~相同，~~但却是和一些蝙蝠贝塔冠状病毒最相似~~但却是和一些蝙蝠乙型冠状病毒最相似，~~序列一致~~超过了 96%基因组序列相同。

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory engineering origin. Some people have alleged that the human SARS-CoV-

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2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4].

当前，种种的推测、谣言和阴谋论认为，SARS-CoV-2 是源自实验室基因工程。一某些人声称，人的 SARS-CoV-2 是从武汉的某个实验室直接泄漏出来的。该实验室最近报道了一种称为 RaTG13 的蝙蝠冠状病毒，和 SARS-CoV-2 基因组序列有 96%的同源性。

However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome [6].

然而，我们知道，人的 SARS 冠状病毒和中间宿主棕榈果子狸~~样~~ SARS 样冠状病毒具有 99.8%的同源性，在整个基因组中~~共鉴定出~~只有 202 个~~单核苷酸变异~~碱基不同。

Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

鉴于人类 SARS-CoV-2 与蝙蝠 RaTG13-CoV 之间~~存在~~有超过 1000 个不同碱基~~单核苷酸的差异~~[4]，且这些差异是按照冠状病毒典型的进化特征以自然发生的模式分布在整个基因组中，因此~~极不可能~~ RaTG13 冠状病毒是 SARS-CoV-2 的直接来源是极不可能的。在新的 SARS-CoV-2 病毒序列中并没有~~一个逻辑上靶向的模式~~基因工程的迹象，且它和野生物种（蝙蝠）~~近亲~~非常相似，这都~~是最~~很明显的~~提示~~揭示~~，一~~和表明 SARS-CoV-2 是通过自然~~进~~演化而来的。这需要~~寻找~~找到蝙蝠与人类之间的中间动物宿主来源~~是需要的~~与 SARS-CoV-2 更相似~~，可以用来确定与人 SARS-CoV-2 更紧密相关~~的动物冠状病毒。有猜测认为穿山甲可能携带与 SARS-CoV-2 密切相关的冠状病毒，但数据尚未发表，无从证实。

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

Commented [SL1]: Disregarded ?

中国社交媒体上的另一种说法指向《自然医学》2015 年发表的一篇论文[7]，该论文报道了在小鼠适应后 SARS 冠状病毒的骨架（MA15 病毒）中构建了带有蝙蝠冠状病毒~~基因~~

（SHC014）S 基因的嵌合冠状病毒，该病毒适应病毒后可以感染小鼠小鼠（MA15 病毒），也能够感染人类细胞[8]。但是，可是该主张说法缺乏任何科学依据，必须予以驳斥，因为该嵌合冠状病毒构建体的遗传序列与 SARS-CoV-2 相比有超过 5,000 个核苷酸的显著的差异。

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patienthumans due to the mouse adaptation.

适应小鼠的 SARS 病毒（MA15）[9]是通过把传染性的克隆野生型 SARS 冠状病毒壳隆体在 BALB / c 小白鼠呼吸道中的连续传代而产生的。在小鼠中传代 15 次后，这个 因 SARS 冠状病毒有了六个编码遗传突变使其适应为与感染小鼠适应性相关的六个编码遗传突变，且 SARS 冠状病毒在老年小鼠中获得了更高的复制和肺部致病性（因此称为 M15）。由于在小鼠内的适应的遗传突变改造，很可能 MA15 在人细胞或者人体内复制很可能是高度降低减毒得以在人细胞或者患者体内复制。

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10,11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6,12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8].

当初分离出~~原始的~~SARS 冠状病毒时，得出的结论是，蝙蝠身上来的冠状病毒的 S 基因不同于人类患者或果子狸身上的病毒，它无法使用人的 ACE2 受体来进入人体细胞[10, 11]。

~~Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6,12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8].~~

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果子狸~~曾~~被认为是~~很多~~蝙蝠冠状病毒的中间宿主，能够将 SARS 冠状病毒传播给人类[6，12]。然而，2013 年，从中国马蹄蝙蝠中分离了出来数种新型蝙蝠冠状病毒~~从中国马蹄蝙蝠中分离了出来~~，~~而且~~这些蝙蝠的 SARS ~~样~~或样冠状病毒（SL-CoV-WIV1）~~病毒~~能够使用~~通过~~人、果子狸和中国马蹄蝙蝠的 ACE2 受体进入和感染细胞[8]。

Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the ~~exact~~ S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, ~~which~~and SL-SHC014-MA15 only cause~~s~~d lethal outcomes in aged mice [7].

另外~~结~~合进化证据表明，在与 SARS 冠状病毒的相互作用上，蝙蝠 ACE2 基因已在与人类 ACE2 基因相同的接触位点上被~~积极~~正选择[13]，因此提出了蝙蝠的 SARS 样冠状病毒传染到人不必需要中间宿主的可能~~不是必需的~~，~~且~~有些蝙蝠 SL-CoV 也许能够直接感染人类宿主。为了直接~~解决~~验证这种可能性，~~来自~~蝙蝠冠状病毒 SL-SHC014 ~~的一样~~的 S 基因被~~合成出来，并~~用~~于~~在~~适应小鼠的~~MA15 SARS-CoV ~~主链~~骨架中产生一个嵌合病毒。所得的 SL-SHC014-MA15 嵌合病毒~~，~~确实可以有效地利用人 ACE2 进入细胞，并在~~原代~~人气呼吸道细胞中复制到与 SARS-CoV 流行株相似的~~浓度~~水平。虽然 SL-SHC014-MA15

可以在年轻和老年小鼠的肺中高效复制，但感染减弱了，并且与 SARS MA15 相比，气道上皮中存在的病毒抗原更少~~。~~，并且只~~而 SARS MA15~~会让老年小鼠致命[7]。

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV with a human SARS virus S gene in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research).

由于 SL-SHC014-MA15 嵌合病毒相对于 SARS-S-MA15 冠状病毒在小鼠中具有更高的致病活性，因此，这种 SL-SHC014-MA15 嵌合病毒的实验后来在美国政府的强制暂停政策之下作为功能获得（GOF）研究而受到限制(https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research)。

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The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5,14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus.

构建这种可能具有大流行病潜力的病毒是否是一种风险，当前的 COVID-2019 ~~流行病已经重新引发子这样的辩论~~流行病又重新引发了这样的辩论，~~可~~虽然这些蝙蝠冠状病毒已经在自然界存在~~，一辩论却无视这个发现~~。无论如何，经过多个~~国际组织~~国家科学家的认真的~~系统发育~~病毒分子进化分析[5，14]，SARS-CoV-2 无疑与 SL-SHC014-MA15 不同，整个基因组有~~的核苷酸差异~~超过 6,000 核苷酸的差异。因此，~~重申一下，~~也是没有可信的证据支持 SARS-CoV-2 是源自嵌合 SL-SHC014-MA15 病毒的说法。

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 virologist Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random [15]. Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

也有传言说，SARS-CoV-2 是实验室中人为人工或有意制造的。在~~提交给~~ BioRxiv（一个同行评审之前的手稿共享网站）的一份手稿~~（任何同行评审之前的手稿共享网站）~~中强调了~~这一~~此传言点，声称 SARS-CoV-2 中含有 HIV 序列，因此很可能是在实验室中产生的。在由 HIV-1 病毒专家 Feng Gao 博士领导的反驳论文中，他们使用了仔细的生物信息

学分析来证明，最初说的 SARS-CoV-2 有多个 HIV-1 插入片段的主张并不是 HIV-1 特有的，而是随机的。由于国际社会提出的许多~~关注~~疑问，提出最初传言~~主张~~的~~提交人~~作者已经撤回了该报告。

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2. We should emphasize that, although SARS-CoV-2 shows no evidence of laboratory origin, viruses with such great public health threats must be handled properly in the laboratory and also properly regulated by the scientific community and governments.

进化是逐步的，并随着时间的推移逐渐产生突变，而合成基因构建体通常会使用已知的骨架并引入逻辑或~~目标~~定向变化，而不是~~用~~像天然分离的病毒（如蝙蝠冠状病毒 RaTG13）中存在的随机发生的突变。我们认为，目前没有可靠的证据支持有关 SARS-CoV-2 源自实验室设计的冠状病毒的说法。 更可能的是，SARS-CoV-2 是一种蝙蝠冠状病毒与中间动物宿主中的另一种冠状病毒之间自然产生的重组冠状病毒。需要更多的研究

来探索这种可能性并解决 SARS-CoV-2 的自然起源。我们应该强调，尽管没有证据显示 SARS-CoV-2 ~~没有证据显示~~是来自实验室，如此对公共健康有威胁的病毒应该在实验室里有恰当的~~处~~管理，也要由科学~~共同体~~界和政府合理监管。

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From:	Lu, Shan
To:	Su, Lishan; Liu, Shan-Lu
Subject:	RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission
Date:	Sunday, February 16, 2020 1:34:20 PM

It is better to keep the credible here.

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Sunday, February 16, 2020 1:33 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I have added the Gao reference and formatted (I have fixed my endnote problem!). Do we need credible here in the title?

No ~~credible~~ evidence supporting claims of laboratory engineering of SARS-CoV-2.

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 1:12 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Ok, let do the 2nd one.

See attached, with Gao ref added for you to put into Endnote

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 16, 2020 1:07 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Second one reads better and is more accurate.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 1:04 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

For shorter, it will be what I suggested, let's put the two below:

No credible claims supporting the laboratory engineering of SARS-CoV-2

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 16, 2020 1:02 PM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I think either of these two should be fine, the shorter the better for a title. Title does not need to be exclusive.

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Sunday, February 16, 2020 at 12:58 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Either is fine, but first is preferred, short and clear.

SARS-CoV-2: no evidence of laboratory engineering
Or
No credible evidence supporting (claims of?) the laboratory engineering of SARS-CoV-2

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 12:53 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I am okay with the change for the title, but "claims" does not seem a good fit here –"evidence" is better I feel.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 12:51 PM

To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Thanks, then let's not having those two parts.

On the title, I do not need to use "current".

How about this:

No credible claims supporting the laboratory engineering of SARS-CoV-2

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 16, 2020 12:43 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Shan,

I agree to delete those two parts. One was added by me, based on Linda's email, and another was also by me, based on Ralph's comments.

I do not seem to prefer using "current", but I get your point - perhaps we can use "convincing"? "Credible" is not good for the title.

Thoughts?

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 12:30 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

See two attached documents:

1. Title of commentary: I agree that by removing "origin", it is better. I also wonder if we can add "current" in it?
2. A slightly revised draft of commentary: I removed certain sentences (with tracking) to make the commentary more focused. For your reference

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Sunday, February 16, 2020 12:22 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Yes, it can be removed from the title. Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 12:21 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Thanks Lishan. The word of “origin” may be removed?

Shan-Lu Liu sent from iPhone

> On Feb 16, 2020, at 12:15 PM, Su, Lishan <lishan_su@med.unc.edu> wrote:
>
> As discussed, see the final version with revised title and the last sentence. best,
>
> -Lishan
>
> ---
>
> **From:** "Liu, Shan-Lu" <liu.6244@osu.edu>
> **Date:** Friday, February 14, 2020 at 7:07 PM
> **To:** "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
> **Subject:** Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission
>
> Agree. For this reason, I think the last sentence to be added will make this perfect point!
>
> SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Friday, February 14, 2020 at 7:02 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I actually am very concerned for the possibility of SARS-2 infection by lab people. It is much more contagious than SARS-1. Now every lab is interested in get a vial of virus to do drug discovery. This can potentially a big issue. I don't think most people have a clue.

I actually was IBC chair at UMMS which is the only university which can do live SARS, and my lab did live SARS work. How to manage such things is very tricky. Not just PPE, but the whole design and logic.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Friday, February 14, 2020 6:46 PM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Yes, he was infected in the lab!

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 14, 2020 at 6:39 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

We are on the same page. Our position on this bio safety ethic issue should be neutral. Your former colleague was infected with sars2 in the lab?

-Lishan
<Liu et al_EMI Commentary_15 references[1]-Final.docx>

From: Lu, Shan
To: Su, Lishan; Liu, Shan-Lu
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission
Date: Sunday, February 16, 2020 1:01:54 PM

Hi, Lishan

Your 2nd choice is very close to what I suggested, and I can go with the following:

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Sunday, February 16, 2020 12:58 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Either is fine, but first is preferred, short and clear.

SARS-CoV-2: no evidence of laboratory engineering
Or
No credible evidence supporting (claims of?) the laboratory engineering of SARS-CoV-2

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 12:53 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I am okay with the change for the title, but “claims” does not seem a good fit here –“evidence” is better I feel.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 12:51 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Thanks, then let's not having those two parts.

On the title, I do not need to use "current".

How about this:

No credible claims supporting the laboratory engineering of SARS-CoV-2

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 16, 2020 12:43 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Shan,

I agree to delete those two parts. One was added by me, based on Linda's email, and another was also by me, based on Ralph's comments.

I do not seem to prefer using "current", but I get your point - perhaps we can use "convincing"? "Credible" is not good for the title.

Thoughts?

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 12:30 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

See two attached documents:

1. Title of commentary: I agree that by removing "origin", it is better. I also wonder if we can add "current" in it?
2. A slightly revised draft of commentary: I removed certain sentences (with tracking) to make the commentary more focused. For your reference

Shan

From: Su, Lishan <lishan_su@med.unc.edu>

Sent: Sunday, February 16, 2020 12:22 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Yes, it can be removed from the title. Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 12:21 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Thanks Lishan. The word of "origin" may be removed?

Shan-Lu Liu sent from iPhone

> On Feb 16, 2020, at 12:15 PM, Su, Lishan <lishan_su@med.unc.edu> wrote:
>
> As discussed, see the final version with revised title and the last sentence. best,
>
> -Lishan
>
> ---
>
> **From:** "Liu, Shan-Lu" <liu.6244@osu.edu>
> **Date:** Friday, February 14, 2020 at 7:07 PM
> **To:** "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
> **Subject:** Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission
>
> Agree. For this reason, I think the last sentence to be added will make this perfect point!
>
> SL
>
> ---
>
> **From:** "Lu, Shan" <Shan.Lu@umassmed.edu>
> **Date:** Friday, February 14, 2020 at 7:02 PM

To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I actually am very concerned for the possibility of SARS-2 infection by lab people. It is much more contagious than SARS-1. Now every lab is interested in get a vial of virus to do drug discovery. This can potentially a big issue. I don't think most people have a clue.

I actually was IBC chair at UMMS which is the only university which can do live SARS, and my lab did live SARS work. How to manage such things is very tricky. Not just PPE, but the whole design and logic.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Friday, February 14, 2020 6:46 PM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Yes, he was infected in the lab!

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 14, 2020 at 6:39 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

We are on the same page. Our position on this bio safety ethic issue should be neutral. Your former colleague was infected with sars2 in the lab?

-Lishan
<Liu et al_EMI Commentary_15 references[1]-Final.docx>

No ~~credible~~ evidence supporting claims of the laborary engineering of SARS-CoV-2~~: no evidence of a laboratory origin~~

Shan-Lu Liu [1, 2,3,4], Linda J. Saif [4,5], Susan Weiss [6], and Lishan Su [7]

[1] Center for Retrovirus Research, The Ohio State University,
Columbus, OH 43210, USA

[2] Department of Veterinary Biosciences, The Ohio State University, Columbus,
OH 43210, USA

[3] Department of Microbial Infection and Immunity, The Ohio State University,
Columbus, OH 43210, USA

[4] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,
The Ohio State University, Columbus, OH 43210, USA

[5] Food Animal Health Research Program,
Ohio Agricultural Research and Development Center, CFAES
Department of Veterinary Preventive Medicine,
The Ohio State University, Wooster, Ohio 44691, USA

[6] Department of Microbiology, Perelman School of Medicine,
University of Pennsylvania, Philadelphia, Pennsylvania, USA

[7] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,
University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1-3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4,5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome~~; among these SNVs, 200 were in the coding sequences, and among the 128 nonsynonymous mutations, 89 led to predicted radical amino acid changes~~ [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted

pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to

use human ACE2 as a receptor for entry into human cells [10,11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6,12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that

could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5,14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus. ~~Finally, we note that the synthetic and chimeric panels of bat and SARS-like CoV led to the identification of remdesivir as a broad-spectrum inhibitor of all group 2b SARS-like coronaviruses tested in vitro or in vivo [15], providing critical pre-clinical data that has led to the ongoing clinical trials in China and is critical for the future development of universal vaccines for all the SARS-like coronaviruses.~~

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 ~~expert~~ virologist Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random [15]~~(Gao et al., EMI paper 2/12/2020 in press)~~. Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Commented [LS1]: Emerging Microbes & Infections, 9:1, 378-381, DOI: 10.1080/22221751.2020.1727299

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated

viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2. We should emphasize that, although SARS-CoV-2 shows no evidence of laboratory origin, such a virus, and closely related, do pose great public health threats and must be handled properly in the laboratory and also properly regulated by governments and scientific community.

References

1. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7.
2. Chang, Lin M, Wei L, et al. Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. JAMA. 2020 Feb 7.
3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Jan 30.
4. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Feb 3.
5. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Jan 24.
6. Song HD, Tu CC, Zhang GW, et al. Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci U S A. 2005 Feb 15;102(7):2430-5.
7. Menachery VD, Yount BL, Jr., Debbink K, et al. A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. Nat Med. 2015 Dec;21(12):1508-13.
8. Ge XY, Li JL, Yang XL, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature. 2013 Nov 28;503(7477):535-8.
9. Roberts A, Deming D, Paddock CD, et al. A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. PLoS Pathog. 2007 Jan;3(1):e5.
10. Li F, Li W, Farzan M, et al. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science. 2005 Sep 16;309(5742):1864-8.
11. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003 Nov 27;426(6965):450-4.
12. Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science. 2003 Oct 10;302(5643):276-8.
13. Demogines A, Farzan M, Sawyer SL. Evidence for ACE2-utilizing coronaviruses (CoVs) related to severe acute respiratory syndrome CoV in bats. J Virol. 2012 Jun;86(11):6350-3.
14. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Feb 3.
15. Xiao C, Li X, Liu S, et al. HIV-1 did not contribute to the 2019-nCoV genome. Emerg Microbes Infect. 2020 Dec;9(1):378-381.

From:	Su, Lishan
To:	Liu, Shan-Lu; Lu, Shan
Subject:	Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission
Date:	Sunday, February 16, 2020 2:14:58 PM
Attachments:	2019 CoV Copy-Converted.enl

No problem. Here is the updated endnote file, in endnote 9 format.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 1:40 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Sorry! I manually edited the reference 15 and just emailed out!

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Sunday, February 16, 2020 at 1:36 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I have added the Gao reference and formatted (I have fixed my endnote problem!). Do we need credible here in the title?

No ~~credible~~ evidence supporting claims of laboratory engineering of SARS-CoV-2.

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 1:12 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Ok, let do the 2nd one.

See attached, with Gao ref added for you to put into Endnote

From: Liu, Shan-Lu <liu.6244@osu.edu>

Sent: Sunday, February 16, 2020 1:07 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Second one reads better and is more accurate.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 1:04 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

For shorter, it will be what I suggested, let's put the two below:

No credible claims supporting the laboratory engineering of SARS-CoV-2

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 16, 2020 1:02 PM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I think either of these two should be fine, the shorter the better for a title. Title does not need to be exclusive.

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Sunday, February 16, 2020 at 12:58 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Either is fine, but first is preferred, short and clear.

SARS-CoV-2: no evidence of laboratory engineering
Or
No credible evidence supporting (claims of?) the laboratory engineering of SARS-CoV-2

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 12:53 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
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I am okay with the change for the title, but "claims" does not seem a good fit here –"evidence" is better I feel.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 12:51 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Thanks, then let's not having those two parts.

On the title, I do not need to use "current".

How about this:

No credible claims supporting the laboratory engineering of SARS-CoV-2

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
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Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Shan,

I agree to delete those two parts. One was added by me, based on Linda's email, and another was also by me, based on Ralph's comments.

I do not seem to prefer using "current", but I get your point - perhaps we can use "convincing"? "Credible" is not good for the title.

Thoughts?

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
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See two attached documents:

1. Title of commentary: I agree that by removing "origin", it is better. I also wonder if we can add "current" in it?
2. A slightly revised draft of commentary: I removed certain sentences (with tracking) to make the commentary more focused. For your reference

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From: Su, Lishan <lishan_su@med.unc.edu>
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Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Yes, it can be removed from the title. Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 12:21 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Thanks Lishan. The word of "origin" may be removed?

Shan-Lu Liu sent from iPhone

> On Feb 16, 2020, at 12:15 PM, Su, Lishan <lishan_su@med.unc.edu> wrote:
>
> As discussed, see the final version with revised title and the last sentence.
> best,

-Lishan

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Date: Friday, February 14, 2020 at 7:07 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Agree. For this reason, I think the last sentence to be added will make this perfect point!

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Friday, February 14, 2020 at 7:02 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I actually am very concerned for the possibility of SARS-2 infection by lab people. It is much more contagious than SARS-1. Now every lab is interested in get a vial of virus to do drug discovery. This can potentially a big issue. I don't think most people have a clue.

I actually was IBC chair at UMMS which is the only university which can do live SARS, and my lab did live SARS work. How to manage such things is very tricky. Not just PPE, but the whole design and logic.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Friday, February 14, 2020 6:46 PM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Yes, he was infected in the lab!

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 14, 2020 at 6:39 PM

To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

We are on the same page. Our position on this bio safety ethic issue should be neutral. Your former colleague was infected with sars2 in the lab?

-Lishan
<Liu et al_EMI Commentary_15 references[1]-Final.docx>

From: Lu, Shan
To: Su, Lishan; Liu, Shan-Lu
Subject: RE: EMI commentary
Date: Wednesday, February 12, 2020 7:25:14 PM
Attachments: image002.png
Liu et al_EMI Commentary_for submission_-0212B.docx

Sorry for slow reply as I have been super busy.

1. I don't have an opinion on who should be the first and who should be the last author. I think either one is fine. One technical consideration is that the last author may need to be the one to do online submission to EMI. At the stage of submission, only one corresponding author is allowed, but you can add back another corresponding author at the stage of Galley.
2. I definitely will not be an author as you guys did everything. It can also keep things somewhat independent as the editor. However (not in contrast), I appreciate your kind offer!
3. At this point, the draft is very good. I made two minor changes and inserted one question (see attached). Either way I am find so you can finalize.
4. No abstract for EMI commentary. Acknowledgement should be fine. If it may take more time to get everyone's grants etc. it is better not listing grants, but only thank people who had input. I am ok if you want to include me for "providing valuable discussion and reading" if you like, and other big name CoV people that SLL had contacted if justified.

Please feel free to move to submission at any time, and let me know if you need any help from EMI office.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Wednesday, February 12, 2020 7:03 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

Either is fine with me too. Let's Shan the editor decide:)

-Lishan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Wednesday, February 12, 2020 6:29:08 PM
To: Su, Lishan <lishan_su@med.unc.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

Hi Lishan:

See both versions attached, either way works for me. It's your call.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Wednesday, February 12, 2020 at 6:26 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

It is probably fine if we cover not only the unc chimeric virus now.

-Lishan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Wednesday, February 12, 2020 6:09:46 PM
To: Su, Lishan <lishan_su@med.unc.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

Lishan:

Now I understand your point of concern. I should be fine either way, as OSU should not care.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Wednesday, February 12, 2020 at 5:55 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

Current we are both senior and corresponding authors. I can be either. I am not sure the UNC affiliation should be listed first or not… let's think about this.

I agree Shan Lu should be a corresponding author too.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Wednesday, February 12, 2020 at 5:51 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>

Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

Hi Shan,

Sure, no problem. I think you deserve senior and corresponding authorship.

Shan did not respond today…

Best.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Wednesday, February 12, 2020 at 5:47 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

Shan-Lu:

Should we switch authorship order, with you first, me last?
I like the idea of adding more from our virology group, if Shan Lu/EMI can wait for the signing delay.

It looks great. I hope it will help to clarify some of the confusions.

Did Feng Gao address the “shuttle vector” sequence claim in his ms? It is very similar to the HIV insertion problem with such short alignments.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Wednesday, February 12, 2020 at 5:12 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>
Cc: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: EMI commentary

Hi Shan,

Attached please find the final version of the commentary for your consideration to be published at EMI.

Kindly advise.

Regards.

Shan-Lu

SARS-CoV-2: no evidence of a laboratory origin

Shan-Lu Liu [1, 2,3,4], Linda J. Saif [4,5], Susan Weiss [6], and Lishan Su [7]

[1] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[2] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[3] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

[4] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[5] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[6] Department of Microbiology, Perelman School of Medicine,

University of Pennsylvania, Philadelphia, Pennsylvania, USA

[7] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1, 2, 3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4, 5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding sequences, and among the 128 nonsynonymous mutations, 89 led to predicted radical amino-acid changes [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that

RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in ~~Chinese~~ social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated ~~to~~ so it can not replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10, 11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6, 12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-

director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5, 14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus. Finally, we note that the synthetic and chimeric panels of bat and SARS-like CoV led to the identification of remdesivir as a broad spectrum inhibitor of all group 2b SARS-like coronaviruses tested in vitro or in vivo [15, 16], providing critical pre-clinical data that has led to the ongoing clinical trials in China and is critical for the future development of universal vaccines for all the SARS-like coronaviruses.

Commented [LS1]: Is this section really needed here?

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 expert Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

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From:	Lu, Shan
To:	Liu, Shan-Lu; Su, Lishan
Subject:	RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission
Date:	Sunday, February 16, 2020 12:56:04 PM

Evidence is too big and vague. Claims are those out there and our commentary addressed these specific claims. So we can defend.

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 16, 2020 12:53 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I am okay with the change for the title, but "claims" does not seem a good fit here –"evidence" is better I feel.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 12:51 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Thanks, then let's not having those two parts.

On the title, I do not need to use "current".

How about this:

No credible claims supporting the laboratory engineering of SARS-CoV-2

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 16, 2020 12:43 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Shan,

I agree to delete those two parts. One was added by me, based on Linda's email, and another was also by me, based on Ralph's comments.

I do not seem to prefer using “current”, but I get your point - perhaps we can use “convincing”? “Credible” is not good for the title.

Thoughts?

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 12:30 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

See two attached documents:

1. Title of commentary: I agree that by removing “origin”, it is better. I also wonder if we can add “current” in it?
2. A slightly revised draft of commentary: I removed certain sentences (with tracking) to make the commentary more focused. For your reference

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Sunday, February 16, 2020 12:22 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Yes, it can be removed from the title. Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 12:21 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Thanks Lishan. The word of “origin” may be removed?

Shan-Lu Liu sent from iPhone

On Feb 16, 2020, at 12:15 PM, Su, Lishan <lishan_su@med.unc.edu> wrote:

As discussed, see the final version with revised title and the last sentence. best,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 14, 2020 at 7:07 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Agree. For this reason, I think the last sentence to be added will make this perfect point!

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Friday, February 14, 2020 at 7:02 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

I actually am very concerned for the possibility of SARS-2 infection by lab people. It is much more contagious than SARS-1. Now every lab is interested in get a vial of virus to do drug discovery. This can potentially a big issue. I don't think most people have a clue.

I actually was IBC chair at UMMS which is the only university which can do live SARS, and my lab did live SARS work. How to manage such things is very tricky. Not just PPE, but the whole design and logic.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Friday, February 14, 2020 6:46 PM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to

your submission

Yes, he was infected in the lab!

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 14, 2020 at 6:39 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

We are on the same page. Our position on this bio safety ethic issue should be neutral. Your former colleague was infected with sars2 in the lab?

-Lishan
<Liu et al_EMI Commentary_15 references[1]-Final.docx>

From:	Su, Lishan
To:	Liu, Shan-Lu; Lu, Shan
Subject:	Re: 2019-nCoV-EMI_commentary
Date:	Wednesday, February 12, 2020 12:58:49 AM
Attachments:	image001.png SHC014-MA15 v 2019 ncoV-SLL-sls-SLL-ref.docx

My endnote is not working with the word, even after loading the X9 verstion. I have put the references in the text. Could either of you format it with your endnote? Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 7:44 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Sounds good, thank you. I still like “however” over “In contrast” – it just reads better

Shan: Are you sure that you prefer not to be included in the coauthorship? Before I send, I think we should have the authorship listed, along with affiliations. Lishan should be the first author, unless he prefers otherwise. Agreed?

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 7:34 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

I made some minor change for the following:

In summary, there is no credible evidence at this point to support the claims that the 2019-nCoV was originated from a laboratory-engineered CoV. In contrast, we cannot rule out the possibility that 2019-nCoV is a recombinant generated in nature between a bat CoV and another coronavirus in an intermediate host. More studies are needed to explore this possibility and resolve the origin of 2019-nCoV.

Maybe now SLL can send the next version to other CoV experts?

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 5:47 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

See the new version with all incorporated.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 4:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I have made additional changes to the Lishan's version, see attached.

Lishan: I share your concern, and that is one reason that Shan, the editor, decides to have a short version.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 4:16 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

The new title is good if we will cover the RaTG13 and HIV insertion issues.
I am still worried if we can shed any light on the major claim of RaTG13 lab escape/evolution in other hosts/humans over the years…?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 3:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Perhaps Lishan can take a look at the latest version, which has the new title I suggested, and modify it as needed.
The last paragraph is also crucial, but I did not have time to work on it because of a meeting this morning.
Once we have almost a final draft, I will contact Linda Saif, Stanley Perlman, Thomas Gallgaher etc. to see if they are willing to join, but this may delay the publishing time.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 1:52 PM

To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I agree that it should be simple and clear. I have included some details in the 1st draft for your information. There is not intention to defend Baric, but to clarify the facts.

Regarding all three, are you combining Goa Feng's piece with this one? For the RaTG13, it involves complicated viral evolution kinetics and maybe hard to simply clarify…
Best,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 1:44 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Sorry here is the attachment with tracking

From: Lu, Shan
Sent: Tuesday, February 11, 2020 1:44 PM
To: 'Su, Lishan' <lishan_su@med.unc.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Hi, I am adding Shuying from my group. She just read the last draft from Lishan and identified a few errors (with tracking).

Also I just had a phone call with SSL and we agreed on the following:

1. We need to make this commentary very simple and short;
2. It is better not going to too much science/tech details as it can only confuse people and provide more room for people to raise more questions;
3. We don't want to appear that we are defending Ralph even though he did nothing wrong.
4. We feel it is best to cover 3 issues in this commentary (for the above reason, plus it is more powerful to cover multiple issues in one summary)
5. ??

SLL: please add anything I missed.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 12:52 PM

To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Looking at Shanlu's version, we may need a separate for the RaTG13 vs lab accident theory...

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 12:44 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

Thanks.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210

Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Tentative Title: Is 2019-nCoV laboratory origin?

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1000 as of Feb. 10, 2020. A novel human coronavirus, 2019-nCoV, was quickly identified, and the associated disease is now referred to as novel coronavirus pneumonia (NCP) or coronavirus disease discovered in 2019 (COVID-19).

According to what has been reported (Wang, D. *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* (2020), Chen, N. *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* (2020). Chang *et al.* Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. *JAMA* (2020).), NCP seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The 2019-nCoV genome sequence also has ~80% identity with SARS-CoV, but is most similar to some bat beta-coronaviruses, with the highest being >96% identity (Zhu, N. *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* (2020); Zhou, P. *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* (2020)).

Currently, there are speculations or rumors that the 2019-CoV is of a laboratory origin. First, certain people suspected that the 2019-nCoV is directly leaked from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the 2019-nCoV (Zhou, P. et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature (2020)). However, as we now know, the SARS-

CoV and palm civets CoV shared 99.8% homology, which is only about 60 nt. Given that there are greater than 1000 nt differences between 2019-nCoV and RaTG13 (Zhou, P. *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* (2020).), it is highly unlikely RaTG13 is the immediate source of 2019-nCoV; this is particularly true in light of the low mutation rate of the coronaviruses. An intermediate host between bats and humans is likely involved.

Another claim points to a Nature Medicine paper published in 2015 (Menachery, V.D. et al. A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. Nat Med 21, 1508-1513 (2015), which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014, Ge, X.Y. et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 503, 535-538 (2013)) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells. However, this claim lacks any scientific basis and must be discounted.

The recombinant mouse-adapted SARS virus (MA15) (PLoS Pathog. 2007 Jan;3(1):e5) was generated by serial passages of an infectious SARS CoV clone in the respiratory tract of BALB/c mice. After 15 rounds of passage in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was not able to use human ACE2 as a receptor for entry (Li, W. et al.

Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426, 450-454 (2003);Li, F., Li, W., Farzan, M. & Harrison, S.C. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science 309, 1864-1868 (2005)). Civets were proposed to be an intermediate host of the bat-CoVs before they spread to humans. However, several novel bat coronaviruses were isolated from Chinese horseshoe bats in 2013 and the bat SARS-like (SL)-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry (Ge, X.Y. et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 503, 535-538 (2013)). Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as human ACE2 gene for interaction with SARS CoV (Demogines, A., Farzan, M. & Sawyer, S.L. Evidence for ACE2-utilizing coronaviruses (CoVs) related to severe acute respiratory syndrome CoV in bats. J Virol 86, 6350-6353 (2012)), it was proposed that intermediate hosts may not be necessary and that some bat SL-CoVs may directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-SHC014 was used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus can indeed efficiently use human ACE2 and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-MA15 can replicate efficiently in the mouse lung, leading to severe pathogenesis (Nat Med 21, 1508-1513 (2015)).

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014-MA15 chimeric virus were considered as gain of function (GOF) studies and briefly paused by the US government. The NCP epidemic has restarted the debate over the risks constructing such viruses with pandemic potentials.

Regardless, upon careful phylogenetic analyses by multiple international groups (Wu, A. et al. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. Cell Host Microbe (2020); Emerg Microbes Infect 9, 313-319 (2020); Zhu, N. et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med (2020)), the 2019-nCoV is unmistakably distinct from SARS-like viruses including SHC014-MA15, with >5000 nt differences across the whole genome. Therefore, there is NO credible evidence to support the claim that the 2019-nCoV is derived from the chimeric SHC014-MA15 virus.

There are also rumors that the 2019-nCoV is artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv, claiming that 2019-nCoV has HIV sequence in it and thus likely generated in the laboratory. A rebuttal paper led by HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the 2019-nCoV is not HIV-1 specific but random (EMI paper 2/12/2020). Because of the many concerns raised by the international community, the authors who made the initial claim have recently decided to withdraw this report.

In summary, we believe that there is no concrete evidence to support the claims that the 2019-nCoV was originated from a laboratory-engineered CoV. However, we cannot rule out the possibility that 2019-nCoV is a recombinant generated in nature between a bat CoV and another coronavirus in humans or an intermediate host. More studies are needed to explore this possibility and resolve the origin of 2019-nCoV.

From: Lu, Shan
To: temi-peerreview@journals.tandf.co.uk; TEMI-production@journals.tandf.co.uk
Cc: lshan_su@med.unc.edu; Editorial Office; Liu, Shan-Lu
Subject: RE: Urgent: revised commentary for Emerging Microbes & Infections - TEMI-2020-0121
Date: Sunday, February 16, 2020 8:13:40 PM
Attachments: image002.png
Liu et al_EMI Commentary_Revision_Final.docx

Dear Jorgie,

I believe the accepted version of TEMI-2020-0121 is already being sent to production, right? If not, then replace it with the one attached (just sent from Dr Shan-Lu Liu (not me) If it has been sent to production, then I will write below to Malathi

Dear Malathi,

If this paper is already in production, please see if you can replace the original version with the attached version If it is too late, the authors can make the change at the galley proofs step Just to make sure that this paper should be treated as very urgent (the fast track)

Thanks

Shan

From: Liu, Shan-Lu <liu 6244@osu edu>
Sent: Sunday, February 16, 2020 8 00 PM
To: temi-peerreview@journals tandf co uk
Cc: Lu, Shan <Shan Lu@umassmed edu>; lishan_su@med unc edu
Subject: Re: Urgent: revised commentary for Emerging Microbes & Infections - TEMI-2020-0121

Here is the attachment, sorry!

_____

Dear Jorgie,

After discussing with Dr. Shan Lu and all coauthors, we have decided to use a new title and also make minor changes to the text, including asscіated references. I have attached the updated commentary and hope that you will be able to help upload the new version for preparing the proof.

Thank you!

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M D , Ph D
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu 6244@osu edu; shan-lu liu@osumc edu

From: "temi-peerreview@journals.tandf.co.uk" <temi-peerreview@journals.tandf.co.uk>
Date: Thursday, February 13, 2020 at 9:14 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: "shan lu@umassmed edu" <shan lu@umassmed edu>, "lishan_su@med unc edu" <lishan_su@med unc edu>
Subject: Re: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission #TrackingId:5633996

Dear Professor Liu,

Thank you very much for sending his file.

Kindly be informed that I have now uploaded in he system on your behalf and proceeded your paper to the editor.

Please let me know if you have further questions or concerns.

Kind regards,

Jorgie Lyn Luna - Journal Editorial Office
Taylor & Francis Group
4 Park Square | Milton Park | Abingdon | Oxon | OX14 4RN UK
Web: www.tandfonline.com

Emerging Microbes & Infections

From:liu.6244@osu.edu
Sent:
To:liu.6244@osu.edu

Cc: Shan.Lu@umassmed.edu,lishan_su@med.unc.edu
Subject: Re: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Hi Jorgie:

I have modified as instructed and attached the new one to this email. Please help upload and proceed.

Thank you.

Shan-Lu

Shan-Lu Liu, M D., Ph D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu 6244@osu edu; shan-lu liu@osumc.edu

On 2/13/20, 8:43 AM, "Emerging Microbes and Infections" <onbehalfof@manuscriptcentral.com> wrote:

13-Feb-2020

Dear Professor Liu,

Your above referenced manuscript, entitled "SARS-CoV-2: no evidence of a laboratory origin" requires some further changes before it is ready for reviewing in Emerging Microbes & Infections. Your submission has been returned to you and is located in your Author Center as a draft, so that you due to these reasons:

1. No line numbering

Kindly add a line numbering in your main document.

2. Exceeded reference count

Kindly be informed that the reference count for the commentary article should not be more than 15.

Your submission along with all files you submitted is now in your Author Center, at https://urldefense.com/v3/__https://mc.manuscriptcentral.com/temi__!!KGKeukY!nGv1RgRJ1P-OGXuZi8b2hKGjXxDFOmBwDONuR_njCdwERJF1HkBIV4Sggqr9udyWYml$ Please read the Quick Guide to Continuing your Submission, which shows how you can access your manuscript, and submit it back to the site. The Guide is located at https://urldefense.com/v3/__http://mc.manuscriptcentral.com/societyimages/tandf_qs0/Continuning*20a*20Submission_screenshot.pdf__JSU!KGKeukY!nGv1RgRJ1P-OGXuZi8b2hKGjXxDFOmBwDONuR_njCdwERJF1HkBIV4Sggqr9re6Z8tA$

You may contact the Editorial Office if you have further questions.

Sincerely,

Jorgie Lyn Luna
Emerging Microbes & Infections Editorial Office
temi-peerreview@journals.tandf.co.uk

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Shan-Lu Liu [1, 2,3,4], Linda J. Saif [4,5], Susan Weiss [6], and Lishan Su [7]

[1] Center for Retrovirus Research, The Ohio State University,
Columbus, OH 43210, USA

[2] Department of Veterinary Biosciences, The Ohio State University, Columbus,
OH 43210, USA

[3] Department of Microbial Infection and Immunity, The Ohio State University,
Columbus, OH 43210, USA

[4] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,
The Ohio State University, Columbus, OH 43210, USA

[5] Food Animal Health Research Program,
Ohio Agricultural Research and Development Center, CFAES
Department of Veterinary Preventive Medicine,
The Ohio State University, Wooster, Ohio 44691, USA

[6] Department of Microbiology, Perelman School of Medicine,
University of Pennsylvania, Philadelphia, Pennsylvania, USA

[7] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,
University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1-3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4,5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural

evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10,11]. Civets were proposed

to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6,12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already

exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5,14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 virologist Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random [15]. Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2. We should emphasize that, although SARS-CoV-2 shows no evidence of laboratory origin, viruses

with such great public health threats must be handled properly in the laboratory and also properly regulated by the scientific community and governments.

References

1. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7.
2. Chang, Lin M, Wei L, et al. Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. JAMA. 2020 Feb 7.
3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Jan 30.
4. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Feb 3.
5. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Jan 24.
6. Song HD, Tu CC, Zhang GW, et al. Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci U S A. 2005 Feb 15;102(7):2430-5.
7. Menachery VD, Yount BL, Jr., Debbink K, et al. A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. Nat Med. 2015 Dec;21(12):1508-13.
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10. Li F, Li W, Farzan M, et al. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science. 2005 Sep 16;309(5742):1864-8.
11. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003 Nov 27;426(6965):450-4.
12. Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science. 2003 Oct 10;302(5643):276-8.
13. Demogines A, Farzan M, Sawyer SL. Evidence for ACE2-utilizing coronaviruses (CoVs) related to severe acute respiratory syndrome CoV in bats. J Virol. 2012 Jun;86(11):6350-3.
14. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Feb 3.
15. Xiao C, Li X, Liu S, et al. HIV-1 did not contribute to the 2019-nCoV genome. Emerg Microbes Infect. 2020 Dec;9(1):378-381.

From: Su, Lishan
To: Liu, Shan-Lu; Lu, Shan
Subject: Re: 2019-nCoV-EMI_commentary
Date: Tuesday, February 11, 2020 5:49:01 PM
Attachments: image001.png
SHC014-MA15 v 2019 ncoV-SLL-sls.docx

See the new version with all incorporated.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 4:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I have made additional changes to the Lishan's version, see attached.

Lishan: I share your concern, and that is one reason that Shan, the editor, decides to have a short version.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 4:16 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

The new title is good if we will cover the RaTG13 and HIV insertion issues.
I am still worried if we can shed any light on the major claim of RaTG13 lab escape/evolution in other hosts/humans over the years…?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 3:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Perhaps Lishan can take a look at the latest version, which has the new title I suggested, and modify it as needed.
The last paragraph is also crucial, but I did not have time to work on it because of a meeting this morning.
Once we have almost a final draft, I will contact Linda Saif, Stanley Perlman, Thomas Gallgaher etc. to see if they are willing to join, but this may delay the publishing time.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 1:52 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I agree that it should be simple and clear. I have included some details in the 1st draft for your information. There is not intention to defend Baric, but to clarify the facts.

Regarding all three, are you combining Goa Feng's piece with this one? For the RaTG13, it involves complicated viral evolution kinetics and maybe hard to simply clarify…
Best,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 1:44 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Sorry here is the attachment with tracking

From: Lu, Shan
Sent: Tuesday, February 11, 2020 1:44 PM
To: 'Su, Lishan' <lishan_su@med.unc.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Hi, I am adding Shuying from my group. She just read the last draft from Lishan and identified a few errors (with tracking).

Also I just had a phone call with SSL and we agreed on the following:

1. We need to make this commentary very simple and short;
2. It is better not going to too much science/tech details as it can only confuse people and provide more room for people to raise more questions;
3. We don't want to appear that we are defending Ralph even though he did nothing wrong.
4. We feel it is best to cover 3 issues in this commentary (for the above reason, plus it is more powerful to cover multiple issues in one summary)
5. ??

SLL: please add anything I missed.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 12:52 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Looking at Shanlu's version, we may need a separate for the RaTG13 vs lab accident theory...

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 12:44 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

Thanks.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor

Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Tentative Title: Is 2019-nCoV laboratory origin ~~of laboratory~~?

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1000 as of Feb. 10, 2020. A novel human coronavirus, 2019-nCoV, was quickly identified, and the associated disease is now referred to as novel coronavirus pneumonia (NCP) or coronavirus disease identified 2019 (COVID-19).

According to what has been reported (Lancet, NEJM 2020), NCP seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The 2019-nCoV genome sequence also has ~80% identity with SARS-CoV, but most similar to some bat beta-coronaviruses, with the highest being >96% identity.

Currently, there are speculations or rumors that the 2019-CoV is of a laboratory origin. First, certain people suspected that the 2019-nCoV is directly leaked from a laboratory in Wuhan as a bat CoV (RaTG13) was recently reported by that laboratory and it shared ~96% homology with the 2019-nCoV (Nature, 2020). However, as we now know, the SARS-CoV and palm civets CoV shared 99.8% homology, which is only about 60 nt. Given that there are greater than 1000 nt differences between 2019-nCoV and RaTG13, it is highly unlikely RaTG13 is the immediate source of 2019-nCoV; this is particular true in light of the low mutation rate of the coronaviruses. Searching for an immediate host between bat and humans is needed.

Another claim points to a Nature Medicine paper published in 2015, which reports the construction of a chimeric CoV with a bat CoV S gene

(SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells. However, this claim lacks any scientific basis and must be discounted.

The recombinant mouse-adapted SARS virus (MA15) (PLoS Pathog. 2007 Jan;3(1):e5) was generated by serial passages of an infectious SARS CoV clone in the respiratory tract of BALB/c mice. After 15 rounds of passage in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was not able to use human ACE2 as a receptor for entry. Civets were proposed to be an intermediate host of the bat-CoVs before they spread to humans (SARS-CoV review?). However, several novel bat coronaviruses were isolated from Chinese horseshoe bats in 2013 and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry (Nature 2013). Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as human ACE2 gene for interaction with SARS CoV (JVI 2012), it was proposed that intermediate hosts may not be necessary and some bat SL-CoVs may directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-SHC014 was used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus can efficiently use human ACE2 and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV.

Importantly, SHC014-MA15 can replicate efficiently in the mouse lung, leading to severe pathogenesis (Nat. Med. 2015).

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies under the US government-mandated pause. ~~No more bat CoV-MA15 chimeric viruses are constructed after the SHC014 MA15 chimeric virus.~~ The NCP epidemic has restarted the debate over the risks constructing such viruses with pandemic potential. Regarding its lineage relationship with 2019 nCoV, however, after careful phylogenetic analyses by multiple international groups (EMI, Nature…2020), the 2019 nCoV is unmistakably distinct from SHC014- MA15 with >5000 nt differences in their genomes. There is NO credible evidence to support the claim that the 2019 nCoV was derived from the chimeric SHC014-MA15 virus.

There are also rumors that the 2019-nCoV is artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv, claiming that 2019-nCoV has HIV sequence in it and thus likely generated in the laboratory. A rebuttal paper led by HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the 2019-nCoV is not HIV-1 specific but random (EMI paper 2/12/2020). Because of the many concerns raised by the international community, the authors who made the initial claim have recently decided to withdraw this report.

In summary, there is no evidence to support the claims that the 2019 nCoV was originated from a laboratory engineered CoV. Phylogenetic analyses of all reported CoV genomes by multiple international groups support the conclusion that 2019 nCoV is a novel virus……?

From: Su, Lishan
To: Liu, Shan-Lu
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)
Date: Friday, February 21, 2020 5:35:47 PM
Attachments: image001.png
TEMI_A_1733440 Proof-Su.pdf

Done, and waiting to be submitted after hearing from Linda.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 3:07 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Lishan,

Do you have the corrected proof? Thanks for doing this. I am almost done with the meeting.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 11:52 AM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

I agree with you on these points, but NIH/government at the time put it as a gof study relative to the original S antigen…

-Lishan

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Friday, February 21, 2020 at 2:51 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Is the adaptation of MA15 to mice considered “gain of function”- that selected virus is more virulent than SHC014-MA15 chimeric virus? Seems to me like more loss of function relative to MA15 when inserting the bat derived spike. MA15 with the urbani spike is like de- adapting the virus to mice.

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 1:40 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

I have noticed that too, probably happened when we tried to simplify the chimeric virus paragraph, and I think Ralph had added the attenuation sentence relative to M15 in mice…

What was reported in the NM paper was that the SHC014-rMA15 chimeric virus was less pathogenic than M15, but more so than the chimeric M15 virus with the original Urbani Spike-gene in M15, probably due to one of the 6 mutations in the M15 S gene.

See old sentence:
Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the original human Urbani S-MA15 chimeric virus in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies…

I will try to fix this.
Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 12:14 PM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Cc: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Lishan: see below comments from Susan.

Susan: thank you. I had the same question before – Lishan, could you explain this?

Shan-Lu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Friday, February 21, 2020 at 9:06 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: Your article proofs for review (ID# TEMI 1733440)

Please list me as Susan R Weiss (with the “R”). there are too many other Susan Weiss’

I noticed what looks like a contradictory statement in the paper- sorry I missed it before- I highlighted in yellow lines 124-133. The first part says chimeric virus is attenuated producing less antigen than MA15 but the next part says it has elevated activity- this seems contradictory

I remain concerned about the insertion of the furin site

Susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 10:05 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: [External] Re: Your article proofs for review (ID# TEMI 1733440)

We agreed to add this link to the proof to the third paragraph regarding RaTG13.

The Proximal Origin of SARS-CoV-2
http://virological.org/t/the-proximal-origin-of-sars-cov-2/398

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: Shan-Lu Liu <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 4:46 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, Susan Weiss <weisssr@pennmedicine.upenn.edu>
Subject: FW: Your article proofs for review (ID# TEMI 1733440)

All,

See message below and also the attached proof.

Please mark your changes in the attached PDF file, and Lishan and I will incorporate to finalize.

Thanks.

Shan-Lu

From: "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
Reply-To: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Date: Friday, February 21, 2020 at 4:13 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Your article proofs for review (ID# TEMI 1733440)

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear Shan-Lu Liu,

Your article proofs are now available for review through the Central Article Tracking System (CATS) at: https://cats.informa.com/PTS/in?ut=B2AB6692AA414D96905B59E6C51FA240 .

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1. Click on 'Review Proofs'.

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3. Follow the guidance on the proof cover sheet to return your corrections. Please limit changes to answering any author queries and to correcting errors. We would not expect to receive more than 30 corrections.

Please check your proofs thoroughly before submitting your corrections as once they have been submitted we are unable to accept further corrections. If you have any queries, please email me.

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• The DOI of your paper is: 10.1080/22221751.2020.1733440. Once your article has published online, it will be available at the following permanent link:
https://doi.org/10.1080/22221751.2020.1733440 .

Thank you,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

TEMI1733440 VOL 0, ISS 0

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Shan-Lu Liu, Linda J. Saif, Susan Weiss, and Lishan Su

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The title and author names are listed on this sheet as they will be published, both on your paper and on the Table of Contents. Please review and ensure the information is correct and advise us if any changes need to be made. In addition, please review your paper as a whole for typographical and essential corrections.

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The CrossRef database (www.crossref.org/) has been used to validate the references. Changes resulting from mismatches are tracked in red font.

AUTHOR QUERIES

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Emerging Microbes & Infections
https://doi.org/10.1080/22221751.2020.1733440

COMMENTARY

OPEN ACCESS Check for updates

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Q1 Shan-Lu Liu[a,b,c,d], Linda J. Saif[d,e], Susan Weiss [f] and Lishan Su[g]

[a]Center for Retrovirus Research, The Ohio State University, Columbus, OH, USA; [b]Department of Veterinary Biosciences, The Ohio State University, Columbus, OH, USA; [c]Department of Microbial Infection and Immunity, The Ohio State University, Columbus, OH, USA; [d]Viruses and Emerging Pathogens Program, Infectious Diseases Institute, The Ohio State University, Columbus, OH, USA; [e]Food Animal Health Research Program, Ohio Agricultural Research and Development Center, CFAES, Department of Veterinary Preventive Medicine, The Ohio State University, Wooster, OH, USA; [f]Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [g]Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

ARTICLE HISTORY Received 13 February 2020; Accepted 13 February 2020

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1–3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4,5].

Currently, there are speculations, rumours and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10,11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6,12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe

CONTACT Shan Lu Liu lsu@med.unc.edu; Lishan Su Liu.6244@osu.edu

bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titres as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5,14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus.

There are also rumours that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 virologist Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random [15]. Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2. We should emphasize that, although SARS-CoV-2 shows no evidence of laboratory origin, viruses with such great public health threats must be handled properly in the laboratory and also properly regulated by the scientific community and governments.

Disclosure statement

No potential conflict of interest was reported by the author(s). Q2

ORCID

Susan Weiss http://orcid.org/0000 0002 8155 4528

References Q3

[1] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus infected pneumonia in Wuhan, China. JAMA. 2020 Feb 7. Q4

[2] Chang LM, Wei L, et al. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. JAMA. 2020 Feb 7. Q5

[3] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Jan 30. Q6

[4] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Feb 3. Q7

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SARS coronavirus. Nature. 2003 Nov 27;426 (6965):450 454.
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[14] Wu F, Zhao S, Yu B, et al. A new coronavirus associ ated with human respiratory disease in China. Nature. 2020 Feb 3.
[15] Xiao C, Li X, Liu S, et al. HIV 1 did not contribute to the 2019 nCoV genome. Emerg Microbes Infect. 2020 Dec;9(1):378 381.

Q9

From: Yost, Mary
To: Liu, Shan-Lu
Subject: Re: Final version of the letter: "COVID-19 and The Virus That Causes It" - OSU
Date: Wednesday, March 25, 2020 1:37:17 PM
Attachments: image001.png
image002.png
image003.png

Shan-Lu,

We are planning to run this in Thursday's paper. Thanks for working with us on it.

Mary

Mary Yost
Editorial Page Editor
Columbus Dispatch
62 E. Broad St.
Columbus, OH 43215
614-461-5040 (office)
614-204-6798 (cell)
myost@dispatch.com

On Tue, Mar 24, 2020 at 12:19 AM Liu, Shan-Lu <liu.6244@osu.edu> wrote:

> Dear Mary,
>
> I have modified the letter by following your instructions. First, I changed the author number to one. Second, I shortened the letter and now its length is ~700 words. Third, I revised the letter by removing “facts” but adding more opinions.
>
> I hope the letter is now acceptable for publication in Columbus Dispatch. Kindly note that the disclaimer in the end is important so please make sure to keep it.
>
> Thank you so much for your help with this effort.
>
> Shan-Lu
>
> THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.

Professor

Co-Director, Viruses and Emerging Pathogens Program

Infectious Diseases Institute

Center for Retrovirus Research

Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology

The Ohio State University

1900 Coffey Rd, Room 480 VMAB

Columbus, Ohio 43210

Phone: (614) 292-8690

Fax: (614) 292-6473

Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Yost, Mary" <myost@dispatch.com>
Date: Monday, March 23, 2020 at 7:38 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: Encarnacion Pyle <epyle@dispatch.com>
Subject: Re: Greetings and inquiry: COIVD-19 commentary

Thank you, but I am not sure it would be suitable for our opinion pages. I encourage you to work with our news side, since it sounds like you are wanting to convey facts, not commentary.

And no, we would not run it with three authors. In cases where multiple individuals want to be credited, we have advised that the others be noted in the body of the article, but that also takes space away from the content you want to present.

We do a weekly review of pending op-eds on Friday afternoons and can let you know after our review if we will publish your submission. The news side could probably share your

information sooner than we can on our opinion pages, even if we are able to publish it.

Mary

Mary Yost

Editorial Page Editor

Columbus Dispatch

62 E. Broad St.

Columbus, OH 43215

614-461-5040 (office)

614-204-6798 (cell)

myost@dispatch.com

On Mon, Mar 23, 2020 at 5:13 PM Liu, Shan-Lu <liu.6244@osu.edu> wrote:

> Hi Mary,
>
> Thank you for your consideration.
>
> Over the last few weeks, I kept receiving requests from people, including local fire departments regarding how this virus is spread and causes the disease, etc. This really motivated me to write something with some updated information that I thought would be helpful to our readers.
>
> Yes, we can cut down to 700 words, with no problem, but I would still prefer to have three authors, because all are co-directors of the OSU program and we have contributed equally.

Thank you so much, and let me know how to proceed.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.

Professor

Co-Director, Viruses and Emerging Pathogens Program

Infectious Diseases Institute

Center for Retrovirus Research

Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology

The Ohio State University

1900 Coffey Rd, Room 480 VMAB

Columbus, Ohio 43210

Phone: (614) 292-8690

Fax: (614) 292-6473

Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Yost, Mary" <myost@dispatch.com>
Date: Monday, March 23, 2020 at 4:56 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: Encarnacion Pyle <epyle@dispatch.com>
Subject: Re: Greetings and inquiry: COIVD-19 commentary

Hi Shan-Lu,

Thank you for offering to send us an op-ed, but it might be better if you could share your expertise with our news side.

As you can imagine, we continue to receive a lot of guest columns around the topic of coronavirus and its impact on all facets of life today. One of the challenges we have with the opinion pages is limited space, just two pages each day, without a lot of flexibility in how we fill our space.

It sounds like the kind of information you have to share is more factual than opinion, which might be better suited for news coverage that doesn't have the space restrictions we do.

A couple of other concerns -- we typically don't run guest columns from more than one author; and our usual length is about 700 words. We made an exception for a guest column that will appear in Tuesday's paper, but that is very rare. I don't know if 700 words would be enough to cover all that you have to share.

I am copying one of our metro editors, Encartia Pyle, in case you would be interested in following up with a news reporter to share your insights.

Thank you for thinking of The Dispatch; and thank you for what you are doing related to the coronavirus.

Mary

Mary Yost

Editorial Page Editor

Columbus Dispatch

62 E. Broad St.

Columbus, OH 43215

614-461-5040 (office)

614-204-6798 (cell)

myost@dispatch.com

On Sat, Mar 21, 2020 at 9:12 PM Liu, Shan-Lu <liu.6244@osu.edu> wrote:

> Dear Alan,
>
> Greetings! Hope this email finds you well.
>
> I am not sure if you are the right person to contact, but please forgive me and help make the connection to the Dispatch.
>
> In 2016 when I joined OSU, Emily Tate wrote a story on me about the Zika virus, see attached article. Now COIVD-19 is here, and as co-director of the OSU Viruses and Emerging Pathogens program, my colleagues Linda Saif, Jacob Yount and I have written a commentary on COIVD-19, which we wish to publish in the Dispatch as commentary or other forms. Our focus is on the virus, SARS-CoV-2, which causes the outbreak and the disease COIVD-19.
>
> The motivation is that I recently have received a lot of requests from local media and even fire department for interview, and I thought that this commentary may be able to address some of the reader's questions.
>
> See below some of my writings published in journals:
>
> https://www.nature.com/articles/d41586-020-00135-z
>
> **New virus in China requires international control effort**
>
> **Emerging Viruses without Borders: The Wuhan Coronavirus**

https://www.mdpi.com/1999-4915/12/2/130

https://www.tandfonline.com/doi/full/10.1080/22221751.2020.1733440

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

SARS-CoV-2 is an appropriate name for the new coronavirus

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30557-2/fulltext

Thank you for your consideration. If your newspaper is interested, please let me know and I will send the article to you shortly.

Sincerely,

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.

Professor

Co-Director, Viruses and Emerging Pathogens Program

Infectious Diseases Institute

Center for Retrovirus Research

Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology

The Ohio State University

1900 Coffey Rd, Room 480 VMAB

Columbus, Ohio 43210

Phone: (614) 292-8690

Fax: (614) 292-6473

Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

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This message may contain confidential and/or privileged information. If you are not the intended recipient or authorized to receive this for the intended recipient, you must not use, copy, disclose or take any action based on this message or any information herein. If you have received this message in error, please advise the sender immediately by sending a reply e-mail and delete this message. Thank you for your cooperation.

From: Savo R
To: Liu, Shan-Lu; lsu@med.unc.edu
Subject: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2
Date: Friday, April 10, 2020 1:41:59 AM

Hello,

What you forget to mention in your review is that four leading scientists have shown both HIV mutations in the genome. Being 100-1000 more infectious then SARS makes no sense on evolution mutations.

And also confirming studies showing HIV drugs are helping in the recovery from COVID-19.

Bob

From: Taylor & Francis
To: Liu, Shan-Lu
Subject: Taylor & Francis author update: access to your article published in an issue of Emerging Microbes & Infections
Date: Thursday, February 27, 2020 12:45:34 AM

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Author Services | **FAQ** | **Twitter** | **Facebook**

Dear author,

Your Open Access article, No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2, published in Emerging Microbes & Infections, Volume 9 Issue 1, is now available to access via tandfonline.com.

Share your article now
You'll hopefully want to share your article with friends or colleagues (and

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then check its downloads, citations and Altmetric data on **Authored Works**, our dedicated center for all Taylor & Francis published authors). Publishing Open Access means your article can be read by anyone, anywhere, and we want to work with you to ensure it reaches as wide (and as appropriate) an audience as possible.

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If you haven't yet registered, you can do so using liu.6244@osu.edu (this is the email you used whilst your manuscript was going through production).

Once you've completed the quick registration you'll be sent an email asking you to confirm. Click on the verification link and you can then login (using the above email address) whenever you want to by going to **Taylor & Francis Online**. Once you have logged in, click on "**Your Account**" at the top of the page to see the latest updates on your article.

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Kind regards,

Stewart Gardiner
Global Production Director, Journals
Taylor & Francis Group

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From: Lu, Shan
To: Su, Lishan; Liu, Shan-Lu
Subject: RE: Revised commentary for EMI - final!
Date: Monday, February 17, 2020 6:08:08 PM

I think each paper has its own focus, like now is very good. Our commentary is directly addressing two particular claims and it did well.

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Monday, February 17, 2020 6:05 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Revised commentary for EMI - final!

I agree with them completely. Based on Shi's two natures papers and the Baric Nature medicine paper, I was trying to make the point as this paper: that the new virus from bats could have jumped into a secondary host or directly to humans and evolve. One of you did not seem to like the direct human possibility and removed it.

Theories of SARS-CoV-2 origins

It is improbable that SARS-CoV-2 emerged through laboratory manipulation of an existing SARS-related coronavirus. As noted above, the RBD of SARS-CoV-2 is optimized for human ACE2 receptor binding with an efficient binding solution different to that which would have been predicted. Further, if genetic manipulation had been performed, one would expect that one of the several reverse genetic systems available for betacoronaviruses would have been used. However, this is not the case as the genetic data shows that SARS-CoV-2 is not derived from any previously used virus backbone[17]. Instead, we propose two scenarios that can plausibly explain the origin of SARS-CoV-2: (i) natural selection in a non-human animal host prior to zoonotic transfer, and (ii) natural selection in humans following zoonotic transfer.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Monday, February 17, 2020 at 5:56 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Revised commentary for EMI - final!

This is the website that people deposit their sequence data and also make relevant comments. Not sure where they will publish it… but it has been widely spread via Twitter.

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Monday, February 17, 2020 at 5:44 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>

Subject: RE: Revised commentary for EMI - final!

Who is first is not critical. But where did you find this new paper? Published?

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Monday, February 17, 2020 5:42 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Revised commentary for EMI - final!

Again, I have no concern at all with our conclusion in the commentary. I believe more scientific articles like this will be out, and EMI will be one of the first to publish them.

Cheers!

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Monday, February 17, 2020 at 5:36 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Revised commentary for EMI - final!

Agreed. Beautifully written.

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Monday, February 17, 2020 5:35 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Revised commentary for EMI - final!

I just carefully read through, very informative and convincing in my view. Those are of course true experts of evolutionary biologists.

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Monday, February 17, 2020 at 5:27 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Revised commentary for EMI - final!

This still has nothing to do with any of the specific claims.

From: Liu, Shan-Lu <liu.6244@osu.edu>

Sent: Monday, February 17, 2020 5:26 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Revised commentary for EMI - final!

The last section is to dispute those rumors.

Theories of SARS-CoV-2 origins

It is improbable that SARS-CoV-2 emerged through laboratory manipulation of an existing SARS-related coronavirus. As noted above, the RBD of SARS-CoV-2 is optimized for human ACE2 receptor binding with an efficient binding solution different to that which would have been predicted. Further, if genetic manipulation had been performed, one would expect that one of the several reverse genetic systems available for betacoronaviruses would have been used. However, this is not the case as the genetic data shows that SARS-CoV-2 is not derived from any previously used virus backbone[17]. Instead, we propose two scenarios that can plausibly explain the origin of SARS-CoV-2: (i) natural selection in a non-human animal host prior to zoonotic transfer, and (ii) natural selection in humans following zoonotic transfer. We also discuss whether selection during passage in culture could have given rise to the same observed features.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Monday, February 17, 2020 at 5:23 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Revised commentary for EMI - final!

Two different things. They are doing SARS2 genome analysis. Your is trying to disapprove the other theories.

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Monday, February 17, 2020 5:17 PM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Revised commentary for EMI - final!

…SARS-CoV-2 is the seventh member of the *Coronaviridae* known to infect humans. Three of these viruses, SARS CoV-1, MERS, and SARS-CoV-2, can cause severe disease; four, HKU1, NL63, OC43 and 229E, are associated with mild respiratory symptoms. Herein, we review what can be deduced about the origin and early evolution of SARS-CoV-2 from the comparative analysis of available genome sequence data. In particular, we offer a perspective on the notable features in the SARS-CoV-2 genome and discuss scenarios by which these features could have arisen. Importantly, this analysis provides evidence that SARS-CoV-2 is not a laboratory construct nor a purposefully manipulated virus.
…

We need to try to get ours out quickly.

SL

From: Lu, Shan
To: Liu, Shan-Lu; Su, Lishan
Subject: RE: 2019-nCoV-EMI_commentary
Date: Tuesday, February 11, 2020 12:46:02 PM
Attachments: image002.png
EMI commentary-20200211_c.docx

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

See my suggested changes.

Thanks.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Title:

Is 2019-nCoV a laboratory origin?

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1000 as of Feb. xx, 2020. A novel human coronavirus, 2019-nCoV, was quickly identified, and the associated disease is now referred to as novel coronavirus pneumonia (NCP).

According to what has been reported in the literature (refs), clinical manifestations of NCP resemble that of severe acute respiratory syndrome (SARS) caused by SARS-CoV. However, the 2019-nCoV genome has only ~80% identity in sequence with SARS-CoV, indicating a quite different beta-coronavirus.

This led to speculations and rumors that the 2019-CoV is of a laboratory origin. First, certain people suspected that the 2019-nCoV is directly leaked from a laboratory in Wuhan as a bat CoV (RaTG13) was recently reported by that laboratory and it shared ~96% homology with the 2019-nCoV (Nature, 2020). However, as we now know, the SARS-CoV and palm civets CoV shared 99.8% homology, which is only about 60 nt. On the other hand, there are greater than 1000 nt differences between 2019-nCoV and RaTG13, suggesting RaTG13 is not the immediate source of 2019-nCoV given the large size genome like beta-coronaviruses (~30 kb) and the slow the mutation rate of the coronaviruses. Searching for an immediate host between bat and humans is needed.

Second, we provide a summary of evidence that supports the conclusion that the 2019-nCoV is not from the chimeric coronavirus (SHC014-rMA15), nor the original bat virus RaTG13 (refs). One particular claim points to a Nature Medicine paper published in 2015, which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS-CoV that has adapted to infect mice (rMA15) and is capable of infecting humans.

Let us first explain how a recombinant mouse-adapted SARS virus (rMA15) was generated. After constructing a full-length infectious SARS-CoV using reverse genetics, Dr. Ralph Baric's lab showed that it replicated in older mice, with low or no pathogenicity They then adapted the SARS-CoV (Urbani strain) by serial passages in the respiratory tract of BALB/c mice. After 15 rounds of passage in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding mutations associated with mouse adaptation. When introduced into the original recombinant SARS-CoV, these six mutations (only one in the S gene) conferred the high virulence and lethality (rMA15). Although not reported in human cells, it is likely that rMA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

It is also important to know how the chimeric SHC014-rMA15 virus was constructed and what key findings were made using this virus. When the SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike its human or civet counterparts, was unable to use the human ACE2 as a receptor for entry. Civets were proposed to be an immediate host before the bat-CoV spreads to humans. However, novel bat coronaviruses were isolated from Chinese horseshoe bats in 2013 and the bat SL-CoV-WIV1 used ACE2 from humans, civets and Chinese horseshoe bats for entry. Based on the evolutionary evidence that the bat ACE2 gene has been positively selected at the same interface as the human ACE2 gene for interacting with SARS-CoV, it was proposed that an intermediate host may not be

necessary for some bat CoVs to directly infect humans. To directly address this possibility, the S gene of the bat coronavirus WIV1-SHC014 was used to generate a chimeric virus in the mouse adapted rMA15 SARS-CoV backbone. The resultant SHC014-rMA15 virus can efficiently use ACE2 from multiple species and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-rMA15 can replicate efficiently in the mouse lung with severe pathogenesis. These findings provide compelling evidence that some bat CoVs can directly use human ACE2 to infect human hosts.

Due to the elevated pathogenic activity of the SHC014-rMA15 chimeric virus relative to the Urbani Spike-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies under the US government-mandated pause (the ban was implemented in 2013/2014 but lifted by NIH in 2017). No more bat-CoV-M15 chimeric viruses have been constructed thereafter the SHC014-rMA15 chimeric virus. The NCP epidemic has triggered a new debate on whether or not it is worth the risks of constructing such viruses with possible pandemic potential (refs), which is not unexpected. However, with careful and in-depth phylogenetic analyses by multiple international groups, the 2019-nCoV is unmistakably, and fortunately, distinct from SHC014- MA15. (we need a good summary here, one, two, three…). Therefore, there is NO credible evidence to support the claim that the 2019 ncoV/NCP virus was derived for the chimeric SHC014- MA15 virus.

Commented [LS1]: necessary?

There are also rumors that the 2019-nCoV is artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv, claiming that 2019-nCoV has HIV sequence in it and thus likely generated in the laboratory. A rebuttal paper led by HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertion into the 2019-nCoV is not HIV-1 specific but random. In addition, the four inserts cannot be held together based on structure modeling as initially claimed (EMI paper 2/12/2020). At the same time, the authors who made the initial claim has withdrawn their report.

From:	vinu arumugham
To:	tiziano.dallavilla@assomagi.org; pietro.chiurazzi@unicatt.it; tommaso.beccari@unipg.it; elisabetta.albi@unipg.it; lucilla.parnetti@unipg.it; silvia.paciotti@unipg.it; stefano.paolacci@assomagi.org; zhng@umich.edu; phao@ips.ac.cn; zhongwu@bmi.ac.cn; lsu@med.unc.edu; Liu, Shan-Lu; kristian@andersen-lab.com; trevor@bedford.io; wil2001@columbia.edu; stanley-perlman@uiowa.edu; jwleduc@utmb.edu; alr2105@columbia.edu; dirk.pfeiffer@cityu.edu.hk
Subject:	Your wrong analysis leads to the wrong conclusion of SARS-CoV-2 origin
Date:	Saturday, May 16, 2020 6:55:41 PM

All,

Regarding the articles:

Bioinformatic analysis indicates that SARS-CoV-2 is unrelated to known artificial coronaviruses.

www.ncbi.nlm.nih.gov/pubmed/32373995

and

Protein Structure and Sequence Reanalysis of 2019-nCoV Genome Refutes Snakes as Its Intermediate Host and the Unique Similarity between Its Spike Protein Insertions and HIV-1

https://pubs.acs.org/doi/10.1021/acs.jproteome.0c00129

You are investigating the wrong problem.

You missed two fundamental facts:

1. The Wuhan lab was transfecting HEK cells with HIV derived plasmids during SLCoV experiments. THIS CHANGES EVERYTHING.

2. You are ASSUMING that RaTG13 is a wild virus. It was "isolated" in 2013 but only sequenced AFTER the COVID-19 outbreak. Why?

You should smell a rat in the RaTG13.

The HIV-1 inserts in SARS-CoV-2 came from HIV derived plasmids. UNINTENTIONAL infection (due to contamination) of HEK cells with SLCoV, resulted in recombination with HIV-1 to produce SARS-Cov-2. All this happened in a BSL2 lab because they were supposed to be pseudovirus experiments. No bioweapon. No gene jockey needed. No GOF needed. Just plain HUMAN STUPIDITY explains everything.

Root cause of COVID-19? Biotechnology's dirty secret: Contamination. Bioinformatics evidence demonstrates that SARS-CoV-2 was created in a laboratory, unlikely to be a bioweapon but most likely a result of sloppy experiments
https://doi.org/10.5281/zenodo.3766462

See Prof. Petrovsky's description below and replace "random mutation" with "HIV-1 recombinations in HEK":

www.scimex.org/newsfeed/expert-reaction-did-covid-19-come-from-a-lab-in-wuhan

https://twitter.com/ArumughamVinu/status/1259208074444734464?s=20

No "intermediate host" was needed because the virus grown in HEK cells was ready for human infection, right out of the lab.

We need to SHUT ALL YOUR LABS DOWN, before you WIPE OUT HUMANITY WITH SUCH STUPIDITY.

Thanks,

Vinu

From: Lu, Shan
To: Su, Lishan; Liu, Shan-Lu
Subject: RE: 2019-nCoV-EMI_commentary
Date: Tuesday, February 11, 2020 1:46:23 PM
Attachments: image001.png
SHC014-MA15 v 2019 ncoVa.docx

Sorry here is the attachment with tracking

From: Lu, Shan
Sent: Tuesday, February 11, 2020 1:44 PM
To: 'Su, Lishan' <lishan_su@med.unc.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Hi, I am adding Shuying from my group. She just read the last draft from Lishan and identified a few errors (with tracking).

Also I just had a phone call with SSL and we agreed on the following:

1. We need to make this commentary very simple and short;
2. It is better not going to too much science/tech details as it can only confuse people and provide more room for people to raise more questions;
3. We don't want to appear that we are defending Ralph even though he did nothing wrong.
4. We feel it is best to cover 3 issues in this commentary (for the above reason, plus it is more powerful to cover multiple issues in one summary)
5. ??

SLL: please add anything I missed.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 12:52 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Looking at Shanlu's version, we may need a separate for the RaTG13 vs lab accident theory...

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 12:44 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

Thanks.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Tentative Title: The mouse adapted SARS chimeric virus with bat-coV S gene (SHC014-MA15) is not related to the NCP ncoV or 2019 nco-V

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1000 as of Feb. 10, 2020. A novel human coronavirus, 2019-nCoV, was quickly identified, and the associated disease is now referred to as novel coronavirus pneumonia (NCP).

According to what has been reported (Lancet, NEJM 2020), NCP seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The 2019-nCoV genome sequence also has ~80% identity with SARS-CoV, but most similar to some bat beta-coronaviruses, with the highest reaching >96% identity. Currently, there are speculations or rumors that the 2019-CoV is of a laboratory origin. One particular claim points to a Nature Medicine paper published in 2015, which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (rMA15) and is capable of infecting human cells. Here, we provide evidence that this claim lacks of scientific basis and must be discounted.

First, we will explain how the recombinant mouse-adapted SARS virus (rMA15) was generated (PLoS Pathog. 2007 Jan;3(1):e5). After constructing a full-length infectious SARS coV by reverse genetics, Dr. Ralph Baric's lab showed that it replicated in old mice with low or no pathogenic activity. They then adapted the SARS-CoV (Urbani strain) by serial passages in the respiratory tract of BALB/c mice. After 15 rounds of passage in mice, the SARS coV gained elevated replication and lung

Commented [SL1]: Specify Urbani strain here?

pathogenesis in aged mice (hence M15), due to six coding mutations associated with mouse adaptation. When introduced into the original recombinant SARS-CoV, these six mutations (only one in the S gene) conferred the high virulence and lethality (rMA15). Although not reported in human cells, it is likely that rMA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

Second, it is important to clarify how the chimeric SHC014-~~ǂ~~MA15 virus was constructed and what key findings were made using that virus. When the SARS coV was isolated, it was concluded that the S gene from bat-derived coV, unlike that from human patients- or civets-derived viruses, was not able to use human ACE2 as a receptor for entry. Civets were proposed as the secondary host for the bat-coV before spreading to humans. However, novel bat coronaviruses were isolated from Chinese horseshoe bats in 2013 and the bat SL-CoV-WIV1 used ACE2 from humans, civets and Chinese horseshoe bats for entry (Nature 2013). Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as human ACE2 gene for interaction with SARS coV (JVI 2012), it was proposed that intermediate hosts may not be necessary and some bat SL-CoVs may directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-~~WIV1~~-SHC014 was used to generate a chimeric virus in the mouse adapted ~~ǂ~~MA15 SARS-CoV backbone. The resultant SHC014-~~ǂ~~MA15 virus can efficiently use ACE2 from multiple species and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-~~ǂ~~MA15 can replicate efficiently in the mouse lung with severe pathogenesis (Nat. Med. 2015). These findings have provided strong evidence that some bat CoVs can directly use human ACE2 to infect human hosts.

Commented [SL2]: In the paper , they use SHC014-MA15

Commented [SL3]: SHC014 and WIVI are two different bat Cov, with some sequence difference in S domain

Due to the elevated pathogenic activity of the SHC014-~~r~~MA15 chimeric virus relative to the Urbani Spike-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies under the US government-mandated pause. No more bat-coV-MA15 chimeric viruses are constructed after the SHC014- MA15 chimeric virus. The NCP epidemic has restarted the debate over the risks constructing such viruses with pandemic potential. Regarding its lineage relationship with 2019 nCoV, however, after careful phylogenetic analyses by multiple international groups (EMI, Nature…2020), the 2019 ncoV/NCP virus is unmistakably, and fortunately, distinct from SHC014-MA15. There is NO credible evidence to support the claim that the 2019 ncoV/NCP virus was derived for the chimeric SHC014- MA15 virus.

From: Lu, Shan
To: Liu, Shan-Lu; Su, Lishan
Subject: RE: Executive summary of EMI commentary
Date: Sunday, February 23, 2020 1:15:50 PM
Attachments: image001.png
Liu et al_EMI Commentary_Revision_中文-Shan Lu.docx

Overall they are very good.

I found one minor error: "Dec" was used for the last reference of your paper. It should be "Feb". You may want to change the current word and pdf, but not change the real paper to be published as it may take a lot of more time to current and reload to online. Readers can find that paper without much problem.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 23, 2020 12:57 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Executive summary of EMI commentary

See my final versions of two files, Word and PDF.

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 23, 2020 at 12:51 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Executive summary of EMI commentary

Your school's email screening system is good! Thanks.

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 23, 2020 12:49 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Executive summary of EMI commentary

Never, just received Shan's email and file! Slow on my end.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 23, 2020 at 12:48 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Executive summary of EMI commentary

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Shan

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Date: Friday, February 21, 2020 at 7:39 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

-Lishan

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THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
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Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology

The Ohio State University
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Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

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Subject: Fwd: Submitted Corrections for article TEMI 1733440

Shan-Lu Liu sent from iPhone

Begin forwarded message:

> **From:** "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
> **Date:** February 21, 2020 at 4:04:41 PM PST
> **To:** "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>, "Liu, Shan-Lu" <liu.6244@osu.edu>
> **Subject: Submitted Corrections for article TEMI 1733440**
> **Reply-To:** TEMI-production@journals.tandf.co.uk
>
> Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2
>
> Journal: *Emerging Microbes & Infections* (TEMI)
>
> Article ID: TEMI 1733440
>
> Dear author,
>
> This email confirms that you have submitted your corrections to your article proofs.
>
> The submitted corrections have been successfully uploaded.
>
> If you want to check your submitted corrections please log into CATS and click on the “Corrections Submitted” button.
>
> Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

没有可信的证据支持 SARS-CoV-2 来自实验室人工合成

Shan-Lu Liu （刘善虑）, 俄亥俄州立大学

Linda J. Saif, 俄亥俄州立大学

Susan Weiss, 宾夕法尼亚大学

Lishan Su,（苏立山） 北卡大学教堂山分校

截止 2020 年 2 月 10 日，在武汉出现和爆发的急性呼吸疾病已波及 4 万多人，导致 1000 多人死亡。研究人员很快找到了一种新型人的冠状病毒，称之为 2019 nCoV 或 SARS-CoV-2，而相应的疾病称之为 COVID-19，意为 2019 年发生的冠状病毒疾病 (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/)。

据现有的报道[1-3]，COVID-2019 与 SARS-CoV 导致的 SARS 有很多相似的临床表现。而 SARS-CoV-2 基因组序列也和 2003 年 SARS-CoV 有 80%同源性，但它与一些蝙蝠的乙型冠状病毒更为相似。当前，种种的推测、谣言和阴谋论到处流行，其中有的认为 SARS-CoV-2 来源于实验室基因工程制造。也有某些人声称，人的 SARS-CoV-2 是从武汉的某个实验室直接泄漏出来的， 其根据是该实验室最近报道了一种称为 RaTG13 的蝙蝠冠状病毒，它和 SARS-CoV-2 基因组序列有高达 96%的同源性。

然而，我们知道，2003 年发现人 SARS 冠状病毒和其中间宿主果子狸 SARS 样冠状病毒具有 99.8％的同源性，在整个基因组中只有 202 个碱基不同。鉴于人类新型 SARS-CoV-2 与蝙蝠 RaTG13-CoV 之间有超过了 1000 个不同碱基[4]，且这些差异是按照冠状病毒典型的进化特征按自然发生的模式分布在整个基因组中，我们认为 SARS-CoV-2 直接来源于 RaTG13 冠状病毒的可能性极小。更为重要的是，在新的人 SARS-CoV-2 病毒基因组序列中并没有任何可信的基因工程改造的迹象，这都揭示 SARS-CoV-2 是通过自然演化而来的。我们认为在蝙蝠与人类之间可以找到中间动物宿主含有类似的冠状病毒，它与 SARS-CoV-2 更相似。最近有消息称穿山甲可能携带与 SARS-CoV-2 密切相关的冠

状病毒，但论文和数据尚未正式发表，无从得以证实(https://www.nature.com/articles/d41586-020-00364-2)。

最近社交媒体上的另一种说法指向2015年在《自然医学》发表的一篇论文[7]。该论文报道了在小鼠适应后的人类SARS冠状病毒（MA15病毒）中，人工构建了带有蝙蝠冠状病毒（SHC014）S基因，这种合成的嵌合冠状病毒，不仅可以可以感染小鼠，也能够感染来源人的细胞[8]。然而，新型冠状病毒SARS-CoV-2与这个嵌合冠状病毒基因组序列有超过了5,000个碱基的不同，所以这种怀疑完全缺乏任何科学依据。

现在我们来理一理来人SARS病毒老鼠适应株MA15和它的衍生病毒的来龙去脉。适应小鼠的SARS病毒（MA15）[9]是通过把SARS冠状病毒在小白鼠呼吸道中连续传代15后产生的；适应后的SARS冠状病毒有六个氨基酸突变，使其能够更有效地感染小鼠，尤其是在老年小鼠中具有了更高的复制活性和肺部致病性能（因此称为M15）。由于在小鼠内适应的遗传突变，MA15在人细胞或者人体内感染很可能降低了。

科学家曾认为从蝙蝠身来的冠状病毒的S基因和人的SARS病毒不同，推测它们无法使用人的SARS病毒受体ACE2进入人体细胞[10, 11]；后来发现果子狸是蝙蝠冠状病毒传给人的中间宿主，能够将SARS冠状病毒传播给人类[6, 12]。然而，2013年以来，科学家陆续从中国马蹄蝠中分离到了数个新型蝙蝠冠状病毒，这些来自蝙蝠的，类似人SARS冠状病毒（SL-CoV-WIV1）能够使用人、果子狸和中国马蹄蝠的ACE2受体进入和感染细胞[8]。进化研究表明，在SARS冠状病毒S蛋白的作用接触位点上，蝙蝠ACE2基因在与人类ACE2基因在相同的位点上同样被进化选择[13]。基于这样的发现，科学家提出了蝙蝠的SARS样冠状病毒具有直接传染到人的能力，不必需要中间宿主环节；也就是说有些蝙蝠冠状病毒有可能直接感染人类宿主细胞。为了直接验证这种可能性，蝙蝠冠状病毒SL-SHC014的S基因被人工嫁接到了MA15 SARS-CoV骨架上，因此产生了一个嵌合病毒。此SL-SHC014-MA15嵌合病毒确实能够有效地利用人ACE2进入细胞，并在人的呼吸道实验细胞中有效复制。SL-SHC014-MA15也可以在小鼠的肺中高效复制，但与SARS MA15相比，感染减弱了，并且只会让老年小鼠致命[7]。

由于SL-SHC014-MA15嵌合病毒相对于另一个人SARS-S/MA15嵌合病毒在小鼠中具有更高的致病活性，这种嵌合冠状病毒的实验后来在美国政府的干预下被暂停(https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-

pause-gain-function-research)。虽然目前 这项禁令在美国已经被解除，但构建这种具有大流行病潜力的病毒是否是一种风险，在当前的COVID-2019流行的形势下又重新引发了讨论，成为热点话题。然而，经过多个国家科学家对病毒的分子进化分析[5，14]，SARS-CoV-2 无疑与 SL-SHC014-MA15 具有非常大的不同，整个基因组有大约 6,000 核苷酸的差异。因此，没有可信的证据支持 SARS-CoV-2 是源自 SL-SHC014-MA15 嵌合病毒的说法。

最近也有传言说，SARS-CoV-2 是实验室中有意人为制造的。其中发表在 BioRxiv（一个同行评审之前的手稿共享网站）的一份手稿中更是此传言的代表，它声称 SARS-CoV-2 中含有 HIV 序列，因此很可能是在实验室中产生的。文章在线后， 舆论哗然，世界各国的多个病毒学者纷纷反驳。 在 HIV-1 病毒专家高峰（Feng Gao）领衔领导的反驳论文中，他们使用了仔细的生物信息学分析来证明，指出最初声称的 SARS-CoV-2 有多个 HIV-1 插入片段并非 HIV-1 特有，而是完全随机的 [15]。由于国际社会提出的种种疑问，这篇手稿的作者已经撤回了该手稿， 不再要求发表。

从科学层面讲，进化是循序渐进的，并随着时间的推移进一步产生有利于病毒的突变，就像天然分离的病毒（如蝙蝠冠状病毒 RaTG13）基因组那样。 相反，人工合成的病毒基因组通常会使用已知的病毒骨架引入一些某些定向的变化。所以我们认为，目前没有可靠的证据支持 SARS-CoV-2 是来源于实验人工设计。 有一种可能不能排除， 就是 SARS-CoV-2 是一种蝙蝠冠状病毒与另一种冠状病毒之间进行了自然重组而产生的；但这种可能性需要更多的研究来证明，来回答 SARS-CoV-2 的自然起源问题。我们需要强调的是，尽管目前没有证据显示新型冠状病毒 SARS-CoV-2 来自实验室人工制造，但对公共健康有威胁的病毒都必须进行恰当的实验室管理，而且需要由科学界和政府合理监管。

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15. Xiao C, Li X, Liu S, et al. HIV-1 did not contribute to the 2019-nCoV genome. Emerg Microbes Infect. 2020 Dec;9(1):378-381.

From: Lu, Shan
To: Liu, Shan-Lu; Su, Lishan
Subject: RE: Executive summary of EMI commentary
Date: Sunday, February 23, 2020 1:40:03 PM
Attachments: image001.png

Perfect。No more changes

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 23, 2020 1:21 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Executive summary of EMI commentary

Now, the final versions, a total of 4 files - hopefully!

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 23, 2020 at 1:15 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Executive summary of EMI commentary

Overall they are very good.

I found one minor error: "Dec" was used for the last reference of your paper. It should be "Feb". You may want to change the current word and pdf, but not change the real paper to be published as it may take a lot of more time to current and reload to online. Readers can find that paper without much problem.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 23, 2020 12:57 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Executive summary of EMI commentary

See my final versions of two files, Word and PDF.

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 23, 2020 at 12:51 PM

To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
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Your school's email screening system is good! Thanks.

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Subject: Submitted Corrections for article TEMI 1733440
Reply-To: TEMI-production@journals.tandf.co.uk

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear author,

This email confirms that you have submitted your corrections to your article proofs.

The submitted corrections have been successfully uploaded.

If you want to check your submitted corrections please log into CATS and click on the “Corrections Submitted” button.

Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

From: Lu, Shan
To: Liu, Shan-Lu; Su, Lishan
Subject: RE: Executive summary of EMI commentary
Date: Sunday, February 23, 2020 12:48:16 PM
Attachments: image003.png
刘善虎苏立山等教授发文分析驳斥新冠病毒阴谋论-Shan Lu.docx

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Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 4:32 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

My bad. How do we fix it? send her a message?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 7:29 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

Lishan:

I just saw that you deleted nt for 1,100 – “nt” should be kept. Could you correct that?

Thanks.

SL

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University

1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 4:28 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

Thanks!

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 7:22 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, Susan Weiss <weisssr@pennmedicine.upenn.edu>
Subject: Fwd: Submitted Corrections for article TEMI 1733440

Shan-Lu Liu sent from iPhone

Begin forwarded message:

> **From:** "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
> **Date:** February 21, 2020 at 4:04:41 PM PST
> **To:** "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>, "Liu, Shan-Lu" <liu.6244@osu.edu>
> **Subject: Submitted Corrections for article TEMI 1733440**
> **Reply-To:** TEMI-production@journals.tandf.co.uk
>
> Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2
>
> Journal: *Emerging Microbes & Infections* (TEMI)
>
> Article ID: TEMI 1733440
>
> Dear author,
>
> This email confirms that you have submitted your corrections to your article proofs.

The submitted corrections have been successfully uploaded.

If you want to check your submitted corrections please log into CATS and click on the “Corrections Submitted” button.

Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论

俄亥俄州立大学教授**刘善虑**，北卡大学教堂山分校教授苏立山联名美国科学院院士 Linda J. Saif 以及美国微生物科学院院士 Susan Weiss，在 国际期刊 Emerging Microbes & Infections (EMI) (中文译名《新发微生物与感染》)发表题为“**没有可信的证据支持 SARS-CoV-2 来自实验室人工合成**”的评论文章，对最近广为流行的传言和阴谋论进行了分析和驳斥。

该文主要论点如下：

1. 新型冠状病毒 SARS-CoV-2 虽然与中国科学院武汉病毒所最近报道的一种称 为 RaTG13 的蝙蝠冠状病毒有高达 96%的同源性， 但两者仍然有超过 1，100 碱基的差别，而且在关键序列序列上有特征性的区别，因此两者是完全不同的冠状病毒。
2. 社交媒体指向 2015 年在《自然医学》一篇论文，认为新型冠状病毒是这篇文章报道的人 SARS 和蝙蝠冠状病毒（SHC014）的嵌合病毒的泄露。分析研究表明，新型冠状病毒 SARS-CoV-2 与这个嵌合冠状病毒在基因组序列上有超过了 5,000 个碱基的不同，所以这种怀疑完全缺乏任何科学依据。
3. 还有一种传言说 SARS-CoV-2 是实验室中有意人为制造的， 并以发表在 BioRxiv 上印度科学家的一份手稿中为依据，声称 SARS-CoV-2 中含有 HIV 序列。实际上这篇文章在线后， 舆论哗然，世界各国病毒学家也纷纷反驳。 在 HIV-1 专家高峰（Feng Gao）领衔领导发表在 EMI 的另一篇反驳论文中，作者使用了仔细的生物信息学分析来证明，指出最初声称的 SARS-CoV-2 有多个 HIV-1 插入片段并非 HIV-1 特有，而是完全随机的。由于国际社会提出的种种疑问，这篇手稿的作者已经撤回了该手稿， 目前~~不再要求~~没有发现再次发表。
4. 从科学层面讲，病毒进化是循序渐进的，并随着时间的推移进一步产生有利于病毒感染人的突变。相反， 人工合成的病毒基因组通常会使用已知的病毒骨架引入一些某些定向的变化。所以， 目前没有可靠的证据支持 SARS-CoV-2 是来源于实验人工设计。
5. 尽管目前没有证据显示新型冠状病毒 SARS-CoV-2 来自实验室人工制造，我们认为对公共健康有威胁的病毒都必须进行恰当的实验室管理，而且需要由科学界和政府合理监管。

From: Su, Lishan
To: Liu, Shan-Lu; Lu, Shan
Subject: Re: URGENT! Submitted Corrections for article TEMI 1733440 #TrackingId:5700591
Date: Monday, February 24, 2020 9:37:47 AM
Attachments: image001.png

Thanks!

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Monday, February 24, 2020 at 9:37 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: URGENT! Submitted Corrections for article TEMI 1733440 #TrackingId:5700591

Lishan:

This is referring to the proof that you missed the “nt” in the submitted proof

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Monday, February 24, 2020 at 9:33 AM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: URGENT! Submitted Corrections for article TEMI 1733440 #TrackingId:5700591

What is this about? I have not seen any other message.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Monday, February 24, 2020 at 8:29 AM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>
Cc: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: URGENT! Submitted Corrections for article TEMI 1733440 #TrackingId:5700591

It’s alright. Lishan did not realize that...
Shan-Lu Liu sent from iPhone

On Feb 24, 2020, at 7:21 AM, Lu, Shan <Shan.Lu@umassmed.edu> wrote:

Now you caused more delay….

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Monday, February 24, 2020 3:12 AM
To: TEMI-production@journals.tandf.co.uk
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: URGENT! Submitted Corrections for article TEMI 1733440 #TrackingId:5700591

Thank you!

SL

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Date: Monday, February 24, 2020 at 1:01 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: URGENT! Submitted Corrections for article TEMI 1733440 #TrackingId:5700591

Dear Shan-Lu Liu,

Thank you for the email. I have sent your additional correction to the team so that they will make the changes in the final PDF.

Have a great day!

Regards,

Malathi
Emerging Microbes & Infections

From:liu.6244@osu.edu
Sent:22-02-2020 06:24
To:malathi@novatechset.com
Cc:
Subject: Re: URGENT! Submitted Corrections for article TEMI 1733440

Dear Malathi Boopalan:

We have just uploaded a corrected proof online, but relegalized a small error: "1,100" should be read as "1,100 nt" – could you kindly help make the correction, or replace the uploaded file with the attached new one?

Thank you! Please confirm.

Shan-Lu Liu & Lishan Su

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Shan-Lu Liu sent from iPhone

> On Feb 21, 2020, at 4:04 PM, TEMI-production@journals.tandf.co.uk <cats@taylorandfrancis.com> wrote:
>
> Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear author,

This email confirms that you have submitted your corrections to your article proofs.

The submitted corrections have been successfully uploaded.

If you want to check your submitted corrections please log into CATS and click on the “Corrections Submitted” button.

Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

From: Su, Lishan
To: Lu, Shan; Liu, Shan-Lu
Subject: Re: 2019-nCoV-EMI_commentary
Date: Tuesday, February 11, 2020 3:39:31 PM
Attachments: image001.png
SHC014-MA15 v 2019 ncoVb.docx

I have inserted your paragraph at he beginning, or we can end with it.

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 2:03 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Sure, we are not saying we are trying to defend Ralph but just don't want to give others the wrong impression.

Feng Gao piece will be published tomorrow so we do not include any details this commentary. There is only one short paragraph at the end of our document to mention it briefly.

The RaTG13 topic can also be very simple. Please take a look at what we wrote below:

This led to speculations and rumors that the 2019-CoV is of a laboratory origin. First, certain people suspected that the 2019-nCoV is directly leaked from a laboratory in Wuhan as a bat CoV (RaTG13) was recently reported by that laboratory and it shared ~96% homology with the 2019-nCoV (Nature, 2020). However, as we now know, the SARS-CoV and palm civets CoV shared 99.8% homology, which is only about 60 nt. On the other hand, there are greater than 1000 nt differences between 2019-nCoV and RaTG13, suggesting RaTG13 is not the immediate source of 2019-nCoV given the large size genome like beta-coronaviruses (~30 kb) and the slow the mutation rate of the coronaviruses. Searching for an immediate host between bat and humans is needed.

My view is that as long as we compared the sequence difference (1000 nt) which is very different from that of SARS (60nt), it is quite clear. Most non-viral people do not understand what does 96% mean. We don't have to explain how long it will take to do the mutations because it will not cover other issues such as some recombination etc. We just say the difference between RaTG13 and 2019-nCoV is very big so they are not the same leaked from Wuhan Virology Lab.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 1:52 PM

To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I agree that it should be simple and clear. I have included some details in the 1st draft for your information. There is not intention to defend Baric, but to clarify the facts.

Regarding all three, are you combining Goa Feng's piece with this one? For the RaTG13, it involves complicated viral evolution kinetics and maybe hard to simply clarify…
Best,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 1:44 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Sorry here is the attachment with tracking

From: Lu, Shan
Sent: Tuesday, February 11, 2020 1:44 PM
To: 'Su, Lishan' <lishan_su@med.unc.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Hi, I am adding Shuying from my group. She just read the last draft from Lishan and identified a few errors (with tracking).

Also I just had a phone call with SSL and we agreed on the following:

1. We need to make this commentary very simple and short;
2. It is better not going to too much science/tech details as it can only confuse people and provide more room for people to raise more questions;
3. We don't want to appear that we are defending Ralph even though he did nothing wrong.
4. We feel it is best to cover 3 issues in this commentary (for the above reason, plus it is more powerful to cover multiple issues in one summary)
5. ??

SLL: please add anything I missed.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 12:52 PM

To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Looking at Shanlu's version, we may need a separate for the RaTG13 vs lab accident theory...

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 12:44 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

Thanks.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210

Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Tentative Title: The mouse adapted SARS chimeric virus with bat-coV S gene (SHC014-MA15) is not related to the NCP ncoV or 2019 nco-V

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1000 as of Feb. 10, 2020. A novel human coronavirus, 2019-nCoV, was quickly identified, and the associated disease is now referred to as novel coronavirus pneumonia (NCP).

According to what has been reported (Lancet, NEJM 2020), NCP seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The 2019-nCoV genome sequence also has ~80% identity with SARS-CoV, but most similar to some bat beta-coronaviruses, with the highest reaching >96% identity. Currently, there are speculations or rumors that the 2019-CoV is of a laboratory origin.

This led to speculations and rumors that the 2019-CoV is of a laboratory origin. First, certain people suspected that the 2019-nCoV is directly leaked from a laboratory in Wuhan as a bat CoV (RaTG13) was recently reported by that laboratory and it shared ~96% homology with the 2019-nCoV (Nature, 2020). However, as we now know, the SARS-CoV and palm civets CoV shared 99.8% homology, which is only about 60 nt. On the other hand, there are greater than 1000 nt differences between 2019-nCoV and RaTG13, suggesting RaTG13 is not the immediate source of 2019-nCoV given the large size genome like beta-coronaviruses (~30 kb) and the slow the mutation rate of the coronaviruses. Searching for an immediate host between bat and humans is needed.

~~One particular~~Another claim points to a Nature Medicine paper published in 2015, which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (rMA15) and is capable of infecting human cells. Here, we provide evidence that this claim lacks ~~of~~ any scientific basis and must be discounted.

~~First, we will explain how t~~The recombinant mouse-adapted SARS virus (~~r~~MA15) ~~was generated~~ (PLoS Pathog. 2007 Jan;3(1):e5)~~.~~ was generated ~~After constructing a full-length infectious~~ SARS coV ~~by reverse genetics, Dr. Ralph Baric's lab showed that it replicated in old mice with low or no pathogenic activity. They then adapted the SARS-CoV (Urbani strain)~~ by serial passages of an infectious SARS coV in the respiratory tract of BALB/c mice. After 15 rounds of passage in mice, the SARS coV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding mutations associated with mouse adaptation. ~~When introduced into the original recombinant SARS-CoV, these six mutations (only one in the S gene) conferred the high virulence and lethality (rMA15). Although not reported in human cells, i~~It is likely that ~~r~~MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

Commented [SL1]: Specify Urbani strain here?

~~Second, it is important to clarify how the chimeric~~ SHC014 ~~rMA15~~ ~~virus was constructed and what key findings were made using that virus.~~ When the SARS coV was isolated, it was concluded that the S gene from bat-derived coV, unlike that from human patients- or civets-derived viruses, was not able to use human ACE2 as a receptor for entry. Civets were proposed as the secondary host for the bat-coV before spreading to humans (SARS coV review?). However, several novel bat coronaviruses

Commented [SL2]: In the paper , they use SHC014-MA15

were isolated from Chinese horseshoe bats in 2013 and the bat SL-CoV-WIV1 used ACE2 from humans, civets and Chinese horseshoe bats for entry (Nature 2013). Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as human ACE2 gene for interaction with SARS coV (JVI 2012), it was proposed that intermediate hosts may not be necessary and some bat SARS-like or SL-CoVs may directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL- ~~WIV1~~ SHC014 was used to generate a chimeric virus in the mouse adapted ~~-~~ ~~r~~MA15 SARS-CoV backbone. The resultant SL-SHC014-~~r~~MA15 virus can efficiently use human ACE2 ~~from multiple species~~ and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-~~r~~MA15 can replicate efficiently in the mouse lung, leading to ~~with~~ severe pathogenesis (Nat. Med. 2015). ~~These findings have provided strong evidence that some bat CoVs can directly use human ACE2 to infect human hosts.~~

Commented [SL3]: SHC014 and WIVI are two different bat Cov, with some sequence difference in S domain

Due to the elevated pathogenic activity of the SHC014-~~r~~MA15 chimeric virus relative to the ~~Urbani Spike~~SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies under the US government-mandated pause. No more bat-coV-MA15 chimeric viruses are constructed after the SHC014-MA15 chimeric virus. The NCP epidemic has restarted the debate over the risks constructing such viruses with pandemic potential. Regarding its lineage relationship with 2019 nCoV, however, after careful phylogenetic analyses by multiple international groups (EMI, Nature…2020, a figure?), the 2019 ncoV/NCP virus is unmistakably, and fortunately, distinct from SHC014- MA15. There is NO credible evidence to support the claim that the 2019 ncoV/NCP virus was derived ~~for~~ from the chimeric SHC014-MA15 virus.

From: Su, Lishan
To: Lu, Shan; Liu, Shan-Lu
Subject: Re: Your article proofs for review (ID# TEMI 1733440)
Date: Friday, February 21, 2020 10:58:37 AM

I agree you are highly suspicious for this one…
I am finishing proofing and will finalize/upload it after considering comments from Susan, Linda and Shan-Lu.
Best,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Friday, February 21, 2020 at 10:36 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: RE: Your article proofs for review (ID# TEMI 1733440)

Yes, just a secret to you two and not share with others.
When I put a super fast review and accept (basically no review), the JEO of T&F, became very suspicious and wanted her boss to check and approve. She probably wonder if we are actually just one person with three fake names

Well, now you guys please coordinate the proof read and get input from Linda and Susan. Then submit it back asap (online, not by emails please). No need to go through me.

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Friday, February 21, 2020 10:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: Your article proofs for review (ID# TEMI 1733440)

Thanks for speeding it up, bro!

We are doing wonders as three confusing/confused musketeers of Shan-Lu, Shan Lu and Lishan Su:)

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Friday, February 21, 2020 at 7:43 AM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Your article proofs for review (ID# TEMI 1733440)

Only 1.5 days. Not 7 days. I feel better towards my brothers (sweating…).

Please go ahead to revise as you two see fit. Only make minimal changes.

Thanks.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Friday, February 21, 2020 7:42 AM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: FW: Your article proofs for review (ID# TEMI 1733440)

From: "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
Reply-To: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Date: Friday, February 21, 2020 at 4:13 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Your article proofs for review (ID# TEMI 1733440)

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear Shan-Lu Liu,

Your article proofs are now available for review through the Central Article Tracking System (CATS) at: https://cats.informa.com/PTS/in?ut=B2AB6692AA414D96905B59E6C51FA240 .

PLEASE NOTE: The CATS system only supports Internet Explorer 6 (and later), or Firefox 3 (and later) browser software. Popup blockers should be disabled. If you have any difficulty using CATS, please contact me.

• Your User Name is: [redacted]

• If you do not know your password, you may reset it here:
http://cats.informa.com/PTS/forgottenPassword.do

1. Click on 'Review Proofs'.

2. Select 'Download PDF'.

3. Follow the guidance on the proof cover sheet to return your corrections. Please limit changes to answering any author queries and to correcting errors. We would not expect to receive more than 30 corrections.

Please check your proofs thoroughly before submitting your corrections as once they have been submitted we are unable to accept further corrections. If you have any queries, please email me.

To avoid delaying publication of your article, please approve these proofs or return any corrections by 26 Feb 2020.

Reprint and issue orders may be placed by logging in to your CATS account and accessing the order form on the "Additional Actions" menu. If you have any questions on this process, please contact me or visit our author services site https://authorservices.taylorandfrancis.com/ordering-print-copies-of-your-article/

• The DOI of your paper is: 10.1080/22221751.2020.1733440. Once your article has published online, it will be available at the following permanent link: https://doi.org/10.1080/22221751.2020.1733440 .

Thank you,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

From: Emerging Microbes and Infections
To: Liu Shan-Lu
Subject: Emerging Microbes & Infections - Invitation to Review Manuscript ID TEMI-2020-0147
Date: Thursday, February 20, 2020 4:27:27 PM

20-Feb-2020
Dear Professor Shan-Lu Liu:

The above manuscript, entitled "The origin of the SARS-CoV-2 coronavirus: a rebuttal to the claim of formation via laboratory recombination" has been submitted to Emerging Microbes & Infections

I would be grateful if you would kindly agree to act as a reviewer for this paper The abstract appears at the end of this letter

(Dear Shan-Lu, since you are an expert in such rebuttals, I would appreciate if you can pick up some key issues and provide a simple and brief points It will be great if you can get back within the next 1-2 days)

Please let me know as soon as possible if you will be able to accept my invitation to review To do this please either click the appropriate link below to automatically register your reply with our online manuscript submission and review system, or e-mail me with your reply

*** PLEASE NOTE: This is a two-step process After clicking on the link, you will be directed to a webpage to confirm ***

Agreed: https://urldefense com/v3/__https://mc manuscriptcentral com/temi?URL_MASK=b79ab5b5cdaf479495e1618435a63e6f__!!KGKeukY!kROoa42fswQs64RsKKYPFDJBYPGTKTfeIEMcF_HEcTLK9iqdqnE7RQ_rCYDGQWDEow8$

Declined: https://urldefense com/v3/__https://mc manuscriptcentral com/temi?URL_MASK=1450a092f3254e64a53747db7513a0e2__!!KGKeukY!kROoa42fswQs64RsKKYPFDJBYPGTKTfeIEMcF_HEcTLK9iqdqnE7RQ_rCYDGJuqBBXI$

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Should you accept my invitation to review this manuscript, you will be sent an email with a direct link to the scoresheet, which will be made available to you You will then have access to the manuscript and reviewer instructions in your Reviewer Center

If you are unable to review the manuscript, click on the “decline” option to register your response This will direct you to a screen where you will be given the opportunity to provide details of any alternative reviewers

I realise that our expert reviewers greatly contribute to the high standards of the Journal, and I thank you for your present and/or future participation

Sincerely,
Professor Shan Lu
Emerging Microbes & Infections

MANUSCRIPT DETAILS

TITLE: The origin of the SARS-CoV-2 coronavirus: a rebuttal to the claim of formation via laboratory recombination

AUTHORS: Professor Wu Zhong

ABSTRACT:

From:	Su, Lishan
To:	Liu, Shan-Lu
Subject:	Re: Executive summary of EMI commentary
Date:	Sunday, February 23, 2020 12:02:06 PM
Attachments:	image001.png image002.png 刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论.pdf

---

See pdf file with no lines.
I can not find a better word than驳斥, but it seems to a be a bit stronger than we intended?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 23, 2020 at 8:57 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Executive summary of EMI commentary

Lishan and Shan – so confusing!

I have wrapped up a summary for the public and media to understand key points of our commentary. Please make suggestions.

I think this can go along with the Chinese translation.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 7:39 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
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Could you send me the PDF of the corrected one?

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
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Lishan:

I just saw that you deleted nt for 1,100 – “nt” should be kept. Could you correct that?

Thanks.

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THE OHIO STATE UNIVERSITY

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Professor
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Date: Friday, February 21, 2020 at 7:22 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, Susan Weiss <weisssr@pennmedicine.upenn.edu>
Subject: Fwd: Submitted Corrections for article TEMI 1733440

Shan-Lu Liu sent from iPhone

Begin forwarded message:

> **From:** "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
> **Date:** February 21, 2020 at 4:04:41 PM PST
> **To:** "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>, "Liu, Shan-Lu" <liu.6244@osu.edu>
> **Subject: Submitted Corrections for article TEMI 1733440**
> **Reply-To:** TEMI-production@journals.tandf.co.uk
>
> Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2
>
> Journal: *Emerging Microbes & Infections* (TEMI)
>
> Article ID: TEMI 1733440
>
> Dear author,
>
> This email confirms that you have submitted your corrections to your article

proofs.

The submitted corrections have been successfully uploaded.

If you want to check your submitted corrections please log into CATS and click on the “Corrections Submitted” button.

Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

刘善虑苏立山等教授发文分析认为新冠病毒阴谋论缺乏病毒学证据

俄亥俄州立大学教授刘善虑，北卡大学教堂山分校教授苏立山联名世界冠状病毒学专家 Linda J. Saif（美国科学院院士）以及 Susan Weiss（美国微生物科学院院士），在 国际期刊 Emerging Microbes & Infections (EMI) (中文译名《新发微生物与感染》)发表题为“**没有可信的证据支持 SARS-CoV-2 来自实验室人工合成**”的评论文章，对最近广为流行的传言和阴谋论进行了分析和驳斥。

该文主要论点如下：

1. 新型冠状病毒 SARS-CoV-2 虽然与中国科学院武汉病毒所最近报道的一种称 为 RaTG13 的蝙蝠冠状病毒有高达 96%的同源性， 但两者仍然有超过 1，100 碱基的差别，而且在关键序列序列上有特征性的区别，因此两者是完全不同的冠状病毒。
2. 社交媒体指向 2015 年在《自然医学》一篇论文，认为新型冠状病毒是这篇文章报道的人 SARS 和蝙蝠冠状病毒（SHC014）的嵌合病毒的泄露。分析研究表明，新型冠状病毒 SARS-CoV-2 与这个嵌合冠状病毒在基因组序列上有超过了 5,000 个碱基的不同，所以这种怀疑完全缺乏任何科学依据。
3. 还有一种传言说 SARS-CoV-2 是实验室中有意人为制造的， 并以发表在 BioRxiv 上印度科学家的一份手稿中为依据，声称 SARS-CoV-2 中含有 HIV 序列。实际上这篇文章在线后， 舆论哗然，世界各国病毒学家也纷纷反驳。 在 HIV-1 专家高峰（Feng Gao）领衔领导发表在 EMI 的反驳论文中，作者使用了仔细的生物信息学分析来证明，指出最初声称的 SARS-CoV-2 有多个 HIV-1 插入片段并非 HIV-1 特有，而是完全随机的。由于国际社会提出的种种疑问，这篇手稿的作者已经撤回了该手稿， 不再要求发表。
4. 从科学层面讲，进化是循序渐进的，并随着时间的推移进一步产生有利于病毒的突变。相反，人工合成的病毒基因组通常会使用已知的病毒骨架引入一些某些定向的变化。所以，目前没有可靠的证据支持 SARS-CoV-2 是来源于实验人工设计。
5. 尽管目前没有证据显示新型冠状病毒 SARS-CoV-2 来自实验室人工制造，我们认为对公共健康有威胁的病毒都必须进行恰当的实验室管理，而且需要由科学界和政府合理监管。

F om u Shan- u
To h h
Subje t Re Eme g ng M c bes & Infect ons - TEMI-20 0-0121 - changes qui ed o ou subm s ion
Date iday eb ua y 4 2020 6 13 2 M

I just finished reading Feng's paper – indeed ery good.

Small e ror noted in he f rst paragraph "Know ng he origin of such a pa hogen is critical to de elop ng means to blocking further transm ssion and to de elop accines". I saw this kind of error frequent for asian people but no big deal.

Feng Gao s my 师兄 in 北京的病毒所 we we e from the same lab where my former director has now been infec ed by SARS CoV 2! Ve y sad but he s doing OK!

Shan-Lu

From Lu, Shan Shan.Lu@umassmed.edu>
Date F iday, Feb ua y 14, 2020 at 5 10 PM
To Shan-Lu L u liu.6244@osu edu>, Su, Lishan l shan_su@med.unc.edu>
Sub ect RE Eme ging Mic obes & Infections - TEMI-2020 0121 - changes equi ed to you subm ssion

I don t have any objec ion. I see the point o add mo e cond tions to make su e the commen a y does not exclude ce tain a e o unusual s tua ions. At the same time, the mo e we t y to be comple e (o mo e like a lawye), it may gene ate mo e ques ions o even suppo t some people to say see these big name autho s also ag ee the e a e possib l ties of this and that… .

Th s is the same eason of t ying o be simple and focused o avoid cove ing compl cated ssues. I don t know how to solve this conflict between be ng tho ough and avoiding confus on. I will ok to take anything once you wo had ca eful thought.

At the same time, I w ll fo wa d to you the comment f om one Biotech ch ef afte I d st ibuted Feng Gao s pape th s mo ning. It was quite su p sing to me and it shows how d ve sity of the po ent al eade s. We can only t y to do ou best.

Shan

F om Liu, Shan-Lu l u 6244@osu.edu>
Sent F iday, Feb ua y 14, 2020 2 19 PM
To Su, L shan l shan_su@med.unc edu> Lu, Shan Shan.Lu@umassmed.edu>
Subject Re Eme g ng Mic obes & Infect ons - TEMI-2020 0121 - changes equi ed to you submiss on

L shan: ooks good o me.
Shan: what do you think?

Thanks.

From Su, L shan l h _ @ >
Date F iday, Feb ua y 14, 2020 at 1 34 PM
To Shan-Lu L u liu.6244@osu edu>, Lu, Shan shan.lu@umassmed.edu>
Sub ect Re Eme ging Mic obes & Infections - TEMI-2020 0121 - changes equi ed to you subm ssion

How about this?

-L shan

From L u, Shan-Lu liu.6244@osu edu>
Date F iday, Feb ua y 14, 2020 at 12 47 PM
To Su, L shan l h _ @ >, Lu, Shan h l @ >
Sub ect Re Eme ging Mic obes & Infections - TEMI-2020 0121 - changes equi ed to you subm ssion

Lishan

I get you point – maybe below one eads bet e ?

We should emphas ze that, although SARS-CoV-2 shows no evidence of labo ato y o igin, vi uses w th such g eat public health th eats must be handled p ope ly in the labo ato y and also p ope ly egulated by scien if c commun ty and gove nments."

Thoughts?

Shan-Lu Liu, M.D., Ph D.
P ofesso
Co-Di ecto , Vi uses and Eme ging Pathogens P og am
Infectious Diseases Inst tu e
Cente fo Ret ovi us Resea ch
Depa ments of Ve e na y Biosciences, Mic obial Infection and Immunity, and M c ob ology
The Oh o State Un ve s ty
1900 Co fey Rd, Room 480 VMAB
Columbu , Oh o 43210
Phone (614) 292-8690
Fax (614) 292-6473
Ema l l u 6244@osu.edu shan lu.liu@osumc.edu

On 2/14/20, 11 08 AM, Su, Lishan l shan su@med.unc edu> w ote

How about adding the last sentence n the p oof?

Evolution s stepwise and acc ues mutations g adually ove t me, whe eas synthet c const uc s would typica ly use a known backbone and nt oduce logical o ta geted changes instead of the andomly occu ing mutations that a e p esent in natu ally sola ed vi uses such as bat CoV RaTG13. In ou view, the e is cu ently no c ed ble evidence to uppo t the cla m that SARS CoV 2 o iginated f om a labo ato y-eng nee ed CoV. It is mo e l kely that SARS-CoV-2 is a ecomb nant CoV gene ated in natu e be ween a bat CoV and anothe co onavi us in an nte mediate animal hos . Mo e studies a e needed to explo e th s possibility and esolve the natu al o g n of SARS CoV-2. Although the SARS2 CoV has shown no evidence of labo ato y o igin, it is impo tant to point out that such vi uses in the labo ato y as d scussed he e do pose public health conce ns and should be ca efu ly moni o ed and egulated.

-Lishan

--- O ig nal Message- ---
F om Liu, Shan-Lu l 62 @ >
Date Thu sday, Feb ua y 13, 2020 at 10 04 AM
To Lu, Shan shan.lu@umassmed.edu>
Cc Su, Lishan l h _ @ >
Subject Re Eme g ng Mic obes & Infect ons - TEMI-2020 0121 - changes equi ed to you submiss on

Thanks, Shan fo you e fic ent ac ion!

On 2/13/20, 9 56 AM, Lu, Shan Sh @ > w ote

You pape is now accepted. Hope you have eceived the dec sion let e .

Best.

Shan

--- -O ginal Message-----
F om L u, Shan-Lu liu.6244@osu edu>
Sent Thu sday, Feb ua y 13, 2020 8 57 AM
To - @j l f
Cc Lu, Shan Shan.Lu@umassmed.edu> Su, Lishan l shan su@med unc edu>
Subject Re Eme ging Mic obes & Infections - TEMI-2020-0121 - changes equi ed to you subm ssion
Impo tance H gh

Hi Jo gie

I have modif ed as inst ucted and at ached the new one to this ema l. Please help upload and p oceed.

Thank you.

Shan-Lu

Shan-Lu L u, M.D., Ph D.
P ofesso
Co-Di ecto , Vi uses and Eme ging Pathogens P og am Infectious Diseases Inst tute Cente fo Ret ovi us Resea ch Depa tments of Vete ina y Biosc ences, M c ob al Infect on and Immun ty, and Mic obiology The Ohio State Unive sity
1900 Co fey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone (614) 292 8690
Fax (614) 292 6473
Ema l l u.6244@osu.edu shan lu.liu@osumc.edu

On 2/13/20, 8 43 AM, Eme ging Mic obes and Infec ions onbehalfo @manusc iptcent al.com> w ote

13-Feb 2020

Dea P ofesso Liu,

You above efe enced manusc ipt, entitled SARS-CoV-2 no evidence of a labo ato y o ig n equi es some fu the changes befo e it is eady fo eviewing n Eme g ng Mic obes & Infec ions. You submiss on has been etu ned to you and is located in you Autho Cen e as a d aft, so that you due to these easons

1. No line numbe ng

K ndly add a l ne numbe ng in you main document.

2. Exceeded efe ence count

K ndly be info med that the efe ence count fo the commenta y a t cle should not be mo e than 15.

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You may contact the Edito ial O fice if you have fu the quest ons.

S nce ely,

Jo g e Lyn Luna
Eme ging M c obes & Infect ons Edi o al Off ce
temi-pee ev ew@ ou nals tandf co uk

From: Su, Lishan
To: Liu, Shan-Lu
Subject: Re: Executive summary of EMI commentary
Date: Sunday, February 23, 2020 12:22:53 PM
Attachments: image001.png
image002.png
刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论.docx

One more time.

-Lishan

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Sunday, February 23, 2020 at 12:16 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: Executive summary of EMI commentary

See revised word/pdf.

-Lishan

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Sunday, February 23, 2020 at 12:07 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: Executive summary of EMI commentary

This may be more accurate? 刘善虑苏立山等教授发文分析认为新冠病毒阴谋论缺乏病毒学证据

-Lishan

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Sunday, February 23, 2020 at 11:54 AM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: Executive summary of EMI commentary

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Subject: Re: Submitted Corrections for article TEMI 1733440

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> **Subject: Submitted Corrections for article TEMI 1733440**
> **Reply-To:** TEMI-production@journals.tandf.co.uk
>
> Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2
>
> Journal: *Emerging Microbes & Infections* (TEMI)
>
> Article ID: TEMI 1733440
>
> Dear author,
>
> This email confirms that you have submitted your corrections to your article proofs.
>
> The submitted corrections have been successfully uploaded.
>
> If you want to check your submitted corrections please log into CATS and click on the “Corrections Submitted” button.
>
> Yours sincerely,
>
> Malathi Boopalan
>
> Email:TEMI-production@journals.tandf.co.uk

刘善虑苏立山等教授发文分析认为新冠病毒阴谋论缺乏病毒学证据

俄亥俄州立大学教授刘善虑，北卡大学教堂山分校教授苏立山联名世界冠状病毒学专家 Linda J. Saif（美国科学院院士）以及 Susan Weiss（美国微生物科学院院士），在 国际期刊 Emerging Microbes & Infections (EMI) (中文译名《新发微生物与感染》)发表题为“**没有可信的证据支持 SARS-CoV-2 来自实验室人工合成**”的评论文章，对最近广为流行的传言和阴谋论进行了分析和驳斥。

该文主要论点如下：

1. 新型冠状病毒 SARS-CoV-2 虽然与中国科学院武汉病毒所最近报道的一种称 为 RaTG13 的蝙蝠冠状病毒有高达 96%的同源性， 但两者仍然有超过 1，100 碱基的差别，而且在关键序列序列上有特征性的区别，因此两者是完全不同的冠状病毒。
2. 社交媒体指向 2015 年在《自然医学》一篇论文，认为新型冠状病毒是这篇文章报道的人 SARS 和蝙蝠冠状病毒（SHC014）的嵌合病毒的泄露。分析研究表明，新型冠状病毒 SARS-CoV-2 与这个嵌合冠状病毒在基因组序列上有超过了 5,000 个碱基的不同，所以这种怀疑完全缺乏任何科学依据。
3. 还有一种传言说 SARS-CoV-2 是实验室中有意人为制造的， 并以发表在 BioRxiv 上印度科学家的一份手稿中为依据，声称 SARS-CoV-2 中含有 HIV 序列。实际上这篇文章在线后， 舆论哗然，世界各国病毒学家也纷纷反驳。 在 HIV-1 专家高峰（Feng Gao）领衔领导发表在 EMI 的反驳论文中，作者使用了仔细的生物信息学分析来证明，指出最初声称的 SARS-CoV-2 有多个 HIV-1 插入片段并非 HIV-1 特有，而是完全随机的。由于国际社会提出的种种疑问，这篇手稿的作者已经撤回了该手稿， 不再要求发表。
4. 从科学层面讲，进化是循序渐进的，并随着时间的推移进一步产生有利于病毒的突变。相反，人工合成的病毒基因组通常会使用已知的病毒骨架引入一些某些定向的变化。所以，目前没有可靠的证据支持 SARS-CoV-2 是来源于实验人工设计。
5. 尽管目前没有证据显示新型冠状病毒 SARS-CoV-2 来自实验室人工制造，我们认为对公共健康有威胁的病毒都必须进行恰当的实验室管理，而且需要由科学界和政府合理监管。

From: Liu, Shan-Lu
To: Su, Lishan; Lu, Shan
Subject: Re: Revised commentary for EMI - final!
Date: Monday, February 17, 2020 6:10:04 PM

I think our points are made in the commentary. Shan did not plan initially to go into much science, but in the end I think we have covered most of it.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Monday, February 17, 2020 at 6:04 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Revised commentary for EMI - final!

I agree with them completely. Based on Shi's two natures papers and the Baric Nature medicine paper, I was trying to make the point as this paper: that the new virus from bats could have jumped into a secondary host or directly to humans and evolve. One of you did not seem to like the direct human possibility and removed it.

Theories of SARS-CoV-2 origins

It is improbable that SARS-CoV-2 emerged through laboratory manipulation of an existing SARS-related coronavirus. As noted above, the RBD of SARS-CoV-2 is optimized for human ACE2 receptor binding with an efficient binding solution different to that which would have been predicted. Further, if genetic manipulation had been performed, one would expect that one of the several reverse genetic systems available for betacoronaviruses would have been used. However, this is not the case as the genetic data shows that SARS-CoV-2 is not derived from any previously used virus backbone[17]. Instead, we propose two scenarios that can plausibly explain the origin of SARS-CoV-2: (i) natural selection in a non-human animal host prior to zoonotic transfer, and (ii) natural selection in humans following zoonotic transfer.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Monday, February 17, 2020 at 5:56 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Revised commentary for EMI - final!

This is the website that people deposit their sequence data and also make relevant comments. Not sure where they will publish it… but it has been widely spread via Twitter.

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>

Date: Monday, February 17, 2020 at 5:44 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Revised commentary for EMI - final!

Who is first is not critical. But where did you find this new paper? Published?

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Monday, February 17, 2020 5:42 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Revised commentary for EMI - final!

Again, I have no concern at all with our conclusion in the commentary. I believe more scientific articles like this will be out, and EMI will be one of the first to publish them.

Cheers!

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Monday, February 17, 2020 at 5:36 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Revised commentary for EMI - final!

Agreed. Beautifully written.

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Monday, February 17, 2020 5:35 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Revised commentary for EMI - final!

I just carefully read through, very informative and convincing in my view. Those are of course true experts of evolutionary biologists.

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Monday, February 17, 2020 at 5:27 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Revised commentary for EMI - final!

This still has nothing to do with any of the specific claims.

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Monday, February 17, 2020 5:26 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Revised commentary for EMI - final!

The last section is to dispute those rumors.

Theories of SARS-CoV-2 origins

It is improbable that SARS-CoV-2 emerged through laboratory manipulation of an existing SARS-related coronavirus. As noted above, the RBD of SARS-CoV-2 is optimized for human ACE2 receptor binding with an efficient binding solution different to that which would have been predicted. Further, if genetic manipulation had been performed, one would expect that one of the several reverse genetic systems available for betacoronaviruses would have been used. However, this is not the case as the genetic data shows that SARS-CoV-2 is not derived from any previously used virus backbone[17]. Instead, we propose two scenarios that can plausibly explain the origin of SARS-CoV-2: (i) natural selection in a non-human animal host prior to zoonotic transfer, and (ii) natural selection in humans following zoonotic transfer. We also discuss whether selection during passage in culture could have given rise to the same observed features.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Monday, February 17, 2020 at 5:23 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Revised commentary for EMI - final!

Two different things. They are doing SARS2 genome analysis. Your is trying to disapprove the other theories.

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Monday, February 17, 2020 5:17 PM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: Revised commentary for EMI - final!

…SARS-CoV-2 is the seventh member of the *Coronaviridae* known to infect humans. Three of these viruses, SARS CoV-1, MERS, and SARS-CoV-2, can cause severe disease; four, HKU1, NL63, OC43 and 229E, are associated with mild respiratory symptoms. Herein, we review what can be deduced about the origin and early evolution of SARS-CoV-2 from the comparative analysis of available genome sequence data. In particular, we offer a perspective on the notable features in the SARS-CoV-2 genome and discuss scenarios by which these features could have arisen. Importantly, this analysis provides evidence that SARS-CoV-2 is not a laboratory construct nor a purposefully manipulated virus.
…

We need to try to get ours out quickly.

SL

From:	Su, Lishan
To:	Liu, Shan-Lu
Subject:	Re: Executive summary of EMI commentary
Date:	Sunday, February 23, 2020 12:24:53 PM
Attachments:	image001.png image002.png 刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论.docx 刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论.Final.pdf

---

See revised word/pdf.

-Lishan

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Sunday, February 23, 2020 at 12:07 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: Executive summary of EMI commentary

This may be more accurate? 刘善虑苏立山等教授发文分析认为新冠病毒阴谋论缺乏病毒学证据

-Lishan

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Sunday, February 23, 2020 at 11:54 AM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Re: Executive summary of EMI commentary

See pdf file with no lines.
I can not find a better word than驳斥, but it seems to a be a bit stronger than we intended?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 23, 2020 at 8:57 AM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Executive summary of EMI commentary

Lishan and Shan – so confusing!

I have wrapped up a summary for the public and media to understand key points of our commentary. Please make suggestions.

I think this can go along with the Chinese translation.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 7:39 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 7:33 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

I just went online to see if we replace with a new one.
Could you send me the PDF of the corrected one?

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 4:32 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

My bad. How do we fix it? send her a message?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 7:29 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

Lishan:

I just saw that you deleted nt for 1,100 – “nt” should be kept. Could you correct that?

Thanks.

SL

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 4:28 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

Thanks!

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 7:22 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, Susan Weiss <weisssr@pennmedicine.upenn.edu>
Subject: Fwd: Submitted Corrections for article TEMI 1733440

Shan-Lu Liu sent from iPhone

Begin forwarded message:

From: "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
Date: February 21, 2020 at 4:04:41 PM PST
To: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: Submitted Corrections for article TEMI 1733440
Reply-To: TEMI-production@journals.tandf.co.uk

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear author,

This email confirms that you have submitted your corrections to your article proofs.

The submitted corrections have been successfully uploaded.

If you want to check your submitted corrections please log into CATS and click on the “Corrections Submitted” button.

Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

刘善虑苏立山等教授发文分析认为新冠病毒阴谋论缺乏病毒学证据

俄亥俄州立大学教授刘善虑，北卡大学教堂山分校教授苏立山联名世界冠状病毒学专家 Linda J. Saif（美国科学院院士）以及 Susan Weiss（美国微生物科学院院士），在 国际期刊 Emerging Microbes & Infections (EMI) (中文译名《新发微生物与感染》)发表题为“**没有可信的证据支持 SARS-CoV-2 来自实验室人工合成**”的评论文章，对最近广为流行的传言和阴谋论进行了分析和驳斥。

该文主要论点如下：

1. 新型冠状病毒 SARS-CoV-2 虽然与中国科学院武汉病毒所最近报道的一种称 为 RaTG13 的蝙蝠冠状病毒有高达 96%的同源性， 但两者仍然有超过 1，100 碱基的差别，而且在关键序列序列上有特征性的区别，因此两者是完全不同的冠状病毒。
2. 社交媒体指向 2015 年在《自然医学》一篇论文，认为新型冠状病毒是这篇文章报道的人 SARS 和蝙蝠冠状病毒（SHC014）的嵌合病毒的泄露。分析研究表明，新型冠状病毒 SARS-CoV-2 与这个嵌合冠状病毒在基因组序列上有超过了 5,000 个碱基的不同，所以这种怀疑完全缺乏任何科学依据。
3. 还有一种传言说 SARS-CoV-2 是实验室中有意人为制造的， 并以发表在 BioRxiv 上印度科学家的一份手稿中为依据，声称 SARS-CoV-2 中含有 HIV 序列。实际上这篇文章在线后， 舆论哗然，世界各国病毒学家也纷纷反驳。 在 HIV-1 专家高峰（Feng Gao）领衔领导发表在 EMI 的反驳论文中，作者使用了仔细的生物信息学分析来证明，指出最初声称的 SARS-CoV-2 有多个 HIV-1 插入片段并非 HIV-1 特有，而是完全随机的。由于国际社会提出的种种疑问，这篇手稿的作者已经撤回了该手稿， 不再要求发表。
4. 从科学层面讲，进化是循序渐进的，并随着时间的推移进一步产生有利于病毒的突变。相反，人工合成的病毒基因组通常会使用已知的病毒骨架引入一些某些定向的变化。所以，目前没有可靠的证据支持 SARS-CoV-2 是来源于实验人工设计。
5. 尽管目前没有证据显示新型冠状病毒 SARS-CoV-2 来自实验室人工制造，我们认为对公共健康有威胁的病毒都必须进行恰当的实验室管理，而且需要由科学界和政府合理监管。

From: Liu, Shan-Lu
To: temi-peerreview@journals.tandf.co.uk
Cc: shan.lu@umassmed.edu; lishan_su@med.unc.edu
Subject: Re: Urgent: revised commentary for Emerging Microbes & Infections - TEMI-2020-0121
Date: Sunday, February 16, 2020 7:59:43 PM
Attachments: Liu et al_EMI Commentary_Revision_Final.docx
image001.png

Here is the attachment, sorry!

_____

Dear Jorgie,

After discussing with Dr. Shan Lu and all coauthors, we have decided to use a new title and also make minor changes to the text, including assciated references. I have attached the updated commentary and hope that you will be able to help upload the new version for preparing the proof.

Thank you!

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M D , Ph D
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "temi-peerreview@journals.tandf.co.uk" <temi-peerreview@journals.tandf.co.uk>
Date: Thursday, February 13, 2020 at 9:14 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: "shan.lu@umassmed.edu" <shan.lu@umassmed.edu>, "lishan_su@med.unc.edu" <lishan_su@med.unc.edu>
Subject: Re: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission #TrackingId:5633996

Dear Professor Liu,

Thank you very much for sending his file.

Kindly be informed that I have now uploaded in he system on your behalf and proceeded your paper to the editor.

Please let me know if you have further questions or concerns.

Kind regards,

Jorgie Lyn Luna - Journal Editorial Office
Taylor & Francis Group
4 Park Square | Milton Park | Abingdon | Oxon | OX14 4RN UK
Web: www.tandfonline.com

Emerging Microbes & Infections

From:liu.6244@osu.edu
Sent:
To:liu.6244@osu.edu
Cc: Shan.Lu@umassmed.edu,lishan_su@med.unc.edu
Subject: Re: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission

Hi Jorgie:

I have modified as instructed and attached the new one to this email. Please help upload and proceed.

Thank you.

Shan-Lu

Shan-Lu Liu, M D., Ph D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210

Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu 6244@osu edu; shan-lu liu@osumc.edu

On 2/13/20, 8:43 AM, "Emerging Microbes and Infections" <onbehalfof@manuscriptcentral.com> wrote:

13-Feb-2020

Dear Professor Liu,

Your above referenced manuscript, entitled "SARS-CoV-2: no evidence of a laboratory origin" requires some further changes before it is ready for reviewing in Emerging Microbes & Infections. Your submission has been returned to you and is located in your Author Center as a draft, so that you due to these reasons:

1. No line numbering

Kindly add a line numbering in your main document.

2. Exceeded reference count

Kindly be informed that the reference count for the commentary article should not be more than 15.

Your submission along with all files you submitted is now in your Author Center, at https://urldefense.com/v3/__https://mc manuscriptcentral com/temi__;!!KGKeukY!nGv1RgRJ1P-OGXuZi8b2hKGjXxDFOmBwDONuR_njCdwERJF1HkBIV4Sggqr9udyWYml$ Please read the Quick Guide to Continuing your Submission, which shows how you can access your manuscript, and submit it back to the site. The Guide is located at https://urldefense.com/v3/__http://mc manuscriptcentral com/societyimages/tandf_qs0/Continuning*20a*20Submission_screenshot.pdf__;JSU! KGKeukY!nGv1RgRJ1P-OGXuZi8b2hKGjXxDFOmBwDONuR_njCdwERJF1HkBIV4Sggqr9re6Z8tA$

You may contact the Editorial Office if you have further questions.

Sincerely,

Jorgie Lyn Luna
Emerging Microbes & Infections Editorial Office
temi-peerreview@journals.tandf.co.uk

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Shan-Lu Liu [1, 2,3,4], Linda J. Saif [4,5], Susan Weiss [6], and Lishan Su [7]

[1] Center for Retrovirus Research, The Ohio State University,
Columbus, OH 43210, USA

[2] Department of Veterinary Biosciences, The Ohio State University, Columbus,
OH 43210, USA

[3] Department of Microbial Infection and Immunity, The Ohio State University,
Columbus, OH 43210, USA

[4] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,
The Ohio State University, Columbus, OH 43210, USA

[5] Food Animal Health Research Program,
Ohio Agricultural Research and Development Center, CFAES
Department of Veterinary Preventive Medicine,
The Ohio State University, Wooster, Ohio 44691, USA

[6] Department of Microbiology, Perelman School of Medicine,
University of Pennsylvania, Philadelphia, Pennsylvania, USA

[7] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,
University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1-3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4,5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural

evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10,11]. Civets were proposed

to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6,12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already

exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5,14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 virologist Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random [15]. Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2. We should emphasize that, although SARS-CoV-2 shows no evidence of laboratory origin, viruses

with such great public health threats must be handled properly in the laboratory and also properly regulated by the scientific community and governments.

References

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From:	Liu, Shan-Lu
To:	Weiss, Susan
Subject:	Re: [External] Re: name for new CoV
Date:	Sunday, February 16, 2020 1:32:08 PM
Attachments:	image001.png image002.png

Not yet, unfortunately!

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Sunday, February 16, 2020 at 1:31 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: name for new CoV

Not in BioRx?
I am anxious to know also

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 1:23 PM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: Re: [External] Re: name for new CoV

Not published yet. I heard that they submitted it Nature for review.
I am very eager to know if the pangolin virus isolated from the market has the RRAR insertion; it is not present in the Viruses paper 2019!

Shan-Lu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Sunday, February 16, 2020 at 1:18 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: name for new CoV

Btw- have you heard any more about the pangolin connection- I see nothing in pub med expect a paper from before the outbreak claiming to find CoV sequences in dead pangolins in the south of China
susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 1:16 PM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: Re: [External] Re: name for new CoV

Susan:

I agree with you. I don't see any evidence of lab origin, as no lab people have been infected, but with some rumors – just rumors!

COVID-19 is the disease name defined by WHO. I still feel SARS-CoV-2 is a good one adopted my Chinese American virologists.

Shan-Lu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Sunday, February 16, 2020 at 1:11 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: name for new CoV

I have a couple of comments

I don't think it is likely that bat virus leaked into humans in the lab- is there any evidence that someone from the Wuhan lab is infected? Also in general the bat viruses have been identified by sequence sand are not actually isolated viruses.

RRAR is a good if not excellent furin site, similar to MERS- MHV A59 is RRAHR, MHV JHM is RRARR (a very good one) – lineage B Bat viruses generally do not have the furin site
I doubt very much it was engineered in in the lab. Doesn't make sense

I wonder if there is some compromise position re the name- the formal name I think has to be SARS-CoV-2 but maybe can be referred to COVID-19 informally- if you look at the internet WHO is calling it COVID-19

Susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 10:05 AM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: Re: [External] Re: name for new CoV

Susan,

I have looked at carefully the RaTG13 sequence, and it is unlikely from it – also see attached file. But we cannot rule out the possibility of other bat viruses from the lab – The Wuhan lab has many bat samples not yet worked out or results published. There are some concerns that some of their samples may not have been handled properly

and leaked out of the lab…But just a possibility.

Right now, it's hard to say an intermediate host or directly from bats, I guess.

Shan-Lu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Sunday, February 16, 2020 at 9:48 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: name for new CoV

Do you think it could come from a bat virus- which one or an unpublished one? RaTg13 is the closest? Is it close enough in sequence? Do you think it came through an intermediate host and sequence drifted?

This is a very chilling idea

susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 9:41 AM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: [External] Re: name for new CoV

Dear Susan,

I strongly support the new name SARS-CoV-2, as I feel that it does reflect what we currently know. I do understand the feeling of those Chinese colleagues, but I dislike their political motivations. They have also approached me, but I have publicly expressed my support of the new name in some Chinese media.

In terms of our commentary to be published in EMI, we may change the title to emphasize that the new virus is not laboratory engineered, "**SARS-CoV-2: no evidence for laboratory engineering",** because we cannot rule out the possibility that it comes from a bat virus leaked out of a lab. When the proof comes, I will write to you and others.

Best wishes.

Shan-Lu

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Infectious Diseases Institute
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Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Sunday, February 16, 2020 at 9:10 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: name for new CoV

Dear Shan-Lu

I was approached about the controversy about the name of the new CoV and asked me to support a request for change in name. When I heard the name SARS-CoV-2 I initially didn't like it at all because it seemed like it would confused with SARS. However, after reading the BioRx article form CGS about the naming, it does makes sense in terms of the other SARS like viruses form bats, I understand that some the Chinese scientists are upset about this and feel it will have a bad psychological effect for China and if it comes back each year like flu it will have a big impact on business investment and tourism etc, which also makes sense.

Which side of this argument are you on?

Susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Wednesday, February 12, 2020 at 10:25 PM
To: Min Yang <min.yang@emi2012.org>, "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>

Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: [External] Re: EMI commentary

Min:

It should have been successfully submitted. See below email:

12-Feb-2020

Dear Professor Liu:

Your manuscript entitled "SARS-CoV-2: no evidence of a laboratory origin" has been successfully submitted online and is presently being given full consideration for publication in Emerging Microbes & Infections.

Your manuscript ID is TEMI-2020-0121.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at https://urldefense.com/v3/__https://mc.manuscriptcentral.com/temi__;!!KGKeukY!klcqOriA-xIzLyrzwwKWtghNAQgvfbCh7pqavzMYm77fJJsm_iShbXJWIKEtRML7ExI$ and edit your user information as appropriate.

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Thank you for submitting your manuscript to Emerging Microbes & Infections.

Sincerely,
Emerging Microbes & Infections Editorial Office

From: Min Yang <min.yang@emi2012.org>
Date: Wednesday, February 12, 2020 at 10:17 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

Dear Dr Liu,

Thank you for your support to EMI.

According to the attachment, it looks like your submission is a DRAFT still which has not been submitted successfully yet.

Could you please check and confirm?

Thanks and regards,

Min Yang

Emerging Microbes & Infections (EMI) Editorial Office
4F Fuxing Building
131 Dongan Road
Shanghai
China
Tel: 86-21-54237992
E-mail: min.yang@emi2012.org

发件人: "Liu, Shan-Lu" <liu.6244@osu.edu>
日期: 2020年2月13日 星期四 上午10:58
收件人: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
抄送: Min Yang <min.yang@emi2012.org>, "Lu, Shan" <Shan.Lu@umassmed.edu>
主题: EMI commentary

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Thank you.

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1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: Liu, Shan-Lu
To: Weiss, Susan
Subject: Re: name for new CoV
Date: Sunday, February 16, 2020 9:40:00 AM
Attachments: image001.png
image002.png

Dear Susan,

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Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Sunday, February 16, 2020 at 9:10 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: name for new CoV

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Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
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Thanks and regards,

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E-mail: min.yang@emi2012.org

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日期**:** 2020年2月13日 星期四 上午10:58
收件人**:** "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
抄送**:** Min Yang <min.yang@emi2012.org>, "Lu, Shan" <Shan.Lu@umassmed.edu>
主题**:** EMI commentary

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Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: Liu, Shan-Lu
To: Su, Lishan; Shan Lu
Subject: FW: Author Publishing Agreement Received for article TEMI 1733440
Date: Wednesday, February 19, 2020 11:52:41 PM

Done, thank you Lishan!

SL

From: "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
Reply-To: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Date: Wednesday, February 19, 2020 at 8:51 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Author Publishing Agreement Received for article TEMI 1733440

Article: SARS-CoV-2: no evidence of a laboratory origin

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear Shan-Lu Liu,

Thank you for submitting your author publishing agreement for the article listed above. You will receive an email once your author publishing agreement has been accepted, or if any problems are identified.

Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

From: Liu, Shan-Lu
To: TEMI-production@journals.tandf.co.uk
Subject: Re: URGENT! Submitted Corrections for article TEMI 1733440 #TrackingId:5700591
Date: Tuesday, February 25, 2020 11:48:07 PM

Thanks. Let me know as soon as it is online.
Thank you.

Shan-Lu Liu sent from iPhone

> On Feb 25, 2020, at 11:28 AM, "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk> wrote:
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> Dear Shan-Lu,
>
> This would be online in one or two days.
>
> Regards,
>
> Malathi
> Emerging Microbes & Infections
>
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>
> **From:**liu.6244@osu.edu
> **Sent:**25-02-2020 08.50 AM
> **To:**TEMI-production@journals.tandf.co.uk
> **Cc:**
> **Subject:**Re: URGENT! Submitted Corrections for article TEMI 1733440
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> Possible to let us know the publication date? Thanks
>
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> > On Feb 24, 2020, at 1:01 AM, "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk> wrote:
> >
> > Dear Shan-Lu Liu,

Thank you for the email. I have sent your additional correction to the team so that they will make the changes in the final PDF.

Have a great day!

Regards,

Malathi
Emerging Microbes & Infections

From:liu.6244@osu.edu
Sent:22-02-2020 06:24
To:malathi@novatechset.com
Cc:
Subject: Re: URGENT! Submitted Corrections for article TEMI 1733440

Dear Malathi Boopalan:

We have just uploaded a corrected proof online, but relegalized a small error: "1,100" should be read as "1,100 nt" – could you kindly help make the correction, or replace the uploaded file with the attached new one?

Thank you! Please confirm.

Shan-Lu Liu & Lishan Su

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
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The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Shan-Lu Liu sent from iPhone

On Feb 21, 2020, at 4:04 PM, TEMI-production@journals.tandf.co.uk <cats@taylorandfrancis.com> wrote:

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear author,

This email confirms that you have submitted your corrections to your article proofs.

The submitted corrections have been successfully uploaded.

If you want to check your submitted corrections please log into CATS and click on the “Corrections Submitted” button.

Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

From: Liu, Shan-Lu
To: Su, Lishan
Cc: Lu, Shan
Subject: Executive summary of EMI commentary
Date: Sunday, February 23, 2020 8:56:59 AM
Attachments: 刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论.docx
image001.png
image002.png

Lishan and Shan – so confusing!

I have wrapped up a summary for the public and media to understand key points of our commentary. Please make suggestions.

I think this can go along with the Chinese translation.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 7:39 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

-Lishan

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Date: Friday, February 21, 2020 at 7:33 PM
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Subject: Re: Submitted Corrections for article TEMI 1733440

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Could you send me the PDF of the corrected one?

THE OHIO STATE UNIVERSITY

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Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690

Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

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Date: Friday, February 21, 2020 at 7:22 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, Susan Weiss <weisssr@pennmedicine.upenn.edu>
Subject: Fwd: Submitted Corrections for article TEMI 1733440

Shan-Lu Liu sent from iPhone

Begin forwarded message:

> **From:** "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
> **Date:** February 21, 2020 at 4:04:41 PM PST
> **To:** "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>, "Liu, Shan-Lu" <liu.6244@osu.edu>
> **Subject: Submitted Corrections for article TEMI 1733440**
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>
> Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2
>
> Journal: *Emerging Microbes & Infections* (TEMI)
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> Article ID: TEMI 1733440
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> If you want to check your submitted corrections please log into CATS and click on the “Corrections Submitted” button.
>
> Yours sincerely,
>
> Malathi Boopalan
>
> Email:TEMI-production@journals.tandf.co.uk

刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论

俄亥俄州立大学教授**刘善虑**，北卡大学教堂山分校教授苏立山联名美国科学院院士 Linda J. Saif 以及美国微生物科学院院士 Susan Weiss，在 国际期刊 Emerging Microbes & Infections (EMI) (中文译名《新发微生物与感染》)发表题为“**没有可信的证据支持 SARS-CoV-2 来自实验室人工合成**”的评论文章，对最近广为流行的传言和阴谋论进行了分析和驳斥。

该文主要论点如下：

1. 新型冠状病毒 SARS-CoV-2 虽然与中国科学院武汉病毒所最近报道的一种称 为 RaTG13 的蝙蝠冠状病毒有高达 96%的同源性， 但两者仍然有超过 1，100 碱基的差别，而且在关键序列序列上有特征性的区别，因此两者是完全不同的冠状病毒。
2. 社交媒体指向 2015 年在《自然医学》一篇论文，认为新型冠状病毒是这篇文章报道的人 SARS 和蝙蝠冠状病毒（SHC014）的嵌合病毒的泄露。分析研究表明，新型冠状病毒 SARS-CoV-2 与这个嵌合冠状病毒在基因组序列上有超过了 5,000 个碱基的不同，所以这种怀疑完全缺乏任何科学依据。
3. 还有一种传言说 SARS-CoV-2 是实验室中有意人为制造的， 并以发表在 BioRxiv 上印度科学家的一份手稿中为依据，声称 SARS-CoV-2 中含有 HIV 序列。实际上这篇文章在线后， 舆论哗然，世界各国病毒学家也纷纷反驳。 在 HIV-1 专家高峰（Feng Gao）领衔领导发表在 EMI 的反驳论文中，作者使用了仔细的生物信息学分析来证明，指出最初声称的 SARS-CoV-2 有多个 HIV-1 插入片段并非 HIV-1 特有，而是完全随机的。由于国际社会提出的种种疑问，这篇手稿的作者已经撤回了该手稿， 不再要求发表。
4. 从科学层面讲，进化是循序渐进的，并随着时间的推移进一步产生有利于病毒的突变。相反，人工合成的病毒基因组通常会使用已知的病毒骨架引入一些某些定向的变化。所以，目前没有可靠的证据支持 SARS-CoV-2 是来源于实验人工设计。
5. 尽管目前没有证据显示新型冠状病毒 SARS-CoV-2 来自实验室人工制造，我们认为对公共健康有威胁的病毒都必须进行恰当的实验室管理，而且需要由科学界和政府合理监管。

From: Liu, Shan-Lu
To: TEMI-production@journals.tandf.co.uk
Subject: URGENT! Submitted Corrections for article TEMI 1733440
Date: Friday, February 21, 2020 7:54:39 PM
Attachments: cidimage001.png@01D3AAF8.8AA7CB20

Dear Malathi Boopalan:

We have just uploaded a corrected proof online, but relegalized a small error: "1,100" should be read as "1,100 nt" – could you kindly help make the correction, or replace the uploaded file with the attached new one?

Thank you! Please confirm.

Shan-Lu Liu & Lishan Su

Shan-Lu Liu, M.D., Ph.D.
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Co-Director, Viruses and Emerging Pathogens Program
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Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

From: Liu, Shan-Lu
To: Liu, Shan-Lu
Subject: FW: Executive summary of EMI commentary
Date: Sunday, February 23, 2020 1:22:20 PM
Attachments: Liu et al_EMI Commentary_Revision_中文-Shan Lu.docx
Liu et al_EMI Commentary_Revision_中文-Shan Lu.pdf
刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论_Final.docx
刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论_Final.pdf
image001.png
image002.png

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Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: Shan-Lu Liu <liu.6244@osu.edu>
Date: Sunday, February 23, 2020 at 1:21 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Executive summary of EMI commentary

Now, the final versions, a total of 4 files - hopefully!

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 23, 2020 at 1:15 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Executive summary of EMI commentary

Overall they are very good.

I found one minor error: "Dec" was used for the last reference of your paper. It should be "Feb". You may want to change the current word and pdf, but not change the real paper to be published as

it may take a lot of more time to current and reload to online. Readers can find that paper without much problem.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 23, 2020 12:57 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Executive summary of EMI commentary

See my final versions of two files, Word and PDF.

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 23, 2020 at 12:51 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Executive summary of EMI commentary

Your school's email screening system is good! Thanks.

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 23, 2020 12:49 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Executive summary of EMI commentary

Never, just received Shan's email and file! Slow on my end.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 23, 2020 at 12:48 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Executive summary of EMI commentary

Great work. However, I made some new changes (see attached). All highlighted or marked, for your reference.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 23, 2020 8:57 AM
To: Su, Lishan <lishan_su@med.unc.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Executive summary of EMI commentary

Lishan and Shan – so confusing!

I have wrapped up a summary for the public and media to understand key points of our commentary. Please make suggestions.

I think this can go along with the Chinese translation.

Shan-Lu

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Date: Friday, February 21, 2020 at 7:39 PM
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没有可信的证据支持 SARS-CoV-2 来自实验室人工合成

Shan-Lu Liu（刘善虑）, 俄亥俄州立大学

Linda J. Saif, 俄亥俄州立大学

Susan Weiss, 宾夕法尼亚大学

Lishan Su,（苏立山）北卡大学教堂山分校

截止 2020 年 2 月 10 日，在武汉出现和爆发的急性呼吸疾病已波及 4 万多人，导致 1000 多人死亡。研究人员很快找到了一种新型人的冠状病毒，称之为 2019 nCoV 或 SARS-CoV-2，而相应的疾病称之为 COVID-19，意为 2019 年发生的冠状病毒疾病 (https://globalbiodefense com/novel-coronavirus-covid-19-portal/)。

据现有的报道[1-3]，COVID-2019 与 SARS-CoV 导致的 SARS 有很多相似的临床表现。而 SARS-CoV-2 基因组序列也和 2003 年 SARS-CoV 有 80%同源性，但它与一些蝙蝠的乙型冠状病毒更为相似。当前，种种的推测、谣言和阴谋论到处流行，其中有的认为 SARS-CoV-2 来源于实验室基因工程制造。也有某些人声称，人的 SARS-CoV-2 是从武汉的某个实验室直接泄漏出来的， 其根据是该实验室最近报道了一种称为 RaTG13 的蝙蝠冠状病毒，它和 SARS-CoV-2 基因组序列有高达 96%的同源性。

然而，我们知道，2003 年发现人 SARS 冠状病毒和其中间宿主果子狸 SARS 样冠状病毒具有 99.8％的同源性，在整个基因组中只有 202 个碱基不同。鉴于人类新型 SARS-CoV-2 与蝙蝠 RaTG13-CoV 之间有超过了 1000 个不同碱基[4]，且这些差异是按照冠状病毒典型的进化特征按自然发生的模式分布在整个基因组中，我们认为 SARS-CoV-2 直接来源于 RaTG13 冠状病毒的可能性极小。更为重要的是，在新的人 SARS-CoV-2 病毒基因组序列中并没有任何可信的基因工程改造的迹象，这都揭示 SARS-CoV-2 是通过自然演化而来的。我们认为在蝙蝠与人类之间可以找到中间动物宿主含有类似的冠状病毒，它与 SARS-CoV-2 更相似。最近有消息称穿山甲可能携带与 SARS-CoV-2 密切相关的冠

状病毒，但论文和数据尚未正式发表，无从得以证实(https://www.nature.com/articles/d41586-020-00364-2)。

最近社交媒体上的另一种说法指向 2015 年在《自然医学》发表的一篇论文[7]。该论文报道了在小鼠适应后的人类 SARS 冠状病毒（MA15 病毒）中，人工构建了带有蝙蝠冠状病毒（SHC014）S 基因，这种合成的嵌合冠状病毒，不仅可以可以感染小鼠，也能够感染来源人的细胞[8]。然而，新型冠状病毒 SARS-CoV-2 与这个嵌合冠状病毒基因组序列有超过了 5,000 个碱基的不同，所以这种怀疑完全缺乏任何科学依据。

现在我们来理一理来人 SARS 病毒老鼠适应株 MA15 和它的衍生病毒的来龙去脉。适应小鼠的 SARS 病毒（MA15）[9]是通过把 SARS 冠状病毒在小白鼠呼吸道中连续传代 15 后产生的；适应后的 SARS 冠状病毒有六个氨基酸突变，使其能够更有效地感染小鼠，尤其是在老年小鼠中具有了更高的复制活性和肺部致病性能（因此称为 M15）。由于在小鼠内适应的遗传突变，MA15 在人细胞或者人体内感染很可能降低了。

科学家曾认为从蝙蝠身来的冠状病毒的 S 基因和人的 SARS 病毒不同，推测它们无法使用人的 SARS 病毒受体 ACE2 进入人体细胞[10, 11]；后来发现果子狸是蝙蝠冠状病毒传给人的中间宿主，能够将 SARS 冠状病毒传播给人类[6，12]。然而，2013 年以来，科学家陆续从中国马蹄蝠中分离到了数个新型蝙蝠冠状病毒，这些来自蝙蝠的，类似人 SARS 冠状病毒（SL-CoV-WIV1）能够使用人、果子狸和中国马蹄蝠的 ACE2 受体进入和感染细胞[8]。进化研究表明，在 SARS 冠状病毒 S 蛋白的作用接触位点上，蝙蝠 ACE2 基因在与人类 ACE2 基因在相同的位点上同样被进化选择[13]。基于这样的发现，科学家提出了蝙蝠的 SARS 样冠状病毒具有直接传染到人的能力，不必需要中间宿主环节；也就是说有些蝙蝠冠状病毒有可能直接感染人类宿主细胞。为了直接验证这种可能性，蝙蝠冠状病毒 SL-SHC014 的 S 基因被人工嫁接到了 MA15 SARS-CoV 骨架上，因此产生了一个嵌合病毒。此 SL-SHC014-MA15 嵌合病毒确实能够有效地利用人 ACE2 进入细胞，并在人的呼吸道实验细胞中有效复制。SL-SHC014-MA15 也可以在小鼠的肺中高效复制，但与 SARS MA15 相比，感染减弱了，并且只会让老年小鼠致命[7]。

由于 SL-SHC014-MA15 嵌合病毒相对于另一个人 SARS-S/MA15 嵌合病毒在小鼠中具有更高的致病活性，这种嵌合冠状病毒的实验后来在美国政府的干预下被暂停(https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-

pause-gain-function-research)。虽然目前 这项禁令在美国已经被解除，但构建这种具有大流行病潜力的病毒是否是一种风险，在当前的COVID-2019流行的形势下又重新引发了讨论，成为热点话题。然而，经过多个国家科学家对病毒的分子进化分析[5，14]，SARS-CoV-2 无疑与 SL-SHC014-MA15 具有非常大的不同，整个基因组有大约 6,000 核苷酸的差异。因此，没有可信的证据支持 SARS-CoV-2 是源自 SL-SHC014-MA15 嵌合病毒的说法。

最近也有传言说，SARS-CoV-2 是实验室中有意人为制造的。其中发表在 BioRxiv（一个同行评审之前的手稿共享网站）的一份手稿中更是此传言的代表，它声称 SARS-CoV-2 中含有 HIV 序列，因此很可能是在实验室中产生的。文章在线后， 舆论哗然，世界各国的多个病毒学者纷纷反驳。 在 HIV-1 病毒专家高峰（Feng Gao）领衔领导的反驳论文中，他们使用了仔细的生物信息学分析来证明，指出最初声称的 SARS-CoV-2 有多个 HIV-1 插入片段并非 HIV-1 特有，而是完全随机的 [15]。由于国际社会提出的种种疑问，这篇手稿的作者已经撤回了该手稿， 不再要求发表。

从科学层面讲，进化是循序渐进的，并随着时间的推移进一步产生有利于病毒的突变，就像天然分离的病毒（如蝙蝠冠状病毒 RaTG13）基因组那样。 相反，人工合成的病毒基因组通常会使用已知的病毒骨架引入一些某些定向的变化。所以我们认为，目前没有可靠的证据支持 SARS-CoV-2 是来源于实验人工设计。 有一种可能不能排除， 就是 SARS-CoV-2 是一种蝙蝠冠状病毒与另一种冠状病毒之间进行了自然重组而产生的；但这种可能性需要更多的研究来证明，来回答 SARS-CoV-2 的自然起源问题。我们需要强调的是，尽管目前没有证据显示新型冠状病毒 SARS-CoV-2 来自实验室人工制造，但对公共健康有威胁的病毒都必须进行恰当的实验室管理，而且需要由科学界和政府合理监管。

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刘善虑苏立山等教授发文分析认为新冠病毒阴谋论缺乏病毒学证据

俄亥俄州立大学教授刘善虑，北卡大学教堂山分校教授苏立山联名国际著名冠状病毒学家 Linda J. Saif（美国科学院院士）以及 Susan Weiss（美国微生物科学院院士），在 国际期刊 Emerging Microbes & Infections (EMI) (中文译名《新发微生物与感染》)发表题为“**没有可信的证据支持 SARS-CoV-2 来自实验室人工合成**”的评论文章，对最近广为流行的传言和阴谋论进行了分析和驳斥。

该文主要论点如下：

1. 新型冠状病毒 SARS-CoV-2 虽与中国科学院武汉病毒所最近报道的一个称为 RaTG13 的蝙蝠冠状病毒有高达 96%的同源性， 但两者仍然有超过 1，100 碱基的差别，而且在关键序列序列上有特征性区别，因此两者是完全不同的冠状病毒。
2. 社交媒体指向 2015 年在《自然医学》（Nature Medicine）一篇论文，认为新型冠状病毒是这篇文章报道的人 SARS 与蝙蝠冠状病毒（SHC014）的嵌合病毒的泄露。然而，分析研究表明，新型冠状病毒 SARS-CoV-2 与这个嵌合冠状病毒在基因组序列上有超过了 5,000 个碱基的不同，所以这种怀疑完全缺乏任何科学依据。
3. 还有一种传言说 SARS-CoV-2 是实验室中有意人为制造的， 并以发表在 BioRxiv 上印度科学家的一份手稿中为依据，声称 SARS-CoV-2 中含有 HIV 序列。实际上这篇文章在线发表后， 舆论哗然，世界各国病毒学家也纷纷反驳。 在 HIV-1 专家高峰（Feng Gao）领衔领导发表在 EMI 的另一篇反驳论文中，作者使用了仔细的生物信息学分析来证明，指出原文作者声称的 SARS-CoV-2 有多个 HIV-1 插入片段并非 HIV-1 特有，而是完全随机的。由于国际社会提出的种种疑问，这篇手稿的作者也已经撤回了该手稿， 目前没有发现再次发表。
4. 从科学层面讲，病毒进化是循序渐进的，并切随着时间的推移进一步产生有利于病毒感染人的突变。相反，人工合成的病毒基因组通常会在已知的病毒骨架引入一些某些定向的变化。所以，目前没有可靠的证据支持 SARS-CoV-2 是来源于实验人工设计。
5. 尽管目前没有证据显示新型冠状病毒 SARS-CoV-2 来自实验室人为制造，我们认为对公共健康有威胁的病毒都必须进行严格恰当的实验室管理，而且需要由科学界和政府联合监管。

From:	Liu, Shan-Lu
To:	Weiss, Susan
Subject:	Re: [External] Re: name for new CoV
Date:	Sunday, February 16, 2020 10:04:27 AM
Attachments:	Tackling Rumors of a Suspicious Origin of nCoV2019 - Novel 2019 coronavirus - nCoV-2019 Evolutionary History - Virological.pdf image001.png image002.png

Susan,

I have looked at carefully the RaTG13 sequence, and it is unlikely from it – also see attached file. But we cannot rule out the possibility of other bat viruses from the lab – The Wuhan lab has many bat samples not yet worked out or results published. There are some concerns that some of their samples may not have been handled properly and leaked out of the lab…But just a possibility.

Right now, it's hard to say an intermediate host or directly from bats, I guess.

Shan-Lu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Sunday, February 16, 2020 at 9:48 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: [External] Re: name for new CoV

Do you think it could come from a bat virus- which one or an unpublished one? RaTg13 is the closest? Is it close enough in sequence? Do you think it came through an intermediate host and sequence drifted?

This is a very chilling idea

susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Sunday, February 16, 2020 at 9:41 AM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: [External] Re: name for new CoV

Dear Susan,

I strongly support the new name SARS-CoV-2, as I feel that it does reflect what we currently know. I do understand the feeling of those Chinese colleagues, but I dislike their political motivations. They have also approached me, but I have publicly expressed my support of the new name in some Chinese media.

In terms of our commentary to be published in EMI, we may change the title to emphasize that the new virus is not laboratory engineered, "**SARS-CoV-2: no evidence for laboratory engineering",** because we cannot rule out the possibility that it comes from a bat virus leaked out of a lab. When the proof comes, I will write to you and others.

Best wishes.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Sunday, February 16, 2020 at 9:10 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: name for new CoV

Dear Shan-Lu

I was approached about the controversy about the name of the new CoV and asked me to support a request for change in name. When I heard the name SARS-CoV-2 I initially didn't like it at all because it seemed like it would confused with SARS. However, after reading the BioRx article form CGS about the naming, it does makes sense in terms of the other SARS like viruses form bats, I understand that some the Chinese scientists are upset about this and feel it will have a bad psychological effect for China and if it comes back each year like flu it will have a big impact on business investment and tourism etc, which also makes sense.

Which side of this argument are you on?

Susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Wednesday, February 12, 2020 at 10:25 PM
To: Min Yang <min.yang@emi2012.org>, "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: [External] Re: EMI commentary

Min:

It should have been successfully submitted. See below email:

12-Feb-2020

Dear Professor Liu:

Your manuscript entitled "SARS-CoV-2: no evidence of a laboratory origin" has been successfully submitted online and is presently being given full consideration for publication in Emerging Microbes & Infections.

Your manuscript ID is TEMI-2020-0121.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at https://urldefense.com/v3/__https://mc.manuscriptcentral.com/temi__;!!KGKeukY!klcqOriA-xIzLyrzwwKWtghNAQgvfbCh7pqavzMYm77fJJsm_iShbXJWIKEtRML7ExI$ and edit your user information as appropriate.

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Thank you for submitting your manuscript to Emerging Microbes & Infections.

Sincerely,
Emerging Microbes & Infections Editorial Office

From: Min Yang <min.yang@emi2012.org>
Date: Wednesday, February 12, 2020 at 10:17 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

Dear Dr Liu,

Thank you for your support to EMI.

According to the attachment, it looks like your submission is a DRAFT still which has not been submitted successfully yet.

Could you please check and confirm?

Thanks and regards,

Min Yang

Emerging Microbes & Infections (EMI) Editorial Office
4F Fuxing Building
131 Dongan Road
Shanghai
China
Tel: 86-21-54237992
E-mail: min.yang@emi2012.org

发件人**:** "Liu, Shan-Lu" <liu.6244@osu.edu>
日期**:** 2020年2月13日 星期四 上午10:58
收件人**:** "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
抄送**:** Min Yang <min.yang@emi2012.org>, "Lu, Shan" <Shan.Lu@umassmed.edu>
主题**:** EMI commentary

Dear all,

I have just submitted a commentary to EMI. See attached the submitted version.

Thank you.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program

Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Tackling Rumors of a Suspicious Origin of nCoV2019

profbillg1901 **4d**

I have been privately dealing with rumors and inquiries, focused on the RRAR potential furin cleavage site, that nCoV2019 may have a suspicious origin as an engineered, laboratory-generated virus either accidentally or deliberately released in the area of the Wuhan seafood and animal market. The publication of the highly similar RaTG13 sequence about a week ago has fueled this type of speculation.

As I have told people privately, I see no evidence at all to support such a claim. In sharp contrast, I have studied the question in detail, using RaTG13 and Wuhan sequence at the S1/S2 boundary, and find convincing proof of exactly opposite conclusion – that RaTG13 could NOT be a proximal source of the Wuhan virus.

At first glance of an alignment of the S protein sequence of both, it is natural that the issue of an engineered insertion should be considered. On either side of the new furin site, the amino acid sequence is identical in both from aa614 to aa1133 – an apparent insert of PRRA is the only difference in an otherwise 100% conserved 519 amino acid region.

But that is at first glance.

One has to consider that the PRRA is an unusual sequence to introduce to generate a furin site – others even among coronaviruses like MHV A59 are so much better. Also that the underlying code CCTCGGCGGGCA introduces an unnecessarily G and C rich region where none otherwise exists. Not likely scenarios for something a gene jockey would do.

Then one looks at the actual RNA alignment. The “insert” is actually not in frame, but CTCCTCGGCGGG, or -2 out of frame. Again, who does that?

But the PROOF lies in looking at the 288 alignable nucleotides on either side of the “insert”. While they cover identical protein sequence, the RNA is not at all identical, but 6.6% different – 19 mutations out of 288. All 19 are mutations in the wobble base of their respective codons. There are so many that the frame can be inferred from the 2/1 pattern even without knowing the beginning or the end, or indeed

that the encoded protein sequence is identical – those are self-evident by looking at the RNA itself.

```
                                                                                                    .
RaTG13 23463  CTAATGTTTTTCAAACACGTGCAGGTTGTTTAATAGGGGCTGAACATGTCAATAACTCGT  23522

Wuhan  23541  ATGAGTGTGACATACCCATTGGTGCAGGTATATGCGCTAGTTATCAGACTCAGACTAATT  23600
              |||||||||||||||| |||||||||| |||||||| ||||||||||||| |||||||
RaTG13 23523  ATGAGTGTGACATACCTATTGGTGCAGGAATATGCGCCAGTTATCAGACTCAAACTAATT  23582

Wuhan  23601  CTCCTCGGCGGGCACGTAGTGTAGCTAGTCAATCCATCATTGCCTACACTATGTCACTTG  23660
                        |||||||||| || |||||||| || ||||||||||||||||||||||
RaTG13 23583  ----------CACGTAGTGTGGCCAGTCAATCTATTATTGCCTACACTATGTCACTTG  23630

Wuhan  23661  GTGCAGAAAATTCAGTTGCTTACTCTAATAACTCTATTGCCATACCCACAAATTTTACTA  23720
              |||||||||||||||||||| |||||||||||||||||||||||| ||||||||||||
RaTG13 23631  GTGCAGAAAATTCAGTTGCTTATTCTAATAACTCTATTGCCATACCTACAAATTTTACTA  23690

Wuhan  23721  TTAGTGTTACCACAGAAATTCTACCAGTGTCTATGACCAAGACATCAGTAGATTGTACAA  23780
              ||||||| ||||| |||||||||||| |||||||||||| |||||||| ||||| |||||||
RaTG13 23691  TTAGTGTGACCACTGAAATTCTACCTGTGTCTATGACAAAGACATCGGTAGACTGTACAA  23750
```

We know from influenza H1N1, for which we have serial isolates from 1918 to the present, that wobble base mutagenesis occurs at a rate of 0.95% per decade. This permits an estimation of the TMRCA of the two sequences nCoV2019 and RaTG13 of 69.5 years ago – roughly 1950 +/- 10 years or so.

RaTG13, or anything nearly identical to it at the RNA level, simply could not be a proximal source of nCoV2019. It just LOOKS like it might be…at first glance.

Given that furin cleavage signals are present in other coronaviruses at exactly that point in the S1/S2 boundary region, it only LOOKS unusual, especially against the backdrop of SARS. The preponderance of evidence, coupled with Ockham's razor (that the simplest explanation is preferred) dictates that the PRRA sequence has been conserved in nCoV2019 from a long ago ancestor virus. It is not of suspicious origin. The closest bat virus sequence is really not close at all.

RNA don't lie.

Bill Gallaher

From: Liu, Shan-Lu
To: TEMI-production@journals.tandf.co.uk
Cc: Su, Lishan
Subject: URGENT CORRECTION: Your article proofs for review (ID# TEMI 1733440)
Date: Friday, February 21, 2020 7:45:16 PM
Attachments: image001.png
Importance: High

Dear Malathi Boopalan:

We have just uploaded a corrected proof online, but relegalized a small error: "1,100" should be read as "1,100 nt" – could you kindly help make the correction, or replace the uploaded file with the attached new one?

Thank you! Please confirm.

Shan-Lu Liu & Lishan Su

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
Reply-To: "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>
Date: Friday, February 21, 2020 at 4:13 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Your article proofs for review (ID# TEMI 1733440)

Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear Shan-Lu Liu,

Your article proofs are now available for review through the Central Article Tracking System (CATS) at: https://cats.informa.com/PTS/in?ut=B2AB6692AA414D96905B59E6C51FA240 .

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• The DOI of your paper is: 10.1080/22221751.2020.1733440. Once your article has published online, it will be available at the following permanent link:
https://doi.org/10.1080/22221751.2020.1733440 .

Thank you,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

From:	Liu, Shan-Lu
To:	Su, Lishan; Lu, Shan
Subject:	Re: Revised commentary for EMI - final!
Date:	Sunday, February 16, 2020 9:49:19 PM
Attachments:	EMI-conspiracy-zlshi.pdf image001.png

See Zhengli's comments. We may not need to make those changes, although some of those are good.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Sunday, February 16, 2020 at 3:17 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: Re: Revised commentary for EMI - final!

See a typo in the title, and the last sentence as we had discussed.
Thanks,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 16, 2020 at 1:55 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Subject: RE: Revised commentary for EMI - final!

Good to me.

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 16, 2020 1:45 PM
To: Su, Lishan <lishan_su@med.unc.edu>; Saif, Linda <saif.2@osu.edu>; Weiss, Susan <weisssr@pennmedicine.upenn.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Revised commentary for EMI - final!

Please look at this new version, sorry!

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.

Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: Shan-Lu Liu <liu.6244@osu.edu>

Date: Sunday, February 16, 2020 at 1:38 PM

To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>

Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>

Subject: Revised commentary for EMI

Dear All,

Following some discussions in the weekend, I had made a change in the title, and also added a sentence to the end of commentary – the latter is based on the concerns of lab safety for this new virus and also other viruses previously.

Let me know what you think.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

SARS-CoV-2: no evidence of a laboratory origin

Journal:	*Emerging Microbes & Infections*
Manuscript ID	Draft
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Complete List of Authors:	Liu, Shan-Lu; The Ohio State University, Infectious Diseases Institute Saif, Linda J.; The Ohio State University Weiss, Susan; University of Pennsylvania Su, Lishan; University of North Carolina at Chapel Hill
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Abstract:	

SARS-CoV-2: no evidence of a laboratory origin

Shan-Lu Liu [1, 2,3,4], Linda J. Saif [4,5], Susan Weiss [6], and Lishan Su [7]

[1] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[2] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[3] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

[4] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[5] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[6] Department of Microbiology, Perelman School of Medicine,

University of Pennsylvania, Philadelphia, Pennsylvania, USA

[7] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1, 2, 3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4, 5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding sequences, and among the 128 nonsynonymous mutations, 89 led to predicted radical amino-acid changes [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that

RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10, 11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6, 12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-

director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5, 14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus. Finally, we note that the synthetic and chimeric panels of bat and SARS-like CoV led to the identification of remdesivir as a broad spectrum inhibitor of all group 2b SARS-like coronaviruses tested in vitro or in vivo [15, 16], providing critical pre-clinical data that has led to the ongoing clinical trials in China and is critical for the future development of universal vaccines for all the SARS-like coronaviruses.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 expert Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

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From: Liu, Shan-Lu
To: Zheng, Yi-Min
Subject: FW: Emerging Microbes & Infections - Decision on Manuscript ID TEMI-2020-0121
Date: Thursday, February 13, 2020 9:50:39 AM

On 2/13/20, 9:49 AM, "Emerging Microbes and Infections" <onbehalfof@manuscriptcentral.com> wrote:

13-Feb-2020

Dear Professor Liu:

Ref: SARS-CoV-2: no evidence of a laboratory origin

Our reviewers have now considered your paper and have recommended publication in Emerging Microbes & Infections. We are pleased to accept your paper in its current form which will now be forwarded to the publisher for copy editing and typesetting. The reviewer comments are included at the bottom of this letter, along with those of the editor who coordinated the review of your paper.

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Thank you for your contribution to Emerging Microbes & Infections and we look forward to receiving further submissions from you.

Sincerely,

Shan Lu
Editor-in-Chief
Emerging Microbes & Infections

Review Editor Comments to the Author:
EMI would like to thank the authors for providing a timely piece. It will have major impact to clear many people's confusion.

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author

This is a timely commentary. It is perfectly written. All four authors are well established virologists. I suggest to publish it right away.

From: Liu, Shan-Lu
To: TEMI-production@journals.tandf.co.uk
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Shan-Lu Liu & Lishan Su

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
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Shan-Lu Liu & Lishan Su

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
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Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
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Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

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From:	Liu, Shan-Lu
To:	Weiss, Susan
Cc:	Su, Lishan; Lu, Shan
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Date:	Wednesday, February 12, 2020 4:05:39 PM
Attachments:	EMI-2019-nCoV_Commentary_Final for submission .docx image001.png image002.png

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Hi Susan,

That is great! Attached please see the final version of the commentary, with you name being added.

Best wishes.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Date: Wednesday, February 12, 2020 at 4:00 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: [External] Commentary for EMI

Shan-LU
I am still in Spain, going home on Saturday.
Yes please add my name as a co-author. This is important!!
Is the new virus now names SARS-2; maybe not a good name – should be different from SARS

I hope I am not too late

susan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Wednesday, February 12, 2020 at 5:26 PM
To: "Weiss, Susan" <weisssr@pennmedicine.upenn.edu>
Cc: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: [External] Commentary for EMI

Dear Susan,

Hope your trip back to Philly was safe and pleasant.

Dr. Lishan Su at UNC and I have just wrapped up a commentary, at invitation by the editor in chief of "Emerging Microbes and Infections", Dr. Shan Lu (don't get confused, it's not me). We are wondering if you would be interested in joining us as a coauthor. We feel that this is an important issue, and as scientist, we should clear this thing up if we can.

Please let us know as soon as possible, as we will try to submit it today. If you feel someone else (other coronavirus experts), whom might be interested in becoming a coauthor, kindly let us know as well.

Best wishes.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
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Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
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Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

SARS-CoV-2: no evidence of a laboratory origin

Lishan Su[1], and Linda J. Saif [2,3], Susan Weiss [4], and Shan-Lu Liu[3, 5,6.7]

[1] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[3] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[4] Department of Microbiology, Perelman School of Medicine,

University of Pennsylvania, Philadelphia, Pennsylvania, USA

[5] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[6] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[7] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1, 2, 3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4, 5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding sequences, and among the 128 nonsynonymous mutations, 89 led to predicted radical amino-acid changes [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring

pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might have CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10, 11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6, 12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was fully attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-

director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5, 14], the SARS-CoV-2 is undoubtedly distinct from SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SHC014-MA15 virus. Finally, we note that the synthetic and chimeric panels of bat and SARS-like CoV led to the identification of remdesivir as a broad spectrum inhibitor of all group 2b SARS-like coronaviruses tested in vitro or in vivo [15, 16], providing critical preIND data that led to the ongoing clinical trials in China and for the future development of universal vaccines for all the SARS-like coronaviruses.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 expert Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of randomly occurring mutations. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

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From: Liu, Shan-Lu
To: Lu, Shan; Su, Lishan
Subject: Re: Executive summary of EMI commentary
Date: Sunday, February 23, 2020 1:21:13 PM
Attachments: Liu et al_EMI Commentary_Revision_中文-Shan Lu.docx
Liu et al_EMI Commentary_Revision_中文-Shan Lu.pdf
刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论_Final.docx
刘善虑苏立山等教授发文分析驳斥新冠病毒阴谋论_Final.pdf
image001.png

Now, the final versions, a total of 4 files - hopefully!

SL

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 23, 2020 at 1:15 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Executive summary of EMI commentary

Overall they are very good.

I found one minor error: "Dec" was used for the last reference of your paper. It should be "Feb". You may want to change the current word and pdf, but not change the real paper to be published as it may take a lot of more time to current and reload to online. Readers can find that paper without much problem.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 23, 2020 12:57 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Executive summary of EMI commentary

See my final versions of two files, Word and PDF.

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 23, 2020 at 12:51 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Executive summary of EMI commentary

Your school's email screening system is good! Thanks.

From: Liu, Shan-Lu <liu.6244@osu.edu>

Sent: Sunday, February 23, 2020 12:49 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: Executive summary of EMI commentary

Never, just received Shan's email and file! Slow on my end.

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Sunday, February 23, 2020 at 12:48 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: Executive summary of EMI commentary

Great work. However, I made some new changes (see attached). All highlighted or marked, for your reference.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Sunday, February 23, 2020 8:57 AM
To: Su, Lishan <lishan_su@med.unc.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Executive summary of EMI commentary

Lishan and Shan – so confusing!

I have wrapped up a summary for the public and media to understand key points of our commentary. Please make suggestions.

I think this can go along with the Chinese translation.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 7:39 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 7:33 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

I just went online to see if we replace with a new one.
Could you send me the PDF of the corrected one?

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 4:32 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

My bad. How do we fix it? send her a message?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 7:29 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

Lishan:

I just saw that you deleted nt for 1,100 – “nt” should be kept. Could you correct that?

Thanks.

SL

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.

Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Friday, February 21, 2020 at 4:28 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Submitted Corrections for article TEMI 1733440

Thanks!

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Friday, February 21, 2020 at 7:22 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Saif, Linda" <saif.2@osu.edu>, Susan Weiss <weisssr@pennmedicine.upenn.edu>
Subject: Fwd: Submitted Corrections for article TEMI 1733440

Shan-Lu Liu sent from iPhone

Begin forwarded message:

> **From:** "TEMI-production@journals.tandf.co.uk" <cats@taylorandfrancis.com>
> **Date:** February 21, 2020 at 4:04:41 PM PST
> **To:** "TEMI-production@journals.tandf.co.uk" <TEMI-production@journals.tandf.co.uk>, "Liu, Shan-Lu" <liu.6244@osu.edu>
> **Subject: Submitted Corrections for article TEMI 1733440**
> **Reply-To:** TEMI-production@journals.tandf.co.uk
>
> Article: No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2
>
> Journal: *Emerging Microbes & Infections* (TEMI)

Article ID: TEMI 1733440

Dear author,

This email confirms that you have submitted your corrections to your article proofs.

The submitted corrections have been successfully uploaded.

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Yours sincerely,

Malathi Boopalan

Email:TEMI-production@journals.tandf.co.uk

没有可信的证据支持 SARS-CoV-2 来自实验室人工合成

Shan-Lu Liu（刘善虑）, 俄亥俄州立大学

Linda J. Saif, 俄亥俄州立大学

Susan Weiss, 宾夕法尼亚大学

Lishan Su,（苏立山）北卡大学教堂山分校

截止 2020 年 2 月 10 日，在武汉出现和爆发的急性呼吸疾病已波及 4 万多人，导致 1000 多人死亡。研究人员很快找到了一种新型人的冠状病毒，称之为 2019 nCoV 或 SARS-CoV-2，而相应的疾病称之为 COVID-19，意为 2019 年发生的冠状病毒疾病 (https://globalbiodefense com/novel-coronavirus-covid-19-portal/)。

据现有的报道[1-3]，COVID-2019 与 SARS-CoV 导致的 SARS 有很多相似的临床表现。而 SARS-CoV-2 基因组序列也和 2003 年 SARS-CoV 有 80%同源性，但它与一些蝙蝠的乙型冠状病毒更为相似。当前，种种的推测、谣言和阴谋论到处流行，其中有的认为 SARS-CoV-2 来源于实验室基因工程制造。也有某些人声称，人的 SARS-CoV-2 是从武汉的某个实验室直接泄漏出来的， 其根据是该实验室最近报道了一种称为 RaTG13 的蝙蝠冠状病毒，它和 SARS-CoV-2 基因组序列有高达 96%的同源性。

然而，我们知道，2003 年发现人 SARS 冠状病毒和其中间宿主果子狸 SARS 样冠状病毒具有 99.8％的同源性，在整个基因组中只有 202 个碱基不同。鉴于人类新型 SARS-CoV-2 与蝙蝠 RaTG13-CoV 之间有超过了 1000 个不同碱基[4]，且这些差异是按照冠状病毒典型的进化特征按自然发生的模式分布在整个基因组中，我们认为 SARS-CoV-2 直接来源于 RaTG13 冠状病毒的可能性极小。更为重要的是，在新的人 SARS-CoV-2 病毒基因组序列中并没有任何可信的基因工程改造的迹象，这都揭示 SARS-CoV-2 是通过自然演化而来的。我们认为在蝙蝠与人类之间可以找到中间动物宿主含有类似的冠状病毒，它与 SARS-CoV-2 更相似。最近有消息称穿山甲可能携带与 SARS-CoV-2 密切相关的冠

状病毒，但论文和数据尚未正式发表，无从得以证实(https://www.nature.com/articles/d41586-020-00364-2)。

最近社交媒体上的另一种说法指向 2015 年在《自然医学》发表的一篇论文[7]。该论文报道了在小鼠适应后的人类 SARS 冠状病毒（MA15 病毒）中，人工构建了带有蝙蝠冠状病毒（SHC014）S 基因，这种合成的嵌合冠状病毒，不仅可以可以感染小鼠，也能够感染来源人的细胞[8]。然而，新型冠状病毒 SARS-CoV-2 与这个嵌合冠状病毒基因组序列有超过了 5,000 个碱基的不同，所以这种怀疑完全缺乏任何科学依据。

现在我们来理一理来人 SARS 病毒老鼠适应株 MA15 和它的衍生病毒的来龙去脉。适应小鼠的 SARS 病毒（MA15）[9]是通过把 SARS 冠状病毒在小白鼠呼吸道中连续传代 15 后产生的；适应后的 SARS 冠状病毒有六个氨基酸突变，使其能够更有效地感染小鼠，尤其是在老年小鼠中具有了更高的复制活性和肺部致病性能（因此称为 M15）。由于在小鼠内适应的遗传突变，MA15 在人细胞或者人体内感染很可能降低了。

科学家曾认为从蝙蝠身来的冠状病毒的 S 基因和人的 SARS 病毒不同，推测它们无法使用人的 SARS 病毒受体 ACE2 进入人体细胞[10, 11]；后来发现果子狸是蝙蝠冠状病毒传给人的中间宿主，能够将 SARS 冠状病毒传播给人类[6，12]。然而，2013 年以来，科学家陆续从中国马蹄蝠中分离到了数个新型蝙蝠冠状病毒，这些来自蝙蝠的，类似人 SARS 冠状病毒（SL-CoV-WIV1）能够使用人、果子狸和中国马蹄蝠的 ACE2 受体进入和感染细胞[8]。进化研究表明，在 SARS 冠状病毒 S 蛋白的作用接触位点上，蝙蝠 ACE2 基因在与人类 ACE2 基因在相同的位点上同样被进化选择[13]。基于这样的发现，科学家提出了蝙蝠的 SARS 样冠状病毒具有直接传染到人的能力，不必需要中间宿主环节；也就是说有些蝙蝠冠状病毒有可能直接感染人类宿主细胞。为了直接验证这种可能性，蝙蝠冠状病毒 SL-SHC014 的 S 基因被人工嫁接到了 MA15 SARS-CoV 骨架上，因此产生了一个嵌合病毒。此 SL-SHC014-MA15 嵌合病毒确实能够有效地利用人 ACE2 进入细胞，并在人的呼吸道实验细胞中有效复制。SL-SHC014-MA15 也可以在小鼠的肺中高效复制，但与 SARS MA15 相比，感染减弱了，并且只会让老年小鼠致命[7]。

由于 SL-SHC014-MA15 嵌合病毒相对于另一个人 SARS-S/MA15 嵌合病毒在小鼠中具有更高的致病活性，这种嵌合冠状病毒的实验后来在美国政府的干预下被暂停(https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-

pause-gain-function-research)。虽然目前 这项禁令在美国已经被解除，但构建这种具有大流行病潜力的病毒是否是一种风险，在当前的COVID-2019流行的形势下又重新引发了讨论，成为热点话题。然而，经过多个国家科学家对病毒的分子进化分析[5，14]，SARS-CoV-2 无疑与 SL-SHC014-MA15 具有非常大的不同，整个基因组有大约 6,000 核苷酸的差异。因此，没有可信的证据支持 SARS-CoV-2 是源自 SL-SHC014-MA15 嵌合病毒的说法。

最近也有传言说，SARS-CoV-2 是实验室中有意人为制造的。其中发表在 BioRxiv（一个同行评审之前的手稿共享网站）的一份手稿中更是此传言的代表，它声称 SARS-CoV-2 中含有 HIV 序列，因此很可能是在实验室中产生的。文章在线后， 舆论哗然，世界各国的多个病毒学者纷纷反驳。 在 HIV-1 病毒专家高峰（Feng Gao）领衔领导的反驳论文中，他们使用了仔细的生物信息学分析来证明，指出最初声称的 SARS-CoV-2 有多个 HIV-1 插入片段并非 HIV-1 特有，而是完全随机的 [15]。由于国际社会提出的种种疑问，这篇手稿的作者已经撤回了该手稿， 不再要求发表。

从科学层面讲，进化是循序渐进的，并随着时间的推移进一步产生有利于病毒的突变，就像天然分离的病毒（如蝙蝠冠状病毒 RaTG13）基因组那样。 相反，人工合成的病毒基因组通常会使用已知的病毒骨架引入一些某些定向的变化。所以我们认为，目前没有可靠的证据支持 SARS-CoV-2 是来源于实验人工设计。 有一种可能不能排除， 就是 SARS-CoV-2 是一种蝙蝠冠状病毒与另一种冠状病毒之间进行了自然重组而产生的；但这种可能性需要更多的研究来证明，来回答 SARS-CoV-2 的自然起源问题。我们需要强调的是，尽管目前没有证据显示新型冠状病毒 SARS-CoV-2 来自实验室人工制造，但对公共健康有威胁的病毒都必须进行恰当的实验室管理，而且需要由科学界和政府合理监管。

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刘善虑苏立山等教授发文分析认为新冠病毒阴谋论缺乏病毒学证据

俄亥俄州立大学教授刘善虑，北卡大学教堂山分校教授苏立山联名国际著名冠状病毒学家 Linda J. Saif（美国科学院院士）以及 Susan Weiss（美国微生物科学院院士），在 国际期刊 Emerging Microbes & Infections (EMI) (中文译名《新发微生物与感染》)发表题为“**没有可信的证据支持 SARS-CoV-2 来自实验室人工合成**”的评论文章，对最近广为流行的传言和阴谋论进行了分析和驳斥。

该文主要论点如下：

1. 新型冠状病毒 SARS-CoV-2 虽与中国科学院武汉病毒所最近报道的一个称为 RaTG13 的蝙蝠冠状病毒有高达 96%的同源性， 但两者仍然有超过 1，100 碱基的差别，而且在关键序列序列上有特征性区别，因此两者是完全不同的冠状病毒。
2. 社交媒体指向 2015 年在《自然医学》（Nature Medicine）一篇论文，认为新型冠状病毒是这篇文章报道的人 SARS 与蝙蝠冠状病毒（SHC014）的嵌合病毒的泄露。然而，分析研究表明，新型冠状病毒 SARS-CoV-2 与这个嵌合冠状病毒在基因组序列上有超过了 5,000 个碱基的不同，所以这种怀疑完全缺乏任何科学依据。
3. 还有一种传言说 SARS-CoV-2 是实验室中有意人为制造的， 并以发表在 BioRxiv 上印度科学家的一份手稿中为依据，声称 SARS-CoV-2 中含有 HIV 序列。实际上这篇文章在线发表后， 舆论哗然，世界各国病毒学家也纷纷反驳。 在 HIV-1 专家高峰（Feng Gao）领衔领导发表在 EMI 的另一篇反驳论文中，作者使用了仔细的生物信息学分析来证明，指出原文作者声称的 SARS-CoV-2 有多个 HIV-1 插入片段并非 HIV-1 特有，而是完全随机的。由于国际社会提出的种种疑问，这篇手稿的作者也已经撤回了该手稿， 目前没有发现再次发表。
4. 从科学层面讲，病毒进化是循序渐进的，并切随着时间的推移进一步产生有利于病毒感染人的突变。相反，人工合成的病毒基因组通常会在已知的病毒骨架引入一些某些定向的变化。所以，目前没有可靠的证据支持 SARS-CoV-2 是来源于实验人工设计。
5. 尽管目前没有证据显示新型冠状病毒 SARS-CoV-2 来自实验室人为制造，我们认为对公共健康有威胁的病毒都必须进行严格恰当的实验室管理，而且需要由科学界和政府联合监管。

From:	Liu, Shan-Lu
To:	Yost, Mary
Cc:	Herb Grant
Subject:	Re: Final version of the letter: "COVID-19 and The Virus That Causes It" - OSU
Date:	Wednesday, March 25, 2020 8:36:18 AM
Attachments:	image001.png image002.png image003.png image004.png image005.png

---

That is great, and thank you Mary and Herb.
Kindly keep me updated.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Yost, Mary" <myost@dispatch.com>
Date: Tuesday, March 24, 2020 at 7:28 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: Herb Grant <hgrant@dispatch.com>
Subject: Re: Final version of the letter: "COVID-19 and The Virus That Causes It" - OSU

Thanks, that should work.

Mary Yost
Editorial Page Editor
Columbus Dispatch
62 E. Broad St.
Columbus, OH 43215
614-461-5040 (office)
614-204-6798 (cell)
myost@dispatch.com

On Tue, Mar 24, 2020 at 7:26 AM Liu, Shan-Lu <liu.6244@osu.edu> wrote:

> Thank you. I have attached my photo. Let me know if the photo does not work or you need anything else.
>
> Once you have decided, kindly let me know, because the OSU communication folks would like to be looped.
>
> Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Yost, Mary" <myost@dispatch.com>
Date: Tuesday, March 24, 2020 at 6:47 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: Encarnacion Pyle <epyle@dispatch.com>, "miller, alan" <amiller@dispatch.com>, Herb Grant <hgrant@dispatch.com>
Subject: Re: Final version of the letter: "COVID-19 and The Virus That Causes It" - OSU

Thank you very much.

If we publish this we would also need your high-resolution head-and-shoulders photo.

If you can submit one, please also copy Herb Grant.

Mary

Mary Yost
Editorial Page Editor

Columbus Dispatch
62 E. Broad St.
Columbus, OH 43215
614-461-5040 (office)
614-204-6798 (cell)
myost@dispatch.com

On Tue, Mar 24, 2020 at 12:19 AM Liu, Shan-Lu <liu.6244@osu.edu> wrote:

> Dear Mary,
>
> I have modified the letter by following your instructions. First, I changed the author number to one. Second, I shortened the letter and now its length is ~700 words. Third, I revised the letter by removing “facts” but adding more opinions.
>
> I hope the letter is now acceptable for publication in Columbus Dispatch. Kindly note that the disclaimer in the end is important so please make sure to keep it.
>
> Thank you so much for your help with this effort.
>
> Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Yost, Mary" <myost@dispatch.com>
Date: Monday, March 23, 2020 at 7:38 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: Encarnacion Pyle <epyle@dispatch.com>
Subject: Re: Greetings and inquiry: COIVD-19 commentary

Thank you, but I am not sure it would be suitable for our opinion pages. I encourage you to work with our news side, since it sounds like you are wanting to convey facts, not commentary.

And no, we would not run it with three authors. In cases where multiple individuals want to be credited, we have advised that the others be noted in the body of the article, but that also takes space away from the content you want to present.

We do a weekly review of pending op-eds on Friday afternoons and can let you know after our review if we will publish your submission. The news side could probably share your information sooner than we can on our opinion pages, even if we are able to publish it.

Mary

Mary Yost
Editorial Page Editor
Columbus Dispatch
62 E. Broad St.
Columbus, OH 43215
614-461-5040 (office)
614-204-6798 (cell)
myost@dispatch.com

On Mon, Mar 23, 2020 at 5:13 PM Liu, Shan-Lu <liu.6244@osu.edu> wrote:

> Hi Mary,
>
> Thank you for your consideration.
>
> Over the last few weeks, I kept receiving requests from people, including local fire departments regarding how this virus is spread and causes the disease, etc. This really motivated me to write something with some updated information that I thought would be helpful to our readers.
>
> Yes, we can cut down to 700 words, with no problem, but I would still prefer to have three authors, because all are co-directors of the OSU program and we have contributed equally.
>
> Thank you so much, and let me know how to proceed.
>
> Shan-Lu
>
> 
> THE OHIO STATE UNIVERSITY
>
> Shan-Lu Liu, M.D., Ph.D.

Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Yost, Mary" <myost@dispatch.com>
Date: Monday, March 23, 2020 at 4:56 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: Encarnacion Pyle <epyle@dispatch.com>
Subject: Re: Greetings and inquiry: COIVD-19 commentary

Hi Shan-Lu,

Thank you for offering to send us an op-ed, but it might be better if you could share your expertise with our news side.

As you can imagine, we continue to receive a lot of guest columns around the topic of coronavirus and its impact on all facets of life today. One of the challenges we have with the opinion pages is limited space, just two pages each day, without a lot of flexibility in how we fill our space.

It sounds like the kind of information you have to share is more factual than opinion, which might be better suited for news coverage that doesn't have the space restrictions we do.

A couple of other concerns -- we typically don't run guest columns from more than one author; and our usual length is about 700 words. We made an exception for a guest column that will appear in Tuesday's paper, but that is very rare. I don't know if 700 words would be enough to cover all that you have to share.

I am copying one of our metro editors, Encartia Pyle, in case you would be interested in following up with a news reporter to share your insights.

Thank you for thinking of The Dispatch; and thank you for what you are doing related to the coronavirus.

Mary

Mary Yost
Editorial Page Editor
Columbus Dispatch
62 E. Broad St.
Columbus, OH 43215
614-461-5040 (office)
614-204-6798 (cell)
myost@dispatch.com

On Sat, Mar 21, 2020 at 9:12 PM Liu, Shan-Lu <liu.6244@osu.edu> wrote:

> Dear Alan,
>
> Greetings! Hope this email finds you well.
>
> I am not sure if you are the right person to contact, but please forgive me and help make the connection to the Dispatch.
>
> In 2016 when I joined OSU, Emily Tate wrote a story on me about the Zika virus, see attached article. Now COIVD-19 is here, and as co-director of the OSU Viruses and Emerging Pathogens program, my colleagues Linda Saif, Jacob Yount and I have written a commentary on COIVD-19, which we wish to publish in the Dispatch as commentary or other forms. Our focus is on the virus, SARS-CoV-2, which causes the outbreak and the disease COIVD-19.
>
> The motivation is that I recently have received a lot of requests from local media and even fire department for interview, and I thought that this commentary may be able to address some of the reader's questions.
>
> See below some of my writings published in journals:
>
> https://www.nature.com/articles/d41586-020-00135-z
>
> **New virus in China requires international control effort**
>
> **Emerging Viruses without Borders: The Wuhan Coronavirus**
>
> **https://www.mdpi.com/1999-4915/12/2/130**
>
> https://www.tandfonline.com/doi/full/10.1080/22221751.2020.1733440
>
> **No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2**

SARS-CoV-2 is an appropriate name for the new coronavirus

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30557-2/fulltext

Thank you for your consideration. If your newspaper is interested, please let me know and I will send the article to you shortly.

Sincerely,

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

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From: Liu_Shan-Lu
To: temi-peerreview@journals.tandf.co.uk
Cc: Lu_Shan; Su_Lishan
Subject: Re: Emerging Microbes & Infections - TEMI-2020-0121 - changes required to your submission
Date: Thursday, February 13, 2020 8 56:46 AM
Attachments: Liu et al_EMI Commentary_15 references.docx
Importance: High

Hi Jorgie:

I have modified as instructed and attached the new one to this email Please help upload and proceed

Thank you

Shan-Lu

Shan-Lu Liu, M D , Ph D
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu 6244@osu edu; shan-lu liu@osumc edu

On 2/13/20, 8:43 AM, "Emerging Microbes and Infections" <onbehalfof@manuscriptcentral com> wrote:

13-Feb-2020

Dear Professor Liu,

Your above referenced manuscript, entitled "SARS-CoV-2: no evidence of a laboratory origin" requires some further changes before it is ready for reviewing in Emerging Microbes & Infections Your submission has been returned to you and is located in your Author Center as a draft, so that you due to these reasons:

1 No line numbering

Kindly add a line numbering in your main document

2 Exceeded reference count

Kindly be informed that the reference count for the commentary article should not be more than 15

Your submission along with all files you submitted is now in your Author Center, at https://urldefense com/v3/__https://mc manuscriptcentral com/temi__!!KGKeukY!nGv1RgRJ1P-OGXuZi8b2hKGjXxDFOmBwDONuR_njCdwERJF1HkBIV4Sgqqr9udyWYmI$ Please read the Quick Guide to Continuing your Submission, which shows how you can access your manuscript, and submit it back to the site The Guide is located at https://urldefense com/v3/__http://mc manuscriptcentral com/societyimages/tandf_qs0/Continuning*20a*20Submission_screenshot pdf__JSU!!KGKeukY!nGv1RgRJ1P-OGXuZi8b2hKGjXxDFOmBwDONuR_njCdwERJF1HkBIV4Sgqqr9re6Z8tA$

You may contact the Editorial Office if you have further questions

Sincerely,

Jorgie Lyn Luna
Emerging Microbes & Infections Editorial Office
temi-peerreview@journals tandf co uk

SARS-CoV-2: no evidence of a laboratory origin

Shan-Lu Liu [1, 2,3,4], Linda J. Saif [4,5], Susan Weiss [6], and Lishan Su [7]

[1] Center for Retrovirus Research, The Ohio State University,
Columbus, OH 43210, USA

[2] Department of Veterinary Biosciences, The Ohio State University, Columbus,
OH 43210, USA

[3] Department of Microbial Infection and Immunity, The Ohio State University,
Columbus, OH 43210, USA

[4] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,
The Ohio State University, Columbus, OH 43210, USA

[5] Food Animal Health Research Program,
Ohio Agricultural Research and Development Center, CFAES
Department of Veterinary Preventive Medicine,
The Ohio State University, Wooster, Ohio 44691, USA

[6] Department of Microbiology, Perelman School of Medicine,
University of Pennsylvania, Philadelphia, Pennsylvania, USA

[7] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,
University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1, 2, 3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4, 5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding sequences, and among the 128 nonsynonymous mutations, 89 led to predicted radical amino-acid changes [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that

RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10, 11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6, 12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-

director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5, 14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus. Finally, we note that the synthetic and chimeric panels of bat and SARS-like CoV led to the identification of remdesivir as a broad spectrum inhibitor of all group 2b SARS-like coronaviruses tested in vitro or in vivo [15], providing critical pre-clinical data that has led to the ongoing clinical trials in China and is critical for the future development of universal vaccines for all the SARS-like coronaviruses.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 expert Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

References

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From:	Liu, Shan-Lu
To:	Stanley Perlman
Cc:	Su, Lishan; Lu, Shan
Subject:	Re: Commentary for EMI
Date:	Wednesday, February 12, 2020 4:13:27 PM
Attachments:	EMI-2019-nCoV_Commentary_Final for submission .docx image001.png image002.png

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Hi Stanley,

I have attached an almost final version of the commentary. Note that Susan Weiss has agreed to become a coauthor. Kindly let us know if you are interested in joining if possible tonight.

Best wishes.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: Shan-Lu Liu <liu.6244@osu.edu>

Date: Wednesday, February 12, 2020 at 11:14 AM

To: Stanley Perlman <stanley-perlman@uiowa.edu>

Cc: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>

Subject: Commentary for EMI

Dear Stanley,

Hope all is well.

As you may know, Lishan at UNC and I have just wrapped up a commentary, at the invitation by the editor in chief of journal “Emerging Microbes and Infections”, Dr. Shan Lu (don’t get confused, it’s not me), and we are wondering if you would be interested in joining us as a coauthor. We feel that this is an important issue, and as

scientist, we should try to clear this thing up.

Let us know as soon as possible, as we will try to submit it today. If you feel someone else (other coronavirus experts), whom might be interested in becoming a coauthor, kindly let us know as well.

Best wishes.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

SARS-CoV-2: no evidence of a laboratory origin

Lishan Su[1], and Linda J. Saif [2,3], Susan Weiss [4], and Shan-Lu Liu[3, 5,6.7]

[1] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[3] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[4] Department of Microbiology, Perelman School of Medicine,

University of Pennsylvania, Philadelphia, Pennsylvania, USA

[5] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[6] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[7] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1, 2, 3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4, 5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding sequences, and among the 128 nonsynonymous mutations, 89 led to predicted radical amino-acid changes [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring

pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might have CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

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When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10, 11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6, 12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was fully attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-

director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5, 14], the SARS-CoV-2 is undoubtedly distinct from SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SHC014-MA15 virus. Finally, we note that the synthetic and chimeric panels of bat and SARS-like CoV led to the identification of remdesivir as a broad spectrum inhibitor of all group 2b SARS-like coronaviruses tested in vitro or in vivo [15, 16], providing critical preIND data that led to the ongoing clinical trials in China and for the future development of universal vaccines for all the SARS-like coronaviruses.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 expert Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of randomly occurring mutations. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

References

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Dec;21(12):1508-13. doi: 10.1038/nm.3985. PubMed PMID: 26552008; PubMed Central PMCID: PMCPMC4797993.

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11. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003 Nov 27;426(6965):450-4. doi: 10.1038/nature02145. PubMed PMID: 14647384.
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From:	Liu, Shan-Lu
To:	Yost, Mary
Cc:	Encarnacion Pyle; miller, alan
Subject:	Final version of the letter: "COVID-19 and The Virus That Causes It" - OSU
Date:	Tuesday, March 24, 2020 12:18:52 AM
Attachments:	Dispatch_commentary_Liu_OSU.docx image001.png image002.png image003.png

Dear Mary,

I have modified the letter by following your instructions. First, I changed the author number to one. Second, I shortened the letter and now its length is ~700 words. Third, I revised the letter by removing “facts” but adding more opinions.

I hope the letter is now acceptable for publication in Columbus Dispatch. Kindly note that the disclaimer in the end is important so please make sure to keep it.

Thank you so much for your help with this effort.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Yost, Mary" <myost@dispatch.com>
Date: Monday, March 23, 2020 at 7:38 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: Encarnacion Pyle <epyle@dispatch.com>
Subject: Re: Greetings and inquiry: COIVD-19 commentary

Thank you, but I am not sure it would be suitable for our opinion pages. I encourage you to work with our news side, since it sounds like you are wanting to convey facts, not commentary.

And no, we would not run it with three authors. In cases where multiple individuals want to be

credited, we have advised that the others be noted in the body of the article, but that also takes space away from the content you want to present.

We do a weekly review of pending op-eds on Friday afternoons and can let you know after our review if we will publish your submission. The news side could probably share your information sooner than we can on our opinion pages, even if we are able to publish it.

Mary

Mary Yost
Editorial Page Editor
Columbus Dispatch
62 E. Broad St.
Columbus, OH 43215
614-461-5040 (office)
614-204-6798 (cell)
myost@dispatch.com

On Mon, Mar 23, 2020 at 5:13 PM Liu, Shan-Lu <liu.6244@osu.edu> wrote:

> Hi Mary,
>
> Thank you for your consideration.
>
> Over the last few weeks, I kept receiving requests from people, including local fire departments regarding how this virus is spread and causes the disease, etc. This really motivated me to write something with some updated information that I thought would be helpful to our readers.
>
> Yes, we can cut down to 700 words, with no problem, but I would still prefer to have three authors, because all are co-directors of the OSU program and we have contributed equally.
>
> Thank you so much, and let me know how to proceed.
>
> Shan-Lu
>
> 
>
> Shan-Lu Liu, M.D., Ph.D.
> Professor
> Co-Director, Viruses and Emerging Pathogens Program
> Infectious Diseases Institute
> Center for Retrovirus Research

Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Yost, Mary" <myost@dispatch.com>
Date: Monday, March 23, 2020 at 4:56 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: Encarnacion Pyle <epyle@dispatch.com>
Subject: Re: Greetings and inquiry: COIVD-19 commentary

Hi Shan-Lu,

Thank you for offering to send us an op-ed, but it might be better if you could share your expertise with our news side.

As you can imagine, we continue to receive a lot of guest columns around the topic of coronavirus and its impact on all facets of life today. One of the challenges we have with the opinion pages is limited space, just two pages each day, without a lot of flexibility in how we fill our space.

It sounds like the kind of information you have to share is more factual than opinion, which might be better suited for news coverage that doesn't have the space restrictions we do.

A couple of other concerns -- we typically don't run guest columns from more than one author; and our usual length is about 700 words. We made an exception for a guest column that will appear in Tuesday's paper, but that is very rare. I don't know if 700 words would be enough to cover all that you have to share.

I am copying one of our metro editors, Encartia Pyle, in case you would be interested in following up with a news reporter to share your insights.

Thank you for thinking of The Dispatch; and thank you for what you are doing related to the coronavirus.

Mary

Mary Yost
Editorial Page Editor
Columbus Dispatch
62 E. Broad St.

Columbus, OH 43215
614-461-5040 (office)
614-204-6798 (cell)
myost@dispatch.com

On Sat, Mar 21, 2020 at 9:12 PM Liu, Shan-Lu <liu.6244@osu.edu> wrote:

> Dear Alan,
>
> Greetings! Hope this email finds you well.
>
> I am not sure if you are the right person to contact, but please forgive me and help make the connection to the Dispatch.
>
> In 2016 when I joined OSU, Emily Tate wrote a story on me about the Zika virus, see attached article. Now COIVD-19 is here, and as co-director of the OSU Viruses and Emerging Pathogens program, my colleagues Linda Saif, Jacob Yount and I have written a commentary on COIVD-19, which we wish to publish in the Dispatch as commentary or other forms. Our focus is on the virus, SARS-CoV-2, which causes the outbreak and the disease COIVD-19.
>
> The motivation is that I recently have received a lot of requests from local media and even fire department for interview, and I thought that this commentary may be able to address some of the reader's questions.
>
> See below some of my writings published in journals:
>
> https://www.nature.com/articles/d41586-020-00135-z
>
> **New virus in China requires international control effort**
>
> **Emerging Viruses without Borders: The Wuhan Coronavirus**
>
> **https://www.mdpi.com/1999-4915/12/2/130**
>
> https://www.tandfonline.com/doi/full/10.1080/22221751.2020.1733440
>
> **No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2**
>
> SARS-CoV-2 is an appropriate name for the new coronavirus

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30557-2/fulltext

Thank you for your consideration. If your newspaper is interested, please let me know and I will send the article to you shortly.

Sincerely,

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

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COVID-19 and The Virus That Causes It

Shan-Lu Liu

COVID-19 is now a global pandemic disease. The disease is caused by a coronavirus that has been officially named SARS-CoV-2. The virus originated in November 2019 in Wuhan, China, a city with a population of 11 million. A seafood wholesale market in the city is thought to be the origin of the virus, with infected wild animals transmitting the virus to humans. SARS-CoV-2 infects the lung in humans, and induces pneumonia. Unlike many animal viruses, it was able to initiate a deadly chain of human-to-human transmission.

Analysis of the virus genome shows that SARS-CoV-2 is most closely related to a virus circulating in bats, suggesting that bats were the source of the virus. Many other viruses have emerged from bats to infect humans, including the SARS coronavirus, Ebola virus and Zika virus. Pangolins, an endangered species of small mammals, harbor a coronavirus similar to SARS-CoV-2 leading to speculation that they may be an intermediate host that transfers virus between bats and humans. Recent data do not support this. Nonetheless, genetic analysis has confirmed that the virus emerged from animals and this finding should dispel unsubstantiated allegations that the virus was manmade.

The transmission rate for a virus can be measured by its reproductive number (R_0), which represents the number of people on average that will acquire the infection from a

single infected person. The R_0 for SARS-CoV-2 is estimated to be 2.7, which is higher than that of seasonal influenza virus (R_0 estimated at 2.0). However, this value for SARS-CoV-2 is likely an underestimate because it is based on confirmed positive cases and does not account for undiagnosed mild or asymptomatic cases.

SARS-CoV-2 can cause severe lung damage with pneumonia and even deaths. However, asymptomatic infections, which some have proposed are the majority of infections, are likely a primary source of transmitted virus. Hence, social distancing currently being practiced in the US and other COVID-19 afflicted countries is critical and should be heeded by all and enhanced as the most effective way to contain the virus in the absence of antivirals and vaccines.

The virus is transmitted by respiratory droplets that can remain airborne for several hours. These droplets can also settle on surfaces and remain infectious for several days. Thus, personal hygiene with frequent handwashing, and social distancing are the most effective means of slowing spread of the virus. Because eye infections may occur in SARS-CoV-2 infected individuals, eye protection is needed for health care workers and individuals should avoid touching their eyes with potentially contaminated hands.

Vaccination is the most effective strategy to prevent infectious diseases. Unfortunately, there is no FDA-approved vaccine for SARS-CoV-2-induced COVID-19. With unprecedented speed, a candidate vaccine has just entered the first phase of a human clinical trial. If successful, this candidate vaccine, or one of the many others in the

pipeline, will be a breakthrough for the control of COVID-19. In the meantime, many researchers are actively screening drugs for antiviral effects on SARS-CoV-2. Media coverage in recent days has focused on an anti-malaria drug known as chloroquine. While we are cautiously optimistic, results of ongoing clinical trials are needed to prove conclusively whether chloroquine is effective and safe for treating COVID-19 patients.

At The Ohio State University, as co-directors of the Viruses and Emerging Pathogens Program of The Infectious Diseases Institute, we are working with the community of immunology and virology researchers as teams to better understand and combat COVID-19. The teams are contributing their collective expertise and new ideas to aid in this battle. Our ultimate goals are to develop effective vaccines and antivirals in order to combat COIVD-19. In addition, the research community is assisting in generating COVID-19 testing reagents to overcome national shortages. Through focused interdisciplinary research, we will be better able to enhance knowledge and devise solutions to combat COVID-19 and viruses that emerge in the future.

Dr. Shan-Lu Liu is co-director of the Viruses and Emerging Pathogens Program of The Infectious Diseases Institute at The Ohio State University. The author acknowledges co-directors Drs. Linda Saif and Jacob Yount for critical input and comments. The opinions expressed in this article do not necessarily represent the viewpoints of The Ohio State University.

Shan-Lu Liu, liu.6244@osu.edu

From: Liu, Shan-Lu
To: Su, Lishan
Cc: Lu, Shan
Subject: Re: EMI commentary
Date: Wednesday, February 12, 2020 6:04:17 PM
Attachments: EMI-2019-nCoV_Commentary_for submission .docx
image001.png

Lishan: My understanding is that Shan does not want to be included as a coauthor… That is why I thought you would be the first author because you had the first draft

Shan: Let us know what you think.

See the updated version, with the new authorship order.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Wednesday, February 12, 2020 at 5:55 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
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I agree Shan Lu should be a corresponding author too.

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Best.

Shan-Lu

THE OHIO STATE UNIVERSITY

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Regards.

Shan-Lu

SARS-CoV-2: no evidence of a laboratory origin

Shan-Lu Liu [1, 2,3,4], Linda J. Saif [4,5], Susan Weiss [6], and Lishan Su [7]

[1] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[2] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[3] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

[4] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[5] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[6] Department of Microbiology, Perelman School of Medicine,

University of Pennsylvania, Philadelphia, Pennsylvania, USA

[7] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

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According to what has been reported [1, 2, 3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4, 5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding sequences, and among the 128 nonsynonymous mutations, 89 led to predicted radical amino-acid changes [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that

RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10, 11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6, 12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-

director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5, 14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus. Finally, we note that the synthetic and chimeric panels of bat and SARS-like CoV led to the identification of remdesivir as a broad spectrum inhibitor of all group 2b SARS-like coronaviruses tested in vitro or in vivo [15, 16], providing critical pre-clinical data that has led to the ongoing clinical trials in China and is critical for the future development of universal vaccines for all the SARS-like coronaviruses.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 expert Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

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From: Liu, Shan-Lu
To: Su, Lishan
Cc: Lu, Shan
Subject: Re: EMI commentary
Date: Wednesday, February 12, 2020 6:29:06 PM
Attachments: Liu et al_ EMI Commentary_for submission .docx
Su et al_ EMI Commentary_Final for submission .docx
image001.png

Hi Lishan:

See both versions attached, either way works for me. It's your call.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Wednesday, February 12, 2020 at 6:26 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

It is probably fine if we cover not only the unc chimeric virus now.

-Lishan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Wednesday, February 12, 2020 6:09:46 PM
To: Su, Lishan <lishan_su@med.unc.edu>
Cc: Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: EMI commentary

Lishan:

Now I understand your point of concern. I should be fine either way, as OSU should not care.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Wednesday, February 12, 2020 at 5:55 PM
To: Shan-Lu Liu <liu.6244@osu.edu>
Cc: "Lu, Shan" <Shan.Lu@umassmed.edu>
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Lishan Su [1], and Linda J. Saif [2,3], Susan Weiss [4], and Shan-Lu Liu [3, 5,6.7]

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[4] Department of Microbiology, Perelman School of Medicine,

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director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5, 14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus. Finally, we note that the synthetic and chimeric panels of bat and SARS-like CoV led to the identification of remdesivir as a broad spectrum inhibitor of all group 2b SARS-like coronaviruses tested in vitro or in vivo [15, 16], providing critical pre-clinical data that has led to the ongoing clinical trials in China and is critical for the future development of universal vaccines for all the SARS-like coronaviruses.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 expert Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

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SARS-CoV-2: no evidence of a laboratory origin

Shan-Lu Liu [1, 2,3,4], Linda J. Saif [4,5], Susan Weiss [6], and Lishan Su [7]

[1] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[2] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[3] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

[4] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[5] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[6] Department of Microbiology, Perelman School of Medicine,

University of Pennsylvania, Philadelphia, Pennsylvania, USA

[7] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Contact: Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1, 2, 3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4, 5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding sequences, and among the 128 nonsynonymous mutations, 89 led to predicted radical amino-acid changes [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that

RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10, 11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6, 12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-

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There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 expert Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

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From: Liu, Shan-Lu
To: Su, Lishan; Lu, Shan
Subject: Re: 2019-nCoV-EMI_commentary
Date: Wednesday, February 12, 2020 6:33:40 AM
Attachments: EMI-2019-nCoV_Commentary LJS_SLL.docx
image001.png
image002.png

I have incorporated Linda's comments into the MS, see attached. I am now working on the references…

Note the new title "**Evidence refuting laboratory origin of SARVS-CoV-2**"…it is now long and more like an article…

SL

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Wednesday, February 12, 2020 at 1:13 AM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

See the endnote file. Thanks,

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 7:44 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Sounds good, thank you. I still like “however” over “In contrast” – it just reads better

Shan: Are you sure that you prefer not to be included in the coauthorship? Before I send, I think we should have the authorship listed, along with affiliations. Lishan should be the first author, unless he prefers otherwise. Agreed?

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 7:34 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

I made some minor change for the following:

In summary, there is no credible evidence at this point to support the claims that the 2019-nCoV was originated from a laboratory-engineered CoV. In contrast, we cannot rule out the possibility that 2019-nCoV is a recombinant generated in nature between a bat CoV and another coronavirus in an intermediate host. More studies are needed to explore this possibility and resolve the origin of 2019-nCoV.

Maybe now SLL can send the next version to other CoV experts?

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 5:47 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

See the new version with all incorporated.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 4:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I have made additional changes to the Lishan’s version, see attached.

Lishan: I share your concern, and that is one reason that Shan, the editor, decides to have a short version.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 4:16 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

The new title is good if we will cover the RaTG13 and HIV insertion issues.
I am still worried if we can shed any light on the major claim of RaTG13 lab escape/evolution in other hosts/humans over the years…?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 3:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Perhaps Lishan can take a look at the latest version, which has the new title I suggested, and modify it as needed.
The last paragraph is also crucial, but I did not have time to work on it because of a meeting this morning.
Once we have almost a final draft, I will contact Linda Saif, Stanley Perlman, Thomas Gallgaher etc. to see if they are willing to join, but this may delay the publishing time.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 1:52 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I agree that it should be simple and clear. I have included some details in the 1st draft for your information. There is not intention to defend Baric, but to clarify the facts.

Regarding all three, are you combining Goa Feng's piece with this one? For the RaTG13, it involves complicated viral evolution kinetics and maybe hard to simply clarify…
Best,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 1:44 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>

Subject: RE: 2019-nCoV-EMI_commentary

Sorry here is the attachment with tracking

From: Lu, Shan
Sent: Tuesday, February 11, 2020 1:44 PM
To: 'Su, Lishan' <lishan_su@med.unc.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Hi, I am adding Shuying from my group. She just read the last draft from Lishan and identified a few errors (with tracking).

Also I just had a phone call with SSL and we agreed on the following:

1. We need to make this commentary very simple and short;
2. It is better not going to too much science/tech details as it can only confuse people and provide more room for people to raise more questions;
3. We don't want to appear that we are defending Ralph even though he did nothing wrong.
4. We feel it is best to cover 3 issues in this commentary (for the above reason, plus it is more powerful to cover multiple issues in one summary)
5. ??

SLL: please add anything I missed.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 12:52 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Looking at Shanlu's version, we may need a separate for the RaTG13 vs lab accident theory...

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 12:44 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs

more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

Thanks.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Evidence refuting laboratory origin of SARVS-CoV-2

Lishan Su[1], and Linda J. Saif [2,3], XXX, XXX, and Shan-Lu Liu[3, 4,5.6]

[1] Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill,

Chapel Hill, North Carolina, USA

[2] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[3] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[4] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[5] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[6] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

Dr. Lishan Su, lsu@med.unc.edu

Dr Linda J. Saif, Saif.2@osu.edu

XXX, XXX

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A novel human coronavirus, SARS-CoV-2 was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (WHO ref here).

According to what has been reported (Lancet, NEJM 2020), COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat betacoronaviruses, with the highest being >96% identity (Nature 2020 refs).

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From: Liu, Shan-Lu
To: Su, Lishan; Lu, Shan
Subject: Re: 2019-nCoV-EMI_commentary
Date: Wednesday, February 12, 2020 6:30:15 AM
Attachments: EMI-2019-nCoV_Commentary LJS_SLL.docx
image001.png

I have incorporated Linda's comments into the MS, see attached. I am now working on the references…

SL

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Date: Wednesday, February 12, 2020 at 1:13 AM
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Subject: 2019-nCoV-EMI_commentary

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Shan-Lu

THE OHIO STATE UNIVERSITY

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Evidence refuting laboratory origin of SARVS-CoV-2

Lishan Su[1], and Linda J. Saif [2,3], XXX, XXX, and Shan-Lu Liu[3, 4,5.6]

[1] Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill,

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Date: Wednesday, February 12, 2020 7:19:39 AM
Attachments: EMI-2019-nCoV_Commentary LJS_SLL_Refs.docx
image001.png

Please use the latest updates, with minor changes.

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[6] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

Dr. Lishan Su, lsu@med.unc.edu

Dr Linda J. Saif, Saif.2@osu.edu

XXX, XXX

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A novel human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (WHO website link ref).

According to what has been reported [1-3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat betacoronaviruses, with the highest being >96% identity [4,5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding DNA sequences (CDSs), and among the 128 nonsynonymous mutations, 89 led to a predicted radical amino-acid changes (Song et al, PNAS 2005). Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern and follow the

evolution characteristics typical of CoVs, including the S gene as the most variable region, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might have CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (website link ref).

Another claim points to a Nature Medicine paper published in 2015 [6], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [7]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2.

The recombinant mouse-adapted SARS virus (MA15) (PLoS Pathog. 2007 Jan;3(1):e5) was generated by serial passage of an infectious SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is also likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [8,9]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans (need to find refs). However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [7]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [10], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-SHC014 was used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-MA15 can replicate efficiently in the mouse lung, leading to severe pathogenesis [6].

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus are now restricted as gain of function (GOF) studies under the US government-mandated pause policy. The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding these bat CoVs already exist in nature. Regardless, upon careful phylogenetic

analyses by multiple international groups [5,11], the SARS-CoV-2 is undoubtedly distinct from SHC014- MA15, with >5000 nt differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SHC014-MA15 virus.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv, (and not yet peer reviewed for accuracy) claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. A rebuttal paper led by an HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (EMI paper 2/12/2020). Because of the many concerns raised by the international community, the authors who made the initial claim have recently withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of randomly occurring mutations. Currently, there is no credible evidence to support the claim that the SARS-CoV-2 originated from a laboratory-engineered CoV. It is much more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

1. Wang, D.*, et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* (2020).
2. Chang*, et al.* Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. *JAMA* (2020).
3. Chen, N.*, et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* (2020).
4. Zhou, P.*, et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* (2020).
5. Zhu, N.*, et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* (2020).
6. Menachery, V.D.*, et al.* A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med* **21**, 1508-1513 (2015).
7. Ge, X.Y.*, et al.* Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature* **503**, 535-538 (2013).
8. Li, F., Li, W., Farzan, M. & Harrison, S.C. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* **309**, 1864-1868 (2005).
9. Li, W.*, et al.* Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* **426**, 450-454 (2003).
10. Demogines, A., Farzan, M. & Sawyer, S.L. Evidence for ACE2-utilizing coronaviruses (CoVs) related to severe acute respiratory syndrome CoV in bats. *J Virol* **86**, 6350-6353 (2012).
11. Wu, F.*, et al.* A new coronavirus associated with human respiratory disease in China. *Nature* (2020).

From:	Liu, Shan-Lu
To:	Stanley Perlman
Cc:	Su, Lishan; Lu, Shan
Subject:	Commentary for EMI
Date:	Wednesday, February 12, 2020 11:14:46 AM
Attachments:	EMI-2019-nCoV_Commentary_Final.docx image001.png

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Dear Stanley,

Hope all is well.

As you may know, Lishan at UNC and I have just wrapped up a commentary, at the invitation by the editor in chief of journal “Emerging Microbes and Infections”, Dr. Shan Lu (don’t get confused, it’s not me), and we are wondering if you would be interested in joining us as a coauthor. We feel that this is an important issue, and as scientist, we should try to clear this thing up.

Let us know as soon as possible, as we will try to submit it today. If you feel someone else (other coronavirus experts), whom might be interested in becoming a coauthor, kindly let us know as well.

Best wishes.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

SARVS-CoV-2: no evidence of a laboratory origin

Lishan Su[1], and Linda J. Saif [2,3], and Shan-Lu Liu[3, 4,5.6]

[1] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[3] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[4] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[5] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[6] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

Contact:

Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A novel human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1, 2, 3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4, 5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding DNA sequences (CDSs), and among the 128 nonsynonymous mutations, 89 led to a predicted radical amino-acid changes [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout

the genome in a naturally occurring pattern and follow the evolution characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might have CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2.

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When the SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10, 11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [12], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-SHC014 was used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-MA15 can replicate efficiently in the mouse lung, leading to severe pathogenesis [7].

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus were restricted as gain of function (GOF) studies under the US government-mandated pause policy (from Oct. 2014 to Dec. 2017: https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding these bat CoVs

already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5, 13], the SARS-CoV-2 is undoubtedly distinct from SHC014-MA15, with >5000 nt differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SHC014-MA15 virus.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. A rebuttal paper led by an HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of randomly occurring mutations. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 was originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

References

1. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7. doi: 10.1001/jama.2020.1585. PubMed PMID: 32031570.
2. Chang, Lin M, Wei L, et al. Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. JAMA. 2020 Feb 7. doi: 10.1001/jama.2020.1623. PubMed PMID: 32031568.
3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Jan 30. doi: 10.1016/S0140-6736(20)30211-7. PubMed PMID: 32007143.
4. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Feb 3. doi: 10.1038/s41586-020-2012-7. PubMed PMID: 32015507.
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7. Menachery VD, Yount BL, Jr., Debbink K, et al. A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. Nat Med. 2015 Dec;21(12):1508-13. doi: 10.1038/nm.3985. PubMed PMID: 26552008; PubMed Central PMCID: PMCPMC4797993.
8. Ge XY, Li JL, Yang XL, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature. 2013 Nov 28;503(7477):535-8. doi: 10.1038/nature12711. PubMed PMID: 24172901; PubMed Central PMCID: PMCPMC5389864.
9. Roberts A, Deming D, Paddock CD, et al. A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. PLoS Pathog. 2007 Jan;3(1):e5. doi: 10.1371/journal.ppat.0030005. PubMed PMID: 17222058; PubMed Central PMCID: PMCPMC1769406.
10. Li F, Li W, Farzan M, et al. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science. 2005 Sep 16;309(5742):1864-8. doi: 10.1126/science.1116480. PubMed PMID: 16166518.
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12. Demogines A, Farzan M, Sawyer SL. Evidence for ACE2-utilizing coronaviruses (CoVs) related to severe acute respiratory syndrome CoV in bats. J Virol. 2012 Jun;86(11):6350-3. doi: 10.1128/JVI.00311-12. PubMed PMID: 22438550; PubMed Central PMCID: PMCPMC3372174.

13. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Feb 3. doi: 10.1038/s41586-020-2008-3. PubMed PMID: 32015508.

From: Liu, Shan-Lu
To: Su, Lishan; Lu, Shan
Subject: 2019-nCoV-EMI_commentary with SOME refs added
Date: Wednesday, February 12, 2020 7:06:54 AM
Attachments: EMI-2019-nCoV_Commentary LJS_SLL_Refs.docx
image001.png
image002.png

Lishan:

Could you help add the following papers to your Endnote library? For some reason, I am unable to add any references! Also, you may help find references for several others and add them as well – I am unable to add for some reason.

Please the updated MS, with refs added.

Shan: I am unable to see the choice of EMI in the Endote library – what similar journal formats can I choose? Sounds like a silly question…

Proc Natl Acad Sci U S A. 2005 Feb 15;102(7):2430-5. Epub 2005 Feb 4.
Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human.
Song HD1, Tu CC, Zhang GW, Wang SY, Zheng K, Lei LC, Chen QX, Gao YW, Zhou HQ, Xiang H, Zheng HJ, Chern SW, Cheng F, Pan CM, Xuan H, Chen SJ, Luo HM, Zhou DH, Liu YF, He JF, Qin PZ, Li LH, Ren YQ, Liang WJ, Yu YD, Anderson L, Wang M, Xu RH, Wu XW, Zheng HY, Chen JD, Liang G, Gao Y, Liao M, Fang L, Jiang LY, Li H, Chen F, Di B, He LJ, Lin JY, Tong S, Kong X, Du L, Hao P, Tang H, Bernini A, Yu XJ, Spiga O, Guo ZM, Pan HY, He WZ, Manuguerra JC, Fontanet A, Danchin A, Niccolai N, Li YX, Wu CI, Zhao GP.

A **mouse-adapted SARS**-coronavirus causes disease and mortality in BALB/c mice.
Roberts A, Deming D, Paddock CD, Cheng A, Yount B, Vogel L, Herman BD, Sheahan T, Heise M, Genrich GL, Zaki SR, Baric R, Subbarao K.
PLoS Pathog. 2007 Jan;3(1):e5.

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 9:40 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I am downloading endnote x9 and hopefully will be able to format the references soon

-Lishan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 8:56:06 PM
To: Su, Lishan <lishan_su@med.unc.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

See my latest version attached. Some small changes have been made.

As of right now, should anyone else be listed as coauthors?

I can send the current draft without references to some coronavirus experts, but thought it will be nice to have all completed to show our due diligence

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 8:31 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I will add the references tonight.

-Lishan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 7:44:27 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Sounds good, thank you. I still like “however” over “In contrast” – it just reads better

Shan: Are you sure that you prefer not to be included in the coauthorship? Before I send, I think we should have the authorship listed, along with affiliations. Lishan should be the first author, unless he prefers otherwise. Agreed?

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 7:34 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

I made some minor change for the following:

In summary, there is no credible evidence at this point to support the claims that the 2019-nCoV was originated from a laboratory-engineered CoV. In contrast, we cannot rule out the possibility that 2019-nCoV is a recombinant generated in nature between a bat CoV and another coronavirus in an intermediate host. More studies are needed to explore this possibility and resolve the origin of 2019-nCoV.

Maybe now SLL can send the next version to other CoV experts?

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 5:47 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

See the new version with all incorporated.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 4:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I have made additional changes to the Lishan's version, see attached.

Lishan: I share your concern, and that is one reason that Shan, the editor, decides to have a short version.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 4:16 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

The new title is good if we will cover the RaTG13 and HIV insertion issues.
I am still worried if we can shed any light on the major claim of RaTG13 lab escape/evolution in other hosts/humans over the years…?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 3:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Perhaps Lishan can take a look at the latest version, which has the new title I suggested, and modify it as needed.
The last paragraph is also crucial, but I did not have time to work on it because of a meeting this morning.
Once we have almost a final draft, I will contact Linda Saif, Stanley Perlman, Thomas Gallgaher etc. to see if they are willing to join, but this may delay the publishing time.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 1:52 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I agree that it should be simple and clear. I have included some details in the 1st draft for your information. There is not intention to defend Baric, but to clarify the facts.

Regarding all three, are you combining Goa Feng's piece with this one? For the RaTG13, it involves complicated viral evolution kinetics and maybe hard to simply clarify…
Best,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 1:44 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Sorry here is the attachment with tracking

From: Lu, Shan
Sent: Tuesday, February 11, 2020 1:44 PM

To: 'Su, Lishan' <lishan_su@med.unc.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Hi, I am adding Shuying from my group. She just read the last draft from Lishan and identified a few errors (with tracking).

Also I just had a phone call with SSL and we agreed on the following:

1. We need to make this commentary very simple and short;
2. It is better not going to too much science/tech details as it can only confuse people and provide more room for people to raise more questions;
3. We don't want to appear that we are defending Ralph even though he did nothing wrong.
4. We feel it is best to cover 3 issues in this commentary (for the above reason, plus it is more powerful to cover multiple issues in one summary)
5. ??

SLL: please add anything I missed.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 12:52 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Looking at Shanlu's version, we may need a separate for the RaTG13 vs lab accident theory...

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 12:44 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>

Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

Thanks.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Evidence refuting laboratory origin of SARVS-CoV-2

Lishan Su[1], and Linda J. Saif [2,3], XXX, XXX, and Shan-Lu Liu[3, 4,5.6]

[1] Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill,

Chapel Hill, North Carolina, USA

[2] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[3] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[4] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[5] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[6] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

Dr. Lishan Su, lsu@med.unc.edu

Dr Linda J. Saif, Saif.2@osu.edu

XXX, XXX

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A novel human coronavirus, SARS-CoV-2 was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (WHO website link ref).

According to what has been reported [1-3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat betacoronaviruses, with the highest being >96% identity [4,5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, and contained a total of 202 single-nucleotide variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding DNA sequences (CDSs), and among the 128 nonsynonymous mutations, 89 led to a predicted radical amino-acid changes (Song et al, PNAS 2005). Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring

pattern and follow the evolution characteristics typical of CoVs, including the S gene as the most variable region, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that 2019-nCoV evolved by natural evolution. Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of randomly occurring mutations. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might have CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (website link ref).

Another claim points to a Nature Medicine paper published in 2015 [6], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [7]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2.

The recombinant mouse-adapted SARS virus (MA15) (PLoS Pathog. 2007 Jan;3(1):e5) was generated by serial passage of an infectious SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic

mutations associated with mouse adaptation. It is also likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [8,9]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans (need to find refs). However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [7]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [10], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-SHC014 was used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-MA15 can replicate efficiently in the mouse lung, leading to severe pathogenesis [6].

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus are now restricted as gain of function (GOF) studies under the US government-mandated

pause policy. The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5,11], the SARS-CoV-2 is undoubtedly distinct from SHC014- MA15, with >5000 nt differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SHC014-MA15 virus.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv, (and not yet peer reviewed for accuracy) claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. A rebuttal paper led by an HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (EMI paper 2/12/2020). Because of the many concerns raised by the international community, the authors who made the initial claim have recently withdrawn this report.

In summary, there is no credible evidence to support the claim that the SARS-CoV-2 originated from a laboratory-engineered CoV. It is much more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

1. Wang, D.*, et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* (2020).
2. Chang*, et al.* Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. *JAMA* (2020).
3. Chen, N.*, et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* (2020).
4. Zhou, P.*, et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* (2020).
5. Zhu, N.*, et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* (2020).
6. Menachery, V.D.*, et al.* A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med* **21**, 1508-1513 (2015).
7. Ge, X.Y.*, et al.* Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature* **503**, 535-538 (2013).
8. Li, F., Li, W., Farzan, M. & Harrison, S.C. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* **309**, 1864-1868 (2005).
9. Li, W.*, et al.* Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* **426**, 450-454 (2003).
10. Demogines, A., Farzan, M. & Sawyer, S.L. Evidence for ACE2-utilizing coronaviruses (CoVs) related to severe acute respiratory syndrome CoV in bats. *J Virol* **86**, 6350-6353 (2012).
11. Wu, F.*, et al.* A new coronavirus associated with human respiratory disease in China. *Nature* (2020).

From: Liu, Shan-Lu
To: Su, Lishan; Lu, Shan
Subject: Re: 2019-nCoV-EMI_commentary
Date: Tuesday, February 11, 2020 7:16:49 PM
Attachments: SHC014-MA15 v 2019 ncoV-SLL-sls-SLL.docx
image001.png
image002.png

See my newest update:

Changes in last paragraph:

"In summary, we believe that there is no concrete evidence to support the claims that the 2019-nCoV was originated from a laboratory-engineered CoV. However, we cannot rule out the possibility that 2019-nCoV is a recombinant generated in nature between a bat CoV and another coronavirus in an intermediate host. More studies are needed to explore this possibility and resolve the origin of 2019-nCoV."

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 5:49 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

See the new version with all incorporated.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 4:26 PM

To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I have made additional changes to the Lishan's version, see attached.

Lishan: I share your concern, and that is one reason that Shan, the editor, decides to have a short version.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 4:16 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

The new title is good if we will cover the RaTG13 and HIV insertion issues.
I am still worried if we can shed any light on the major claim of RaTG13 lab escape/evolution in other hosts/humans over the years…?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 3:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Perhaps Lishan can take a look at the latest version, which has the new title I suggested, and modify it as needed.
The last paragraph is also crucial, but I did not have time to work on it because of a meeting this morning.
Once we have almost a final draft, I will contact Linda Saif, Stanley Perlman, Thomas Gallgaher etc. to see if they are willing to join, but this may delay the publishing time.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 1:52 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I agree that it should be simple and clear. I have included some details in the 1st draft for your information. There is not intention to defend Baric, but to clarify the facts.

Regarding all three, are you combining Goa Feng's piece with this one? For the RaTG13, it involves complicated viral evolution kinetics and maybe hard to simply clarify…
Best,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 1:44 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Sorry here is the attachment with tracking

From: Lu, Shan
Sent: Tuesday, February 11, 2020 1:44 PM
To: 'Su, Lishan' <lishan_su@med.unc.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Hi, I am adding Shuying from my group. She just read the last draft from Lishan and identified a few errors (with tracking).

Also I just had a phone call with SSL and we agreed on the following:

1. We need to make this commentary very simple and short;
2. It is better not going to too much science/tech details as it can only confuse people and provide more room for people to raise more questions;
3. We don't want to appear that we are defending Ralph even though he did nothing wrong.
4. We feel it is best to cover 3 issues in this commentary (for the above reason, plus it is more powerful to cover multiple issues in one summary)
5. ??

SLL: please add anything I missed.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 12:52 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Looking at Shanlu's version, we may need a separate for the RaTG13 vs lab accident theory...

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 12:44 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

Thanks.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Tentative Title: Is 2019-nCoV laboratory origin ~~of laboratory~~?

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1000 as of Feb. 10, 2020. A novel human coronavirus, 2019-nCoV, was quickly identified, and the associated disease is now referred to as novel coronavirus pneumonia (NCP) or coronavirus disease discovered in ~~identified~~ 2019 (COVID-19).

According to what has been reported (Lancet, NEJM 2020), NCP seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The 2019-nCoV genome sequence also has ~80% identity with SARS-CoV, but is most similar to some bat beta-coronaviruses, with the highest being >96% identity.

Currently, there are speculations or rumors that the 2019-CoV is of a laboratory origin. First, certain people suspected that the 2019-nCoV is directly leaked from a laboratory in Wuhan whereas ~~as~~ a bat CoV (RaTG13) was recently reported, which ~~by that laboratory and it~~ shared ~96% homology with the 2019-nCoV (Nature, 2020). However, as we now know, the SARS-CoV and palm civets CoV shared 99.8% homology, which is only about 60 nt. Given that there are greater than 1000 nt differences between 2019-nCoV and RaTG13, it is highly unlikely RaTG13 is the immediate source of 2019-nCoV; this is particular true in light of the low mutation rate of the coronaviruses. Searching for an inter~~m~~mediate host between bat and humans is needed.

Another claim points to a Nature Medicine paper published in 2015, which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014)

in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells. However, this claim lacks any scientific basis and must be discounted.

The recombinant mouse-adapted SARS virus (MA15) (PLoS Pathog. 2007 Jan;3(1):e5) was generated by serial passages of an infectious SARS CoV clone in the respiratory tract of BALB/c mice. After 15 rounds of passage in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was not able to use human ACE2 as a receptor for entry. Civets were proposed to be an intermediate host of the bat-CoVs before they spread to humans (SARS-CoV review?). However, several novel bat coronaviruses were isolated from Chinese horseshoe bats in 2013 and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry (Nature 2013). Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as human ACE2 gene for interaction with SARS CoV (JVI 2012), it was proposed that intermediate hosts may not be necessary and that some bat SL-CoVs may directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-SHC014 was used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus can indeed efficiently use human ACE2 and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-MA15

can replicate efficiently in the mouse lung, leading to severe pathogenesis (Nat. Med. 2015).

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014-MA15 chimeric virus are considered as gain of function (GOF) studies under the US government-mandated pause. ~~No more bat CoV MA15 chimeric viruses are constructed after the SHC014 MA15 chimeric virus.~~ The NCP epidemic has restarted the debate over the risks constructing such viruses with pandemic potential. Regardless, ~~Regarding its lineage relationship with 2019 nCoV, however,~~ upon~~after~~ careful phylogenetic analyses by multiple international groups (EMI, Nature…2020), the 2019-nCoV is unmistakably distinct from SHC014- MA15, with >5000 nt differences across the whole~~in their~~ genome~~s~~. Therefore, t~~T~~here is NO credible evidence to support the claim that the 2019-nCoV is~~was~~ derived from the chimeric SHC014-MA15 virus.

There are also rumors that the 2019-nCoV is artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv, claiming that 2019-nCoV has HIV sequence in it and thus likely generated in the laboratory. A rebuttal paper led by HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the 2019-nCoV is not HIV-1 specific but random (EMI paper 2/12/2020). Because of the many concerns raised by the international community, the authors who made the initial claim have recently decided to withdraw this report.

In summary, we believe that there is no concrete evidence to support the claims that the 2019-nCoV was originated from a laboratory-engineered CoV. However, we cannot rule out the possibility that 2019-nCoV is a recombinant generated in nature between a bat CoV and another coronavirus in an intermediate host. More studies are needed to explore this possibility and resolve the origin of 2019-nCoV. ~~Phylogenetic analyses~~

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~~of all reported CoV genomes by multiple international groups support the conclusion that 2019 nCoV is a novel virus……?~~

From: Liu, Shan-Lu
To: Lu, Shan; Su, Lishan
Cc: Liu, Shan-Lu
Subject: 2019-nCoV-EMI_commentary
Date: Tuesday, February 11, 2020 11:21:41 AM
Attachments: EMI commentary-20200211_SLL.docx
image001.png

See my suggested changes.

Thanks.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Title:

The current concerns on the source of 2019 nCoV

Is 2019-nCoV a laboratory origin?

The emergence and outbreak of a newly discovered ~~new~~ acute respiratory disease~~s outbreak~~ in Wuhan, China, has affected greater than 40,000 people, and killed more than 1000 as of Feb. xx, 2020. A novel human coronavirus, 2019-nCoV, ~~(or NCP),~~ was~~has been~~ quickly identified, and the associated disease is now referred to as novel coronavirus pneumonia (NCP).

According to what has been reported in the literature (refs), NCP has many (?) clinical manifestations that are similar to that of severe acute respiratory syndrome (SARS) caused by SARS-CoV. ~~the cause of this emerging infection.~~ The 2019-nCoV genome also has ~80% identity in sequence with SARS-CoV but most similar to some bat ~~same full-length gene sequences were found among multiple NCP viruses isolated from different countries and confirmed that it is a~~ beta-coronaviruses, with the highest being >96% identity. Currently, there are ~~like SAR-CoV. However, NCP only has ~80% identity with SARS-CoV.~~

~~Because of NCP's similar clinical manifestation as SARS, several mis-guided~~ speculations and rumors that the 2019-CoV is of a ~~have been circulating about the origin of the new virus, including its possible~~ laboratory origin. One particular claim~~speculation~~ points to~~at~~ a Nature Medicine paper published in 2015, which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS-CoV that has adapted to infect mice (rMA15) and is capable of infecting humans. There is also a rumor that the 2019-nCoV is directly from a bat virus (RaTG13) originally isolated from a laboratory in Wuhan China. Here we provide a summary of evidence that supports the conclusion that the 2019-nCoV is not from the chimeric coronavirus (SHC014-rMA15) nor the original bat virus RaTG13 (refs).

L~~First, et us~~we will first explain how a~~the~~ recombinant mouse-adapted SARS virus (rMA15) was generated. After constructing a full-length infectious SARS-C-eoV using~~by~~ reverse genetics, Dr. Ralph Baric's lab showed that it replicated in older mice with low or no pathogenicity ~~activity.~~ They then adapted the SARS-CoV (Urbani strain) by serial passages in the respiratory tract of BALB/c mice. After 15 rounds of passage in mice, the SARS-C-eoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding mutations associated with mouse adaptation. When introduced into the original recombinant SARS-CoV, these six mutations (only one in the S gene) conferred the high virulence and lethality (rMA15). Although not reported in human cells, it is likely that rMA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

I~~Second, i~~t is also i~~m~~portant to know~~clarify~~ how the chimeric SHC014-rMA15 virus was constructed and what key findings were made using this~~at~~ virus. When the SARS-C-eoV was isolated, it was concluded that the S gene from bat-derived Ceo~~V~~, unlike its~~that from~~ human ~~patients~~ or civet~~s~~ counterparts

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~~derived viruses~~, was un~~not~~ able to use the human ACE2 as a receptor for entry. Civets were proposed to be an immediate ~~as the secondary~~ host before~~for~~ the bat-CoV ~~before~~ spread~~sing~~ to humans. However, novel bat coronaviruses were isolated from Chinese horseshoe bats in 2013 and the bat SL-CoV-WIV1 used ACE2 from humans, civets and Chinese horseshoe bats for entry. Based on the evolutionary evidence that the bat ACE2 gene has been positively selected at the same ~~contact sites~~interface as the human ACE2 gene for interacting~~on~~ with SARS-C-~~o~~oV, it was proposed that an intermediate host~~s~~ may not be necessary for ~~and~~ some bat CoVs to ~~may~~ directly infect human~~s hosts~~. To directly address this possibility, the S gene ~~from~~ of the bat coronavirus WIV1-SHC014 was used to generate a chimeric virus in the mouse adapted -rMA15 SARS-CoV backbone. The resultant SHC014-rMA15 virus can efficiently use ACE2 from multiple species and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-rMA15 can replicate efficiently in the mouse lung with severe pathogenesis. These findings ~~have~~ provide ~~d~~ compelling~~strong~~ evidence that some bat CoVs can directly use human ACE2 to infect human hosts.

Due to the elevated pathogenic activity of the SHC014-rMA15 chimeric virus relative to the Urbani Spike-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies under the US government-mandated pause (the ban was implemented in 2013/2014 but lifted by NIH in 2017). No more bat-Co~~c~~V-M15 chimeric viruses have been~~are~~ constructed thereafter the SHC014-r-MA15 chimeric virus. The NCP epidemic has triggered a new ~~restarted the~~ debate on~~over~~ whether or not it is worth the risks of constructing such viruses with possible pandemic potential (refs), which is not unexpected. However, w~~, W~~ith careful and in-depth ~~careful~~ phylogenetic analyses by multiple international groups, the 2019-nC~~n~~eoV~~/NCP virus~~ is unmistakably, and fortunately, distinct from SHC014- MA15. (we need a good summary here one two three…). Therefore t~~T~~here is NO credible evidence to support the claim that the 2019 ncoV/NCP virus was derived for the chimeric SHC014- MA15 virus.

Another ~~The next~~ speculation is that 2019-nCoV~~NCP~~ is directly mutated from a recently ~~newly~~ reported bat-CoV isolate RaTG13) (Ref), ~~-~~because these two viruses share~~d~~ more than ~~≈~~96% sequence homology. With a large size genome like beta-coronaviruses (~20 kb), there are still ~1000 nt differences between these two viruses (ref), indicating RaTG13 is un~~not~~ likely the source of 2019-nCov. ~~NCP,~~ Moreover the mutation rate of the coronaviruses is considered to be very low (need a number here) due to the existence of a proofreading enzyme ExoN (nsp14). Most important, the 2019-nCoV contains a potential furin-cleavage signature sequence "RRAR", which is not present in most coronaviruses, including the RaTG13, although recombination between RaTG13 and other coronaviruses cannot be ruled out. ~~and thus denied the speculation that NCP is somehow a leaked relative of RaTG13 from the laboratory who originally identified RaTG13.~~

There are also rumors that the 2019-nCoV is artificially and intentionally made by humans in the lab and this is highlighted one manuscript submitted to BioRxiv,~~also~~ claiming that 2019-nCoV has HIV sequence in it and thus likely generated in the laboratory. ~~other people who claimed the finding of other viral sequences within HCP genome, implying that someone artificially created the NCP. One such claim suggested finding of four inserts related to HIV-1 sequences.~~ A rebuttal paper led by HIV-1 expert Dr. Feng Gao has used~~did~~ careful bioinformatics analyses~~is~~ to~~and~~ demonstrate~~showed~~ that the original claim of multiple HIV insertion into the 2019-nCoV is not ~~do not have data to show these 4 insert~~

Commented [LS2]: necessary?

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~~sequences are actually~~ HIV-1 specific but random.. In addition, the four inserts can not be held together based on structure modeling as initially claimed (ref.). At the same time, those authors who made the initial claim has withdrawn their report.

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From:	Liu, Shan-Lu
To:	Weiss, Susan
Cc:	Su, Lishan; Lu, Shan
Subject:	Commentary for EMI
Date:	Wednesday, February 12, 2020 11:25:38 AM
Attachments:	EMI-2019-nCoV_Commentary_Final.docx image001.png

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Dear Susan,

Hope your trip back to Philly was safe and pleasant.

Dr. Lishan Su at UNC and I have just wrapped up a commentary, at invitation by the editor in chief of “Emerging Microbes and Infections”, Dr. Shan Lu (don’t get confused, it’s not me). We are wondering if you would be interested in joining us as a coauthor. We feel that this is an important issue, and as scientist, we should clear this thing up if we can.

Please let us know as soon as possible, as we will try to submit it today. If you feel someone else (other coronavirus experts), whom might be interested in becoming a coauthor, kindly let us know as well.

Best wishes.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

SARVS-CoV-2: no evidence of a laboratory origin

Lishan Su[1], and Linda J. Saif [2,3], and Shan-Lu Liu[3, 4,5.6]

[1] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[3] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[4] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[5] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[6] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

Contact:

Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A novel human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1, 2, 3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4, 5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding DNA sequences (CDSs), and among the 128 nonsynonymous mutations, 89 led to a predicted radical amino-acid changes [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout

the genome in a naturally occurring pattern and follow the evolution characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might have CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2.

The recombinant mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is also likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10, 11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [12], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-SHC014 was used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-MA15 can replicate efficiently in the mouse lung, leading to severe pathogenesis [7].

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus were restricted as gain of function (GOF) studies under the US government-mandated pause policy (from Oct. 2014 to Dec. 2017: https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding these bat CoVs

already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5, 13], the SARS-CoV-2 is undoubtedly distinct from SHC014-MA15, with >5000 nt differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SHC014-MA15 virus.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. A rebuttal paper led by an HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of randomly occurring mutations. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 was originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

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From:	Liu, Shan-Lu
To:	Su, Lishan; Lu, Shan
Subject:	Re: 2019-nCoV-EMI_commentary
Date:	Tuesday, February 11, 2020 8:56:05 PM
Attachments:	EMI-2019-nCoV_Commentary.docx image001.png

See my latest version attached. Some small changes have been made.

As of right now, should anyone else be listed as coauthors?

I can send the current draft without references to some coronavirus experts, but thought it will be nice to have all completed to show our due diligence

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 8:31 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I will add the references tonight.

-Lishan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 7:44:27 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Sounds good, thank you. I still like “however” over “In contrast” – it just reads better

Shan: Are you sure that you prefer not to be included in the coauthorship? Before I send, I think we should have the authorship listed, along with affiliations. Lishan should be the first author, unless he prefers otherwise. Agreed?

Shan-Lu

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 7:34 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

I made some minor change for the following:

In summary, there is no credible evidence at this point to support the claims that the 2019-nCoV was

originated from a laboratory-engineered CoV. In contrast, we cannot rule out the possibility that 2019-nCoV is a recombinant generated in nature between a bat CoV and another coronavirus in an intermediate host. More studies are needed to explore this possibility and resolve the origin of 2019-nCoV.

Maybe now SLL can send the next version to other CoV experts?

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 5:47 PM
To: Liu, Shan-Lu <liu.6244@osu.edu>; Lu, Shan <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

See the new version with all incorporated.

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 4:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I have made additional changes to the Lishan's version, see attached.

Lishan: I share your concern, and that is one reason that Shan, the editor, decides to have a short version.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 4:16 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

The new title is good if we will cover the RaTG13 and HIV insertion issues.
I am still worried if we can shed any light on the major claim of RaTG13 lab escape/evolution in other hosts/humans over the years…?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 3:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Perhaps Lishan can take a look at the latest version, which has the new title I suggested, and modify it as needed.
The last paragraph is also crucial, but I did not have time to work on it because of a meeting this morning.
Once we have almost a final draft, I will contact Linda Saif, Stanley Perlman, Thomas Gallgaher etc. to see if they are willing to join, but this may delay the publishing time.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 1:52 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

I agree that it should be simple and clear. I have included some details in the 1st draft for your information. There is not intention to defend Baric, but to clarify the facts.

Regarding all three, are you combining Goa Feng's piece with this one? For the RaTG13, it involves complicated viral evolution kinetics and maybe hard to simply clarify…
Best,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 1:44 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Sorry here is the attachment with tracking

From: Lu, Shan
Sent: Tuesday, February 11, 2020 1:44 PM
To: 'Su, Lishan' <lishan_su@med.unc.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Hi, I am adding Shuying from my group. She just read the last draft from Lishan and identified a few errors (with tracking).

Also I just had a phone call with SSL and we agreed on the following:

1. We need to make this commentary very simple and short;
2. It is better not going to too much science/tech details as it can only confuse people and

provide more room for people to raise more questions;
3. We don't want to appear that we are defending Ralph even though he did nothing wrong.
4. We feel it is best to cover 3 issues in this commentary (for the above reason, plus it is more powerful to cover multiple issues in one summary)
5. ??

SLL: please add anything I missed.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 12:52 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Looking at Shanlu's version, we may need a separate for the RaTG13 vs lab accident theory...

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 12:44 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

Thanks.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Is 2019-nCoV a laboratory origin?

Lishan Su[1], and Shan-Lu Liu[2, 3,4.5]

[1] Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2] Center for Retrovirus Research, The Ohio State University, Columbus, OH 43210, USA

[3] Department of Veterinary Biosciences, The Ohio State University, Columbus, OH 43210, USA

[4] Department of Microbial Infection and Immunity, The Ohio State University, Columbus, OH 43210, USA

[5] Viruses and Emerging Pathogens Program, Infectious Diseases Institute, The Ohio State University, Columbus, OH 43210, USA

Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1000 as of Feb. 10, 2020. A novel human coronavirus, 2019-nCoV, was quickly identified, and the associated disease is now referred to as novel coronavirus pneumonia (NCP) or coronavirus disease discovered in 2019 (COVID-19).

According to what has been reported (Lancet, NEJM 2020), NCP seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The 2019-nCoV genome sequence also has ~80% identity with SARS-CoV, but is most similar to some bat beta-coronaviruses, with the highest being >96% identity (refs).

Currently, there are speculations or rumors that the 2019-CoV is of a laboratory origin. First, certain people suspected that the 2019-nCoV is directly leaked from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the 2019-nCoV (Nature, 2020). However, as we know, the SARS-CoV and palm civets CoV shared 99.8% homology, which is only about 60 nt differences in the whole genome sequence (refs). Given that there are greater than 1000 nt differences between the 2019-nCoV and the RaTG13-CoV (refs), it is highly unlikely RaTG13 is the immediate source of 2019-nCoV; this is particularly true in light of a low mutation rate of the coronaviruses (refs). Searching for an intermediate host between bat and humans is needed.

Another claim points to a Nature Medicine paper published in 2015, which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells (refs). However, this claim lacks any scientific basis and must be discounted.

The recombinant mouse-adapted SARS virus (MA15) (PLoS Pathog. 2007 Jan;3(1):e5) was generated by serial passages of an infectious SARS CoV clone in the respiratory tract of BALB/c mice. After 15 rounds of passage in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was not able to use human ACE2 as a receptor for entry (refs). Civets were proposed to be an intermediate host of the bat-CoVs before they spread to humans (refs). However, several novel bat coronaviruses were isolated from Chinese horseshoe bats in 2013 and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry (Nature 2013). Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as human ACE2 gene for interacting with SARS CoV (JVI 2012), it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts (refs). To directly address this possibility, the S gene from bat coronavirus

SL-SHC014 was used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus can indeed efficiently use human ACE2 and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-MA15 can replicate efficiently in the mouse lung, leading to severe pathogenesis (Nat. Med. 2015).

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies under the US government-mandated pause policy (refs). The current NCP epidemic has restarted the debate over the risks constructing such viruses with pandemic potential. Regardless, upon careful phylogenetic analyses by multiple international groups (EMI, Nature…2020), the 2019-nCoV is undoubtedly distinct from SHC014- MA15, with >5000 nt differences across the whole genome. Therefore, there is no credible evidence to support the claim that the 2019-nCoV is derived from the chimeric SHC014-MA15 virus.

There are also rumors that the 2019-nCoV is artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv, claiming that 2019-nCoV has HIV sequence in it and is thus likely generated in the laboratory. A rebuttal paper led by an HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the 2019-nCoV is not HIV-1 specific but random (EMI paper 2/12/2020). Because

of the many concerns raised by the international community, the authors who made the initial claim have recently decided to withdraw this report.

In summary, we believe that there is no credible evidence to support the claim that the 2019-nCoV was originated from a laboratory-engineered CoV. However, we cannot rule out the possibility that 2019-nCoV is a recombinant generated in nature between a bat CoV and another coronavirus in an intermediate host. More studies are needed to explore this possibility and resolve the origin of 2019-nCoV.

From: Liu, Shan-Lu
To: Su, Lishan; Lu, Shan
Subject: Re: 2019-nCoV-EMI_commentary
Date: Tuesday, February 11, 2020 4:25:47 PM
Attachments: SHC014-MA15 v 2019 ncoV-SLL.docx
image001.png

I have made additional changes to the Lishan's version, see attached.

Lishan: I share your concern, and that is one reason that Shan, the editor, decides to have a short version.

Shan-Lu

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 4:16 PM
To: Shan-Lu Liu <liu.6244@osu.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

The new title is good if we will cover the RaTG13 and HIV insertion issues.
I am still worried if we can shed any light on the major claim of RaTG13 lab escape/evolution in other hosts/humans over the years…?

-Lishan

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 at 3:26 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Perhaps Lishan can take a look at the latest version, which has the new title I suggested, and modify it as needed.
The last paragraph is also crucial, but I did not have time to work on it because of a meeting this morning.
Once we have almost a final draft, I will contact Linda Saif, Stanley Perlman, Thomas Gallgaher etc. to see if they are willing to join, but this may delay the publishing time.

SL

From: "Su, Lishan" <lishan_su@med.unc.edu>
Date: Tuesday, February 11, 2020 at 1:52 PM
To: "Lu, Shan" <Shan.Lu@umassmed.edu>, Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

st

I agree that it should be simple and clear. I have included some details in the 1 draft for your information. There is not intention to defend Baric, but to clarify the facts.

Regarding all three, are you combining Goa Feng's piece with this one? For the RaTG13, it involves complicated viral evolution kinetics and maybe hard to simply clarify…
Best,

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 1:44 PM
To: "Su, Lishan" <lishan_su@med.unc.edu>, "Liu, Shan-Lu" <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Sorry here is the attachment with tracking

From: Lu, Shan
Sent: Tuesday, February 11, 2020 1:44 PM
To: 'Su, Lishan' <lishan_su@med.unc.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Hi, I am adding Shuying from my group. She just read the last draft from Lishan and identified a few errors (with tracking).

Also I just had a phone call with SSL and we agreed on the following:

1. We need to make this commentary very simple and short;
2. It is better not going to too much science/tech details as it can only confuse people and provide more room for people to raise more questions;
3. We don't want to appear that we are defending Ralph even though he did nothing wrong.
4. We feel it is best to cover 3 issues in this commentary (for the above reason, plus it is more powerful to cover multiple issues in one summary)
5. ??

SLL: please add anything I missed.

Shan

From: Su, Lishan <lishan_su@med.unc.edu>
Sent: Tuesday, February 11, 2020 12:52 PM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Liu, Shan-Lu <liu.6244@osu.edu>
Subject: Re: 2019-nCoV-EMI_commentary

Thanks. Looking at Shanlu's version, we may need a separate for the RaTG13 vs lab accident theory...

-Lishan

From: "Lu, Shan" <Shan.Lu@umassmed.edu>
Date: Tuesday, February 11, 2020 at 12:44 PM
To: "Liu, Shan-Lu" <liu.6244@osu.edu>, "Su, Lishan" <lishan_su@med.unc.edu>
Subject: RE: 2019-nCoV-EMI_commentary

Here is my new version based on SLL's. highlighted areas are my new version (I did not leave tracking as it is too messy). Please take a look then we can focus on the chimeric one which needs more simplification as I can see. We may not need to go too deep in science as it can only confuse more people and found more issues from those who has suspicion.

Shan

From: Liu, Shan-Lu <liu.6244@osu.edu>
Sent: Tuesday, February 11, 2020 11:22 AM
To: Lu, Shan <Shan.Lu@umassmed.edu>; Su, Lishan <lishan_su@med.unc.edu>
Cc: Liu, Shan-Lu <liu.6244@osu.edu>
Subject: 2019-nCoV-EMI_commentary

Thanks.

Shan-Lu

THE OHIO STATE UNIVERSITY

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

Tentative Title: The mouse adapted SARS chimeric virus with bat-coV S gene (SHC014-MA15) is not related to the NCP ncoV or 2019 nco-V

A new suggested title: Is 2019-nCoV origin of laboratory?

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The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1000 as of Feb. 10, 2020. A novel human coronavirus, 2019-nCoV, was quickly identified, and the associated disease is now referred to as novel coronavirus pneumonia (NCP) or coronavirus disease identified 2019 (COVID-19).

According to what has been reported (Lancet, NEJM 2020), NCP seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The 2019-nCoV genome sequence also has ~80% identity with SARS-CoV, but most similar to some bat beta-coronaviruses, with the highest ~~reaching~~ being >96% identity. ~~Currently, there are speculations or rumors that the 2019-CoV is of a laboratory origin.~~

Currently, there are speculations or rumors that the 2019-CoV is of a laboratory origin. ~~This led to speculations and rumors that the 2019-CoV is of a laboratory origin~~. First, certain people suspected that the 2019-nCoV is directly leaked from a laboratory in Wuhan as a bat CoV (RaTG13) was recently reported by that laboratory and it shared ~96% homology with the 2019-nCoV (Nature, 2020). However, as we now know, the SARS-CoV and palm civets CoV shared 99.8% homology, which is only about 60 nt. Given that ~~On the other hand,~~ there are greater than 1000 nt differences between 2019-nCoV and RaTG13, it is highly unlikely~~suggesting~~ RaTG13 is not the immediate source of 2019-nCoV; this is particular true in light of the low

~~given the large size genome like beta coronaviruses (~30 kb) and the slow the~~ mutation rate of the coronaviruses. Searching for an immediate host between bat and humans is needed.

~~One particular~~Another claim points to a Nature Medicine paper published in 2015, which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (rMA15) and is capable of infecting human cells. Here, we provide evidence that this claim lacks ~~of~~ any scientific basis and must be discounted. (However, this claim lacks any scientific basis and must be discounted. – we can use this sentence if the editor decides to have a shorter/simpler version)

~~First, we will explain how t~~The recombinant mouse-adapted SARS virus (~~r~~MA15) ~~was generated~~ (PLoS Pathog. 2007 Jan;3(1):e5)~~.~~ was generated ~~After constructing a full-length infectious~~ SARS coV ~~by reverse genetics, Dr. Ralph Baric's lab showed that it replicated in old mice with low or no pathogenic activity. They then adapted the SARS-CoV (Urbani strain)~~ by serial passages of an infectious SARS coV in the respiratory tract of BALB/c mice. After 15 rounds of passage in mice, the SARS-~~C~~coV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding mutations associated with mouse adaptation. ~~When introduced into the original recombinant SARS-CoV, these six mutations (only one in the S gene) conferred the high virulence and lethality (rMA15). Although not reported in human cells, i~~It is likely that ~~r~~MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

~~Second, it is important to clarify how the chimeric~~ ~~SHC014-rMA15~~ ~~virus was constructed and what key findings were made using that virus.~~ When the SARS-~~C~~coV was isolated, it was concluded that the S gene from bat-

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Commented [SL1]: Specify Urbani strain here?

Commented [SL2]: In the paper , they use SHC014-MA15

derived Cc~~c~~oV, unlike that ~~-~~from human patients- or civets-derived viruses, was not able to use human ACE2 as a receptor for entry. Civets were proposed to be an intermediate~~as the secondary~~ host of ~~for~~ the bat-Cc~~c~~oVs before they spread~~ing~~ to humans (SARS-~~-~~Cc~~c~~oV review?). However, several novel bat coronaviruses were isolated from Chinese horseshoe bats in 2013 and the bat SL-CoV-WIV1 used ACE2 from humans, civets and Chinese horseshoe bats for entry (Nature 2013). Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as human ACE2 gene for interaction with SARS coV (JVI 2012), it was proposed that intermediate hosts may not be necessary and some bat SARS-like or SL-CoVs may directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-~~- WIV1-~~ SHC014 was used to generate a chimeric virus in the mouse adapted-~~r~~MA15 SARS-CoV backbone. The resultant SL-SHC014-~~r~~MA15 virus can efficiently use human ACE2 ~~from multiple species~~ and replicate efficiently in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-~~r~~MA15 can replicate efficiently in the mouse lung, leading to ~~with~~ severe pathogenesis (Nat. Med. 2015). ~~These findings have provided strong evidence that some bat CoVs can directly use human ACE2 to infect human hosts.~~

Commented [SL3]: SHC014 and WIVI are two different bat Cov, with some sequence difference in S domain

Due to the elevated pathogenic activity of the SHC014-~~r~~MA15 chimeric virus relative to the ~~Urbani Spike~~SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus are considered as gain of function (GOF) studies under the US government-mandated pause. No more bat-coV-MA15 chimeric viruses are constructed after the SHC014-MA15 chimeric virus. The NCP epidemic has restarted the debate over the risks constructing such viruses with pandemic potential. Regarding its lineage relationship with 2019 nCoV, however, after careful phylogenetic analyses by multiple international groups (EMI, Nature…2020, a figure?), the 2019 ncoV/NCP virus is unmistakably, and fortunately, distinct from

SHC014- MA15. There is NO credible evidence to support the claim that the 2019 ncoV/NCP virus was derived ~~for~~ from the chimeric SHC014- MA15 virus.

There are also rumors that the 2019-nCoV is artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv, claiming that 2019-nCoV has HIV sequence in it and thus likely generated in the laboratory. A rebuttal paper led by HIV-1 expert Dr. Feng Gao has used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertion into the 2019-nCoV is not HIV-1 specific but random. Moreover, the four inserts cannot be held together as was initially claimed (EMI paper 2/12/2020). Because of the many concerns raided by the international community, the authors who made the initial claim have recently decided to withdraw this report.

Concluding sentence?

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Commented [LS4]: "Do not seem to cluster to the same interface"?

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From: Liu, Shan-Lu
To: Su, Lishan; Lu, Shan
Subject: FW: Commentary for Emerging Microbes & Infections
Date: Wednesday, February 12, 2020 1:26:52 PM
Attachments: EMI-2019-nCoV_Commentary_Final LJS 2020.docx
image001.png

See below.
I am now finalzing it. Not sure if we need to wait for Stanely, but may be good to add Peter? Should I try?

SL

From: "Saif, Linda" <saif.2@osu.edu>
Date: Wednesday, February 12, 2020 at 11:35 AM
To: Shan-Lu Liu <liu.6244@osu.edu>
Subject: Re: Commentary for Emerging Microbes & Infections

Hi Shan-Lu,
A few minor edits—nice job on this write up!
Experts to add include Stan and Peter Daszak (daszak@ecohealthalliance.org), but maybe not essential since with Peter we have prepared a similar statement to denounce the conspiracies with multiple signatories of respected scientists including internationally recognized coronavirologists! However our statement does not add the details that are in this commentary which I think are very important to cite as supporting scientific evidence.
Also Peter told me the NAS is preparing a similar statement to denounce these conspiracy theories circulating on the internet but I have not seen this yet.
I will send this to Ralph to review, but as I noted he may be too busy to respond!
Regards,
Linda

Linda J. Saif, PhD
Distinguished University Professor
Food Animal Health Research Program
OARDC/The Ohio State University
1680 Madison Ave
Wooster, Oh 44691

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Wednesday, February 12, 2020 11:01 AM
To: Linda Saif <saif.2@osu.edu>
Cc: "Su, Lishan" <lishan_su@med.unc.edu>, "Lu, Shan" <Shan.Lu@umassmed.edu>
Subject: Re: Commentary for Emerging Microbes & Infections

Dear Linda;

Attached please find almost the final version of the commentary for EMI, so please feel free to share it with Ralph. Let me know if you have additional suggestions – all your points are incorporated into the new version, please check.

Note that I was trying to find official website links for the new names of the virus (ICTV) and diseases (WHO), but failed; I therefore decided to use the following website, which contains both.

https://globalbiodefense.com/novel-coronavirus-covid-19-portal/

We will try to submit it today, but are considering to add a few more coronavirus experts – anyone that you would like to suggest? We will contact Stanley Perlman right now.

Shan-Lu

Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

From: "Saif, Linda" <saif.2@osu.edu>

Date: Wednesday, February 12, 2020 at 9:37 AM

To: Shan-Lu Liu <liu.6244@osu.edu>

Subject: Re: Commentary for Emerging Microbes & Infections

Can you please send me the updated version first and then I will try to share with Ralph!

Thanks

Linda

Linda J. Saif, PhD

Distinguished University Professor

Food Animal Health Research Program

OARDC/The Ohio State University
1680 Madison Ave
Wooster, Oh 44691

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Wednesday, February 12, 2020 12:47 AM
To: Linda Saif <saif.2@osu.edu>
Subject: Re: Commentary for Emerging Microbes & Infections

Hi Linda.
Thanks so much, and your comments are extremely helpful. Please feel free to share with Ralph to get his feedback if possible. We would like to publish this in the next few days.
I will work on reference tomorrow and send you a updated version.

Shan-Lu Liu sent from iPhone

> On Feb 11, 2020, at 11:54 PM, Saif, Linda <saif.2@osu.edu> wrote:
>
> Hi Shan-Lu,
> I edited this version and added my name as I too feel strongly about denouncing this.
> Here are more comments and some refs that I have made in replies to some reporters about this issue if you think any are useful to include. I also wonder if we might share this with Ralph Baric since he is a conspiracy target and maybe he could add additional points, but I know he would not want to be a co-author—not sure if he has time to answer.
>
> The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that 2019-nCoV evolved by natural evolution. Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of randomly occurring mutations.
>
> The closest virus relative to 2019-nCoV is bat CoV RaTG13. There are 4% nt differences between 2019-nCoV and RaTG13, corresponding to >1000 nt based on a genome size of 29k. These changes (SNP) are distributed throughout the genome in a naturally occurring pattern and follow the evolution characteristics

typical of CoVs, including the S gene as the most variable region.
(Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature doi:10.1038/s41586-020-2012-7.

Regarding differences between civet cat SARSr-CoV and SARS-CoV, here is the accurate data: . A total of 202 SNVs with multiple occurrences were identified, among which 200 were in the CDSs. Among the 128 nonsynonymous mutations, 89 led to a predicted radical amino acid changes
Proc Natl Acad Sci U S A. 2005 Feb 15;102(7):2430-5. Epub 2005 Feb 4.
Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human.
Song HD1, Tu CC, Zhang GW, Wang SY, Zheng K, Lei LC, Chen QX, Gao YW, Zhou HQ, Xiang H, Zheng HJ, Chern SW, Cheng F, Pan CM, Xuan H, Chen SJ, Luo HM, Zhou DH, Liu YF, He JF, Qin PZ, Li LH, Ren YQ, Liang WJ, Yu YD, Anderson L, Wang M, Xu RH, Wu XW, Zheng HY, Chen JD, Liang G, Gao Y, Liao M, Fang L, Jiang LY, Li H, Chen F, Di B, He LJ, Lin JY, Tong S, Kong X, Du L, Hao P, Tang H, Bernini A, Yu XJ, Spiga O, Guo ZM, Pan HY, He WZ, Manuguerra JC, Fontanet A, Danchin A, Niccolai N, Li YX, Wu CI, Zhao GP.

Linda J. Saif, PhD
Distinguished University Professor
Food Animal Health Research Program

OARDC/The Ohio State University
1680 Madison Ave
Wooster, Oh 44691

From: "Liu, Shan-Lu" <liu.6244@osu.edu>
Date: Tuesday, February 11, 2020 10:32 PM
To: Linda Saif <saif.2@osu.edu>
Subject: Commentary for Emerging Microbes & Infections

Hi Linda,

Invited by the editor in chief of EMI, Lushan Su from UNC and I have written a commentary on the possible origin of the 2019-nCoV or SARS-CoV-2 in order to dispute some rumors, and we would like to invite you as a coauthor. Attached please find an almost complete draft (references needed) of the commentary, so kindly let me know what you think. Your comments and suggestions are very much appreciated.

Thanks.

Shan-Lu

<image001.png>
Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Departments of Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu

<image001.png>
<EMI-2019-nCoV_Commentary LJS.docx>

SARVS-CoV-2: no evidence of a laboratory origin

Lishan Su[1], and Linda J. Saif [2,3], and Shan-Lu Liu[3, 4,5.6]

[1] Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology,

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2] Food Animal Health Research Program,

Ohio Agricultural Research and Development Center, CFAES

Department of Veterinary Preventive Medicine,

The Ohio State University, Wooster, Ohio 44691, USA

[3] Viruses and Emerging Pathogens Program, Infectious Diseases Institute,

The Ohio State University, Columbus, OH 43210, USA

[4] Center for Retrovirus Research, The Ohio State University,

Columbus, OH 43210, USA

[5] Department of Veterinary Biosciences, The Ohio State University, Columbus,

OH 43210, USA

[6] Department of Microbial Infection and Immunity, The Ohio State University,

Columbus, OH 43210, USA

Contact:

Dr. Lishan Su, lsu@med.unc.edu

Dr. Shan-Lu Liu, Liu.6244@osu.edu

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new ~~novel~~ human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1, 2, 3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4, 5].

Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide variations (SNVs) identified across the genome; among these SNVs, 200 were in the coding DNA sequences (CDSs), and among the 128 nonsynonymous mutations, 89 led to ~~a~~ predicted radical amino-acid changes [6]. Given that there are greater than 1000 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout

the genome in a naturally occurring pattern ~~and~~ following the evolutionary characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might have CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2.

The recombinant mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is also likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

When the original SARS-CoV was isolated, it was concluded that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10, 11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [12], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the S gene from bat coronavirus SL-SHC014 was used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titers as epidemic strains of SARS-CoV. Importantly, SHC014-MA15 can replicate efficiently in the mouse lung, leading to severe pathoglogyenesis [7].

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to the SARS-MA15 CoV in mice, such experiments with SHC014- MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (from Oct. 2014 to Dec. 2017: https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding

that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5, 13], the SARS-CoV-2 is undoubtedly distinct from SHC014- MA15, with >5000 nt differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SHC014-MA15 virus.

There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a~~A~~ rebuttal paper led by an HIV-1 expert Dr. Feng Gao, they ~~has~~ used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random (Gao et al., EMI paper 2/12/2020 in press). Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of randomly occurring mutations. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 ~~was~~ originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2.

References

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From: Liu, Shan-Lu
To: Liu, Shan-Lu
Date: Sunday, December 20, 2020 10:52:32 AM

For the following item “Feb 23, 2020: Themed discussion on the possible origin of SARS-CoV-2 and RaTG13, especially whether or not SARS-CoV-2 is artificially engineered; this led to an article entitled “No credible evidence supporting claims of the laboratory engineering of SARS- CoV-2” by Lishan Su and Shan-Lu Liu and others published in EMI.” I wonder if you can add: “This paper received 75000 download read ranking #3 of the top 10 papers among over 2500 journals in the Taylor & Francis family”.

Thanks.

Shan-Lu

From:	Bergan, Rachel
To:	Liu, Shan-Lu
Subject:	Your paper features in T&F"s top ten OA articles of 2020
Date:	Thursday, October 22, 2020 4:59:57 AM
Attachments:	image001.png image002.png

Dear Shan-Lu,

I'm very pleased to let you know that your recent article "No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2" was one of the most-downloaded open access articles published by Taylor & Francis so far this year.

Many congratulations!

To mark Open Access Week, we have published a blog post on our Author Services website about the Top 10, including links to the articles, and details of each Altmetric score to reflect the discussion of your article online and in the media.

This is a great excuse to further highlight your research to your contacts and communities. We will be promoting the blog post on our social media platforms: Twitter, LinkedIn, and Facebook. You could share our posts/tweets or write your own (please use the same hashtags).

We'll also be featuring the Top 10 in our Insights newsletter, to further reach researchers and the wider academic community.

Please do not hesitate to contact me if you have any further questions or queries.

Kind Regards,
Rachel

Rachel Bergan (she/her)
Communications Coordinator
Taylor & Francis Group

Email: rachel.bergan@tandf.co.uk
Tel: +44 (0) 20 755 19259
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

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From:	Bergan, Rachel
To:	Liu, Shan-Lu; lsu@med.unc.edu
Subject:	Top 10 most-read open access articles of 2020
Date:	Friday, January 22, 2021 5:45:31 AM
Attachments:	image001.png

Hi there,

I'm very pleased to let you know that your recent article "No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2" was one of the most-downloaded open access articles published by Taylor & Francis in 2020.

Many congratulations!

We have published a report on our Author Services website about the Top 10, including links to the articles, and details of their Altmetric score, to reflect the discussion about this research online and in the media.

This is another great excuse to highlight your research to your contacts. We will be promoting the blog post on our social media platforms - here's a tweet from our Twitter account that you can like and share with your network.

We'll also be featuring the Top 10 in our Insights newsletter and Open Access Bulletin, to share this popular feature with the wider academic community.

Please do not hesitate to contact me if you have any questions.

Kind regards,
Rachel

Rachel Bergan (she/her)
Marketing Communications Coordinator
Taylor & Francis Group

Email: rachel.bergan@tandf.co.uk
Tel: +44 (0) 20 755 19259
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

From:	Liu, Shan-Lu
To:	Liu, Shan-Lu
Cc:	Shan-Lu Liu
Subject:	<no subject>
Date:	Monday, December 21, 2020 11:13:40 AM
Attachments:	image001.png image002.png Liu_EMI.pdf

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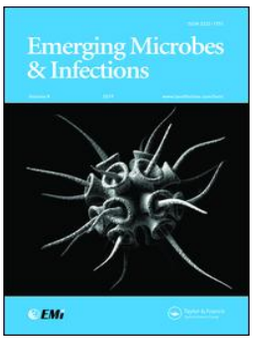
Shan-Lu Liu, M.D., Ph.D.
Professor
Co-Director, Viruses and Emerging Pathogens Program
Infectious Diseases Institute
Center for Retrovirus Research
Veterinary Biosciences, Microbial Infection and Immunity, and Microbiology
The Ohio State University
1900 Coffey Rd, Room 480 VMAB
Columbus, Ohio 43210
Phone: (614) 292-8690
Fax: (614) 292-6473
Email: liu.6244@osu.edu; shan-lu.liu@osumc.edu



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COMMENTARY

OPEN ACCESS Check for updates

No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2

Shan-Lu Liu[a,b,c,d], Linda J. Saif[d,e], Susan R. Weiss [f] and Lishan Su[g]

[a]Center for Retrovirus Research, The Ohio State University, Columbus, OH, USA; [b]Department of Veterinary Biosciences, The Ohio State University, Columbus, OH, USA; [c]Department of Microbial Infection and Immunity, The Ohio State University, Columbus, OH, USA; [d]Viruses and Emerging Pathogens Program, Infectious Diseases Institute, The Ohio State University, Columbus, OH, USA; [e]Food Animal Health Research Program, Ohio Agricultural Research and Development Center, CFAES, Department of Veterinary Preventive Medicine, The Ohio State University, Wooster, OH, USA; [f]Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [g]Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

ARTICLE HISTORY Received 13 February 2020; Accepted 13 February 2020

The emergence and outbreak of a newly discovered acute respiratory disease in Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and the associated disease is now referred to as coronavirus disease discovered in 2019 (COVID-19) (https://globalbiodefense.com/novel-coronavirus-covid-19-portal/).

According to what has been reported [1–3], COVID-2019 seems to have similar clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96% identity [4,5].

Currently, there are speculations, rumours and conspiracy theories that SARS-CoV-2 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know, the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8% homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the genome [6]. Given that there are greater than 1,100 nt differences between the human SARS-CoV-2 and the bat RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted pattern in the new viral sequences and a close relative in a wildlife species (bats) are the most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an intermediate animal host between bats and humans is needed to identify animal CoVs more closely related to human SARS-CoV-2. There is speculation that pangolins might carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet published (https://www.nature.com/articles/d41586-020-00364-2).

Another claim in Chinese social media points to a Nature Medicine paper published in 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and is capable of infecting human cells [8]. However, this claim lacks any scientific basis and must be discounted because of significant divergence in the genetic sequence of this construct with the new SARS-CoV-2 (>5,000 nucleotides).

The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in aged mice (hence M15), due to six coding genetic mutations associated with mouse adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients due to the mouse adaptation.

It was proposed that the S gene from bat-derived CoV, unlike that from human patients- or civets-derived viruses, was unable to use human ACE2 as a receptor for entry into human cells [10,11]. Civets were proposed to be an intermediate host of the bat-CoVs, capable of spreading SARS CoV to humans [6,12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary

CONTACT Shan Lu Liu Liu.6244@osu.edu; Lishan Su lsu@med.unc.edu

evidence that the bat ACE2 gene has been positively selected at the same contact sites as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an intermediate host may not be necessary and that some bat SL-CoVs may be able to directly infect human hosts. To directly address this possibility, the exact S gene from bat coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus could indeed efficiently use human ACE2 and replicate in primary human airway cells to similar titres as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate efficiently in young and aged mouse lungs, infection was attenuated, and less virus antigen was present in the airway epithelium as compared to SARS MA15, which causes lethal outcomes in aged mice [7].

Due to the elevated pathogenic activity of the SHC014-MA15 chimeric virus relative to MA15 chimeric virus with the original human SARS S gene in mice, such experiments with SL-SHC014-MA15 chimeric virus were later restricted as gain of function (GOF) studies under the US government-mandated pause policy (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research). The current COVID-2019 epidemic has restarted the debate over the risks of constructing such viruses that could have pandemic potential, irrespective of the finding that these bat CoVs already exist in nature. Regardless, upon careful phylogenetic analyses by multiple international groups [5,14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15, with >6,000 nucleotide differences across the whole genome. Therefore, once again there is no credible evidence to support the claim that the SARS-CoV-2 is derived from the chimeric SL-SHC014-MA15 virus.

There are also rumours that the SARS-CoV-2 was artificially, or intentionally, made by humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by an HIV-1 virologist Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific but random [15]. Because of the many concerns raised by the international community, the authors who made the initial claim have already withdrawn this report.

Evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat CoV and another coronavirus in an intermediate animal host. More studies are needed to explore this possibility and resolve the natural origin of SARS-CoV-2. We should emphasize that, although SARS-CoV-2 shows no evidence of laboratory origin, viruses with such great public health threats must be handled properly in the laboratory and also properly regulated by the scientific community and governments.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Susan R. Weiss http://orcid.org/0000 0002 8155 4528

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