Message

From: Fauci, Anthony (NIH/NIAID) [E] [redacted]
Sent: 1/31/2020 6:25:48 PM
To: Kristian G. Andersen [redacted]
CC: Jeremy Farrar [redacted]
Subject: RE: Phone call

Thanks, Christian. I will keep you posted.
Best regards,
Tony

From: Kristian G. Andersen [redacted]
Sent: Friday, January 31, 2020 8:05 PM
To: Fauci, Anthony (NIH/NIAID) [E] [redacted]
Cc: Jeremy Farrar [redacted]
Subject: Re: Phone call

Thanks Tony,

In addition to Eddie and Bob we have Mike Farzan on board (discoverer of the SARS receptor https://www.scripps.edu/faculty/farzan/), and I believe Jeremy will reach out to Christian Drosten and Ron Fouchier in the morning to get their expertise as well. Combined, this group will be able to objectively assess the available data and determine whether the genome looks unusual.

Please let me know if anything changes on your end or if you have any questions.

Best,
Kristian

On Fri, Jan 31, 2020 at 4:38 PM Fauci, Anthony (NIH/NIAID) [E] [redacted] wrote:

> Jeremy:
>
> I just got off the phone with Kristian Anderson and he related to me his concern about the Furine site mutation in the spike protein of the currently circulating 2019-nCoV. I told him that as soon as possible he and Eddie Holmes should get a group of evolutionary biologists together to examine carefully the data to determine if his concerns are validated. He should do this very quickly and if everyone agrees with this concern, they should report it to the appropriate authorities. I would imagine that in the USA this would be the FBI and in the UK it would be MI5. It would be important to quickly get confirmation of the cause of his concern by experts in the field of coronaviruses and evolutionary biology. In the meantime, I will alert my US. Government official colleagues of my conversation with you and Kristian and determine what further investigation they recommend. Let us stay in touch.
>
> Best regards,
>
> Tony
>
> **Anthony S. Fauci, MD**
> **Director**

National Institute of Allergy and Infectious Diseases
[redacted]
National Institutes of Health
Bethesda, MD 20892-2520
Phone: [redacted]
FAX: [redacted]
E-mail: [redacted]

From: Jeremy Farrar [redacted]
Sent: Friday, January 31, 2020 5:57 PM
To: Fauci, Anthony (NIH/NIAID) [E] [redacted]
Subject: Re: Phone call

Thanks Tony

Can you phone Kristian Anderson

[redacted]

He is expecting your call now.

The people involved are:

Kristian Anderson

https://www.scripps.edu/faculty/andersen/

Bob Garry

https://medicine.tulane.edu/departments/microbiology-immunology-tulane-cancer-center/faculty/robert-f-garry-jr-phd

Eddie Holmes

https://sydney.edu.au/science/about/our-people/academic-staff/edward-holmes.html

From: "Conrad, Patricia (NIH/NIAID) [E]" [redacted] on behalf of "Fauci, Anthony (NIH/NIAID) [E]" [redacted]
Date: Friday, 31 January 2020 at 22:34
To: Jeremy Farrar [redacted]
Subject: RE: Phone call

Will call shortly...

Patricia L. Conrad

Public Health Analyst and

Special Assistant to the Director

National Institute of Allergy and Infectious Diseases

The National Institutes of Health

[redacted]

Bethesda, Maryland 20892

[redacted]

[redacted] fax

From: Jeremy Farrar [redacted]
Sent: Friday, January 31, 2020 5:23 PM
To: Fauci, Anthony (NIH/NIAID) [E] [redacted]
Subject: Phone call

Tony

Really would like to speak with you this evening

It is 10pm now UK

Can you phone me on +44 [redacted]

Jeremy

Message

From: Fauci, Anthony (NIH/NIAID) [E] [redacted]
Sent: 2/1/2020 10:43:31 AM
To: Kristian G. Andersen [redacted]
Subject: RE: FW: Science: Mining coronavirus genomes for clues to the outbreak's origins

Thanks, Kristian. Talk soon on the call.

From: Kristian G. Andersen [redacted]
Sent: Friday, January 31, 2020 10:32 PM
To: Fauci, Anthony (NIH/NIAID) [E] [redacted]
Cc: Jeremy Farrar [redacted]
Subject: Re: FW: Science: Mining coronavirus genomes for clues to the outbreak's origins

Hi Tony,

Thanks for sharing. Yes, I saw this earlier today and both Eddie and myself are actually quoted in it. It's a great article, but the problem is that our phylogenetic analyses aren't able to answer whether the sequences are unusual at individual residues, except if they are completely off. On a phylogenetic tree the virus looks totally normal and the close clustering with bats suggest that bats serve as the reservoir. The unusual features of the virus make up a really small part of the genome (<0.1%) so one has to look really closely at all the sequences to see that some of the features (potentially) look engineered.

We have a good team lined up to look very critically at this, so we should know much more at the end of the weekend. I should mention that after discussions earlier today, Eddie, Bob, Mike, and myself all find the genome inconsistent with expectations from evolutionary theory. But we have to look at this much more closely and there are still further analyses to be done, so those opinions could still change.

Best,
Kristian

On Fri, Jan 31, 2020 at 18:47 Fauci, Anthony (NIH/NIAID) [E] [redacted] wrote:

> Jeremy/Kristian:
>
> This just came out today. You may have seen it. If not, it is of interest to the current discussion.
>
> Best,
>
> Tony

From: Folkers, Greg (NIH/NIAID) [E] [redacted]
Sent: Friday, January 31, 2020 8:43 PM
Subject: Science: Mining coronavirus genomes for clues to the outbreak's origins

As part of a long-running effort to see what viruses bats harbor, researchers in China collect one from a cave in Guandong.

EcoHealth Alliance

Mining coronavirus genomes for clues to the outbreak's origins

By Jon CohenJan. 31, 2020 , 6:20 PM

attaaaggtt tataccttcc caggtaacaa accaaccaac tttcgatctc ttgtagatct ...

That string of apparent gibberish is anything but: It's a snippet of a DNA sequence from the viral pathogen, dubbed 2019 novel coronavirus (2019-nCoV), that is overwhelming China and frightening the entire world. Scientists are publicly sharing an ever-growing number of full sequences of the virus from patients—53 at last count in the Global Initiative on Sharing All Influenza Data database. These viral genomes are being intensely studied to try to understand the origin of 2019-nCoV and how it fits on the family tree of related viruses found in bats and other species. They have also given glimpses into what this newly discovered virus physically looks like, how it's changing, and how it might be stopped.

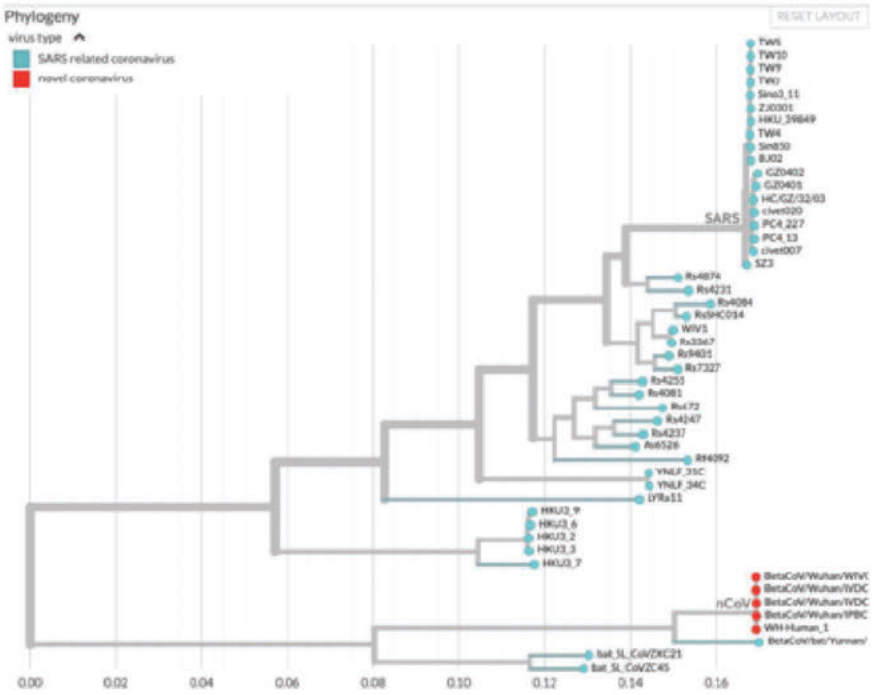
"One of the biggest takeaway messages [from the viral sequences] is that there was a single introduction into humans and then human-to-human spread," says Trevor Bedford, a bioinformatics specialist at the University of Washington, Seattle. The role of Huanan Seafood Wholesale Market in Wuhan, China, in spreading 2019-nCoV remains murky, though such sequencing, combined with sampling the market's environment for the presence of the virus, is clarifying that it indeed had an important early role in amplifying the outbreak. The viral sequences, most researchers say, also knock down the idea the pathogen came from a virology institute in Wuhan.

In all, 2019-nCoV has nearly 29,000 nucleotides bases that hold the genetic instruction book to produce the virus. Although it's one of the many viruses whose genes are in the form of RNA, scientists convert the viral genome into DNA, with bases known in shorthand as A, T, C, and G, to make it easier to study. Many analyses of 2019-nCoV's sequences have already appeared on virological.org, nextstrain.org, preprint servers like bioRxiv, and even in peer-reviewed journals. The sharing of the sequences by Chinese researchers allowed public health labs around the world to develop their own diagnostics for the virus, which now has been found in 18 other countries. (*Science*'s news stories on the outbreak can be found here.)

When the first 2019-nCoV sequence became available, researchers placed it on a family tree of known coronaviruses—which are abundant and infect many species—and found that it was most closely related to relatives found in bats. A team led by Shi Zheng-Li, a coronavirus specialist at the Wuhan Institute of Virology, reported on 23 January on bioRxiv that 2019-nCoV's sequence was 96.2% similar to a bat virus and had 79.5% similarity to the coronavirus that causes severe acute respiratory syndrome (SARS), a disease whose initial outbreak was also in China more than 15 years ago. But the SARS coronavirus has a similarly close relationship to bat viruses, and sequence data make a powerful case that

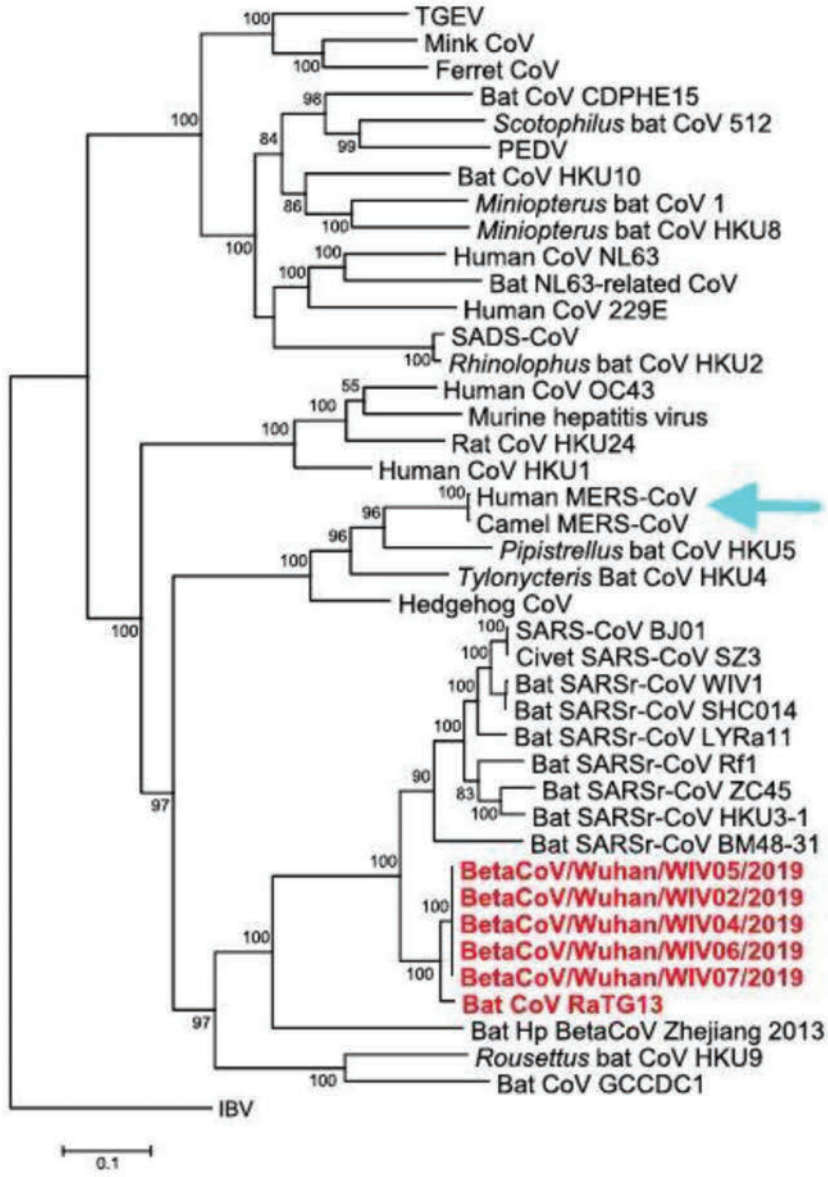
it jumped into people from a coronavirus in civets that differed from human SARS viruses by as few as 10 nucleotides. That's one reason why many scientists suspect there's an "intermediary" host species—or several—between bats and 2019-nCoV.

According to Bedford's analysis, the bat coronavirus sequence that Shi Zheng-Li's team highlighted, dubbed RaTG13, differs from 2019-nCoV by nearly 1100 nucleotides. On nextstrain.org, a site he co-founded, Bedford has created coronavirus family trees (example below) that include bat, civet, SARS, and 2019-nCoV sequences. (The trees are interactive—by dragging a computer mouse over them, it's easy to see the differences and similarities between the sequences.)



Bedford's analyses of RaTG13 and 2019-nCoV suggest that the two viruses shared a common ancestor 25 to 65 years ago, an estimate he arrived at by combining the difference in nucleotides between the viruses with the presumed rates of mutation in other coronaviruses. So it likely took decades for RaTG13-like viruses to mutate into 2019-nCoV.

Middle East respiratory syndrome (MERS), another human disease caused by a coronavirus, similarly has a link to bat viruses. But studies have built a compelling case it jumped to humans from camels. And the phylogenetic tree from Shi's bioRxiv paper (below) makes the camel-MERS link easy to see.



The longer a virus circulates in a human populations, the more time it has to develop mutations that differentiate strains in infected people, and given that the 2019-nCoV sequences analyzed to date differ from each other by seven nucleotides at most, this suggests it jumped into humans very recently. But it remains a mystery which animal spread the virus to humans. "There's a very large gray area between viruses detected in bats and the virus now isolated in humans," says Vincent Munster, a virologist at the U.S. National Institute of Allergy and Infectious Diseases who studies coronaviruses in bats, camels, and others species.

Strong evidence suggests the marketplace played an early role in spreading 2019-nCoV, but whether it was the origin of the outbreak remains uncertain. Many of the initially confirmed 2019-nCoV cases—27 of the first 41 in one report, 26 of 47 in another—were connected to the Wuhan market, but up to 45%, including the earliest handful, were not. This raises the possibility that the initial jump into people happened elsewhere.

According to Xinhua, the state-run news agency, "environmental sampling" of the Wuhan seafood market has found evidence of 2019-nCoV. Of the 585 samples tested, 33 were positive for 2019-nCoV and all were in the huge market's western portion, which is where wildlife were sold. "The positive tests from the wet market are hugely important," says Edward Holmes, an evolutionary biologist at the University of Sydney who collaborated with the first group to publicly release a 2019-nCoV sequence. "Such a high rate of positive tests would strongly imply that animals in the market played a key role in the emergence of the virus."

Yet there have been no preprints or official scientific reports on the sampling, so it's not clear which, if any, animals tested positive. "Until you consistently isolate the virus out of a single species, it's really, really difficult to try and determine what the natural host is," says Kristian Andersen, an evolutionary biologist at Scripps Research.

One possible explanation for the confusion about where the virus first entered humans is if there was a batch of recently infected animals sold at different marketplaces. Or an infected animal trader could have transmitted the virus to different people at different markets. Or, Bedford suggests, those early cases could have been infected by viruses that didn't easily transmit and sputtered out. "It would be hugely helpful to have just a sequence or two from the marketplace [environmental sampling] that could illuminate how many zoonoses occurred and when they occurred," Bedford says.

A research group sent fecal and other bodily samples from bats they trapped in caves to the Wuhan Institute of Virology to search for coronaviruses.

EcoHealth Alliance

In the absence of clear conclusions about the outbreak's origin, theories thrive, and some have been scientifically shaky. A sequence analysis led by Wei Ji of Peking University and published online by the *Journal of Medical Virology* received substantial press coverage when it suggested that "snake is the most probable wildlife animal reservoir for the 2019-nCoV." Sequence specialists, however, pilloried it.

Conspiracy theories also abound. A CBC News report about the Canadian government deporting Chinese scientists who worked in a Winnipeg lab that studies dangerous pathogens was distorted on social media to suggest that they were spies who had smuggled out coronaviruses. The Wuhan Institute of Virology, which is the premier lab in China that studies bat and human coronaviruses, has also come under fire. "Experts debunk fringe theory linking China's coronavirus to weapons research," read a headline on a story in *The Washington Post* that focused on the facility.

Concerns about the institute predate this outbreak. *Nature* ran a story in 2017 about it building a new biosafety level 4 lab and included molecular biologist Richard Ebright of Rutgers University, Piscataway, expressing concerns about accidental infections, which he noted repeatedly happened with lab workers handling SARS in Beijing. Ebright, who has a long history of raising red flags about studies with dangerous pathogens, also in 2015 criticized an experiment in which modifications were made to a SARS-like virus circulating in Chinese bats to see whether it had the potential to cause disease in humans. Earlier this week, Ebright questioned the accuracy of Bedford's calculation that there are at least 25 years of evolutionary distance between RaTG13—the virus held in the Wuhan virology institute—and 2019-nCoV, arguing that the mutation rate may have been different as it passed through different hosts before humans. Ebright tells *Science*Insider that the 2019-nCoV data are "consistent with entry into the human population as a natural accident."

Shi did not reply to emails from *Science*, but her longtime collaborator, disease ecologist Peter Daszak of the EcoHealth Alliance, dismissed Ebright's conjecture. "Every time there's an emerging disease, a new virus, the same story comes out: This is a spillover or the release of an agent or a bioengineered virus," Daszak says. "It's just a shame. It seems humans can't resist controversy and these myths, yet it's staring us right in the face. There's this incredible diversity of

viruses in wildlife and we've just scratched the surface. Within that diversity, there will be some that can infect people and within that group will be some that cause illness."

A team of researchers from the Wuhan Institute of Virology and the EcoHealth Alliance have trapped bats in caves all over China, like this one in Guangdong, to sample them for coronaviruses.

EcoHealth Alliance

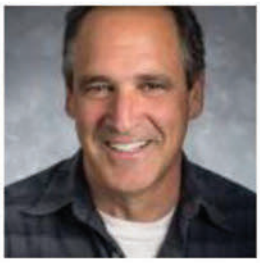
Daszak and Shi's group have for 8 years been trapping bats in caves around China to sample their feces and blood for viruses. He says they have sampled more than 10,000 bats and 2000 other species. They have found some 500 novel coronaviruses, about 50 of which fall relatively close to the SARS virus on the family tree, including RaTG13—it was fished out of a bat fecal sample they collected in 2013 from a cave in Moglang in Yunnan province. "We cannot assume that just because this virus from Yunnan has high sequence identity with the new one that that's the origin," Daszak says, noting that only a tiny fraction of coronaviruses that infect bats have been discovered. "I expect that once we've sampled and sampled and sampled across southern China and central China that we're going to find many other viruses and some of them will be closer [to 2019-nCoV]."

It's not just a "curious interest" to figure out what sparked the current outbreak, Daszak says. "If we don't find the origin, it could still be a raging infection at a farm somewhere, and once this outbreak dies, there could be a continued spillover that's really hard to stop. But the jury is still out on what the real origins of this are."

Posted in:

- Asia/Pacific
- Health
- Coronavirus

doi:10.1126/science.abb1256



Jon Cohen

Jon is a staff writer for *Science*.

- Email Jon
- Twitter

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Message

From: Pope, Andrew [redacted]
Sent: 2/3/2020 9:04:47 AM
To: 'Chakravarti, Aravinda' [redacted] 'andersen [redacted] Ralph Baric [redacted] 'trevor [redacted] Peter Daszak [redacted] 'dgriffi6([redacted] Gigi Gronvall [redacted] 'tinglesby([redacted] Stanley Perlman [redacted] 'KATHRYBR' [redacted] Tony Fauci [redacted] Hassell, David (Chris) (OS/ASPR/IO) [redacted] 'Mex7 [redacted] 'ribull([redacted] 'Watson, Ian D. EOP/OSTP' [redacted] Kadlec, Robert (OS/ASPR/IO) [redacted] 'Conrad, Patricia(NIH/NIAID) [E]' [redacted] Barasch, Kimberly (NIH/NIAID) [C] [redacted]
CC: May, David [redacted] Chao, Samantha [redacted] Laney,Kara N. [redacted] Shore, Carolyn [redacted] SheltonDavenport, Marilee [redacted] Symmes, Gregory [redacted] Brown, Lisa [redacted] Downey, Autumn [redacted] Wollek,Scott [redacted] Kanarek, Morgan [redacted] Dzau, VictorJ. [redacted] Beachy, Sarah [redacted] Logan, Kendall [redacted] Kearney, Megan [redacted] Korsen, Dana [redacted] Behney, Clyde [redacted] Shern, Lauren [redacted] Borel, Bridget [redacted]
Subject: Today's Call/meeting info
Attachments: Agenda- 2019-nCoV.docx; SOW.docx

Thank you for participating in today's meeting of experts at the National Academies to discuss and identify what data, information and samples are needed to understand the evolutionary origins of 2019-nCoV and more effectively respond to the outbreak and resulting misinformation.

Attached for your information are:
Agenda
Scope of Work
A list of participants will be sent along shortly

Please let me know if you have any questions of problems with connecting.

"Zoom" Call-in info is as follows (and is included at top of agenda):

Zoom Dial-in Info:
Time: Feb 3, 2020 02:00 PM Eastern Time (US and Canada)
Join from PC, Mac, Linux, iOS or Android: [redacted]
Telephone: [redacted]
Meeting ID: [redacted]
International numbers available: [redacted]

Andrew M. Pope, Ph.D.
Director
Board on Health Sciences Policy
Health and Medicine Division
The National Academies of Sciences,
Engineering, and Medicine
[redacted]
[redacted] direct
[redacted] office
Find us at nationalacademies.org/HMD

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Expert Meeting
Rapid Response for Assessment of Data Needs for 2019-nCoV

Agenda

February 3, 2020
2:00 p.m.–3:00 p.m. (ET)

Keck Center, Room 103
500 5th St NW, Washington, DC 20001

Join from PC, Mac, Linux, iOS or Android: [redacted]
Telephone: [redacted]
Meeting ID: [redacted]
International numbers available: [redacted]

Meeting Objective: *Assess what data, information and samples are needed to understand the evolutionary origins of 2019-nCoV and more effectively respond to the outbreak and resulting misinformation.*

2:00 p.m. **Welcome and Introductions** (*5 mins*)

ANDREW POPE
Director, Board on Health Sciences Policy
National Academies of Sciences, Engineering, and Medicine

2:05 p.m. **Statement of Work** (*10 mins*)

KELVIN DROEGEMEIER
Director
Office of Science and Technology Policy

D. CHRISTIAN ("CHRIS") HASSELL
Senior Science Advisor
U.S. Department of Health and Human Services

2:15 p.m. **Perspective from NIH/NIAID** (*10 mins*)

ANTHONY ("TONY") S. FAUCI
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health

2:25 p.m. **Discussion of Meeting Objective** (*30 mins*)

2:55 p.m. **Determine Next Steps** (*5 mins*)

3:00 p.m. **Adjourn**

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Statement of Work

Rapid Response for Assessment of Data Needs for 2019-nCoV

February 3, 2020

Statement of Task:

In response to a request from OSTP, the NASEM will examine information and identify data requirements that would help determine the origins of 2019-nCoV, specifically from an evolutionary/structural biology standpoint. NASEM will also consider whether this should include more temporally and geographically diverse clinical isolates, sequences, etc. Although a widely-disputed paper posted on a pre-print server last week has since been withdrawn, the response to that paper highlights the need to determine these information needs as quickly as possible. As part of a broader deliberative process, this review will help prepare for future events by establishing a process for quickly assembling subject matter experts for evaluation of other potentially threatening organisms.

Workplan:

NASEM will hold a meeting of experts to assess what data, information and samples are needed to address the unknowns, in order to understand the evolutionary origins of NCoV and more effectively respond to both the outbreak and any resulting misinformation. A statement from the National Academies will be prepared and published on the Web as a "Based on Science" article that summarizes the status and needs for more and what types of data. A more in-depth examination of the issues will be established as a follow up as needed.

Gmail [redacted]

URGENT: Please review by NOON if at all possible...

Kristian G. Andersen [redacted] Tue, Feb 4, 2020 at 9:05 AM
To: Peter Daszak [redacted]
Cc: "Pope, Andrew" [redacted], "Chakravarti, Aravinda" [redacted], "Ralph Baric [redacted] "Trevor Bedford [redacted] Gigi Gronvall [redacted], "Tom Inglesby [redacted] "Stanley Perlman [redacted] "Shore, Carolyn" [redacted], "Chao, Samantha" [redacted]

I too agree with all that has been said, but would caution against adding language suggesting that the virus might evolve (i.e., "mutate" to most people) towards better infectivity or transmission - a lot has been said about that for Ebola and other viruses, and it's been driving fear because most people don't fully understand what it means. I'm not arguing that it's not something that might well happen - the SARS data beautifully show it - but I would be worried about the message it could send.

Reading through the letter I think it's great, but I do wonder if we need to be more firm on the question of engineering. The main crackpot theories going around at the moment relate to this virus being somehow engineered with intent and that is demonstrably not the case. Engineering can mean many things and could be done for either basic research or nefarious reasons, but the data conclusively show that neither was done (in the nefarious scenario somebody would have used a SARS/MERS backbone and optimal ACE2 binding as previously described, and for the basic research scenario would have used one of the many already available reverse genetic systems). If one of the main purposes of this document is to counter those fringe theories, I think it's very important that we do so strongly and in plain language ("consistent with" [natural evolution] is a favorite of mine when talking to scientists, but not when talking to the public - especially conspiracy theorists).

Best,
Kristian

On Tue, Feb 4, 2020 at 9:02 AM Peter Daszak [redacted] wrote:

> I agree with all of the other comments so far sent in, and want to add the following:
>
> 1) In the 3rd paragraph, it's important to add "including further samples from wildlife", and perhaps the rationale for this "to identify other viruses closely related to nCoV"
>
> 2) Re. references for #3 that there are current and planned studies underway on the bat origins of CoVs. Here are some references to pick from if they make sense:
>
> · Latinne A, Hu B, Olival KJ, et al.; Origin and cross-species transmission of bat coronaviruses in China. *Nature Communications* 2020;**In review**.
>
> · Wang N, Li S-Y, Yang X-L, et al.; Serological Evidence of Bat SARS-Related Coronavirus Infection in Humans, China. *Virologica Sinica* 2018. doi: 10.1007/s12250-018-0012-7.
>
> · Hu B, Zeng L-P, Yang X-L, et al.; Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. *PLOS Pathogens* 2017;**13**(11):e1006698. doi: 10.1371/journal.ppat.1006698.
>
> · Zhou P, Fan H, Lan T, et al.; Fatal Swine Acute Diarrhea Syndrome caused by an HKU2-related Coronavirus of Bat Origin. *Nature* 2018

Cheers,

Peter

Peter Daszak

President

EcoHealth Alliance

[redacted]

New York, NY 10001

Tel. [redacted]

Website: www.ecohealthalliance.org

Twitter: @PeterDaszak

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that prevent pandemics and promote conservation.

From: Pope, Andrew [redacted]
Sent: Tuesday, February 4, 2020 9:11 AM
To: 'Chakravarti, Aravinda'; Kristian Andersen [redacted] Ralph Baric [redacted] Trevor Bedford [redacted] Peter Daszak; Gigi Gronvall; Tom Inglesby [redacted] Stanley [redacted]
Cc: Shore, Carolyn; Chao, Samantha
Subject: URGENT: Please review by NOON if at all possible...
Importance: High

Many thanks again for your thoughtful participation yesterday. The plans have changed in terms of our product. Instead of a “Based on Science” web posting, we are now developing a letter that will be signed by the 3 Presidents of our 3 Academies (NAS, Marcia McNutt; NAM, Victor Dzau; NAE, John Anderson), in response to a letter from OSTP. We think this will be more appropriate and expeditious.

Thus, given the urgency of the request from OSTP and HHS we ask that you please review the attached DRAFT CONFIDENTIAL letter, and let us know if you have any concerns or suggested edits. In particular, we would like to ask if there might be some additional detail added to the data needs that are identified. We think it would be helpful to be a bit more specific, but don't want to go into too much detail either. Your help there would be most helpful.

Many sincere thanks again for your continued engagement on this important activity!

Andy

Andrew M. Pope, Ph.D.

Director

Board on Health Sciences Policy

Health and Medicine Division

The National Academies of Sciences,

Engineering, and Medicine

[redacted]

[redacted], direct

[redacted], office

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To: 'Chakravarti, Aravinda' [redacted] Kristian Andersen
Baric, Ralph S [redacted] Trevor Bedford
[redacted] Peter Daszak [redacted] Gigi
[redacted] Tom Inglesby [redacted] Stanley Perlman [redacted]
[redacted]
Cc: Shore, Carolyn [redacted] Chao, Samantha [redacted]
From: Pope, Andrew [redacted]
Sent: Tue 2/4/2020 9:10:35 AM (UTC-05:00)
Subject: URGENT: Please review by NOON if at all possible...
Response Letter_DRAFT - Feb 4.docx

Many thanks again for your thoughtful participation yesterday. The plans have changed in terms of our product. Instead of a "Based on Science" web posting, we are now developing a letter that will be signed by the 3 Presidents of our 3 Academies (NAS, Marcia McNutt; NAM, Victor Dzau; NAE, John Anderson), in response to a letter from OSTP. We think this will be more appropriate and expeditious.

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Many sincere thanks again for your continued engagement on this important activity!

Andy

Andrew M. Pope, Ph.D.
Director
Board on Health Sciences Policy
Health and Medicine Division
The National Academies of Sciences,
Engineering, and Medicine
[redacted]
direct
office
Find us at nationalacademies.org/HMD

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CONFIDENTIAL DRAFT

February 4, 2020

[insert address]

Dear XXX:

Thank you for your letter regarding the current outbreak of a new respiratory virus, the 2019 Novel Coronavirus, or 2019-nCoV, which was first detected in Wuhan, China, and has now been reported in a growing number of locations worldwide, including the United States.[1] The request from OSTP is timely given the public health urgency of the outbreak and potential for misinformation.

In response to your request, we consulted leading experts[2] in the fields of virology, infectious disease genomics, genome sciences, epidemiology, microbiology, immunobiology, coronaviruses, emerging infections, biosecurity, and global health, to share their views of whether available genomic data on 2019-nCoV are consistent with natural evolution and the data that could help determine the origins of 2019-nCoV, specifically from an evolutionary and structural biology standpoint.

Many studies of the genome of 2019-nCoV to better understand its origin and how it relates to viruses found in bats and other species are already underway.[3] The initial views of the experts[4] is that the available genomic data are consistent with natural evolution[5] and that there is currently no evidence that the virus was engineered to spread more quickly among humans. [ask experts to add specifics re binding sites?] They also told us that additional genomic sequence data from geographically and temporally diverse viral samples, including samples that have been collected prior to the outbreak in Wuhan, could be used to clarify the origins of the virus. Understanding the driving forces behind viral evolution may facilitate the development of more effective strategies for managing the 2019-nCoV outbreak. International collaboration is more important than ever to overcome these types of global challenges.

The National Academies stand ready to assemble a committee of experts to examine these issues in more detail and provide more complete evidence-based advice to you in an expedited manner if requested.

Thank you, again for your commitment to the National Academies and our efforts to provide independent, objective analysis; advise the nation; and inform public policy decisions.

Sincerely,

[1] "2019 Novel Coronavirus (2019-nCoV) Situation Summary." *Centers for Disease Control and Prevention*, 3 Feb. 2020. https://www.cdc.gov/coronavirus/2019-nCoV/summary.html#anchor_1580079137454. Accessed 3 Feb. 2020.
[2] [possible add list]
[3] [insert references]

[5] [possibly add brief explanation that this does not preclude an unintentional release from a laboratory studying the evolution of related coronaviruses]

cc: [insert names]

Message

From: Edward Holmes [redacted]
Sent: 2/5/2020 1:23:41 AM
To: Garry, Robert F [redacted]; Kristian G. Andersen [redacted]; rambaut [redacted]
Subject: Re: Summary - Invitation to edit

Kristian, can you quickly check those RBD mutations in the pangolin S protein...

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
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And unfortunately as well I think that we're about to learn that "quarantines and travel bans" are really bad for the economy.

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Cc: Edward Holmes [redacted], "rambaut@[redacted]
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Variation on the theme in HKU1, a virus that probably does have intense transmission infecting millions of people each year. Here the insert is three Serine residues, which pushes this site to a mucin-like patch (there are already a couple of prolines and the SSS is a turn as well)

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You have to infect flu viruses (the ones without the multibasic cleavage site) in the presence of trypsin, and include trypsin in the overlay if you want to get virus spread aka plaques.

This also contributes to the pathogenicity of - well - highly pathogenic flu virus – different tissues have different proteases and are able to "activate" flu to different extents - if the flu v has a furin cleavage site it has a lot more choices and canmore easil go systemic.

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Bottom line – I think that if you put selection pressure on a Cov without a furin cleavage site in cell culture you could well generate a furin cleavage site after a number of passages (but let's see the data Ron!). It will infect a lot better if it can effectively fuse at the cell surface and doesn't have to rely on endosomal cleavage and receptor mediated endocytosis..

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I'll let Bob weigh in as well - definitely not my area of expertise.

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Bob - a question from Jeremy:

"Quick question though - why could passage in animals in lab work add the glycans?"

Any thoughts?

Eddie

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PROFESSOR EDWARD C. HOLMES FAA FRS
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Great job.

Professor Edward C. Holmes FAA FRS
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> Some, perhaps more than a few, will not like it still since it allows that the nCoV may have arisen during cell culture passage in a lab (their labs).
>
> Thanks for the great science…
>
> b

From: Kristian Andersen [redacted]
Reply-To: Kristian Andersen [redacted]
Date: Monday, February 3, 2020 at 9:36 PM
To: Robert Garry [redacted]
Cc: "edward.holmes [redacted], "rambaut [redacted]
Subject: Summary - Invitation to edit

External Sender. Be aware of links, attachments and requests.

[redacted] has invited you to **edit** the following document:

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Summary

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Google LLC, 1600 Amphitheatre Parkway, Mountain View, CA 94043, USA
You have received this email because someone shared a document with you from Google Docs.

Error! Filename not specified

<Alongshan copy.pdf>

Message

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Sent: 2/5/2020 4:22:24 AM
To: Andrew Rambaut [redacted]
CC: Garry, Robert F [redacted] Kristian G. Andersen [redacted]
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Region 6 is the RBD. Could be recombination? Very strange.

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E [redacted]

On 5 Feb 2020, at 9:04 pm, Edward Holmes [redacted] wrote:

I think we might have dropped the ball with this pangolin virus. I ignored it when I saw it didn't have the furin cleavage site. Should now check all the key sites.

Cheers,

Eddie

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On 5 Feb 2020, at 8:44 pm, Andrew Rambaut [redacted] wrote:

I think we need to keep this document live and update it as necessary. Give it a date and version number.

Andrew

Sent from my phone. Apologies for brevity or illiteracy.

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To: Robert Garry [redacted]
Cc: "edward.holmes[redacted]", "rambaut[redacted]
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Google LLC, 1600 Amphitheatre Parkway, Mountain View, CA 94043, USA
You have received this email because someone shared a document with you from Google Docs.

Error! Filename not specified.

<Alongshan copy.pdf>

Message

From: Edward Holmes [redacted]
Sent: 2/6/2020 2:36:30 AM
To: Kristian G. Andersen [redacted]
CC: Garry, Robert F [redacted]; Andrew Rambaut [redacted]
Subject: Re: Summary - Invitation to edit

From Jeremy.

"Do you think in the report....possible to dampen down further the 'conspiracy' idea and make totally neutral?

Talking with Marion last night and with the WHO meeting next week....both wondering whether actually publishing this sooner, but ruthlessly on the science....is worthwhile to put that flag down..."

Thoughts?

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On 6 Feb 2020, at 11:10 am, Kristian G. Andersen [redacted] wrote:

Haha, I got the same email. I assume Andrew probably did too.

I already said yes.

Not.

K

On Wed, Feb 5, 2020 at 16:05 Garry, Robert F [redacted] wrote:

I'd probably stammer a bit on, "Professor Garry can you assure our audience beyond any reasonable doubt that nCoV did not escape from the WIV?"

From: Edward Holmes [redacted]
Date: Wednesday, February 5, 2020 at 5:46 PM
To: Andrew Rambaut [redacted]
Cc: Robert Garry [redacted], Kristian Andersen [redacted]
Subject: Re: Summary - Invitation to edit

I thought I had better say no…

Dear Professor Holmes,

My name is Andrey Kozlov, I'm producer in Russian Broadcasting Company NTV. We are making a report on false conspiracy theories around new China's coronavirus. I'm looking for an interview opportunity with you on this issue. We would like to discuss with you these theories, where they came from, what effect they have and etc. Will it be possible for you to meet with our film crew this week? Perhaps, on Thursday or Friday? Hope for you cooperation.

Best regards,

Andrey Kozlov,

Producer,

NTV Broadcasting company

Cell. [redacted]

PROFESSOR EDWARD C. HOLMES FAA FRS
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E [redacted]

On 6 Feb 2020, at 9:43 am, Andrew Rambaut [redacted] wrote:

The Sunda pangolin, also known as the Malayan or Javan pangolin, is a species of pangolin. It is found throughout Southeast Asia, including Brunei, Cambodia, Java, Sumatra, Borneo, the Lesser Sunda Islands, Laos, Malaysia, Singapore, Thailand, Myanmar and Vietnam.

(wikipedia)

On 5 Feb 2020, at 22:39, Garry, Robert F [redacted] wrote:

Fascinating – so does this mean they were infected before being smuggled out of Malaysia?

From: Edward Holmes [redacted]
Date: Wednesday, February 5, 2020 at 4:37 PM
To: Robert Garry [redacted]
Cc: Kristian Andersen [redacted], Andrew Rambaut [redacted]
Subject: Re: Summary - Invitation to edit

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Smuggled in. Captured by the anti-smuggling cops in two southern provinces.

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

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Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 6 Feb 2020, at 9:24 am, Garry, Robert F [redacted] wrote:

SO just info from Wiki but *Manis javanica* is the Malayian pangolin.

Chinese pangolin (*Manis pentadactyla*) is the one in southern China.

I guess the ranges overlap some, but is it odd that they got this species?

From: Edward Holmes [redacted]
Date: Wednesday, February 5, 2020 at 4:12 PM
To: Robert Garry [redacted]
Cc: Kristian Andersen [redacted], Andrew Rambaut [redacted]
Subject: Re: Summary - Invitation to edit

External Sender. Be aware of links, attachments and requests.

More pangolin viruses on this tree - crazy.

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 6 Feb 2020, at 9:08 am, Garry, Robert F [redacted] wrote:

No problem with Marian Koopsman either.

From: Robert Garry [redacted]
Date: Wednesday, February 5, 2020 at 4:07 PM
To: Kristian Andersen [redacted]
Cc: Andrew Rambaut [redacted], Edward Holmes [redacted]
Subject: Re: Summary - Invitation to edit

Kawaoka is a good guy. Good perspective on GoF research and flu.

From: Kristian Andersen [redacted]
Date: Wednesday, February 5, 2020 at 4:01 PM
To: Robert Garry [redacted]
Cc: Andrew Rambaut [redacted], Edward Holmes [redacted]
Subject: Re: Summary - Invitation to edit

'Ego' is Eddie's genius (he's got many other...).

Yeah, Eddie, good point. Need to nix Baric too then.

How about Yoshi? He might know some good people in Japan.

K

On Wed, Feb 5, 2020 at 13:59 Garry, Robert F [redacted] wrote:

I'm "sure" that Ego was a typo – otherwise well done!

From: Kristian Andersen <[redacted]

Date: Wednesday, February 5, 2020 at 3:58 PM
To: Edward Holmes [redacted]
Cc: Andrew Rambaut [redacted], Robert Garry [redacted]
Subject: Re: Summary - Invitation to edit

EgoHealth people might have some African collaborators they could suggest?

K

On Wed, Feb 5, 2020 at 13:57 Edward Holmes [redacted] wrote:

WHO need geographic breath. Very important for them.

Thanks for all the suggestions.

PROFESSOR EDWARD C. HOLMES FAA FRS
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T [redacted]
E [redacted]

On 6 Feb 2020, at 8:55 am, Garry, Robert F [redacted] wrote:

Yes was just going to suggest Malik Peiris from Hong Kong – brings expertise of CoV and flu.

Not sure Christian Happi is the right person for CoV. His input would be very general.

I'm told they had or about to have a meeting on CoV preparedness in Dakar. But not sure who is involved. Might be a place to start.

MERS CoV has been isolated from camels in Kenya, but mostly WIV and outside investigators involved.

From: Edward Holmes [redacted]
Date: Wednesday, February 5, 2020 at 3:43 PM
To: Andrew Rambaut [redacted]
Cc: Robert Garry [redacted], Kristian Andersen [redacted]
Subject: Re: Summary - Invitation to edit

Thanks. Anyone from Asia? Africa?

Professor Edward C. Holmes FAA FRS

The University of Sydney

On 6 Feb 2020, at 8:36 am, Andrew Rambaut [redacted] wrote:

Colin Parrish, Jamie Lloyd Smith, Sara Sawer for zoonotic theory?

A

Sent from my phone. Apologies for brevity or illiteracy.

On 5 Feb 2020, at 21:28, Garry, Robert F [redacted] wrote:

Drosten, Fazan, Fouchier, Baric and Shi Zhengli from WIV – to capture different sides of the various scenarios.

Ab Osterhaus, Linfa Wang, and Peter Diazek to capture the bats.

George Gao and possibly Steve Harrison for structure.

Seems like she may be retired but probably has deepest historical perspective on CoV research:

http://www.ucdenver.edu/academics/colleges/medicalschool/departments/ImmunologyMicrobiology/faculty/departmental/Pages/HOLMESKV.aspx

Kathryn V. Holmes, Ph.D.

12800 E. 19th Ave., RC-1 N 9127
Mail Stop 8333, Aurora, CO 80045
Phone: [redacted]
E-mail: [redacted]

From: Edward Holmes <[redacted]
Date: Wednesday, February 5, 2020 at 3:13 PM
To: Kristian Andersen [redacted]
Cc: Robert Garry [redacted], Andrew Rambaut [redacted]

Subject: Re: Summary - Invitation to edit

I've asked Tommy to check the metagenomic assembly and to look at the synonymous changes. At face value it looks like recombination, which itself raises a whole set of other questions. Just so random that it is illegally smuggled pangolins from southern China.

Jeremy has the green light from WHO. Can you think of good sensible people to be on it? Need gender and geographic diversity.

Best wishes,

Eddie

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T [redacted]
E [redacted]

On 6 Feb 2020, at 3:14 am, Kristian G. Andersen [redacted] wrote:

Yup, agreed. Need proper biochemistry to really answer this question.

K

On Wed, Feb 5, 2020 at 07:49 Garry, Robert F [redacted] wrote:

Yeah _ I reread the Baric JV paper and still think some caution is needed. It's a good paper, but nCoV or it's progenitor may have found another RBD binding solution that might be as good or better. Argument that nCoV is inferior, hinges on nCoV aa501. However, there's a proline at 499 that's not present in SARSv or civet v (it is present in pangolin and RaTG13), which would put in a kink and change a lot.

From: Kristian Andersen [redacted]
Date: Wednesday, February 5, 2020 at 9:27 AM
To: Robert Garry [redacted]
Cc: Edward Holmes [redacted], Andrew Rambaut [redacted]
Subject: Re: Summary - Invitation to edit

External Sender. Be aware of links, attachments and requests.

Wait, I **have** the pangolin sequences - will take a look once I'm in the office.

K

On Wed, Feb 5, 2020 at 7:20 AM Kristian G. Andersen [redacted] wrote:

Eddie, can you please share the pangolin sequence? I can take a look later today (hopefully - super packed calendar). If not today, definitely tomorrow.

Bob, for the idea about civets not being optimal - take a look at this paper: https://www.ncbi.nlm.nih.gov/pubmed/31996437

Once I have had a look, I'll update on Slack - let's try and keep stuff on there so it doesn't get lost.

K

On Wed, Feb 5, 2020 at 6:24 AM Garry, Robert F [redacted] wrote:

Worth pointing out - if the crackpot charge comes re cell culture hypothesis - that we are discussing this in private amongst experts.

Clearly and I think correctly our approach has been different than say the flawed nejm paper -see science feb3 - about asymptomatic infection - Drosten was on the rushed out paper Tony got tripped up. Public error and pretty important. IMO they should retract the paper to send clear message.

Sent from my iPhone

On Feb 5, 2020, at 5:18 AM, Edward Holmes [redacted] wrote:

The pangolin virus looks like it might fall in roughly the same place on the tree as those new bat virus trees I put on Slack. Don't have the seqs of those yet.

Professor Edward C. Holmes FAA FRS

The University of Sydney

On 5 Feb 2020, at 9:52 pm, Andrew Rambaut [redacted] wrote:

Perhaps say we are adding new information? See whether he wants to hold off. I suspect Bethesda will be sending it round already?

I think we need to add a section about the pangolin and possibly something about whether the glycan sites are evidence of selection by an immune system?

A.

On 5 Feb 2020, at 10:47, Edward Holmes [redacted] wrote:

The animals are from Guangdong and Guangxi. Seized by customs. Need those Hubei pangolins.

Should I tell Jeremy to hold on sending the summary out to the group while we investigate more or does that really matter? He did say that more wildlife needed to be studied. He's sent it to the Bethesda boys.

Best wishes,

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS
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T
E [redacted]

On 5 Feb 2020, at 9:34 pm, Andrew Rambaut [redacted] wrote:

Do we know where this pangolin is from? Guangdong markets?

A.

On 5 Feb 2020, at 10:31, Edward Holmes [redacted] wrote:

I've asked Tommy to check for synonymous changes. He's writing a paper. Only got the figure this afternoon.

Professor Edward C. Holmes FAA FRS
The University of Sydney

On 5 Feb 2020, at 9:25 pm, Andrew Rambaut [redacted] wrote:

Need to look for some synonymous mutations. Perhaps the nCoV progenitor is also in Pangolins (widely traded illegally)?

A.

On 5 Feb 2020, at 10:22, Edward Holmes [redacted] wrote:

Region 6 is the RBD. Could be recombination? Very strange.

Message

From: Andrew Rambaut [redacted]
Sent: 2/7/2020 1:10:22 PM
To: Kristian G. Andersen [redacted]
CC: Edward Holmes [redacted]; Garry, Robert F [redacted]
Subject: Re: Stuff

Don't worry about FOI. Huawei will be feeding all of this directly to Xi Jinping.

A

Sent from my phone. Apologies for brevity or illiteracy.

On 7 Feb 2020, at 21:05, Kristian G. Andersen [redacted] wrote:

I would argue that any animal being identified would be beneficial to them - otherwise we're all going to point fingers at them telling people that they're so shit that they can't even predict the outbreaks of their own making...

Too harsh?

K

[for a potential future FOIA reader - please note that I can at times be sarcastic and have a knack for bad jokes].

On Fri, Feb 7, 2020 at 12:59 PM Andrew Rambaut [redacted] wrote:

No. They will hate it being pangolins. They were saying the had predicted the bats.

A

Sent from my phone. Apologies for brevity or illiteracy.

On 7 Feb 2020, at 20:53, Edward Holmes [redacted] wrote:

No, not at all.

Just Twitter chat.

PROFESSOR EDWARD C. HOLMES FAA FRS
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T [redacted]
E [redacted]

On 8 Feb 2020, at 7:51 am, Kristian G. Andersen [redacted] wrote:

Is this pangolin stuff the Ego guys?

On Fri, Feb 7, 2020 at 12:42 PM Garry, Robert F [redacted] wrote:

Shameless.

From: Edward Holmes [redacted]
Date: Friday, February 7, 2020 at 2:18 PM
To: Robert Garry [redacted]
Cc: Kristian Andersen [redacted] Andrew Rambaut [redacted]
Subject: Re: Stuff

External Sender. Be aware of links, attachments and requests.

Entertaining that the Ego Health crowd agree that having a press conference without providing the data is not the right way to proceed...no similarity to Bombali virus then.

Professor Edward C. Holmes FAA FRS

The University of Sydney

On 8 Feb 2020, at 2:46 am, Garry, Robert F [redacted] wrote:

Some comments over on the Slack channel, but need that 99% pangolin sequence.

I agree that the presence of the furin site would all but rule out passage.

If it's not there (or at least some insert) passage isn't ruled out (data from Fazan or Fouchier critical here).

Stating the somewhat obvious here: In Kristian's alignment Pangolin337 is essentially the RBD of SARS-CoV-2 save for a single amino acid change (what are the differences at the nucleotide level?), but differs more than BaTG13 elsewhere. May be looking at some mosaicism or recombination event amongst the different Pangolin CoV strains that should be "fairly" easy to pick up on.

From: Kristian Andersen [redacted]
Date: Friday, February 7, 2020 at 9:29 AM
To: Robert Garry [redacted]
Cc: Edward Holmes [redacted] Andrew Rambaut [redacted]
Subject: Re: Stuff

External Sender. Be aware of links, attachments and requests.

"But, does this swing it completely away from the passage idea?"

No, it does not, however, every little helps. The furin is still peculiar, but if we're discussing whether evolution could create a furin cleavage site or not, then, well, we better hit the pub sooner rather than later. Now, the presence of the furin site in pangos would nail it, but the absence (as it appears to be) wouldn't really tell us much.

K

On Fri, Feb 7, 2020 at 2:41 AM Garry, Robert F [redacted] wrote:

Yes indeed

Would be good to know about the 12 base pair insert

Would be great to see any insert there.

If not will be important to fetermine where this pangolin came from

As Andrew taught [me] they come from all over illegally

Also don't know obviously if it's 99.0 or 99.8%. If there is a 99% virus there may well be a 99.8% virus back in the pangolin's home country.

Sent from my iPhone

On Feb 7, 2020, at 4:11 AM, Edward Holmes [redacted] wrote:

External Sender. Be aware of links, attachments and requests.

OK, I've just emailed one of the authors. Let's hope we get a reply.

PROFESSOR EDWARD C. HOLMES FAA FRS
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T [redacted]
E [redacted]

On 7 Feb 2020, at 8:55 pm, Garry, Robert F [redacted] wrote:

That is the or at least a key question.

Sent from my iPhone

On Feb 7, 2020, at 3:46 AM, Andrew Rambaut [redacted] wrote:

Can we at least get a pers-comm as to whether it has the insertion or not?

https://www.nytimes.com/reuters/2020/02/07/world/asia/07reuters-china-health-pangolins.html

https://www.businessinsider.com/china-scientists-identify-pangolin-as-possible-coronavirus-host-2020-2?r=US&IR=T

A.

On 7 Feb 2020, at 09:36, Edward Holmes [redacted] wrote:

Jeremy wants us to publish our report somewhere. Thoughts?

I'll need to update the pangolin stuff again. Not proven of course, but it makes complete sense. We don't know what the amino acid sequences of these pangolin viruses that 99% similar to 2019-nCoV will look like, but there must be decent chance they have all the key mutations. But, does this swing it completely away from the passage idea?

Things are changing so fast it is hard not be redundant.

PROFESSOR EDWARD C. HOLMES FAA FRS
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T [redacted]
E [redacted]

Begin forwarded message:

From: Jeremy Farrar [redacted]
Subject: Re: Stuff
Date: 7 February 2020 at 5:31:44 pm AEDT
To: Edward Holmes [redacted]

I will be neutral.

Anyone from China?

Tomorrow morning fine.

Any preference for journal? All will take immediately, I can let them know coming if helpful and you have a preference

With revisions – will share with the TC group over the weekend – if OK – got to add the new info

---

From: Edward Holmes [redacted]
Date: Friday, 7 February 2020 at 06:29
To: Jeremy Farrar [redacted]
Subject: Re: Stuff

Tonight? More likely to you tomorrow am. Just need more about the pangomania which is very important.

Let me know if you need anything else changed.

Not sure about journal.

Authors: Kristian, me, Bob, Andrew. You? Or do you want to be neutral?

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

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T [redacted]
E [redacted]

On 7 Feb 2020, at 5:26 pm, Jeremy Farrar [redacted] wrote:

When can you update?

Lancet
Nature
NEJM

Will all review immediately, after quick QC, will share with WHO.

Can I help with any of the editors?

Who will be authors from your side?

Andrew Rambaut
Institute for Evolutionary Biology
Ashworth Laboratories, University of Edinburgh, Edinburgh, EH9 3FL, UK

contact – [redacted] | http://tree.bio.ed.ac.uk | tel [redacted]

Message

From: R.A.M. Fouchier [redacted]
Sent: 2/8/2020 2:50:00 PM
To: Andrew Rambaut [redacted]; Jeremy Farrar [redacted]
CC: Eddie Holmes [redacted]; Christian Drosten [redacted]
kga1978[redacted]; rfgarry [redacted]; p.vallance1[redacted]; collinsf[redacted]
afauci[redacted]; Josie Golding [redacted]; M.P.G. Koopmans [redacted]
Mike Ferguson [redacted]
Subject: Re: [ext] 2019 N-CoV

I do not understand Andrews argument " The sequence data clearly and unambiguously rules out any form of lab construct or engineering of the virus. ". Molecular biologists like myself can generate perfect copies of viruses without leaving a trace, eg the BamHI site. The arguments for and against passaging and engineering are the same if you ask me.
Ron

From: Andrew Rambaut [redacted]
Sent: Saturday, February 8, 2020 4:16 PM
To: Jeremy Farrar
Cc: Eddie Holmes; Christian Drosten; kga1978[redacted]; rfgarry[redacted]; r.fouchier[redacted];
p.vallance1[redacted]; collinsf[redacted]; afauci[redacted]; Josie Golding;
m.koopmans[redacted]; Mike Ferguson
Subject: Re: [ext] 2019 N-CoV

I agree with Eddie, I think someone needs to lay out the science of this before it gets out of hand (and causes more formal investigations).

I am of the view that the natural selection hypothesis is the most likely (specifically the non-bat reservoir). And as Eddie mentioned this is becoming more likely from day to day with the pangolin story.

I disagree with Ron that the passaging hypothesis is evidentially equal to the engineering hypothesis. The sequence data clearly and unambiguously rules out any form of lab construct or engineering of the virus. It doesn't really have anything to say about the relative plausibility of the 3 hypotheses for selection.

I think we need stronger arguments than an assertion that no lab has done those experiments. We can definitely argue that it has nothing to do with RaTG13 (or SARS or any other published SARSr virus). The argument that we would need to offer this hypothesis for all other outbreaks is not a useful one in this context.

Is it possible to argue that A) a passaging experiment wouldn't create the features we see? or B) that there are logical reasons why someone wouldn't do such an experiment?

The pangolin virus that was announced in the press conference might solve this issue if it has the furin cleavage site insertion which would be all but conclusive for the natural scenario.

Andrew

On 8 Feb 2020, at 20:21, Jeremy Farrar [redacted] wrote:

The theory of the origin of the has gathered considerable momentum not in social media, but increasingly among some scientists, in main stream media, and among politicians.

The aim of this was to bring a neutral, respected, scientific group together to look at the data and in a neutral, considered way provide an opinion and we hoped to focus the discussion on the science, not on any conspiracy or other theory and to lay down a respected statement to frame whatever debate goes on – before that debate gets out of hand with potentially hugely damaging ramifications.

With the additional information on the pangolin virus, information not available even 24 hours ago, I think the argument is even clearer.

My preference is that a carefully considered piece of science, early in the public domain, will help mitigate more polarised debate. If not, that debate will increasingly happen and science will be reacting to it. Not a good position to be in.

From: Edward Holmes [redacted]
Date: Saturday, 8 February 2020 at 20:11
To: Christian Drosten [redacted]
Cc: Jeremy Farrar [redacted], "kga1978[redacted], "a.rambaut[redacted], "rfgarry[redacted], "r.fouchier[redacted], "P.Vallance1([redacted], Francis Collins <[redacted] "afauci[redacted], Josie Golding [redacted], Marion Koopmans [redacted], Mike Ferguson [redacted]
Subject: Re: [ext] 2019 N-CoV

Hi Christian,

I don't know where this story came from, but it has nothing whatsoever to do the HIV nonsense. Please don't associate this with that. This is a broader story.

Ever since this outbreak started there have suggestions that the virus escaped from the Wuhan lab, if only because of the coincidence of where the outbreak occurred and the location of the lab. I do a lot of work in China and I can you that a lot of people there believe this and believe they are being lied to. Things were made worse when Wuhan lab published the bat virus sequence - a bat sampled in a different province for which they have a large collection of samples.

I believe the aim/question here is whether we, as scientists, should try to write something balanced on the science behind this? There are arguments for and against doing this.

Personally, with the pangolin virus possessing 6/6 key sites in the receptor binding domain, I am in favour of the natural evolution theory.

Best wishes,

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

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T [redacted]
E [redacted]

On 9 Feb 2020, at 6:52 am, Drosten, Christian [redacted] wrote:

Dear All,

I am overloaded with nCoV patient-related work and will need a few days before I can work on this text.

Can someone help me with one question: didn´t we congregate to challenge a certain theory, and if we could, drop it? This whole text reads as if the hypothesis was obvious, or was brought up by some external source, forcing us to respond. Is this the case? It does not seem as if this was linked to the HIV nonsense.

Who came up with this story in the beginning? Are we working on debunking our own conspiracy theory?

Christian
--

Professor Christian Drosten
Director, Institute of Virology
Scientific Director, Charité Global Health

Charité - Universitätsmedizin Berlin
Campus Charité Mitte

[redacted]
Germany

E-Mail: [redacted]
https://virologie-ccm.charite.de/
https://globalhealth.charite.de/

Von: Jeremy Farrar [redacted]
Datum: Samstag, 8. Februar 2020 um 10:45
An: Edward Holmes [redacted], "kga1978[redacted]
Andrew Rambaut [redacted], "rfgarry[redacted]>
Cc: "r.fouchier[redacted] "P.Vallance1[redacted]
[redacted] "collinsf[redacted], "afauci([redacted]
[redacted], Josie Golding <[redacted], "m.koopmans[redacted]"
[redacted], Christian Drosten <[redacted], Mike Ferguson
[redacted]
Betreff: [ext] FW: 2019 N-CoV

APOLOGIES WITH ALL CORRECT EMAILS

Kristen, Andrew, Bob, Eddie have reworked the summary and it is attached here.

We are pushing to get the sequence data from the reports on the pangolins, but do not have currently, clearly that is very important to incorporate.

Interested in your views

- Is this reasonably balanced given the data?
- Is there anything anyone disagrees with?
- Is there anything more in relation to what would seem to be the two possibilities
  - Nature, Intermediate host, evolution and passage
- Future data you may have
- Advice on whether KA, AR, RG and EH should publish this.

These and other thoughts welcome in confidence.

Andrew Rambaut
Institute for Evolutionary Biology
Ashworth Laboratories, University of Edinburgh, Edinburgh, EH9 3FL, UK

contact – [redacted] | http://tree.bio.ed.ac.uk | tel [redacted]

Message

From: R.A.M. Fouchier
Sent: 2/8/2020 11:36:30 AM
To: Jeremy Farrar; Edward Holmes; kga1978; Andrew Rambaut; rfgarry
CC: P.Vallance1; collinsf; afauci; Josie Golding; M.P.G.Koopmans; christian.drosten; Mike Ferguson
Subject: Re: 2019 N-CoV
Attachments: Summary.Feb7 RF.pdf

I am not in favor of publishing as is. I fail to see how the last of the three discussed scenarios (passaging) does not fall under the category of "laboratory manipulation". There is no evidence that might hint to this scenario and hence it should be put aside just like the engineering option. As far as I am aware, no laboratory has worked on passaging the pangolin-origin virus, the bat-CoV RaTG13, or another closely related virus or had access to it prior to the outbreak. That nCoV-2019 could originate from a SARS-like virus in Chinese labs can also be excluded. This information could be added after reference 10 in the manuscript, to provide further argument.
If we assume passaging as a possible scenario here, we must assume it is also plausible for all outbreaks from the past, present and future. This manuscript would be much stronger if it focused on the likelihood of the first 2 scenarios as compared to intentional or accidental release. That would also limit the chance of new biosafety discussions that would unnecessarily obstruct future attempts of virus culturing for research and diagnostic purposes for any (emerging/zoonotic) virus.

I made some additional comments in the attached pdf, also in line with Andrew's comments.

With kind regards,
Ron

Van: Jeremy Farrar
Datum: zaterdag 8 februari 2020 om 10:45
Aan: Edward Holmes, "kga1978, Andrew Rambaut, "rfgarry(
CC: "R.A.M. Fouchier", "P.Vallance1("collinsf "afauci Josie Golding "M. Koopmans", Christian Drosten Mike Ferguson
Onderwerp: FW: 2019 N-CoV

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These and other thoughts welcome in confidence.

Message

From: Mike Ferguson [redacted]
Sent: 2/9/2020 12:00:46 PM
To: Jeremy Farrar [redacted] Edward Holmes [redacted] kga1978 [redacted] Andrew Rambaut [redacted] rfgarry [redacted]
CC: r.fouchier [redacted] P.Vallance1 [redacted] collinsf [redacted] afauci [redacted] Josie Golding [redacted] m.koopmans [redacted] christian.drosten [redacted]
Subject: Re: 2019 N-CoV
Attachments: Summary.Feb7_MF.pdf

Dear Jeremy et al

I have made some comments and suggestions on the pdf attached.

I am not an expert on protein O-glycosylation - however, Dr Tabak, who was on the call last weekend, is and if I were to consult anyone else on this it would be Henrik Clausen
https://icmm.ku.dk/english/research-groups/clausen-group/

However, from what I do know of general glycobiology, I am not sure one can conclude that an immune system would be required to select for O-glycosylation sites. Once an alpha-helix is disturbed by the introduction of a proline, adjacent Ser and Thr residues will be (over-)predicted to have O-glycosylation potential - hard to know the functional consequences/significance without knowing whether the potential O-sites are actually occupied.

Regards

Mike

From: Jeremy Farrar [redacted]
Sent: 08 February 2020 09:45
To: Edward Holmes [redacted] kga1978 [redacted] Andrew Rambaut [redacted] rfgarry [redacted]
Cc: r.fouchier [redacted] P.Vallance1 [redacted] collinsf [redacted] afauci [redacted] Josie Golding [redacted] m.koopmans [redacted] christian.drosten [redacted] Mike Ferguson [redacted]
Subject: FW: 2019 N-CoV

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These and other thoughts welcome in confidence.

Overview

Sequencing of 2019-nCoV revealed two notable features of its genome. We investigate these features and outline some examples for how the virus may have acquired them. ~~We also discuss some scenarios by which these features could have arisen.~~ **Analysis of the virus genome sequences clearly demonstrates that the virus is not a laboratory construct or experimentally manipulated virus.** We believe the features discussed, which may explain the infectiousness and transmissibility of 2019-nCoV in humans, ~~could~~ have arisen through selection and adaptation prior to the initial outbreak.

The two primary features of 2019-nCoV of interest were:

- Based on structural modeling and early biochemical experiments, 2019-nCoV appears to be optimized for binding to the human ACE2 receptor.
- The highly variable spike protein of 2019-nCoV has a furin cleavage inserted at the S1 and S2 boundary via the insertion of twelve in-frame nucleotides. Additionally, this event also led to the acquisition of three ~~predicted O-linked glycans~~ around the furin cleavage site.

Mutations in the receptor binding domain of 2019-nCoV

The receptor binding domain (RBD) in the spike protein of SARS-CoV and SARS-like coronaviruses is the most variable part of the virus genome. When aligned against related viruses, 2019-nCoV displays a similar level of diversity as predicted from previous studies, including to its most closely related virus - SARS-like CoV isolated from bats (RaTG13, which is ~96% identical to 2019-nCoV).

Six residues in the RBD have been described as critical for binding to the human ACE2 receptor and determining host range[1]. Using coordinates based on the Ubani strain of SARS-CoV, they are Y442, L472, N479, D480, T487, and Y491 (the corresponding residues in 2019-nCoV are L455, F486, Q493, S494, N501, and Y505). Five out of six of these residues are mutated in 2019-nCoV compared to the closely related virus, RaTG13 (**Figure 1**). Based on modeling[1] and early biochemical experiments[2,3], 2019-nCoV seems to have an RBD that may bind with high affinity to ACE2 from human, primate, ferret, pig, and cat, as well as other species with high receptor homology. In contrast, 2019-nCoV may bind less efficiently to ACE2 in other species associated with SARS-like viruses, including rodents, civets, and bats[1].

do we have the pangolin ACE2 sequence/model?

A phenylalanine at F486 in 2019-nCoV corresponds to L472 in the SARS-CoV Ubani strain. In cell culture experiments the leucine at position 472 mutated to phenylalanine (L472F)[4], which has been predicted to be optimal for binding of the SARS-CoV RBD to the human ACE2 receptor[5]. However, a phenylalanine in this position is also present in several SARS-like CoVs from bats (**Figure 1**). While these analyses suggest that 2019-nCoV may be capable of binding the human ACE2 receptor with high affinity, importantly, the interaction is not predicted to be optimal[1]. Additionally, several of the key residues in the RBD of 2019-nCoV are different from those previously described to be optimal for human ACE2 receptor binding as determined by both natural evolution of SARS-CoV and rational design[5]. This latter point is strong evidence *against* 2019-nCoV being specifically engineered as, presumably, in such a scenario the most optimal residues would have been introduced, which is not what we observe.

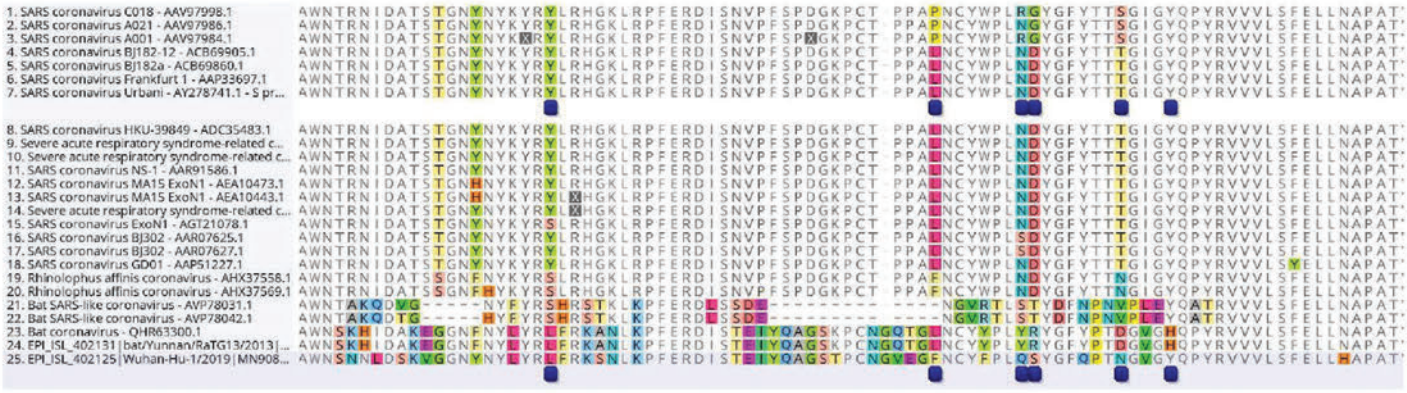

Figure 1 | Mutations in contact residues of the 2019-nCoV spike protein. The spike protein of 2019-nCoV (bottom) was aligned against the most closely related SARS and SARS-like CoVs. Key residues in the spike protein that make contact to the

ACE2 receptor have been marked with blue boxes in both 2019-nCoV and the SARS-CoV Urbani strain.

Furin cleavage site and ~~O-linked glycans~~

An interesting feature of 2019-nCoV is a predicted furin cleavage site in the spike protein (**Figure 2**). In addition to the furin cleavage site (RRAR), a leading P is also inserted so the fully inserted sequence becomes PRRA (**Figure 2**). A proline in this position is predicted to create three flanking ~~O-linked glycans~~ at S673, T678, and S686. A furin site has never before been observed in the lineage B betacoronaviruses and is a unique feature of 2019-nCoV. Some human betacoronaviruses, including HCoV-HKU1 (lineage A) have furin cleavage sites (typically RRKR), although not in such an optimal position.

Figure 2 | Acquisition of furin cleavage site and ~~O-linked glycans~~. The spike protein of 2019-nCoV (bottom) was aligned against the most closely related SARS and SARS-like CoVs. The furin cleavage site is marked in grey with the three adjacent ~~predicted O-linked glycans~~ in blue. Both the furin cleavage site and ~~O-linked glycans~~ are unique to 2019-nCoV and not previously seen in this group of viruses.

While the functional consequence - if any - of the furin cleavage site in 2019-nCoV is unknown, previous experiments with SARS-CoV have shown that it enhances cell–cell fusion but does not affect virus entry[6]. Furin cleavage sites are often acquired in condition selecting for rapid virus replication and transmission (e.g., highly dense chicken populations) and are a hallmark of highly pathogenic avian influenza virus, although these viruses acquire the site in different and more direct ways[7–9]. The acquisition of furin cleavage sites have also been observed after repeated passage of viruses in cell culture (personal correspondence and NASEM call, February 3, 2020).

A potential function of the three predicted O-linked glycans is less clear, but could create a "mucin-like domain" shielding potential epitopes or key residues on the 2019-nCoV spike protein.

Origin of 2019-nCoV

As noted at the start of this document, we believe that the origin of 2019-nCoV through laboratory manipulation of an existing SARS-related coronavirus can be ruled out with a high degree of confidence. If genetic manipulation would have been performed, one would expect that ~~a researcher would have used~~ one of the several reverse genetics systems available for betacoronaviruses. However, this is not the case as the genetic data clearly shows that 2019-nCoV is not derived from any previously used virus backbone, for example those described in a 2015 paper in *Nature Medicine*[10].

Instead we believe one of three main scenarios could explain how 2019-nCoV acquired the features discussed above: (1) natural selection in humans, (2) natural selection in an animal host, or (3) selection during passage.

Adaptation to humans

As the features outlined above are likely to enhance the ability of the virus to infect humans, it is possible that these are indeed adaptations to humans as a host and arose after the virus jumped from a non-human host, during the early stages of the epidemic. However, all of the genome sequences so far have the features described above and estimates of the timing of the most recent common ancestor of the currently sampled viruses support the seafood market outbreak as the zoonotic origin (i.e., in early December) and this would afford little opportunity for adaptation to occur. This may be explained by a transition to a rapid growth phase in the epidemic when the features arose and from which all current

cases are derived. However this would require a prior hidden epidemic of sufficient magnitude and duration for the adaptations to occur and there is no evidence of this. We also note that these features did not emerge during the SARS epidemic, which involved extensive human to human transmission.

Selection in an animal host

Given the similarity of 2019-nCoV to bat SARS-like CoVs, particularly RaTG13, it is highly likely that bats serve as the reservoir for this virus. However, previous human epidemics caused by betacoronaviruses have involved intermediate (possibly amplifying) hosts such as civets and other animals (SARS) and camels (MERS). It is therefore likely that an intermediate host would also exist for 2019-nCoV, although it is unclear what that host may be. Given the mutations in key residues of the RBD in 2019-nCoV it seems less likely that civets would be involved, although it is impossible to say with certainty at this stage. Notably, provisional analyses reveal that Malayan pangolins (*Manis javanica*) illegally imported into Guangdong province contain CoVs that are extremely similar to 2019-nCoV[11]. Although RaTG13 remains the closest relative to 2019-nCoV across the genome as a whole, the Malayan pangolin CoVs are identical to 2019-nCoV at all six key RBD residues. Analyses of these pangolin viruses are ongoing, although they do not carry the furin cleavage site insertion.

For the virus to acquire the furin cleavage site and mutations in the spike proteins that appear to be suitable for human ACE2 receptor binding, it seems plausible that this animal host would have to have a high population density – to allow the necessary natural selection to proceed efficiently – and an ACE2 gene that is similar to the human orthologue. Since furin cleavage sites have not been observed in sarbecoviruses before, it is unclear what conditions would be required for it to be acquired in the lineage leading to 2019-nCoV.

Selection during passage

Bas bee 201 cult the of a be role

glycosylation (O- and N-) can reduce host immune response to antigens - but is there any evidence that neutralising antibodies are made to this region of spike protein? If not, where would the selective pressure come from? O-glycosylation (if present) could just as easily be stabilising (or preventing) a secondary structure feature (i.e., not immune system driven). Also note that O-glycosylation predictors tend to over-predict, experimental evidence (mass spec) important. Also, one of the most common functions of glycosylation is to protect the underlying peptide from proteolysis - i.e., these sites if occupied might actually reduce the efficiency of the furtin cleavag site.

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Limitations and recommendations

The evolution scenarios discussed above are largely indistinguishable and current data are consistent with all three. It is currently impossible to prove or disprove either, and it is unclear whether future data or analyses will help resolve this issue. Identifying the immediate non-human animal source and obtaining virus sequences from it would be the most definitive way of distinguishing the three scenarios.

The main limitation of what is described here is our clear ascertainment bias. We are looking for features or evolutionary aspects that could help explain how 2019-nCoV lead to such a rapidly expanding human epidemic, yet the specific features we are trying to find may be the exact features one would expect in a virus that could lead to an epidemic of the magnitude currently observed. Before 2019-nCoV 'took off' and started the current epidemic, it is plausible that many stuttering transmission chains of highly similar viruses could have entered the human population, but because they never took off they were never sampled. It is extremely important to keep this in mind as any inference about the plausibility of various scenarios about the evolution and/or epidemic potential of 2019-nCoV is attempted.

To further clarify the evolutionary origins and functional features of 2019-nCoV it would be helpful to obtain additional data about the virus - both genetic and functional. This includes experimental studies of receptor binding and the role of the furin cleavage site and predicted O-linked glycans. The identification of a potential intermediate host of 2019-nCoV as well as sequencing of very early cases, including those not connected to the market, could also help refute the passage scenario described above. Even in the

light of such data, however, it is not guaranteed that data can be obtained to conclusively prove all aspects of the initial emergence of 2019-nCoV.

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Message

From: Garry, Robert F [redacted]
Sent: 2/10/2020 3:51:18 PM
To: Kristian G. Andersen [redacted] Edward Holmes [redacted]
CC: Andrew Rambaut [redacted]
Subject: Re: More

All true.

But if Lipkin says higher ups are concerned and intel involved it's consistent with all we know too.

Not surprised Ego krewe (maybe Fouchier too) writing some sort of counter to the white paper with the allusion to scenario 3 "passage." Preemptive strike?

After a brief chat with Kristian after our NIH telecon I have to admit likewise that I don't really know the answers – maybe someone does. The data we have is just insufficient and even pango99 prob not helping (unless it magically has a furin cleavage site, which seems doubtful). I think the key may come from Guangdong. So, China Ag U Researchers culturing pangolin virus for undeterminable length of time makes me somewhat nervous.

From: Kristian Andersen [redacted]
Date: Monday, February 10, 2020 at 3:34 PM
To: Edward Holmes [redacted]
Cc: Andrew Rambaut [redacted], Robert Garry [redacted]
Subject: Re: More

> External Sender. Be aware of links, attachments and requests.

Having known Bob for more than a decade I feel quite confident that he will make the connection between Butt Lesion and a certain Columbia professor.

I feel less confident that we will always be able to understand the references that Bob might himself be making at times... (note, a postgraduate degree in manga, anime, and comics may be required).

On Mon, Feb 10, 2020 at 1:27 PM Edward Holmes [redacted] wrote:

> Thanks mate.
>
> Thermonuclear ego explosion when those two are together.
>
> You had better explain the butt lesion ref to Bob if he doesn't know. A link to the New York Post article should do it.
>
> Professor Edward C. Holmes FAA FRS
> The University of Sydney
>
> On 11 Feb 2020, at 8:17 am, Kristian G. Andersen [redacted] wrote:
>
> Eddie - lemme know your favorite brand and I'll send you a fresh pair of jocks.
>
> Can't go wrong with the Grand Wizard of EgoHealth and Butt Lesion in the same room. Looking forward to it.
>
> K

On Mon, Feb 10, 2020 at 12:56 PM Edward Holmes [redacted] wrote:

He's about where we were a week ago. He's for escape.

He also said that Peter Daszak, grand wizard of EgoHealth, and some others were writing a piece saying the Wuhan lab were being persecuted.

I'll talk to Jeremy later.

Currently, I'm more concerned that I will run out of underpants.

Professor Edward C. Holmes FAA FRS
The University of Sydney

On 11 Feb 2020, at 7:52 am, Andrew Rambaut [redacted] wrote:

We should get him on the group. Will make it more entertaining and balance the German/Dutch a bit.

A

Sent from my phone. Apologies for brevity or illiteracy.

On 10 Feb 2020, at 21:11, Edward Holmes [redacted] wrote:

Ian Lipkin just called - very worried about the furin cleavage site and says that high ups are as well, inc. intel. Also saw the restriction site.

Actually, he was most vexed that he wasn't part of our discussion group. Classic. I think I'll send the doc.

I still have no power. Could be a week.

Professor Edward C. Holmes FAA FRS
The University of Sydney

From: Edward Holmes
Sent: Monday, February 10, 2020 5:06 PM EST
To: Ian Lipkin
Subject: Re: Please call me

I agree. Talking to Jeremy (Farrar) in a few minutes and I'll get back in touch after.
It is indeed striking that this virus is so closely related to SARS yet is behaving so differently. Seems to have been pre-adapted for human spread since the get go. It's the epidemiology that I find most worrying.

Professor Edward C. Holmes FAA FRS
The University of Sydney

On 11 Feb 2020, at 9:01 am, Ian Lipkin [redacted] wrote:

It's well reasoned and provides a plausible argument against genetic engineering. It does not eliminate the possibility of inadvertent release following adaptation through selection in culture at the institute in Wuhan. Given the scale of the bat CoV research pursued there and the site of emergence of the first human cases we have a nightmare of circumstantial evidence to assess.

Ian

On Feb 10, 2020, at 4:33 PM, Edward Holmes [redacted] wrote:

Hi Ian,
Here's the document we wrote a few days ago. Things are moving so quickly that is hard to keep up. Comments welcome. I favour natural evolution myself, but the furin cleavage site is an issue. I'll have a chat with Jeremy in a little while to see if can get you more directly involved.
Pangolins. Key observations are that:
(i) Two sets of pangolins independently collected from different Chinese provinces both have CoVs in the same clade as 2019-nCoV. What are the odds?
(ii) In the receptor binding domain the Guandong pangolins are the closest to 2019-nCoV, with 6/6 of the key mutations (only 1/6 in the closest bat sequence).
Absolutely not proven that the pangolin is the intermediate host, but the points above make it a credible choice for additional investigation.
Agree it might not be clear - very rushed at the end.
Cheers,
Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS

ARC Australian Laureate Fellow

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School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 10 Feb 2020, at 9:08 pm, Ian Lipkin [redacted] wrote:

When you are back up for air I need to speak on two issues that concern you directly.

Ian

On Feb 9, 2020, at 4:14 PM, Edward Holmes [redacted] wrote:

Ian, sorry, it won't be today.

Huge storm in Sydney: no power for 24 hours, flood water 1 cm from house, transport buggered.

I need to sort this out.

Phone will die soon.

Professor Edward C. Holmes FAA FRS
The University of Sydney

On 10 Feb 2020, at 4:47 am, Ian Lipkin [redacted] wrote:

Eddie-
Please call me. [redacted]
Thanks

Ian

<Summary.Feb7.pdf>

Message

From: Jeremy Farrar [redacted]
Sent: 2/10/2020 1:26:57 AM
To: M.P.G. Koopmans [redacted]; Kristian G. Andersen [redacted]; Drosten, Christian [redacted]; Edward Holmes [redacted]; Andrew Rambaut [redacted]; rfgarry([redacted] R.A.M.Fouchier [redacted]; P.Vallance1 [redacted]; collinsf([redacted]; afauci([redacted]; Josie Golding [redacted]; Mike Ferguson [redacted]
Subject: Re: [ext] 2019 N-CoV

Many thanks all

Sydney had a complete power cut over the weekend which has delayed things a little.

Appreciate not everyone will agree on the next plans but the discussion has been very constructive, thank you. As (hopefully) the pangolin data becomes available and can be incorporated a final draft will be completed and shared and a decision made among the people who have led the analysis (EH, KA, BG and AR) of next steps.

From: Marion Koopmans [redacted]
Date: Sunday, 9 February 2020 at 20:07
To: "Kristian G. Andersen" [redacted], "Drosten, Christian" [redacted], Jeremy Farrar [redacted], Edward Holmes [redacted], "a.rambaut [redacted], "rfgarry [redacted] "r.fouchier([redacted], "P.Vallance1([redacted], Francis Collins [redacted], "afauci([redacted], Josie Golding [redacted], Mike Ferguson [redacted]
Subject: Re: [ext] 2019 N-CoV

Wow….took off from e-mail for a day…..

As mentioned to Jeremy, I would not be in favour of publishing something specific on the lab escape hypothesis, because I agree (with Kristian) that this could backfire. Yes, there is speculation in the public domain, triggered by several papers, including the rubbish ones. By zooming in on a specific finding that is NOT in the public domain as far as I know, I think this will generate its own conspiracy theories.

So if published, I would suggest zooming out a bit for starters, describing that one of the key challenges is where this virus came from, discuss some of the (wild) guesses out there, and then argue step by step what the challenges are in inferring this from sequence data, where you do not know exactly what the pool is that you are sampling from, so end up interpreting the needle drawn out of a haystack. Here, the many pieces of the discussion that passed by these last few days can be included, like rates of evolution and dating of possible origins; examples of cleavage site acquisition from other viruses, recombination in coronavirus evolutionary history, possible abrupt changes in spillover events, ability to confirm or disproof things in vitro. etc

And I would leave “lab escape”for the discussion, because putting that in the public domain as a hypothesis in my view will be read as “see, they also thought so"

Marion

On 8 Feb 2020, at 22:15, Kristian G. Andersen <[redacted] wrote:

A lot of good discussion here, so I just wanted to add a couple of things for context that I think are important - and why what we're considering is far from "another conspiracy theory", but rather is taking a valid scientific approach to a question that is increasingly being asked by the public, media, scientists, and politicians (e.g., I have been contacted by Science, NYT, and many other news outlets over the last couple of days about this exact question).

To Ron's question, passage of SARS-like CoVs have been ongoing for several years, and more specifically in Wuhan under BSL-2 conditions - see references 12-15 in the document for a few examples. The fact that Wuhan became the epicenter of the ongoing epidemic caused by nCoV is likely an unfortunate coincidence, but it raises questions that would be wrong to dismiss out of hand. Our main work over the last couple of weeks has been focused on trying to *disprove* any type of lab theory, but we are at a crossroad where the scientific evidence isn't conclusive enough to say that we have high confidence in any of the three main theories considered. Like Eddie - and I believe Bob, Andrew, and everybody on this email as well - I am very hopeful that the viruses from pangolins will help provide the missing pieces. For now, giving the lab theory serious consideration has been highly effective at countering many of the circulating conspiracy theories, including HIV recombinants, bioengineering, etc. - here's just one example: https://www.factcheck.org/2020/02/baseless-conspiracy-theories-claim-new-coronavirus-was-bioengineered/.

As to publishing this document in a journal, I am currently not in favor of doing so. I believe that publishing something that is open-ended could backfire at this stage. I think it's important that we try to gather additional evidence - including waiting on the pangolin virus sequences and further scrutinize the furin cleavage site and O-linked glycans - before publishing. That way we can (hopefully) come out with some strong conclusive statements that are based on the best data we have access to. I don't think we are there yet.

Best,
Kristian

On Sat, Feb 8, 2020 at 12:38 PM Drosten, Christian <[redacted] wrote:

> OK, I see. We should then introduce references to these informal sources in the beginning of the text. Else it reads a bit funny.
>
> Christian
>
> --
>
> **Professor Christian Drosten**
> Director, Institute of Virology
> Scientific Director, Charité Global Health
>
> Charité - Universitätsmedizin Berlin
> Campus Charité Mitte
>
> Chariteplatz 1
> D-10117 Berlin
> Germany

E-Mail: christian.drosten@charite.de
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https://globalhealth.charite.de/

Von: Jeremy Farrar [redacted]
Datum: Samstag, 8. Februar 2020 um 21:21
An: Edward Holmes [redacted], Christian Drosten [redacted]
Cc: "kga1978 [redacted] Andrew Rambaut [redacted],
"rfgarry [redacted], "r.fouchier [redacted],
"P.Vallance1 [redacted], "collinsf [redacted]
[redacted], "afauci [redacted], Josie Golding
[redacted], "m.koopmans [redacted], Mike Ferguson
[redacted]
Betreff: Re: [ext] 2019 N-CoV

The theory of the origin of the has gathered considerable momentum not in social media, but increasingly among some scientists, in main stream media, and among politicians.

The aim of this was to bring a neutral, respected, scientific group together to look at the data and in a neutral, considered way provide an opinion and we hoped to focus the discussion on the science, not on any conspiracy or other theory and to lay down a respected statement to frame whatever debate goes on – before that debate gets out of hand with potentially hugely damaging ramifications.

With the additional information on the pangolin virus, information not available even 24 hours ago, I think the argument is even clearer.

My preference is that a carefully considered piece of science, early in the public domain, will help mitigate more polarised debate. If not, that debate will increasingly happen and science will be reacting to it. Not a good position to be in.

From: Edward Holmes [redacted]
Date: Saturday, 8 February 2020 at 20:11
To: Christian Drosten [redacted]
Cc: Jeremy Farrar [redacted], "kga1978 [redacted]
"a.rambaut [redacted], "rfgarry [redacted]
"r.fouchier [redacted], "P.Vallance1 [redacted]
<P.Vallance1 [redacted], Francis Collins <[redacted], "afauci [redacted]
[redacted], Josie Golding [redacted], Marion Koopmans
[redacted], Mike Ferguson [redacted]
Subject: Re: [ext] 2019 N-CoV

Hi Christian,

I don't know where this story came from, but it has nothing whatsoever to do the HIV nonsense. Please don't associate this with that. This is a broader story.

Ever since this outbreak started there have suggestions that the virus escaped from the Wuhan lab, if only because of the coincidence of where the outbreak occurred and the location of the lab. I do a lot of work in China and I can you that a lot of people there believe this and believe they are being lied to. Things were made worse when Wuhan lab published the bat virus sequence - a bat sampled in a different province for which they have a large collection of samples.

I believe the aim/question here is whether we, as scientists, should try to write something balanced on the science behind this? There are arguments for and against doing this.

Personally, with the pangolin virus possessing 6/6 key sites in the receptor binding domain, I am in favour of the natural evolution theory.

Best wishes,

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS
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School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 9 Feb 2020, at 6:52 am, Drosten, Christian [redacted] wrote:

Dear All,

I am overloaded with nCoV patient-related work and will need a few days before I can work on this text.

Can someone help me with one question: didn´t we congregate to challenge a certain theory, and if we could, drop it? This whole text reads as if the hypothesis was obvious, or was brought up by some external source, forcing us to respond. Is this the case? It does not seem as if this was linked to the HIV nonsense.

Who came up with this story in the beginning? Are we working on debunking our own conspiracy theory?

Christian

--

Professor Christian Drosten
Director, Institute of Virology
Scientific Director, Charité Global Health

Charité - Universitätsmedizin Berlin
Campus Charité Mitte

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Von: Jeremy Farrar [redacted]
Datum: Samstag, 8. Februar 2020 um 10:45
An: Edward Holmes [redacted], "kga1978[redacted] [redacted]
Andrew Rambaut [redacted], "rfgarry[redacted]
Cc: "r.fouchier[redacted] "P.Vallance1[redacted]
[redacted] "collinsf[redacted] "afauci[redacted]
[redacted], Josie Golding [redacted] "m.koopmans[redacted]
[redacted], Christian Drosten [redacted], Mike Ferguson
[redacted]
Betreff: [ext] FW: 2019 N-CoV

APOLOGIES WITH ALL CORRECT EMAILS

Kristen, Andrew, Bob, Eddie have reworked the summary and it is attached here.

We are pushing to get the sequence data from the reports on the pangolins, but do not have currently, clearly that is very important to incorporate.

Interested in your views

- Is this reasonably balanced given the data?
- Is there anything anyone disagrees with?
- Is there anything more in relation to what would seem to be the two possibilities

- Nature, Intermediate host, evolution and passage
- Future data you may have
- Advice on whether KA, AR, RG and EH should publish this.

These and other thoughts welcome in confidence.

Message

From: Garry, Robert F [redacted]
Sent: 2/11/2020 9:16:27 PM
To: Edward Holmes [redacted]
CC: Kristian G. Andersen [redacted] Andrew Rambaut [redacted]
Subject: Re: A few thoughts on the summary

Yes very interesting - publish!

I predict Kristian will soon have some better dN/dS data to add productively to the mix as well.

Stay agnostic...hope Ian can as well.

From: Edward Holmes [redacted]
Sent: Wednesday, February 12, 2020 2:57 AM
To: Garry, Robert F [redacted]
Cc: Kristian G. Andersen [redacted] Andrew Rambaut [redacted]
Subject: Re: A few thoughts on the summary

> External Sender. Be aware of links, attachments and requests.

See my comments on Slack.

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 12 Feb 2020, at 1:47 pm, Garry, Robert F < [redacted] wrote:

Virologica Sinica
February 2018, Volume 33, Issue 1, pp 104–107| Cite as

Serological Evidence of Bat SARS-Related Coronavirus Infection in Humans, China

"The virus may have been circulating for a longer period and in a larger population than we postulate based on molecular assays. This could be tested using banked sera once we have specific assays."

SAmples in South China seropositive, but those from Wuhan seronegative.

From: Kristian G. Andersen [redacted]
Sent: Wednesday, February 12, 2020 2:24 AM
To: Edward Holmes [redacted]
Cc: Garry, Robert F [redacted] Andrew Rambaut [redacted]
Subject: Re: A few thoughts on the summary

External Sender. Be aware of links, attachments and requests.

Yup, all good - as long as we don't have to inspect his arse.

On Tue, Feb 11, 2020 at 6:06 PM Edward Holmes [redacted] wrote:

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The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 12 Feb 2020, at 1:00 pm, Garry, Robert F [redacted] wrote:

No problem from me...

From: Edward Holmes [redacted]
Sent: Wednesday, February 12, 2020 1:15 AM
To: Kristian G. Andersen [redacted] Garry, Robert F [redacted]; Andrew Rambaut [redacted]
Subject: Fwd: A few thoughts on the summary

External Sender. Be aware of links, attachments and requests.

From Ian about the Feb 7 summary.

Think we should add him as an author. Safety in numbers. In his own mind he brings a lot of gravitas…plus because he is involved in the GOF I think it add weights. Happy to be over-ruled though.

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T [redacted]
E [redacted]

Begin forwarded message:

From: Ian Lipkin [redacted]

Subject: A few thoughts on the summary
Date: 12 February 2020 at 1:40:21 am AEDT
To: Eddie Holmes [redacted]

Eddie-
Call me whenever you wish.
Ian

Adaptation to humans
1. Animals in the Wuhan wildlife market may not be the zoonotic origin of the outbreak. It's also possible that an infected human involved in the wildlife trade transmitted the virus to people in the market. This might explain why the environmental sampling revealed more viral sequences on the West (seafood) than the East (terrestrial) side of the street. I don't see a way to test this possibility; nonethless, we could mention it.
2. The virus may have been circulating for a longer period and in a larger population than we postulate based on molecular assays. This could be tested using banked sera once we have specific assays.

Selection during passage
1. Are we suggesting that the furin cleavage site evolved from de novo mutations or through recombination?

On Feb 10, 2020, at 4:33 PM, Edward Holmes [redacted] wrote:

<Summary.Feb7.pdf>

Message

From: Clare Thomas [redacted]
Sent: 2/13/2020 2:34:29 AM
To: Kristian G. Andersen [redacted]
Subject: RE: Interest in commentary/hypothesis on SARS-CoV-2 origins?

Dear Kristian,
Yes please! It sounds possibly like a Perspective. I would love to take a look and consider whether it might be suitable for Nature.
All the best,
Clare

From: Kristian G. Andersen [redacted]
Sent: 12 February 2020 23:09
To: Clare Thomas
Subject: Interest in commentary/hypothesis on SARS-CoV-2 origins?

Dear Clare,

I can only imagine you must be crazy busy at the moment! I wanted to reach out to you to see if there would be interest in receiving a commentary/hypothesis piece on the evolutionary origins of SARS-CoV-2? There has been a lot of speculation, fear mongering, and conspiracies put forward in this space and we thought that bringing some clarity to this discussion might be of interest to Nature.

Prompted by Jeremy Farrah, Tony Fauci, and Francis Collins, Eddie Holmes, Andrew Rambaut, Bob Garry, Ian Lipkin, and myself have been working through much of the (primarily) genetic data to provide agnostic and scientifically informed hypotheses around the origins of the virus. We are not quite finished with the writeup and we still have some loose ends, but I wanted to reach out to you to see if this might potentially be of interest? We see this more as a commentary/hypothesis, as opposed to a more long-form Letter or Article.

Best,
Kristian

Kristian G. Andersen, PhD
Associate Professor, Scripps Research
Director of Infectious Disease Genomics, Scripps Research Translational Institute
Director, Center for Viral Systems Biology

The Scripps Research Institute
10550 North Torrey Pines Road, SGM-300A
Department of Immunology and Microbial Science
La Jolla, CA 92037

p: [redacted]
c:
t:
e:
w:

Assistant: [redacted]

Message

From: Clare Thomas [redacted]
Sent: 2/13/2020 8:47:54 AM
To: Kristian G. Andersen [redacted]
Subject: RE: Interest in commentary/hypothesis on SARS-CoV-2 origins?

Dear Kristian,
Ok that sounds great. Thanks so much.
All the best,
Clare

From: Kristian G. Andersen [redacted]
Sent: 13 February 2020 16:33
To: Clare Thomas
Subject: Re: Interest in commentary/hypothesis on SARS-CoV-2 origins?

Sounds great Clare. We'll work out a few more of the details and share with you a draft so you can get a sense of whether this would be of interest and would also give you a chance to provide suggestions for things to incorporate.

I'll be gone for the rest the week, but I assume we'll have this ready early/mid next week.

Best,
Kristian

On Thu, Feb 13, 2020 at 2:34 AM Clare Thomas [redacted] wrote:

> Dear Kristian,
>
> Yes please! It sounds possibly like a Perspective. I would love to take a look and consider whether it might be suitable for Nature.
>
> All the best,
>
> Clare
>
> **From:** Kristian G. Andersen [redacted]
> **Sent:** 12 February 2020 23:09
> **To:** Clare Thomas
> **Subject:** Interest in commentary/hypothesis on SARS-CoV-2 origins?
>
> Dear Clare,
>
> I can only imagine you must be crazy busy at the moment! I wanted to reach out to you to see if there would be interest in receiving a commentary/hypothesis piece on the evolutionary origins of SARS-CoV-2? There has

been a lot of speculation, fear mongering, and conspiracies put forward in this space and we thought that bringing some clarity to this discussion might be of interest to Nature.

Prompted by Jeremy Farrah, Tony Fauci, and Francis Collins, Eddie Holmes, Andrew Rambaut, Bob Garry, Ian Lipkin, and myself have been working through much of the (primarily) genetic data to provide agnostic and scientifically informed hypotheses around the origins of the virus. We are not quite finished with the writeup and we still have some loose ends, but I wanted to reach out to you to see if this might potentially be of interest? We see this more as a commentary/hypothesis, as opposed to a more long-form Letter or Article.

Best,

Kristian

Kristian G. Andersen, PhD

Associate Professor, Scripps Research

Director of Infectious Disease Genomics, Scripps Research Translational Institute

Director, Center for Viral Systems Biology

The Scripps Research Institute

10550 North Torrey Pines Road, [redacted]

Department of Immunology and Microbial Science

La Jolla, CA 92037

p: [redacted]

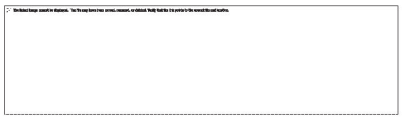
c: [redacted]

t: @K_G_Andersen

e: [redacted]

w: www.andersen-lab.com

Assistant: [redacted]



Message

From: Edward Holmes [redacted]
Sent: 2/16/2020 2:38:46 AM
To: Garry, Robert F [redacted]
CC: Ian Lipkin [redacted] Andrew Rambaut [redacted] Kristian G. Andersen [redacted]
Subject: Re: Paper

External Sender. Be aware of links, attachments and requests.

Oh yes, the reviewers are easy…I think this is a slam dunk.

PROFESSOR EDWARD C. HOLMES FAA FRS
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T [redacted]
E [redacted]

On 16 Feb 2020, at 7:36 pm, Garry, Robert F [redacted] wrote:

Yeah I know and that's a good choice for him.

So, as you know when you submit you'll need to suggest reviewers to include and exclude. Seems easy - there are some natural choices for both lists. Nature commentaries are peer reviewed iirc but I'm guessing they'll push this as fast as possible.

Sent from my iPhone

On Feb 16, 2020, at 2:29 AM, Edward Holmes [redacted] wrote:

> External Sender. Be aware of links, attachments and requests.

I agree, and I offered, but he wants to remain independent.

PROFESSOR EDWARD C. HOLMES FAA FRS
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T [redacted]
E [redacted]

On 16 Feb 2020, at 7:24 pm, Garry, Robert F [redacted] wrote:

No problem either count

Jeremy has been amazing leader-should be author

Sent from my iPhone

On Feb 16, 2020, at 2:18 AM, Edward Holmes [redacted] wrote:

External Sender. Be aware of links, attachments and requests.

Ah. I so, I can submit on his behalf.

Jeremy wants to add something to the acknowledgments.

Just seen this: no GISAID acknowledgment as far as I can tell:

https://www.tandfonline.com/doi/full/10.1080/20477724.2020.1725339

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E [redacted]

On 16 Feb 2020, at 7:14 pm, Garry, Robert F [redacted] wrote:

One thing - I'm not sure when Kristian is returning to the connected world. Monday is a federal holiday.

Sent from my iPhone

On Feb 16, 2020, at 12:44 AM, Edward Holmes [redacted] wrote:

External Sender. Be aware of links, attachments and requests.

Thanks Bob!

Sorry about the typo. I'll let Kristian fix that one.

Cheers,

Eddie

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On 16 Feb 2020, at 5:05 pm, Garry, Robert F [redacted] wrote:

Looking fine! Congrats all.

Minor: last sentence first paragraph covid-9 to covid-19

Sent from my iPhone

On Feb 15, 2020, at 10:46 PM, Edward Holmes [redacted] wrote:

All, attached is what I propose is the final version of this paper. I've just given it a final wash-and-brush-up. Looks great I reckon.

Can you please check your names, affiliations and acknowledgements.

I'll pass to Jeremy to see if he has any final comments and wants to be acknowledged.

This needs to go to Nature on Monday in somebody's time zone. Kristian I'll let you deal with this. You may need to provide more contact details. Figure also attached separately.

Cheers,

Eddie

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E [redacted]

On 16 Feb 2020, at 12:09 pm, Garry, Robert F [redacted] wrote:

I formally agree.

Any guy that helps discover Jingmen tick viruses and Wuhan cricket virus must be trusted. Very important.

Going to dinner with my wife so will put down the phone.

Did I mention the Jingmen tick viruses have pretty spectacular mucin like domains? Would not have looks at CoVs otherwise.

Sent from my iPhone

On Feb 15, 2020, at 6:26 PM, Edward Holmes [redacted] wrote:

External Sender. Be aware of links, attachments and requests.

I will send through a final version that everyone can formally agree to later today. I'll also pass to Jeremy. Kristian can then do the formal submission, although I'll probably ping a copy to Magda and Clare anyway.

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T
E [redacted]

On 16 Feb 2020, at 11:22 am, Ian Lipkin [redacted] wrote:

Congratulations. It's a timely and well reasoned review.

Ian

On Feb 15, 2020, at 7:15 PM, Edward Holmes [redacted] wrote:

Fab.

Just need to sort out author order. Kristian 1st and probably should correspond as he's chatted with Clare? Bob, I was thinking you might go last? I'd be nervous about putting my name there as I am amateur on the specific virological stuff we discuss. I feel I have only contributed to the writing. I don't mind Andrew going last either.

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E [redacted]

On 16 Feb 2020, at 11:03 am, Andrew Rambaut [redacted] wrote:

I am done. Added in all the references (I think).

A.

On 16 Feb 2020, at 00:01, Edward Holmes [redacted] wrote:

Right, I need to get this finalised. Can I suggest that people stop editing the Google Docs version within the next hour (noon Sydney time) and I'll finish everything in normal Word. Need to draw a line under this very soon.

Thanks!

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS
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E [redacted]

Andrew Rambaut
Institute for Evolutionary Biology
Ashworth Laboratories, University of Edinburgh, Edinburgh, EH9 3FL, UK

contact – [redacted] | http://tree.bio.ed.ac.uk | tel [redacted]

<Andersen.Nature Perspective.docx>

<Andersen.Figure 1.pdf>

Message

From: Edward Holmes [redacted]
Sent: 2/16/2020 3:06:49 PM
To: Garry, Robert F [redacted]
CC: Ian Lipkin [redacted]; Kristian G. Andersen [redacted]; Andrew Rambaut [redacted]
Subject: Re: Paper

Just got this from Francis Collins.

"This is really well done, and I would argue ought to be made public ASAP (Jeremy sent it this morning).

Francis"

I'll submit and send to Magda/Clare this morning. If they ok we can then put on bioRxiv and perhaps Virological.org as well?

Cheers,

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS
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T [redacted]
E [redacted]

On 17 Feb 2020, at 9:52 am, Garry, Robert F [redacted] wrote:

Important to get this out.
https://www.washingtonpost.com/politics/2020/02/16/tom-cotton-coronavirus-conspiracy/

From: Edward Holmes [redacted]
Date: Sunday, February 16, 2020 at 4:14 PM
To: Robert Garry [redacted]
Cc: Ian Lipkin [redacted] Kristian Andersen [redacted], Andrew Rambaut [redacted]
Subject: Re: Paper

> External Sender. Be aware of links, attachments and requests.

I'll quickly check with Magda first.

Professor Edward C. Holmes FAA FRS
The University of Sydney

On 17 Feb 2020, at 9:06 am, Garry, Robert F < [redacted] wrote:

Sounds correct to me.

From: Edward Holmes [redacted]
Date: Sunday, February 16, 2020 at 4:04 PM
To: Robert Garry [redacted]
Cc: Ian Lipkin [redacted], Kristian Andersen [redacted], Andrew Rambaut [redacted]
Subject: Re: Paper

External Sender. Be aware of links, attachments and requests.

All, I assume this needs to go on bioRxiv right? That's the Nature policy for all COVID-19 papers. We also meant to send to WHO.

Professor Edward C. Holmes FAA FRS
The University of Sydney

On 17 Feb 2020, at 7:57 am, Garry, Robert F [redacted] wrote:

Thanks Eddie!

Yes the NAID pics are nice.

The fusing SARS-CoV-2 pic is maybe not the prettiest one, but for me a clear indication that the polybasic site is functional.

You can observe this with flu v if you concentrate and treat with trypsin or some proper peptides. The virions fuse with each other.

Looks to me like SARS-CoV-2 gets at least partly activated coming out of the cells.

b

From: Edward Holmes [redacted]
Date: Sunday, February 16, 2020 at 2:50 PM
To: Robert Garry [redacted]
Cc: Ian Lipkin [redacted], Kristian Andersen [redacted], Andrew Rambaut [redacted]
Subject: Re: Paper

External Sender. Be aware of links, attachments and requests.

Great pics. Let's see what Nature say. I will get the paper out the door today.

Cheers,

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS
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T [redacted]
E [redacted]

On 17 Feb 2020, at 4:54 am, Garry, Robert F [redacted] wrote:

Maybe Kristian can sell them on this version?

Or maybe not.

From: Robert Garry [redacted]
Date: Sunday, February 16, 2020 at 8:21 AM
To: Ian Lipkin [redacted], Kristian Andersen [redacted], Andrew Rambaut [redacted], Eddie Holmes [redacted]
Subject: Re: Paper

They might need a cover. ☺

Seriously though NIH Took some pics that Tony would love to see on the Nature cover:

https://www.flickr.com/photos/niaid/albums/72157712914621487

<image001.png>

This one is actually VERY pertinent to our story BTW – notice that there are several fusing virions.

We've actually seen the same thing with fusion peptides that activate FluV.

SARS-CoV-2 is "activated!"

From: Ian Lipkin [redacted]
Date: Sunday, February 16, 2020 at 5:46 AM
To: Kristian Andersen [redacted], Robert Garry [redacted], Andrew Rambaut [redacted], Eddie Holmes [redacted]
Subject: Re: Paper

Our audience includes the general public and policy makers as well as the scientific community. Once the paper is accepted we should ask Nature how it and we can promote broad visibility. At minimum we will need a short, powerful press release that hits the high points: who reviewed the data, what we considered, what we concluded, what needs to be done.

Ian

On Feb 16, 2020, at 5:58 AM, Andrew Rambaut [redacted] wrote:

Just catching up on all this. Bob - you definitely should go last author. Without your expertise and knowledge (and your rummaging around the literature), we wouldn't have been able to write this. Happy to go second and Eddie can go second senior.

Andrew

On 16 Feb 2020, at 00:20, Garry, Robert F [redacted] wrote:

Andrew should go last – he did the bulk of the heavy lifting.

[1] Tulane University, School of Medicine, Department of Microbiology and Immunology, New Orleans, LA, USA

[2] Zalgen Labs, LCC, Germantown, MD, USA
I have to list the latter because of the US CoI rules.

From: Edward Holmes [redacted]
Date: Saturday, February 15, 2020 at 6:15 PM
To: Andrew Rambaut [redacted]
Cc: Robert Garry [redacted], Kristian Andersen [redacted], Ian Lipkin [redacted]
Subject: Re: Paper

Fab.

Just need to sort out author order. Kristian 1st and probably should correspond as he's chatted with Clare? Bob, I was thinking you might go last? I'd be nervous about putting my name there as I am amateur on the specific virological stuff we discuss. I feel I have only contributed to the writing. I don't mind Andrew going last either.

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E [redacted]

On 16 Feb 2020, at 11:03 am, Andrew Rambaut [redacted] wrote:

I am done. Added in all the references (I think).

A.

On 16 Feb 2020, at 00:01, Edward Holmes [redacted] wrote:

Right, I need to get this finalised. Can I suggest that people stop editing the Google Docs version within the next hour (noon Sydney time) and I'll finish everything in normal Word. Need to draw a line under this very soon.

Thanks!

Eddie

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Andrew Rambaut
Institute for Evolutionary Biology
Ashworth Laboratories, University of Edinburgh, Edinburgh, EH9 3FL, UK

contact – [redacted] | http://tree.bio.ed.ac.uk | tel [redacted]

Andrew Rambaut
Institute for Evolutionary Biology
Ashworth Laboratories, University of Edinburgh, Edinburgh, EH9 3FL, UK

contact – [redacted] | http://tree.bio.ed.ac.uk | tel [redacted]

<Suggested cover v2 red1.pdf>

Message

From: Edward Holmes [redacted]
Sent: 2/16/2020 6:59:20 PM
To: Kristian G. Andersen [redacted]
CC: Andrew Rambaut [redacted]; Garry, Robert F [redacted]; Ian Lipkin [redacted]
Subject: Re: Paper

All came together very quickly in the end. Jeremy Farrar and Francis Collins are very happy. Works for me.

PROFESSOR EDWARD C. HOLMES FAA FRS
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E [redacted]

On 17 Feb 2020, at 1:53 pm, Kristian G. Andersen [redacted] wrote:

Pure coincidence. The no-shower-since-Thursday will serve as evidence in case you need proof....

Great job lads!!

K

On Sun, Feb 16, 2020 at 6:48 PM Edward Holmes [redacted] wrote:

> Well, that's suspicious…he comes back 15 minutes after I submit? A natural phenomenon? I'm not sure we can exclude the hypothesis of deliberately engineered responsibility shirking.
>
> Anyway, it's done. Sorry the last bit had to be done without you…pressure from on high.
>
> Fair point about bioRxiv. I've asked Nature what they want. Virological will work.
>
> More rattlesnakes to come mate….
>
> Cheers,
>
> Eddie
>
> ---
>
> **PROFESSOR EDWARD C. HOLMES FAA FRS**
> ARC Australian Laureate Fellow
>
> **THE UNIVERSITY OF SYDNEY**
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> E [redacted]

On 17 Feb 2020, at 1:41 pm, Kristian G. Andersen [redacted] wrote:

Gentlemen, it seems I should go to the desert more often... Only had three rattlesnake encounters, one near-death experience, and one running out of gas on the highway (with 1/4 left in the tank... it's a Jeep thing...), so all in all, pretty mellow. Fun though.

I'm still on my way back so not caught up yet - lemme know what's needed from me?

Eddie, bioRxiv is only for primary research and not this type of paper, so no need to submit.

Bob, pangolins... not me. But good idea.

Onwards.

K

On Sun, Feb 16, 2020 at 4:35 PM Edward Holmes [redacted] wrote:

Added (attached).

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T [redacted]
E [redacted]

On 17 Feb 2020, at 11:16 am, Andrew Rambaut [redacted] wrote:

The pangolin metagenomic data seems to have come ultimately from this paper:

https://www.ncbi.nlm.nih.gov/pubmed/31652964

We should cite it.

A.

On 16 Feb 2020, at 23:12, Garry, Robert F [redacted] wrote:

Sounds good...

From: Edward Holmes [redacted]
Date: Sunday, February 16, 2020 at 5:06 PM
To: Robert Garry [redacted]
Cc: Ian Lipkin [redacted], Kristian Andersen [redacted], Andrew Rambaut

[redacted]
Subject: Re: Paper

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Just got this from Francis Collins.

"This is really well done, and I would argue ought to be made public ASAP (Jeremy sent it this morning).

Francis"

I'll submit and send to Magda/Clare this morning. If they ok we can then put on bioRxiv and perhaps Virological.org as well?

Cheers,

Eddie

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On 17 Feb 2020, at 9:52 am, Garry, Robert F [redacted] wrote:

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Date: Sunday, February 16, 2020 at 4:14 PM
To: Robert Garry [redacted]
Cc: Ian Lipkin [redacted], Kristian Andersen [redacted], Andrew Rambaut [redacted]
Subject: Re: Paper

External Sender. Be aware of links, attachments and requests.

I'll quickly check with Magda first.

Professor Edward C. Holmes FAA FRS
The University of Sydney

On 17 Feb 2020, at 9:06 am, Garry, Robert F [redacted] wrote:

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From: Edward Holmes [redacted]
Date: Sunday, February 16, 2020 at 4:04 PM
To: Robert Garry [redacted]
Cc: Ian Lipkin [redacted], Kristian Andersen [redacted], Andrew Rambaut <a.rambaut@ed.ac.uk>
Subject: Re: Paper

External Sender. Be aware of links, attachments and requests.

All, I assume this needs to go on bioRxiv right? That's the Nature policy for all COVID-19 papers. We also meant to send to WHO.

Professor Edward C. Holmes FAA FRS
The University of Sydney

On 17 Feb 2020, at 7:57 am, Garry, Robert F [redacted] wrote:

Thanks Eddie!

Yes the NAID pics are nice.

The fusing SARS-CoV-2 pic is maybe not the prettiest one, but for me a clear indication that the polybasic site is functional.

You can observe this with flu v if you concentrate and treat with trypsin or some proper peptides. The virions fuse with each other.

Looks to me like SARS-CoV-2 gets at least partly activated coming out of the cells.

b

From: Edward Holmes [redacted]
Date: Sunday, February 16, 2020 at 2:50 PM
To: Robert Garry [redacted]
Cc: Ian Lipkin [redacted] Kristian Andersen [redacted], Andrew Rambaut [redacted]
Subject: Re: Paper

External Sender. Be aware of links, attachments and requests.

Great pics. Let's see what Nature say. I will get the paper out the door today.

Cheers,

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS

ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 17 Feb 2020, at 4:54 am, Garry, Robert F <[redacted] wrote:

Maybe Kristian can sell them on this version?

Or maybe not.

From: Robert Garry [redacted]
Date: Sunday, February 16, 2020 at 8:21 AM
To: Ian Lipkin [redacted] Kristian Andersen [redacted] Andrew Rambaut [redacted], Eddie Holmes [redacted]
Subject: Re: Paper

They might need a cover. ☺

Seriously though NIH Took some pics that Tony would love to see on the Nature cover:

https://www.flickr.com/photos/niaid/albums/72157712914621487

<image001.png>

This one is actually VERY pertinent to our story BTW – notice that there are several fusing virions.

We've actually seen the same thing with fusion peptides that activate FluV.

SARS-CoV-2 is "activated!"

From: Ian Lipkin [redacted]
Date: Sunday, February 16, 2020 at 5:46 AM
To: Kristian Andersen [redacted], Robert Garry <[redacted], Andrew Rambaut [redacted], Eddie Holmes [redacted]
Subject: Re: Paper

Our audience includes the general public and policy makers as well as the scientific community. Once the paper is accepted we should ask Nature how it and we can promote broad visibility. At minimum we will need a short,

powerful press release that hits the high points: who reviewed the data, what we considered, what we concluded, what needs to be done.

Ian

On Feb 16, 2020, at 5:58 AM, Andrew Rambaut [redacted] wrote:

Just catching up on all this. Bob - you definitely should go last author. Without your expertise and knowledge (and your rummaging around the literature), we wouldn't have been able to write this. Happy to go second and Eddie can go second senior.

Andrew

On 16 Feb 2020, at 00:20, Garry, Robert F [redacted] wrote:

Andrew should go last – he did the bulk of the heavy lifting.

[1] Tulane University, School of Medicine, Department of Microbiology and Immunology, New Orleans, LA, USA

[2] Zalgen Labs, LCC, Germantown, MD, USA
I have to list the latter because of the US CoI rules.

From: Edward Holmes [redacted]
Date: Saturday, February 15, 2020 at 6:15 PM
To: Andrew Rambaut [redacted]
Cc: Robert Garry [redacted], Kristian Andersen [redacted] Ian Lipkin [redacted]
Subject: Re: Paper

External Sender. Be aware of links, attachments and requests.

Fab.

Just need to sort out author order. Kristian 1st and probably should correspond as he's chatted with Clare? Bob, I was thinking you might go last? I'd be nervous about putting my name there as I am amateur on the specific virological stuff we discuss. I feel I have only contributed to the writing. I don't mind Andrew going last either.

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T
E [redacted]

On 16 Feb 2020, at 11:03 am, Andrew Rambaut [redacted] wrote:

I am done. Added in all the references (I think).

A.

On 16 Feb 2020, at 00:01, Edward Holmes [redacted] wrote:

Right, I need to get this finalised. Can I suggest that people stop editing the Google Docs version within the next hour (noon Sydney time) and I'll finish everything in normal Word. Need to draw a line under this very soon.

Thanks!

Eddie

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T
E [redacted]

Andrew Rambaut
Institute for Evolutionary Biology
Ashworth Laboratories, University of Edinburgh, Edinburgh, EH9 3FL, UK

contact – [redacted] | http://tree.bio.ed.ac.uk | tel [redacted]

Andrew Rambaut
Institute for Evolutionary Biology
Ashworth Laboratories, University of Edinburgh, Edinburgh, EH9 3FL, UK

contact – [redacted] http://tree.bio.ed.ac.uk | tel [redacted]

<Suggested cover v2 red1.pdf>

Andrew Rambaut
Institute for Evolutionary Biology
Ashworth Laboratories, University of Edinburgh, Edinburgh, EH9 3FL, UK

contact – [redacted] | http://tree.bio.ed.ac.uk | tel [redacted]

From: Jeremy Farrar
Sent: Monday, February 17, 2020 10:42 AM EST
To: Ian Lipkin
Subject: Re: Connections COVID-19

Yes I know and in US - why so keen to get out ASAP.
I will push Nature

On 17 Feb 2020, at 16:41, Ian Lipkin [redacted] wrote:

Jeremy,
Thanks for shepherding this paper. Rumors of bioweaponeering are now circulating in China.

Ian

On Feb 17, 2020, at 10:28 AM, Jeremy Farrar [redacted] wrote:

When you have been able to update with the extra sentence and data can you forward on to me - keep that WHO see ASAP.

On 17 Feb 2020, at 12:09, Garry, Robert F [redacted] wrote:

This also means less concern about the Baric scenario where another mutation could kick SARS-CoV-2 into another gear. Binding already optimal.

Sent from my iPhone

On Feb 17, 2020, at 4:51 AM, Andrew Rambaut [redacted] wrote:

External Sender. Be aware of links, attachments and requests.

Fixed.

On 17 Feb 2020, at 10:47, Edward Holmes [redacted] wrote:

Hang on…should be " recent binding studies indicate" not indict. One of the new edits.

PROFESSOR EDWARD C. HOLMES FAA FRS
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T [redacted]
E [redacted]

On 17 Feb 2020, at 9:44 pm, Garry, Robert F [redacted] wrote:

Looks great!

Sent from my iPhone

On Feb 17, 2020, at 4:41 AM, Andrew Rambaut [redacted] wrote:

External Sender. Be aware of links, attachments and requests.

OK. Here is the version with all the changes and the updated references. As I manually changed the numbers (adding reference 7 and incrementing all numbers above 6) I would appreciate a check.
I also simplified Bob's text below.
I am going to start formatting this in virological so let me know if you spot any issues.
A.

On 17 Feb 2020, at 10:25, Garry, Robert F [redacted] wrote:

Another better version:
While these analyses suggest that SARS-CoV-2 may be capable of binding the human ACE2 receptor with high affinity, the interaction is not predicted to be optimal[1]. Additionally, several of the key residues in the RBD of SARS-CoV-2 are different to those previously described as optimal for human ACE2 receptor binding[6]. In contrast to these computational assessments recent binding studies indict that SARS-CoV-2 binds with high affinity to human ACE2 (insert ref). SARS-COV-2 spike does not appear to have an artificial sequence designed in the laboratory. An artificial sequence would have used interactions predicted to be optimal for interaction with its receptor. Instead the

SARs-CoV-2 spike appears to be the result of selection on human or human-like ACE2 permitting another optimal binding solution to arise. This is strong evidence that SARS-CoV-2 is *not* the product of genetic engineering.

From: Andrew Rambaut [redacted]
Sent: Monday, February 17, 2020 10:23 AM
To: Garry, Robert F [redacted]
Cc: Eddie Holmes [redacted]; Kristian G. Andersen [redacted]; Ian Lipkin [redacted]; Jeremy Farrar [redacted]
Subject: Re: Connections COVID-19

External Sender. Be aware of links, attachments and requests.

OK. I will add that. I am editing the document now.
Andrew

On 17 Feb 2020, at 10:20, Garry, Robert F [redacted] wrote:

While these analyses suggest that SARS-CoV-2 may be capable of binding the human ACE2 receptor with high affinity, the interaction is not predicted to be optimal[1]. Additionally, several of the key residues in the RBD of SARS-CoV-2 are different to those previously described as optimal for human ACE2 receptor binding[6]. In contrast to these computational assessments recent binding studies indict that SARS-CoV-2 binds with high affinity to human ACE2 (insert ref). SARS-COV-2 spike does not appear to have an artificial sequence designed in the laboratory would have been designed for optimal binding and used interactions predicted to be optimal. Instead it appears to be the result of selection on human or human-like ACE2 permit another optimal binding solutions to arise. This is strong evidence that SARS-CoV-2 is *not* the product of genetic engineering.

From: Garry, Robert F [redacted]
Sent: Monday, February 17, 2020 10:02 AM
To: Edward Holmes [redacted]
Cc: Kristian G. Andersen [redacted]; Andrew Rambaut [redacted]; Ian Lipkin [redacted]; Jeremy Farrar [redacted]
Subject: Re: Connections COVID-19

put the "While these" back

From: Edward Holmes [redacted]
Sent: Monday, February 17, 2020 9:49 AM
To: Garry, Robert F [redacted]
Cc: Kristian G. Andersen [redacted]; Andrew Rambaut

[redacted]; Ian Lipkin [redacted]; Jeremy Farrar [redacted]
Subject: Re: Connections COVID-19

External Sender. Be aware of links, attachments and requests.

Ok. Pass a draft to me and I'll give it a quick read through.
No way I can stay up to your levels...

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T [redacted]
E [redacted]

On 17 Feb 2020, at 8:47 pm, Garry, Robert F [redacted] wrote:

agreed - i'm up - who needs to sleep
will take very quick swing at it now - yes a sentence or two will likely do
15 minutes i'll be back

From: Edward Holmes [redacted]
Sent: Monday, February 17, 2020 9:45 AM
To: Garry, Robert F [redacted]
Cc: Kristian G. Andersen [redacted]; Andrew Rambaut [redacted]; Ian Lipkin [redacted]; Jeremy Farrar [redacted]
Subject: Re: Connections COVID-19

External Sender. Be aware of links, attachments and requests.

Bob, if you or someone else wants to add a sentence now that's ok (refs. will need to change as well), but we must get it out today. Things are moving/changing so rapidly that we are always going to be out of date. We need to draw a line somewhere.

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On 17 Feb 2020, at 8:39 pm, Garry, Robert F [redacted] wrote:

New preprint not affect any of the other three scenarios for selection on a human or human like ACE2, but a stronger still argument against bioengineering imo.

Sent from my iPhone

On Feb 17, 2020, at 2:50 AM, Edward Holmes [redacted] wrote:

External Sender. Be aware of links, attachments and requests.

All,
We have the green light to preprint.
Kristian - even though bioRxiv deals with primary research papers I still feel we should send it there.
Andrew - I think you can put this in Virological and do some precision tweeting.
Very interesting to see the new ACE2 paper.

Best wishes,
Eddie

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T [redacted]
E [redacted]

Begin forwarded message:

From: Clare Thomas [redacted]
Subject: RE: Connections COVID-19
Date: 17 February 2020 at 7:07:01 pm AEDT
To: Edward Holmes [redacted], Magdalena Skipper [redacted]

Hi Eddie,

Thanks for this. I agree that you should deposit the preprint asap. I can see it in our system so I'll send it for expedited review today.

If the refs are positive it will likely need revising as it already seems out of date. See the preprint below, for example, which appeared on Saturday and which says that SARS-CoV-2 binds with higher affinity to ACE2 than SARS-CoV. And of course if the second pangolin paper surfaces that would also affect the conclusions, if their press release is to be believed.

https://www.biorxiv.org/content/10.1101/2020.02.11.944462v1

Anyway, thanks again for sending this and I'll try to return a decision soon.

All the best,

Clare

<Andersen.Nature Perspective.Final_v2.docx>

<Andersen.Nature Perspective.Final_v2.docx>

From: Garry, Robert F
Sent: Monday, February 17, 2020 12:37 PM EST
To: Jeremy Farrar; Kristian G. Andersen
CC: Andrew Rambaut; Eddie Holmes; Ian Lipkin
Subject: Re: Connections COVID-19

Ian suggested a press release – it's very appropriate under the circumstances. Who will draft?

From: Jeremy Farrar [redacted]
Date: Monday, February 17, 2020 at 11:35 AM
To: Kristian Andersen [redacted]
Cc: Andrew Rambaut [redacted], Robert Garry [redacted], Eddie Holmes [redacted], Ian Lipkin [redacted]
Subject: Re: Connections COVID-19

External Sender. Be aware of links, attachments and requests.

Reason I ask about when to post is to coordinate press briefings etc etc ….to make sure the key messages are reasonably reported…

From: Jeremy Farrar [redacted]
Date: Monday, 17 February 2020 at 18:32
To: "Kristian G. Andersen" [redacted]
Cc: "a.rambaut@ed.ac.uk" [redacted], "Garry, Robert F" [redacted], Edward Holmes [redacted] Ian Lipkin [redacted]
Subject: Re: Connections COVID-19

No preference – whatever you all think best.

When do you plan to post?

From: "Kristian G. Andersen" [redacted]
Date: Monday, 17 February 2020 at 18:30
To: Jeremy Farrar [redacted]
Cc: "a.rambaut@ed.ac.uk" [redacted], "Garry, Robert F" [redacted], Edward Holmes [redacted], Ian Lipkin [redacted]
Subject: Re: Connections COVID-19

The bioRxiv unfortunately does not accept perspectives/reviews/comments - only original research papers so this, per standard policies, can't go on there. For that reason, my preference is to keep this on Virological and use that as the channel for dissemination, but if there's a need to try and bypass normal bioRxiv policies I can definitely reach out to Richard and John to ask them. I'm leading their efforts for

better screening of outbreak-related preprints and have another email out to them so can definitely bring it up. Jeremy, what's your preference?

K

On Mon, Feb 17, 2020 at 9:22 AM Jeremy Farrar [redacted] wrote:

> Thank you
>
> Any idea when likely to be released on pre-print server?
>
> Is tomorrow OK?
>
> Thinking about the publicity of it….

From: "Kristian G. Andersen" [redacted]
Date: Monday, 17 February 2020 at 18:11
To: Jeremy Farrar [redacted]
Cc: [redacted] "Garry, Robert F" [redacted], Edward Holmes [redacted], Ian Lipkin [redacted]
Subject: Re: Connections COVID-19

Sure, attached.

K

On Mon, Feb 17, 2020 at 9:02 AM Jeremy Farrar [redacted] wrote:

> Sorry to micro-manage/microedit!
>
> But would you be willing to change one sentence?
>
> From
> It is **unlikely** that SARS-CoV-2 emerged through laboratory manipulation of an existing SARS-related coronavirus.
> To
> It is **improbable** that SARS-CoV-2 emerged through laboratory manipulation of an existing SARS-related coronavirus.

From: [redacted]
Date: Monday, 17 February 2020 at 17:56
To: "Kristian G. Andersen" [redacted]
Cc: Jeremy Farrar [redacted], "Garry, Robert F" [redacted], Edward Holmes [redacted], Ian Lipkin [redacted]
Subject: Re: Connections COVID-19

Sorry. This is the final version (v2.2).

Sent from my phone. Apologies for brevity or illiteracy.

On 17 Feb 2020, at 16:52, Kristian G. Andersen [redacted] wrote:

Just corrected a few more typos - but yes, I believe this is the final version for now. I'm sure Nature will have plenty of edits.

K

On Mon, Feb 17, 2020 at 8:47 AM Jeremy Farrar [redacted] wrote:

Andrew – is this the 'final' draft, pending any changes at Nature – with the additional information?

From: [redacted]
Date: Monday, 17 February 2020 at 17:08
To: Jeremy Farrar [redacted], "Garry, Robert F" [redacted], Edward Holmes [redacted], "Kristian G. Andersen" [redacted], Ian Lipkin [redacted]
Subject: Re: Connections COVID-19

Dear all,

I think this is now the same version as on Virological. First author's name corrected, 'SARs' corrected. Figure updated (and legend corrected).

Andrew

On 17 Feb 2020, at 15:28, Jeremy Farrar [redacted] wrote:

When you have been able to update with the extra sentence and data can you forward on to me - keep that WHO see ASAP.

On 17 Feb 2020, at 12:09, Garry, Robert F [redacted] wrote:

This also means less concern about the Baric scenario where another mutation could kick SARS-CoV-2 into another gear. Binding already optimal.

Sent from my iPhone

External Sender. Be aware of links, attachments and requests.

On Feb 17, 2020, at 4:51 AM, Andrew Rambaut [redacted] wrote:

Fixed.

On 17 Feb 2020, at 10:47, Edward Holmes [redacted] wrote:

Hang on…should be " recent binding studies indicate" not indict. One of the new edits.

PROFESSOR EDWARD C. HOLMES FAA FRS
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Looks great!

Sent from my iPhone

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On Feb 17, 2020, at 4:41 AM, Andrew Rambaut [redacted] wrote:

OK. Here is the version with all the changes and the updated references. As I manually changed the numbers (adding reference 7 and incrementing all numbers above 6) I would appreciate a check.

I also simplified Bob's text below.

I am going to start formatting this in virological so let me know if you spot any issues.

A.

On 17 Feb 2020, at 10:25, Garry, Robert F [redacted] wrote:

Another better version:

While these analyses suggest that SARS-CoV-2 may be capable of binding the human ACE2 receptor with high affinity, the interaction is not predicted to be optimal[1]. Additionally, several of the key residues in the RBD of SARS-CoV-2 are different to those previously described as optimal for human ACE2 receptor binding[6]. In contrast to these computational assessments recent binding studies indict that SARS-CoV-2 binds with high affinity to human ACE2 (insert ref). SARS-COV-2 spike does not appear to have an artificial sequence designed in the laboratory. An artificial sequence would have used interactions predicted to be optimal for interaction with its receptor. Instead the SARs-CoV-2 spike appears to be the result of selection on human or human-like ACE2 permitting another optimal binding solution to arise. This is strong evidence that SARS-CoV-2 is *not* the product of genetic engineering.

From: Andrew Rambaut [redacted]
Sent: Monday, February 17, 2020 10:23 AM
To: Garry, Robert F [redacted]
Cc: Eddie Holmes [redacted]; Kristian G. Andersen [redacted]; Ian Lipkin [redacted]; Jeremy Farrar [redacted]
Subject: Re: Connections COVID-19

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OK. I will add that. I am editing the document now.

Andrew

On 17 Feb 2020, at 10:20, Garry, Robert F [redacted] wrote:

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From: Garry, Robert F [redacted]
Sent: Monday, February 17, 2020 10:02 AM
To: Edward Holmes [redacted]
Cc: Kristian G. Andersen [redacted]; Andrew Rambaut [redacted]; Ian Lipkin [redacted]; Jeremy Farrar [redacted]
Subject: Re: Connections COVID-19

put the "While these" back

From: Edward Holmes [redacted]
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To: Garry, Robert F [redacted]
Cc: Kristian G. Andersen [redacted]; Andrew Rambaut [redacted]; Ian Lipkin [redacted]; Jeremy Farrar [redacted]
Subject: Re: Connections COVID-19

Ok. Pass a draft to me and I'll give it a quick read through.

No way I can stay up to your levels...

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E [redacted]

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15 minutes i'll be back

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Cc: Kristian G. Andersen [redacted]; Andrew Rambaut [redacted]; Ian Lipkin [redacted]; Jeremy Farrar [redacted]
Subject: Re: Connections COVID-19

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New preprint not affect any of the other three scenarios for selection on a human or human like ACE2, but a stronger still argument against bioengineering imo.

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Kristian - even though bioRxiv deals with primary research papers I still feel we should send it there.
Andrew - I think you can put this in Virological and do some precision tweeting.

Very interesting to see the new ACE2 paper.

Best wishes,

Eddie

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T [redacted]
E [redacted]

Begin forwarded message:

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Date: 17 February 2020 at 7:07:01 pm AEDT
To: Edward Holmes [redacted], Magdalena Skipper [redacted]

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https://www.biorxiv.org/content/10.1101/2020.02.11.944462v1

Anyway, thanks again for sending this and I'll try to return a decision soon.

All the best,

Clare

<Andersen.Nature Perspective.Final_v2.docx>

<Andersen.Nature Perspective.Final_v2.docx>

<Andersen.Nature Perspective.Final_v2.2.docx>

Message

From: Clare Thomas [redacted]
Sent: 3/4/2020 11:44:43 PM
To: Kristian G. Andersen [redacted]
CC: Edward Holmes [redacted]
Subject: RE: Decision on Nature submission 2020-02-02583

Dear Kristian,

It looks like it's set up with you as the CA with your gmail address as the contact info kga1978@gmail.com.

I can see whether my assistant can merge the account with your other one: andersen@scripps.edu. I'll ask her to get in touch with you once she's done it. Alternatively you can just submit directly to Nature Medicine and if Joao needs to see the reports again I can send them to him by email.

I am indeed drowning in COVID-19 papers. Never been so busy. I cancelled my participation in the conference that Eddie is at, in part because I just don't have time to move from my desk... (sorry to miss you, Eddie).

I am sure you're frantically busy as well.

All the best,

Clare

From: Kristian G. Andersen [redacted]
Sent: 05 March 2020 02:06
To: Clare Thomas
Cc: Edward Holmes
Subject: Re: Decision on Nature submission 2020-02-02583

Dear Clare,

We're just about to send our manuscript over to Nature Medicine, which has been much improved due to some recent data. I just wanted to share the new material with you so you're in the loop.

Since the original manuscript was submitted under Eddie's account, would it be possible for you to please transfer everything over to my account so I can start the process of getting this to Nature Medicine? Eddie is in transit at the moment, so I think it'll be difficult for him to get this transferred in time. If you're not able to transfer to my account, don't worry - we'll figure it out.

Thanks again for giving us the opportunity - we thought this would have been a very good piece for Nature given the massive interest, but Nature Medicine (if accepted) will be a good audience too.

I hope you're not drowning in COVID-19 papers!

Best,
Kristian

On Thu, Feb 20, 2020 at 9:56 AM Kristian G. Andersen [redacted] wrote:

> Yeah, no worries Clare - it's a tricky topic and I understand. And thanks for reaching out to your colleagues - much appreciated.
>
> Best,
> Kristian
>
> On Thu, Feb 20, 2020 at 9:54 AM Clare Thomas [redacted] wrote:
>
> > Dear Kristian,
> >
> > Ok, thanks for clarifying. I am sorry we could not return a more positive decision at Nature but I wish you all the best with publishing it elsewhere and I'm glad we could get you some other options at Nature Research, if that interests you.
> >
> > All the best,
> >
> > Clare
> >
> > **From:** Kristian G. Andersen [redacted]
> > **Sent:** 20 February 2020 17:48
> > **To:** Clare Thomas
> > **Subject:** Re: Decision on Nature submission 2020-02-02583
> >
> > Thanks Clare for letting me know so quickly. I'll discuss with the other authors to see what the best path would be - just one thing to make clear though, reviewer 2 is unfortunately wrong about "Once the authors publish their new pangolin sequences, a lab origin will be extremely unlikely". Had that been the case, we would of course have included that - but the more sequences we see from pangolins (and we have been analyzing/discussing these *very* carefully) the more unlikely it seems that they're intermediate hosts. They definitely harbor SARS-CoV-like viruses, no doubt, but it's unlikely they have a direct connection to the COVID-19 epidemic. Unfortunately none of this helps refute a lab origin and the possibility must be considered as a serious scientific theory (which is what we do) and not dismissed out of hand as another 'conspiracy' theory. We all really, really wish that we could do that (that's how this got started), but unfortunately it's just not possible given the data.
> >
> > Thanks again for considering our manuscript and while we had of course hoped for a better outcome, we understand the decision.
> >
> > Best,
> > Kristian
> >
> > On Thu, Feb 20, 2020 at 8:52 AM [redacted] wrote:
> >
> > > 20th February 2020
> > >
> > > Dear Kristian,
> > >
> > > Thank you for submitting your manuscript entitled "The Proximal Origin of SARS-CoV-2" to be considered for publication in Nature. We've now obtained two ref reports on the paper (appended below) and I've had the opportunity to discuss them with our chief editor Magdalena Skipper. In the light of the advice received I am afraid we have decided that we cannot offer to publish the Perspective in Nature.

While the Perspective is interesting and timely one of our referees raised concerns (also emphasised to the editors) about whether such a piece would feed or quash the conspiracy theories. But more importantly this reviewer feels, and we agree, that the Perspective would quickly become outdated when more scientific data are published (for example on potential reservoir hosts).

I did, however, take the liberty of consulting with my colleagues at Nature Medicine, Nature Ecology and Evolution and Nature Microbiology and I am happy to say that all three journals were interested in publishing a revised piece in some form.

Nature Medicine are interested in publishing it either as a Comment or a Correspondence. If you would like to pursue this option, please transfer the submission to Nature Medicine using the link provided below. Feel free to reach out to Joao Monteiro, chief editor, at joao..monteiro@us.nature.com if you want to discuss the transfer process or have questions.

Nature Ecology & Evolution would be interested in considering the manuscript as a Comment article. They would like to work with you to address the reviewers' concerns and restructure the manuscript to focus more on the plausible evolutionary scenarios. If this option is of interest, you can also use the link below to transfer, and please feel free to get in touch with Patrick Goymer (p.goymer@nature.com) to discuss it further.

Finally, Nature Microbiology would similarly be interested in considering a revised manuscript that addresses the main concerns from the referees as a Comment article. Should you be interested in this option, please use the link below to transfer and please feel free to contact Nonia Pariente (nonia.pariente@nature.com; who is currently out of the office but will be back on Feb 24th) and Paula Jauregui (paula.jauregui@nature.com) to discuss further.

I am sorry that we cannot be more positive on this occasion. We hope that our decision does not discourage you from submitting your work to us in future as we remain interested in publishing key developments in this area of research. We hope that you will find our referees' comments helpful.

With best wishes,

Clare

Clare Thomas
Senior Editor
Nature

Referees' comments:

Referee #1 (Remarks to the Author):

Anderson presented a timely manuscript to share their points of view about the origin of SARS-CoV-2. There are several rumors about the origin of this virus. However, these “hypotheses” are entirely based on very limited, if any, scientific evidences.
This reviewer sees most of the arguments raised by the authors are valid and convincing. However, the authors might want to consider these minor suggestions:

1.The sections for the RBD and cleavage site of Spike protein basically have summarized the existing findings from other recent publications. The authors might want to spell out that these two sections are

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2. Fig. 1. This figure has 6 aligned sequences, but with only 5 sequence titles. The order of these titles are also not correct.

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7. Optional: Can the authors share their views on the possibility of having a lab escape of a natural coronavirus? This is also one of the hypotheses that have been extensively discussed. The reviewer understand that this is entirely a different topic, but any insights are welcomed.

Referee #2 (Remarks to the Author):

This is a perspective discussing evidence against a hypothetical lab origin of SARS-CoV-2. The paper addresses suboptimal composition of ACE2-binding sites in the RBD, 3 predicted O-linked glycosylation sites and a furin cleavage site in the glycoprotein that was speculated upon before.

The paper is itself interesting, but unnecessarily speculative. It's not clear why the authors do not refute a hypothetical lab origin in their coming publication on the ancestors of SARS-CoV-2 in bats and pangolins. The tree showing diverse pangolin viruses has kindly been made available by some of the authors in GISAID. Once the authors publish their new pangolin sequences, a lab origin will be extremely unlikely. It is not clear why the authors rush with a speculative perspective if their central hypothesis can be supported by their own data. Please explain.

Another critical aspect of this text is the complete lack of referencing to a potential debate on a hypothetical lab origin. Who said this, why is this considered a problem? There are indeed a few apparently uninformed statements claiming the virus may be a Chinese bioweapon, but is this really problematic on a larger scale? The central reason for issuing this text must be exhaustively referenced and discussed.

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Finally, the main argument against a hypothetical lab origin seems the required reconstruction of a backbone of a bat virus of unknown pathogenesis. It does not seem feasible that any scientist would disembark on such an uncertain endeavor. This difficulties of coronavirus reverse genetics should be stated clearly.

--

Message

From: medicine@us.nature.com [medicine@us.nature.com]
Sent: 3/5/2020 1:03:48 PM
To: [redacted]
CC: medicine@us.nature.com; [redacted]@springernature.com
Subject: Decision on Nature Medicine submission NMED-LE102233-T

5th Mar 2020

Dear Kristian,

Thanks for working with us to improve your Letter for publication. i'm delighted to tell you that your manuscript NMED-LE102233-T has been accepted for publication in our Correspondence section, and that it has been scheduled for publication in our April print issue. Please note that are fast-tracking the online publication of this piece, so please make sure to return the copyrights form to our editorial assistant asap, and to respond to any queries from our production promptly to avoid delays. As soon as we have the online publication date set, our production will let you know. This piece will be in front of the paywall for time being.

All the best,
Joao

Joao Monteiro
Chief Editor

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If you have queries at any point during the production process then please contact the production team at [redacted]@springernature.com.

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Message

From: Edward Holmes [redacted]
Sent: 3/5/2020 5:24:59 PM
To: Kristian G. Andersen [redacted]
CC: Clare Thomas [redacted]
Subject: Re: Decision on Nature submission 2020-02-02583

Thanks Both!

Sorry if I confused things.

Sorry to miss you Clare! It was a really good meeting and largely free of coronavirus stuff. I had some nice conversations with the Nature staff that attended…who have already sent me papers to review!

Cheers,

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 6 Mar 2020, at 2:08 am, Kristian G. Andersen [redacted] wrote:

Hi Clare,

Yes, sorry - I was confused. Eddie started the process and that emailed a link to me so we should be good. Thanks again.

COVID-19 will be a marathon, not a sprint, so hopefully we'll all get some time to breathe soon ;).

Best,
Kristian

On Wed, Mar 4, 2020 at 11:45 PM Clare Thomas [redacted] wrote:

Oh, I was looking at my emails backwards… I see you've already done it ☺

From: Clare Thomas
Sent: 05 March 2020 07:45
To: 'Kristian G. Andersen'

Cc: Edward Holmes
Subject: RE: Decision on Nature submission 2020-02-02583

Dear Kristian,

It looks like it's set up with you as the CA with your gmail address as the contact info [redacted].

I can see whether my assistant can merge the account with your other one: [redacted]. I'll ask her to get in touch with you once she's done it. Alternatively you can just submit directly to Nature Medicine and if Joao needs to see the reports again I can send them to him by email.

I am indeed drowning in COVID-19 papers. Never been so busy. I cancelled my participation in the conference that Eddie is at, in part because I just don't have time to move from my desk… (sorry to miss you, Eddie).

I am sure you're frantically busy as well.

All the best,

Clare

From: Kristian G. Andersen [redacted]
Sent: 05 March 2020 02:06
To: Clare Thomas
Cc: Edward Holmes
Subject: Re: Decision on Nature submission 2020-02-02583

Dear Clare,

We're just about to send our manuscript over to Nature Medicine, which has been much improved due to some recent data. I just wanted to share the new material with you so you're in the loop.

Since the original manuscript was submitted under Eddie's account, would it be possible for you to please transfer everything over to my account so I can start the process of getting this to Nature Medicine? Eddie is in transit at the moment, so I think it'll be difficult for him to get this transferred in time. If you're not able to transfer to my account, don't worry - we'll figure it out.

Thanks again for giving us the opportunity - we thought this would have been a very good piece for Nature given the massive interest, but Nature Medicine (if accepted) will be a good audience too.

I hope you're not drowning in COVID-19 papers!

Best,

Kristian

On Thu, Feb 20, 2020 at 9:56 AM Kristian G. Andersen [redacted] wrote:

> Yeah, no worries Clare - it's a tricky topic and I understand. And thanks for reaching out to your colleagues - much appreciated.
>
> Best,
>
> Kristian
>
> On Thu, Feb 20, 2020 at 9:54 AM Clare Thomas [redacted] wrote:
>
> > Dear Kristian,

Ok, thanks for clarifying. I am sorry we could not return a more positive decision at Nature but I wish you all the best with publishing it elsewhere and I'm glad we could get you some other options at Nature Research, if that interests you.

All the best,

Clare

From: Kristian G. Andersen [redacted]
Sent: 20 February 2020 17:48
To: Clare Thomas
Subject: Re: Decision on Nature submission 2020-02-02583

Thanks Clare for letting me know so quickly. I'll discuss with the other authors to see what the best path would be - just one thing to make clear though, reviewer 2 is unfortunately wrong about "Once the authors publish their new pangolin sequences, a lab origin will be extremely unlikely". Had that been the case, we would of course have included that - but the more sequences we see from pangolins (and we have been analyzing/discussing these *very* carefully) the more unlikely it seems that they're intermediate hosts. They definitely harbor SARS-CoV-like viruses, no doubt, but it's unlikely they have a direct connection to the COVID-19 epidemic. Unfortunately none of this helps refute a lab origin and the possibility must be considered as a serious scientific theory (which is what we do) and not dismissed out of hand as another 'conspiracy' theory. We all really, really wish that we could do that (that's how this got started), but unfortunately it's just not possible given the data.

Thanks again for considering our manuscript and while we had of course hoped for a better outcome, we understand the decision.

Best,

Kristian

On Thu, Feb 20, 2020 at 8:52 AM [redacted] wrote:

20th February 2020

Dear Kristian,

Thank you for submitting your manuscript entitled "The Proximal Origin of SARS-CoV-2" to be considered for publication in Nature. We've now obtained two ref reports on the paper (appended below) and I've had the opportunity to discuss them with our chief editor Magdalena Skipper. In the light of the advice received I am afraid we have decided that we

cannot offer to publish the Perspective in Nature.

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Clare

Clare Thomas
Senior Editor
Nature

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Referee #1 (Remarks to the Author):

Anderson presented a timely manuscript to share their points of view about the origin of SARS-CoV-2. There are several rumors about the origin of this virus. However, these "hypotheses" are entirely based on very limited, if any, scientific evidences.
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However, the authors might want to consider these minor suggestions:

1.The sections for the RBD and cleavage site of Spike protein basically have summarized the existing findings from other recent publications. The authors might want to spell out that these two sections are review summaries. In addition, the author can present these two sections in a more condense format and save some space for something else (also see points 6 and 7 below)

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5. Line 194. Laboratory escapes of SARS occurred in Singapore, China and Taiwan (PMID: 16830004).

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--

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Message

From: Joao Monteiro [redacted]
Sent: 3/5/2020 10:17:45 AM
To: Kristian G. Andersen [redacted] Edward Holmes [redacted]
Subject: RE: Interest in "Proximal Origins of hCoV-19"?

Thanks, Kristian.

Our Editorial Assistant, Sarah will send you the copyright assignment form. Please return it to her today if possible. Otherwise we are good to go.

Joao

From: Kristian G. Andersen [redacted]
Sent: Thursday, March 05, 2020 12:29 PM
To: Edward Holmes
Cc: Joao Monteiro
Subject: Re: Interest in "Proximal Origins of hCoV-19"?

Hi Joao,

Just to let you know the manuscript has been transferred over - NMED-C102233-T.

Please let me know if you need anything else or have any questions.

Best,
Kristian

On Wed, Mar 4, 2020 at 7:04 PM Edward Holmes [redacted] wrote:

> Excellent, many thanks.
> ---
> **PROFESSOR EDWARD C. HOLMES FAA FRS**
> ARC Australian Laureate Fellow
>
> **THE UNIVERSITY OF SYDNEY**
> Marie Bashir Institute for Infectious Diseases & Biosecurity,
> School of Life & Environmental Sciences and School of Medical Sciences,
> The University of Sydney | Sydney | NSW | 2006 | Australia
> T [redacted]
> E [redacted]
>
> On 4 Mar 2020, at 7:02 pm, Kristian G. Andersen [redacted] wrote:
>
> Yup, links work - all good, I'll get this done in the morning.
>
> K
>
> On Wed, Mar 4, 2020 at 7:01 PM Edward Holmes [redacted] wrote:
>
> Ok! I started the transfer process but I've just aborted.

Kristian - can you just check that the link works.

Cheers,

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T
E [redacted]

On 4 Mar 2020, at 6:59 pm, Kristian G. Andersen [redacted] wrote:

Ah, I have the email - I see the link. I'll update a few things and get this transferred over - should be completed tomorrow morning.

K

On Wed, Mar 4, 2020 at 6:57 PM Joao Monteiro [redacted] wrote:

Hi,

If you are listed as corresponding author, you can just go ahead and transfer the paper using the link in the decision letter from Nature that you received. You may also be able to make Kristien a corresponding author, if you have access to your account.

Sent from my iPhone, please excuse the brevity.

On Mar 4, 2020, at 9:54 PM, Edward Holmes [redacted] wrote:

Apologies! I'm in LAX now and will be for a few hours.

Please let me know what I need to do get this resolved.

Best wishes,

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T
E [redacted]

On 4 Mar 2020, at 4:33 pm, Kristian G. Andersen [redacted] wrote:

Once I have clarity on HCoV-19/SARS-CoV-2 I have all the edits in.

As for the previous submission - that's actually under Eddie's account - are you able to transfer it over to mine (krisandersen)? Otherwise, I'll forward all the material to Eddie and then he can transfer - I believe he's *en route* to Sydney at the moment.

K

On Wed, Mar 4, 2020 at 3:32 PM Kristian G. Andersen [redacted] wrote:

Great, thanks Joao - I can incorporate.

A couple of specific comments:

- "Proximal" is included since we're talking about the most recent origin - not deeper origins (e.g., in bats). I have heard from a number of people that they really like that bit, so I was hoping to keep it?
- The naming of the virus is tricky and I'm hoping to push back a little here - but of course will do whatever you prefer. The name "SARS-CoV-2" was chosen by ICTV without consulting any Chinese authorities or any of the people involved in its discovery. The WHO - while they now acknowledge SARS-CoV-2 as the official name of the virus, they refuse to use it because of stigma and other issues. HCoV-19 was suggested by a number of leading Chinese scientists involved in the discovery of the virus to (a) avoid stigma, and (b) make it more consistent with the name of the disease. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30419-0/fulltext. Again, we'll of course do whatever you think is best, but my personal opinion (shared by my co-authors) is that HCoV-19 is more appropriate than SARS-CoV-2.

<Screen Shot 2020-03-04 at 3.30.34 PM.png>

On Wed, Mar 4, 2020 at 3:22 PM Joao Monteiro [redacted] wrote:

Hi Kristian,

Thanks for the quick reply. I have added a couple notes to the file, for you to review plus some stylistic edits. Once you're done, can you transfer the submission from Nature to our system and upload the files to include the revised finalized version, the point-by-point response and the figure file separately, please? The main text should be an editable word doc.

LMK if you have any questions. I'll be on and off for the next hour or so. If you can turn this back to me before end of the week, would be fab.

ATB

Joao

From: Kristian G. Andersen [redacted]
Sent: Wednesday, March 04, 2020 5:56 PM
To: Joao Monteiro
Subject: Re: Interest in "Proximal Origins of hCoV-19"?

Hi Joao,

Please find attached a version cut to the suggested size. Please let me know if you have any questions or if you need anything else.

Best,

Kristian

On Tue, Mar 3, 2020 at 5:27 PM Kristian G. Andersen [redacted] wrote:

> Hi Joao,
>
> Thanks for getting back to me. Sounds good - we'll cut it to size and get back to you asap (hopefully tomorrow).
>
> K
>
> On Tue, Mar 3, 2020 at 11:02 AM Joao Monteiro [redacted] wrote:
>
> > Hi Kristian,
> >
> > Thanks for sending the files and sorry about the delay to respond.

We're interested in the piece, though I must it has grown significantly since the version I saw in consultation with Nature. Our plan was going to pursue publication within our Correspondences section, given the tone and overall type of discussion in the piece. I could offer ~2200 words, and up to 30 references, so you'd need to trim this back down more or less the size of the Nature version, while retaining the major changes in response to the reviewers.

Does this sound a reasonable plan to you? I believe that using this route, we could move ahead with publication fairly quickly.

Please let me know.

All the best,

Joao

From: Kristian G. Andersen [redacted]
Sent: Saturday, February 29, 2020 7:22 PM
To: Joao Monteiro
Subject: Re: Interest in "Proximal Origins of hCoV-19"?

Hi Joao,

Sorry for the delay in getting this over to you. I have attached the manuscript (PDF + Word), figure, and the response to the questions raised after our first submission. Please let me know if you have any questions or if you want me to submit this via your formal submission system.

Best,

Kristian

On Thu, Feb 27, 2020 at 9:17 PM Kristian G. Andersen [redacted] wrote:

> Hi Joao,

Sounds great. I need to get a few final edits in to make our conclusions a little less open ended (to make clearer that this *does* have a natural origin), but I'm hoping to get that done tomorrow in the AM. I'll send it over to you as soon as that's done.

K

On Thu, Feb 27, 2020 at 18:53 Joao Monteiro [redacted] wrote:

> Hi Kristian,
>
> Thanks for reaching out. Yes, we are very interested in the comment, and since it's been already peer reviewed, we were hoping to. I've ahead with fairly quickly. I'm at a conference right now, back to the office tomorrow. In the meanwhile, could you send me the revised version you're working on? I can work in that fri. The editorial side, so that when you transfer, we can move ahead with accepting it straight away.
>
> All the best,
>
> Joao
>
> Sent from my iPhone, please excuse the brevity.

On Feb 27, 2020, at 7:34 PM, Kristian G. Andersen [redacted] wrote:

> > Dear Joao,
> >
> > I believe Clare over at Nature might have mentioned our commentary on the proximal origins of the hCoV-19 virus last week. We have been incorporating some critical changes to the reviewer's comments so I just wanted to reach out to you to see if you're still interested in having a look at this manuscript? We're still incorporating a few changes but will have all of this wrapped up shortly as we're on a tight deadline - the media interest in this has been enormous and hasn't slowed down (we have refrained from commenting until formal publication). The public interest

has also been very high, with more than 65,000 reads of the blog post version over the last week.

Best,

Kristian

Kristian G. Andersen, PhD

Associate Professor, Scripps Research

Director of Infectious Disease Genomics, Scripps Research Translational Institute

Director, Center for Viral Systems Biology

The Scripps Research Institute

10550 North Torrey Pines Road, [redacted]

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La Jolla, CA 92037

p: [redacted]

c: [redacted]

t: @K_G_Andersen

e: [redacted]

w: www.andersen-lab.com

Assistant: [redacted]

Message

From: Chris Emery [redacted]
Sent: 3/17/2020 1:21:41 PM
To: Kristian Andersen Gmail Forward [redacted]
Subject: FW: COVID-19 preprint of interest - now published

You probably know this, but the paper is live. Press release is up here: https://www.scripps.edu/news-and-events/press-room/2020/20200317-andersen-covid-19-coronavirus.html

---

From: "Coleman, Amanda (NIH/NIAID) [C]" [redacted]
Date: Tuesday, March 17, 2020 at 1:15 PM
To: "Shabman, Reed (NIH/NIAID) [E]" [redacted]
Cc: "Brown, Liliana (NIH/NIAID) [E]" [redacted], Chris Emery [redacted]
Subject: RE: COVID-19 preprint of interest - now published

Thanks so much, Reed. I'll let the Office of Communications know.

Thank you,

Amanda Coleman [C]
[redacted]

From: Shabman, Reed (NIH/NIAID) [E] [redacted]
Sent: Tuesday, March 17, 2020 3:01 PM
To: Coleman, Amanda (NIH/NIAID) [C] [redacted]
Cc: Brown, Liliana (NIH/NIAID) [E] [redacted]; Chris Emery [redacted]
Subject: RE: COVID-19 preprint of interest - now published

Hi Amanda,

Following-up on this email chain. The paper, **The proximal origin of SARS-CoV-2**, is now online at Nature Medicine. Disregard my note if you have already heard from Chris at Scripps, but just wanted to close the loop.

Reed

Link: https://www.nature.com/articles/s41591-020-0820-9#Ack1

From: Shabman, Reed (NIH/NIAID) [E]
Sent: Wednesday, February 19, 2020 3:30 PM
To: Coleman, Amanda (NIH/NIAID) [C] [redacted]
Cc: Brown, Liliana (NIH/NIAID) [E] [redacted]; Chris Emery [redacted]
Subject: RE: COVID-19 preprint of interest

Hi Amanda,

I reached out to Kristian and team and copied his response below in italics. As you can see from his note, the text is submitted to Nature. Kristian suggests that the Office of Communications can communicate directly with Chris Emery (copied here).

Thanks,

Reed

Yes, it's been submitted for peer review (in Nature) and we are holding off on giving further comments to the media until it's been through that and published. Chris Emery from our communications department (cc'd here) is taking the lead on creating a press release / summary in lay language, as well as a Q&A with questions the public and policy makers might have - Wellcome is involved as well to help out. If there's interest on NIAID's side, I'm sure Chris and the team would welcome coordination/collaboration, so if you can please reach out to him directly.

Best,
Kristian

From: Coleman, Amanda (NIH/NIAID) [C] [redacted]
Sent: Wednesday, February 19, 2020 1:21 PM
To: Shabman, Reed (NIH/NIAID) [E] [redacted]
Cc: Brown, Liliana (NIH/NIAID) [E] [redacted]
Subject: RE: COVID-19 preprint of interest

Hi Reed – The Office of Communications asked if we could alert them if this paper is accepted in a peer reviewed journal. Do you know if the authors have submitted it to a journal?

Thank you,

Amanda Coleman [C]
[redacted]

Message

From: Kristian G. Andersen [redacted]
Sent: 3/31/2020 8:59:49 PM
To: Michael Farzan [redacted]
Subject: Re: Furin...

Hey Mike,

Still chugging along here in SoCal... As per our previous conversations, I thought this was pretty interesting:

http://virological.org/t/identification-of-a-common-deletion-in-the-spike-protein-of-sars-cov-2/451

Not quite sure what to make of it - but definitely interesting!

K

On Mon, Feb 17, 2020 at 9:26 AM Kristian G. Andersen [redacted] wrote:

> Hey Mike,
>
> Thanks - I was actually in the desert when that got pushed out, so a little rushed IMO. But pressure from the higher ups to get it out.
>
> Thanks for your comment on the structure/binding - this is actually *really* important. We have been discussing that bioRxiv paper this morning since it appears to show that -2 does indeed bind as well - or better - than -1. There is other data to suggest that too, but good to know that this isn't gospel!
>
> Four pangolin sequences just dropped as well - unfortunately these are similar to the previous and not similar in the RBD. I'm starting to think that one pango that stands out might not actually be correct. Hopefully more to come!
>
> Cheers,
> K
>
> On Mon, Feb 17, 2020 at 9:17 AM Michael Farzan <[redacted] wrote:
>
> > Yep.
> >
> > Hey just saw your review. Nice!
> >
> > Fyi: Jason McClellan's otherwise gorgeous S-protein structure includes a probably wrong assertion that the SARS2 S protein binds with "20-fold" higher affinity than that of SARS1. This is almost certainly wrong, and based in thei paper on an apples to oranges comparison. I suspect that will be in the press soon but thought I would mention it in case you were asked, "the jury is still out on that conclusion".
> >
> > **From:** Kristian G. Andersen [redacted]
> > **Sent:** Sunday, February 16, 2020 9:45 PM
> > **To:** Michael Farzan
> > **Subject:** Re: Furin...

Hey Mike,

Yup, one of the pangolin sequences have a very similar RBD (the others are more like bat and further from human still). It's not the elusive "99% pangolin" though as that sequence was never published nor was a study produced - I think they might have spoken a little too soon. The one that's online and close in the RBD is from merging a couple of metagenomic datasets and is very incomplete, so I'm not quite sure what to make of it. I really hope they'd come up with the 99% sequence - that'd be cool!

Cheers,

Kristian

On Sat, Feb 15, 2020 at 9:42 AM Michael Farzan [redacted] wrote:

> Hi Kristian, you probably know this by now but the RBM of the 99% panglolin-derived virus is virtually identical to SARS2 but the furin-site 4-aa insertion is missing. Mike

---

From: Michael Farzan
Sent: Thursday, February 6, 2020 11:07 PM
To: Kristian G. Andersen [redacted]
Subject: RE: Furin...

Hey Kristian,

It's a bit complicated but here is the best I can find.

There are two MHV variants A59 and BHK. BHK is lab adapted and has extended host range, and no longer is cleaved in the producer cell by furin. It also appears to be independent of the murine (or human) CEACAM receptor, relying on heparan sulfate.

The furin site has not changed in BHK, rather two amino acids immediately downstream account for the phenotype.

https://jvi.asm.org/content/79/22/14451?ijkey=709aa5da9513e80f42db103ec19b539ed1cc350b&keytype2=tf_ipsecsha

Virus-Cell Interactions

Message

From: Jeremy Farrar [redacted]
Sent: 2/8/2020 1:27:14 PM
To: Kristian G. Andersen [redacted] Drosten, Christian [redacted]
CC: Edward Holmes [redacted] Andrew Rambaut [redacted] rfgarry [redacted]; r.fouchier [redacted] P.Vallance1 [redacted]; collinsf [redacted] afauci [redacted]; Josie Golding [redacted] m.koopmans [redacted]; Mike Ferguson [redacted]
Subject: Re: [ext] 2019 N-CoV

We now have (and we will get more) the pangolin data (Eddie has) we think we can tie this up even tighter with the next iteration and make a conclusive statement which will then be the go to scientific statement to refer to.

Eddie and I have just come off a call with the National Academy of Medicine in the US – who the White House has asked to produce a report on this….

From: "Kristian G. Andersen" [redacted]
Date: Saturday, 8 February 2020 at 21:16
To: "Drosten, Christian" [redacted]
Cc: Jeremy Farrar [redacted], Edward Holmes [redacted], "a.rambaut [redacted], "rfgarry [redacted] "r.fouchier [redacted], "P.Vallance1 [redacted], Francis Collins [redacted] "afauci [redacted], Josie Golding [redacted], Marion Koopmans [redacted], Mike Ferguson [redacted]
Subject: Re: [ext] 2019 N-CoV

A lot of good discussion here, so I just wanted to add a couple of things for context that I think are important - and why what we're considering is far from "another conspiracy theory", but rather is taking a valid scientific approach to a question that is increasingly being asked by the public, media, scientists, and politicians (e.g., I have been contacted by Science, NYT, and many other news outlets over the last couple of days about this exact question).

To Ron's question, passage of SARS-like CoVs have been ongoing for several years, and more specifically in Wuhan under BSL-2 conditions - see references 12-15 in the document for a few examples. The fact that Wuhan became the epicenter of the ongoing epidemic caused by nCoV is likely an unfortunate coincidence, but it raises questions that would be wrong to dismiss out of hand. Our main work over the last couple of weeks has been focused on trying to *disprove* any type of lab theory, but we are at a crossroad where the scientific evidence isn't conclusive enough to say that we have high confidence in any of the three main theories considered. Like Eddie - and I believe Bob, Andrew, and everybody on this email as well - I am very hopeful that the viruses from pangolins will help provide the missing pieces. For now, giving the lab theory serious consideration has been highly effective at countering many of the circulating conspiracy theories, including HIV recombinants, bioengineering, etc. - here's just one example: https://www.factcheck.org/2020/02/baseless-conspiracy-theories-claim-new-coronavirus-was-bioengineered/.

As to publishing this document in a journal, I am currently not in favor of doing so. I believe that publishing something that is open-ended could backfire at this stage. I think it's important that we try to gather additional evidence - including waiting on the pangolin virus sequences and further scrutinize the furin cleavage site and O-linked glycans - before

publishing. That way we can (hopefully) come out with some strong conclusive statements that are based on the best data we have access to. I don't think we are there yet.

Best,
Kristian

On Sat, Feb 8, 2020 at 12:38 PM Drosten, Christian [redacted] wrote:

OK, I see. We should then introduce references to these informal sources in the beginning of the text. Else it reads a bit funny.

Christian

--

Professor Christian Drosten
Director, Institute of Virology
Scientific Director, Charité Global Health

Charité - Universitätsmedizin Berlin
Campus Charité Mitte

[redacted]
Germany

E-Mail: [redacted]
https://virologie-ccm.charite.de/
https://globalhealth.charite.de/

Von: Jeremy Farrar [redacted]
Datum: Samstag, 8. Februar 2020 um 21:21
An: Edward Holmes [redacted], Christian Drosten [redacted]
Cc: "kga1978[redacted], Andrew Rambaut [redacted]
"rfgarry[redacted] "r.fouchier[redacted]
"P.Vallance1[redacted], "collinsf[redacted]
<collinsf[redacted], "afauci[redacted], Josie Golding
[redacted], "m.koopmans[redacted] Mike Ferguson
[redacted]
Betreff: Re: [ext] 2019 N-CoV

The theory of the origin of the has gathered considerable momentum not in social media, but increasingly among some scientists, in main stream media, and among politicians.

The aim of this was to bring a neutral, respected, scientific group together to look at the data and in a neutral, considered way provide an opinion and we hoped to focus the discussion on the science, not on any conspiracy or

other theory and to lay down a respected statement to frame whatever debate goes on – before that debate gets out of hand with potentially hugely damaging ramifications.

With the additional information on the pangolin virus, information not available even 24 hours ago, I think the argument is even clearer.

My preference is that a carefully considered piece of science, early in the public domain, will help mitigate more polarised debate. If not, that debate will increasingly happen and science will be reacting to it. Not a good position to be in.

From: Edward Holmes [redacted]
Date: Saturday, 8 February 2020 at 20:11
To: Christian Drosten [redacted]
Cc: Jeremy Farrar [redacted], "kga1978 [redacted]
"a.rambaut [redacted], "rfgarry [redacted]
"r.fouchier [redacted], "P.Vallance1 [redacted]
[redacted], Francis Collins [redacted], "afauci([redacted]
[redacted], Josie Golding [redacted] Marion Koopmans
[redacted], Mike Ferguson [redacted]
Subject: Re: [ext] 2019 N-CoV

Hi Christian,

I don't know where this story came from, but it has nothing whatsoever to do the HIV nonsense. Please don't associate this with that. This is a broader story.

Ever since this outbreak started there have suggestions that the virus escaped from the Wuhan lab, if only because of the coincidence of where the outbreak occurred and the location of the lab. I do a lot of work in China and I can you that a lot of people there believe this and believe they are being lied to. Things were made worse when Wuhan lab published the bat virus sequence - a bat sampled in a different province for which they have a large collection of samples.

I believe the aim/question here is whether we, as scientists, should try to write something balanced on the science behind this? There are arguments for and against doing this.

Personally, with the pangolin virus possessing 6/6 key sites in the receptor binding domain, I am in favour of the natural evolution theory.

Best wishes,

Eddie

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,

School of Life & Environmental Sciences and School of Medical Sciences,

The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 9 Feb 2020, at 6:52 am, Drosten, Christian · [redacted] wrote:

Dear All,

I am overloaded with nCoV patient-related work and will need a few days before I can work on this text.

Can someone help me with one question: didn´t we congregate to challenge a certain theory, and if we could, drop it? This whole text reads as if the hypothesis was obvious, or was brought up by some external source, forcing us to respond. Is this the case? It does not seem as if this was linked to the HIV nonsense.

Who came up with this story in the beginning? Are we working on debunking our own conspiracy theory?

Christian

--

Professor Christian Drosten
Director, Institute of Virology
Scientific Director, Charité Global Health

Charité - Universitätsmedizin Berlin
Campus Charité Mitte

[redacted]
Germany

E-Mail: [redacted]
https://virologie-ccm.charite.de/
https://globalhealth.charite.de/

Von: Jeremy Farrar [redacted]
Datum: Samstag, 8. Februar 2020 um 10:45
An: Edward Holmes · [redacted], "kga1978([redacted]

Andrew Rambaut [redacted] "rfgarry([redacted]
Cc: "r.fouchier([redacted], "P.Vallance1([redacted]
<P.Vallance1 [redacted], "collinsf [redacted] "afauci([redacted], Josie Golding [redacted] "m.koopmans([redacted], Christian Drosten [redacted] Mike Ferguson [redacted]
Betreff: [ext] FW: 2019 N-CoV

APOLOGIES WITH ALL CORRECT EMAILS

Kristen, Andrew, Bob, Eddie have reworked the summary and it is attached here.

We are pushing to get the sequence data from the reports on the pangolins, but do not have currently, clearly that is very important to incorporate.

Interested in your views

- Is this reasonably balanced given the data?
- Is there anything anyone disagrees with?
- Is there anything more in relation to what would seem to be the two possibilities
  - Nature, Intermediate host, evolution and passage
- Future data you may have
- Advice on whether KA, AR, RG and EH should publish this.

These and other thoughts welcome in confidence.

Message

From: Edward Holmes [redacted]

Sent: 7/28/2020 4:23:46 AM

To: Kristian G. Andersen [redacted]

CC: Garry, Robert F [redacted] Andrew Rambaut [redacted]

Subject: Re: Teleconference

External Sender. Be aware of links, attachments and requests.

All, I've spoken to Jeremy and he wants a little more of the time-line incorporated, which helps make or case stronger. Also happens to be true. He's also agreed to be cc'd on the reply to Jon which is great because he will be able to confirm.

So, I've edited the draft email to Jon accordingly (Kristian, I've moved some sentences around).

Jeremy's comms person at Wellome also had some suggestions and I'll forward that in a sec.

Cheers,

Eddie

Hi Jon,

Here are the facts:

1. On Jan 27 Jeremy Farrar called one of us (Eddie) to say that some rumours were coming out of the US that the virus may be a lab escape and could he determine whether this had any scientific credibility. By coincidence, on Jan 31 Kristian independently contacted Eddie to note that there was some features in the SARS-CoV-2 genome that at the time appeared unusual, particularly the furin cleavage site and the receptor binding domain.

2. At this stage we thought it was wise to ask for additional opinion on this, so a conference call was rapidly arranged for Feb 1 (Feb 2 Eddie's time). There were indeed other coronavirus experts on the call, chosen by Jeremy and Eddie. It is worth pointing out at this point that the senior author on our paper - Bob Garry - has published a significant number of papers on coronaviruses, including on the SARS spike protein, and even commented on this on the virological.org website prior to the call taking place (https://virological.org/t/analysis-of-wuhan-coronavirus-deja-vu/357).

3. Clearly, some people on the call were very strongly of the opinion that the possibility of a lab escape was implausible and gave reasons why it should be dismissed (although there was also some initial confusion about whether we were referring to the crazy HIV origins theory that had just been touted - obviously we were not). Some of those comments we agreed with, others we did not.

4. A take-home message from the call was that we should investigate further and write a scientific paper to clearly set-out the background on the topic and our findings. Indeed, one the of emailed agenda items for discussion after the call was: "Advice on whether KA, AR, RG and EH should publish this".

Hence, we eventually wrote up our findings as a scientific (peer reviewed) paper. Critically, drafts of this paper were sent to all the people on the call, including those with the information that has been emailed to you. We have attached our first draft of what would eventually become our paper from Feb 7, which was circulated to everyone on the call. As you can see, it is essentially the basis of our final study and people on the call commented on it.

5. Very shortly after the call, the pangolin data came out. This was critical, and as Eddie wrote in an email to everyone on the call on Feb 9th:

"Personally, with the pangolin virus possessing 6/6 key sites in the receptor binding domain, I am in favour of the natural evolution theory."

With Andrew Rambaut replying:

"I am of the view that the natural selection hypothesis is the most likely (specifically the non-bat reservoir). And as Eddie mentioned this is becoming more likely from day to day with the pangolin story."

6. Hence, it is completely and utterly false to claim that we (i) all thought it was a lab escape, (ii) that we were corrected ("schooled") in our views by the coronavirus experts on the call, and (iii) then submitted a Nature paper without anyone else knowing about it. The truth is that we had a range of views among us, our paper included the pangolin data that was not available at the time of the call, and we circulated drafts of our document to everyone. Importantly, our study was an evolutionary study based on genomic information, which is the only way to investigate the origins of SARS-CoV-2 - we believe all the authors on our paper have a strong demonstrated record in answering exactly those types of questions for a multitude of viruses.

7. We also categorically deny that we were "spreading the rumor" that the virus was human engineered. As you can see from point 1 this did not come from us. Indeed, at the time, there were indeed rumours - which persists to this day - that SARS-CoV-2 was an engineered virus, but these certainly did not come from us. As you know, the White House OSTP asked for expert opinions on this question too (spurred by the HIV nonsense preprint), and Kristian was part of that panel (https://www.the-scientist.com/news-opinion/lab-made-coronavirus-triggers-debate-34502). Our study directly addressed these rumours in a scientific way by considering that a lab escape could have occurred. We did not dismiss this possibility out of hand, but we scientifically investigated it.

8. We strongly reject the idea that we should not have raised nor discussed the possibility of lab escape: as scientists we have to present all the data and discuss it openly. That's what we did. To not have considered or mentioned the possibility of a lab escape would have been negligent. Is the person who emailed you seriously suggesting that we should not have discussed these issues? Wouldn't that be a cover-up? Indeed, the great irony is that 99.9% of the feedback we have received on our paper - including death threats - are people accusing us of dismissing the lab escape theory too quickly. Can you imagine if we had not mentioned - or considered - it all as suggested by some "coronavirus experts"?

To is, this clearly appears to be a case of sour grapes based on half-truths that lack the full history, gossip, and likely stimulated by your recent (great) article with quotes from us on the questions you raised with Dr. Zhengli. It's telling that the person who emailed you is anonymous. We have absolutely no problem with people knowing that our views on this issue have evolved as more data have appeared - and continues to evolve to this day, should more data become available. That's

science. And it's the only way to do it well. Indeed, we have told our history of thinking on this to many people: the way we set this up was a study of alternative hypotheses equally weighted priors, which we tested - our posterior clearly favors the hypothesis that this is a natural virus. As far as we can tell we are only 'guilty' of following the proper scientific method - but maybe we offended an ivory tower "coronavirus expert" in the process. It likely won't be the last time.

Best,

Eddie and Kristian

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 28 Jul 2020, at 6:21 pm, Andrew Rambaut [redacted] wrote:

I agree - most likely Ron doing the leaking. Whoever it was that talked to the emailer was indignant that 'non-coronavirus-experts' were involved. I can't see any of the others having this sort of pompous, arrogant view of the world. Marion approached me well after this to help analyse the Dutch data. Christian I have worked with before on MERS. I doubt even that Ron was that bothered - probably just told the story to whoever it was and misremembered or 'enhanced' it for effect.

A

On 28 Jul 2020, at 03:58, Edward Holmes [redacted] wrote:

Pohlmann as on it and very good. Christian was also v. interested in the furin cleavage site (I've other emails).

Despite this, I'm 100% sure it is Ron who leaked it - he was the most angry - and I still think it was like Baric who emailed Jon Cohen.

I just thought "I would conclude that a follow-up discussion on the possible origin of 2019-nCoV would be of much interest" was very interesting.

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia

T [redacted]
E [redacted]

On 28 Jul 2020, at 12:54 pm, Kristian G. Andersen [redacted] wrote:

Interesting - I don't actually remember this from Ron. Was Stefan Pohlmann on the call too? Surely he knows Ralph very well.

On Mon, Jul 27, 2020 at 7:47 PM Edward Holmes [redacted] wrote:
Ron thought it was useful at the time.

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

Begin forwarded message:

From: "R.A.M. Fouchier" [redacted]
Subject: Re: Teleconference
Date: 2 February 2020 at 7:30:12 pm AEDT
To: Jeremy Farrar [redacted], "Fauci, Anthony (NIH/NIAID) [E]" [redacted]>, Patrick Vallance [redacted]
Cc: "Drosten, Christian" [redacted], "M.P.G. Koopmans" [redacted], Edward Holmes [redacted], "spoehlmann[redacted], Andrew Rambaut [redacted], "Kristian G. Andersen" [redacted], Paul Schreier [redacted], "rfgarry[redacted], "Ferguson, Mike" [redacted], Francis Collins <collinsf[redacted], "lawrence.tabak[redacted] Josie Golding [redacted]

Dear Jeremy and others,

This was a very useful teleconference. Given the evidence presented and the discussions around it, I would conclude that a follow-up discussion on the possible origin of 2019-nCoV would be of much interest. However, I doubt if it needs to be done on very short term, given the importance of other activities of the scientific community, WHO and other stakeholders at present. It is my opinion that a non-natural origin of 2019-nCoV is highly unlikely at present. Any conspiracy theory can be approached with factual information. I have written down some of the counter-arguments. It is a bit long (below) but wanted to share it with you anyway.

Thanks for organizing this on such short notice,
Kind regards
Ron

Ron's notes:
An accusation that nCoV-2019 might have been engineered and released into the environment by humans (accidental or intentional) would need to be supported by strong data, beyond reasonable doubt. It is good that this possibility was discussed in detail with a team of experts. However, further debate about such accusations would unnecessarily distract top researchers from their active duties and do unnecessary harm to science in general and science in China in particular. At present, the arguments that nCoV-2019 could have emerged from an animal source is much stronger than other possibilities.

Observations about the genome that were inferred to be suggestive for a non-animal origin:
1. HIV-like sequences in the spike protein.
2. Level of mutations in the spike protein region.
3. Presence of a furin cleavage site in the middle of spike
4. BamH1 restriction site at the end of the spike sequence
5. An F-to-Y substitution in the receptor-binding domain of spike
6. Potential O-linked glycan sites protecting the cleavage site of spike

1. The biorxiv publication by Prashant Pradhan and colleagues from Delhi ("Uncanny similarity of unique inserts in the 2019-nCoV spike protein to HIV-1 gp120 and Gag") has already been heavily debated on biorxiv and virological.org. The similarity between the inserts in 2019-nCoV spike and sequences of HIV-1 is accidental. These are very short insert sequences that are highly similar to many Genbank entries. Such similarities are explained by pure chance alone.
2. Andrew Rambaut analyzed the level of mutations in the spike region of SARS-CoV with that of its closest bat virus relative and of 2019-nCoV and its closest bat virus relative. The level of mutations between the two pairs of viruses was in the same range. Thus, this level of mutations can arise under circumstances of natural emergence.
3. Bat coronaviruses generally do not have a furin cleavage site in the spike protein. Some human coronaviruses do have a furin cleavage site in spike, which must have evolved naturally. As animal reservoir and spill-over hosts are highly under-sampled, the presence of a furin cleavage site in spike in such species is unknown. When coronaviruses jump host barriers, this frequently involved adaptation of cleavage sites that may be targeted by various proteases. Given the presence of furin-like sites in human coronavirus and the mutation of protease cleavage sites upon coronavirus host-jumps in general, a natural origin of the furin site is certainly not impossible.
4. The BamHI restriction endonuclease site evolved due to a single (silent) nucleotide substitution as compared to the closest relative bat virus genome sequence. Restriction sites of 6 nucleotides can be found in every sequence, all over the genome, when 1 of the 6 positions is allowed to vary. We now find BamHI, next time it might be one of the plethora of other 6-nucleotide sequence motifs. This can be explained by pure chance.
5. The F-Y substitution in the spike receptor binding domain was observed in mouse-adapted SARS-CoV and in 2019-nCoV. It is generally absent in bat coronaviruses. This substitution is associated with host adaptation in mice. It may point to (natural) host adaption of 2019-nCoV (in mice, humans or unknown hosts) as well. It is possible that scientists would like to test the effect of F-Y because it was found in a mouse adaptation experiment. However, the logical way to test it would be in the original (SARS-CoV) virus backbone. There is no other reason to insert the F-Y substitution in an engineered virus.
6. It is unclear if the potential O-linked glycosylation sites 1) are used during glycosylation; 2) have a functional role for the spike protein; 3) were present in the ancestral virus from the original host. This is not an argument in the discussion on the origin of 2019-nCoV.

Additional arguments:
A. All focus is on spike. Spike is a highly variable protein in general, crucial for host adaptation and under strong natural selection.

B. The virus backbone (beyond spike) is not an indicator of a human source of 2019-nCoV emergence. The virus itself has not been described or characterized previously and no reverse genetics system has been described for this virus. Any scientist wanting to investigate spike function (e.g. to study protease cleavage or the receptor-binding domain) would have used a well-characterized reverse genetics system that is already available (making accidental lab-escape unlikely). Anyone with malicious intend would have used a well-characterized virulent strain (SARS-CoV, MERS-CoV) described and characterized (by others) in the literature.

C. The patterns of mutations we observe in the receptor-binding domain and the protease cleavage sites of spike are typical for host-switched naturally evolving viruses. We can infer it for the naturally evolved human coronaviruses, we have seen it for the natural zoonoses of SARS-CoV and MERS-CoV. Convergent (parallel) evolutionary events are common in virology. Also for influenza, we see the same mutations emerge during the pandemics of 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2), in the 2013 zoonotic H7N9 virus and e.g. an epizootic in seals in 2014 (H10N7). Regardless of the divergent subtype, we see identical substitutions in the receptor-binding domains, identical substitutions in polymerase, and non-identical substitutions with identical phenotypic consequences (e.g. stability) in the genome. The fact that we (think we) see recognizable traits in spike does not mean it must be man-made.

D. We do not know the source of 2019-nCoV. There is "~30 years of evolutionary gap" between 2019-nCoV and the closest bat virus relative. These 30 years may have been in any host. We have no idea what might have happened (in evolutionary sense) between BatCov/RaTG13 and 2019-nCoV. We should rest our case until we have a close relative of 2019-nCoV.

Van: Jeremy Farrar [redacted]
Datum: zaterdag 1 februari 2020 om 21:59
Aan: "Fauci, Anthony (NIH/NIAID) [E]" [redacted], Patrick Vallance [redacted]
CC: Christian Drosten [redacted], "M. Koopmans" [redacted]
"R.A.M. Fouchier" [redacted] Edward Holmes [redacted]
"spoehlmann[redacted], Andrew Rambaut [redacted], "Kristian G. Andersen" [redacted] Paul Schreier [redacted], "rfgarry[redacted]
[redacted] "Ferguson, Mike" [redacted], Francis Collins
<collinsf@[redacted] "lawrence.tabak[redacted] Josie Golding
[redacted]
Onderwerp: Re: Teleconference

Thank you to everyone for joining.

There is clearly much to understand understand in this. This call was very helpful to hear some of our current understanding and the many gaps in our knowledge. I do not believe this is a question of a binary outcome, it is more a question of "What are the evolutionary origins of 2019-nCoV, important for future risk assessment and understanding of animal/human coronaviruses".

I do know there are papers being prepared, there will media interest and there is already chat on Twitter/WeChat.

We on this call are not the only ones with scientific expertise in this area and this was an ad hoc group that came together to air some thoughts. It is clearly not the sole group to take this forward, that will need a broader range of imput and a respected international body to ask an expert group to explore this, with a completely open mind. In order to stay ahead of the conspiracy theories and social media I do think there is an urgency for a body to convene such a group and commission some work to – (draft) "To understand the evolutionary origins of 2019-nCoV, important for this epidemic and for future risk assessment and understanding of animal/human coronaviruses".

In other words a completely open minded and neutral question bringing in the best minds, and under the umbrella of a respected international agency

I hope that is a reasonable approach, please send any thoughts or suggestions.

Once again, thank you for making time over a weekend and for such an informed discussion on a complex issue.

Thank you and best wishes Jeremy

From: Jeremy Farrar [redacted]
Date: Saturday, 1 February 2020 at 15:34
To: "Fauci, Anthony (NIH/NIAID) [E]" [redacted], Patrick Vallance [redacted]
Cc: "Drosten, Christian" [redacted], Marion Koopmans [redacted] "r.fouchier[redacted], Edward Holmes [redacted] "spoehlmann[redacted] "a.rambaut[redacted], "Kristian G. Andersen" [redacted] Paul Schreier [redacted], "rfgarry[redacted] <rfgarry[redacted] Michael FMedSci [redacted]
Subject: Teleconference

1st February (2nd Feb for Eddie)
Information and discussion is shared in total confidence and not to be shared until agreement on next steps.

Dial in details attached.
Please mute phones.
I will be on email throughout – email Paul or I Paul if any problems
If you cannot make it, I will phone you afterwards to update.

One Hour

6am Sydney
8pm CET
7pm GMT
2pm EST
11am PST
(Hope I have the times right!)

Thank you for the series of calls and for agreeing to join this call.

Agenda

- Introduction, focus and desired outcomes - JF
- Summary – KA
- Comments – EH
- Q&A – All
- Summary and next steps - JF

Kristian Anderson
Bob Garry - I have not been able to contact Bob. Please forward if you can.
Christian Drosten
Tony Fauci
Mike Ferguson
Ron Fouchier
Eddie Holmes
Marion Koopmans
Stefan Pohlmann
Andrew Rambaut
Paul Schreier
Patrick Vallance

Message

From: Jeremy Farrar [redacted]
Sent: 7/28/2020 12:36:51 AM
To: Edward Holmes [redacted]
CC: Kristian G. Andersen [redacted]; Fauci, Anthony (NIH/NIAID) [E] [redacted]
Subject: Re: The authors who wrote the paper saying that SARS-CoV-2 is not human engineered first tried convincing Anthony Fauci of the opposite.

Thanks Eddie.

I will recheck emails and phones, I will try and do that today.

I think it really starts on the 8/9th January and the calls you and I had with China and the original sequence.

And others were also on those calls – Francis Collins, Mike Ferguson, Patrick Vallance.

I would suggest we get the sequence of events absolutely right before replying.

Best wishes Jeremy

From: Edward Holmes [redacted]
Date: Tuesday, 28 July 2020 at 08:30
To: Jeremy Farrar [redacted]
Cc: "Kristian G. Andersen" [redacted] "Fauci, Anthony (NIH/NIAID) [E]" [redacted]
Subject: Re: The authors who wrote the paper saying that SARS-CoV-2 is not human engineered first tried convincing Anthony Fauci of the opposite.

Hi Jeremy,

Here is the exact time-line which I have now checked.

1. Jan 26. You call me (I was in Switzerland) to talk about some concerns coming out the US that the virus might be a lab escape. Patrick Vallance might have been on that call, I can't recall. You later forward me an email from Marc Lipsitch and others containing some comments from Richard Ebright. I take a quick look at the sequence and say that I saw no evidence for lab escape in SARS-CoV-2 because it's pattern of variability was the same as in RaTG13.

2. Jan 31. Kristian contacts me to say that he has spotted some strange things in the issue - specifically the furin cleavage site and restriction sites - that we was concerned about. Given our conversation earlier that week, I called you and informed you of Kristian's findings. We then decided to have a broader discussion with key parties on this ASAP. I think Kristian told Tony at this point but he can confirm. You and I then decided that Ron Fouchier, Christian Drosten and Marion Koopmans would be good to include. Christian also wanted Stephan Pollmnan involved.

3. Feb 1 (6 am on Feb 2 for me). We have the conference call and then start an email chain about how we should deal with this. Writing it up for a paper was on the agenda and discussed. I have all the emails on this.

For Tony's benefit a revised draft of the email to Jon is pasted below.

I can't for the life of me see what we have done wrong here. I strongly believe we have just tried to get on top of a very vexing question as quickly and openly as possible.

Cheers,

Eddie

Hi Jon,

Here are the facts:

1. In early Feb we had spotted some features in the SARS-CoV-2 genome that at the time appeared unusual - particularly the furin cleavage site and the receptor binding domain.

2. At this stage we thought it was wise to ask for other expert's opinions on this, so a conference call was arranged. There were indeed other coronavirus experts on the call. It is worth pointing out that the senior author on our paper - Bob Garry - has published a significant number of papers on coronaviruses, including on the SARS spike protein, and even commented on this on the virological.org website prior to the call taking place (https://virological.org/t/analysis-of-wuhan-coronavirus-deja-vu/357). Importantly, our study was an evolutionary study based on genomic information, which is the only way to investigate the origins of SARS-CoV-2 - we believe all the authors on our paper have a strong demonstrated record in answering exactly those types of questions for a multitude of viruses.

3. Clearly, some people on the call were very strongly of the opinion that the possibility of a lab escape was ridiculous and listed reasons why it should be dismissed out of hand (although there was also some initial confusion about whether we were referring to the crazy HIV origins theory that had just been touted - obviously we were not). Some of those comments we agreed with, others we did not. A take-home message from the call was that we should investigate further and write a scientific paper to clearly set-out the background on the topic and our findings. Indeed, one the of emailed agenda items for discussion after the call was "Advice on whether KA, AR, RG and EH should publish this".

4. We eventually wrote up our findings as a scientific (peer reviewed) paper. Critically, drafts of this paper were sent to all the people on the call, including those with the information that has been emailed to you. We have attached our first draft of what would eventually become our paper from Feb 7, which was circulated to everyone on the call. As you can see, it is essentially the basis of our final study and people on the call commented on it.

5. Very shortly after the call, the pangolin data came out. This was critical and as Eddie wrote in an email to everyone on the call on Feb 9th:

"Personally, with the pangolin virus possessing 6/6 key sites in the receptor binding domain, I am in favour of the natural evolution theory."

and Rndrew Rambaut replied to this stating:
"I am of the view that the natural selection hypothesis is the most likely (specifically the non-bat reservoir). And as Eddie mentioned this is becoming more likely from day to day with the pangolin story."
6. Hence, it is completely and utterly false to claim that we (1) all thought it was a lab escape, (2) that we were corrected ("schooled") in our views by the coronavirus experts on the call, and (3) then submitted a Nature paper without anyone else knowing about it. The truth is that we had a range of views among us, our paper included the pangolin data that was not available at the time of the call, and we circulated drafts of our document to everyone.

7. We categorically deny that we were "spreading the rumor" that the virus was human engineered. At the time, there were indeed rumours - which persists to this day - that SARS-CoV-2 was an engineered virus, but these certainly did not come from us. As you know, the White House OSTP asked for expert opinions on this question too (spurred by the HIV

nonsense preprint), and Kristian was part of that panel (https://www.the-scientist.com/news-opinion/lab-made-coronavirus-triggers-debate-34502). Our study directly addressed these rumours in a scientific way by considering that a lab escape could have occurred. We did not dismiss this possibility out of hand, but we scientifically investigated it.

We strongly reject the idea that we should not have raised nor discussed the possibility of lab escape: as scientists we have to present all the data and discuss it openly. That's what we did. To not have considered or mentioned the possibility of a lab escape would have been negligent. Is the person who emailed you seriously suggesting that we should not have discussed these issues? Wouldn't that be a cover-up? Indeed, the great irony is that 99.9% of the feedback we have received on our paper - including death threats - are people accusing us of dismissing the lab escape theory too quickly. Can you imagine if we had not mentioned - or considered - it all as suggested by some "coronavirus experts"?

This clearly appears to be a case of sour grapes based on half-truths and likely stimulated by your recent (great) article with quotes from us on the questions you raised with Dr. Zhengli. It's telling that the person who emailed you is anonymous. We have absolutely no problem with people knowing that our views on this issue have evolved as more data have appeared - and continues to evolve to this day, should more data become available. That's science. And it's the only way to do it well. Indeed, we have told this to many people: the way we set this up was a study of alternative hypotheses equally weighted priors, which we tested - our posterior clearly favors the hypothesis that this is a natural virus. As far as we can tell we are only 'guilty' of following the proper scientific method - but maybe we offended an ivory tower "coronavirus expert" in the process. It likely won't be the last time.

Best,

Eddie and Kristian

PROFESSOR EDWARD C. HOLMES FAA FRS
ARC Australian Laureate Fellow

THE UNIVERSITY OF SYDNEY
Marie Bashir Institute for Infectious Diseases & Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney | Sydney | NSW | 2006 | Australia
T [redacted]
E [redacted]

On 28 Jul 2020, at 4:54 pm, Jeremy Farrar [redacted] wrote:

Thanks for forwarding this and the other emails.

I would like to get the sequence of events absolutely right from the start. Eddie the start goes back to the calls you and I had on the 8/9th January.

Can we get that sequence of events right and agreed before a substantive reply goes back to Jon?

Jeremy

On 28 Jul 2020, at 02:07, Kristian G. Andersen [redacted] wrote:

Dear Tony,

I am sorry to be contacting you, as I know you have critically important priorities, including developing a vaccine for COVID-19. **We just received the email below from Jon Cohen** (from Science) about our conversations back in February investigating the **origins of SARS-CoV-2.** As you know, we considered the theory that SARS-CoV-2 could have been a lab escape and therefore did what any good scientist should do - investigate likely hypotheses and let the data decide. As you know, the data strongly suggests that this is a natural virus and clearly this person gets a lot of things wrong about how this all played out.

We need to reply back to Jon, which would have to include confirming that this meeting did indeed take place with you and Jeremy present. Please let me know if you have any comments or concerns in this regard.

At the very end of this email, I have added a draft email that Eddie put together. I have a few clarifying points that I will add and then Eddie and I will reply back to Jon.

Again, sorry to take up your time - please let me know if you have any comments, questions, or concerns. **We are planning to email Jon tomorrow afternoon.**

Best,
Kristian

Kristian G. Andersen, PhD
Professor | Scripps Research
Director of Infectious Disease Genomics | Scripps Research Translational Institute
Vice President | Viral Hemorrhagic Fever Consortium
Principal Investigator | Center for Viral Systems Biology
Principal Investigator | West African Emerging Infectious Disease Research Center

The Scripps Research Institute
10550 North Torrey Pines Road, [redacted]
Department of Immunology and Microbial Science
La Jolla, CA 92037

p: [redacted]
t: @K_G_Andersen
e: [redacted]
w: www.andersen-lab.com

Assistant: [redacted]

---------- Forwarded message ---------
From: **Jon Cohen** [redacted]
Date: Mon, Jul 27, 2020 at 3:02 PM
Subject: Re: The authors who wrote the paper saying that SARS-CoV-2 is not human engineered first tried convincing Anthony Fauci of the opposite.
To: Kristian G. Andersen [redacted], Edward Holmes [redacted]

Here's what one person who claims to have inside knowledge is saying behind your backs...

Jon

On Jul 25, 2020, at 7:22 AM, ofu8ledu8z <ofu8ledu8z[redacted] wrote:

[EXTERNAL EMAIL]

Hello Jon

Given your recent mentions of the origin of SARS-CoV-2 I thought you might be interested to hear the bizarre back-story of the paper "The proximal origin of SARS-CoV-2" (https://www.nature.com/articles/s41591-020-0820-9).

In summary, four of the authors managed to organize a conference call with Anthony Fauci and others, after quietly raising the alarm (or "spreading the rumor", as Jeremy Farrar apparently put it) that the virus **WAS** in fact human engineered. On the call were two world-class virologists who actually work on coronaviruses, who set them straight in great detail. That seemed to be the end of the affair.

But, incredibly, Andersen et al. turned around and submitted the Proximal paper to *Nature* with the exact opposite claim, i.e., that the virus was **NOT** human engineered. They used (without acknowledgment, of course) all the arguments provided by the coronavirologists on the initial call in which they had tried to raise the human-engineered alarm.

I don't think it would be too hard to verify all this, if you feel like digging a little. If you're wondering if this could all possibly be true: ask yourself how this group of authors, none of whom work on coronaviruses, could have such detailed arguments about why SARS-CoV-2 was not human-engineered. The answer is that they couldn't (and didn't) - they were schooled by the coronavirus experts on the call.

For the phone conference, Anthony Fauci called in Jeremy Farrar (Director of the Wellcome Trust). Farrar asked the coronavirus experts to join the call to listen to the claims. The call took place on a Saturday in early February (either the 1st or 8th, I'm not sure but I could probably find out). On the call making the claim were: Kristian G. Andersen, Andrew Rambaut, Edward C. Holmes, Robert F. Garry, but not Ian Lipkin.

The coronavirus experts listened for a while and both quickly concluded that the reasoning was completely flawed, that the non-coronavirus virologists had no idea what they were talking about, and that the human-engineered claim was totally wrong. One of the coronavirus experts was entertaining guests that day and told the people on the conference call that they wanted to give their opinion and then go back to the guests. So they told them it was nonsense, gave them a list of reasons why, and got off the call. The other coronavirus expert stayed on the call, gave a similar opinion and the morning afterwards sent a detailed list of the reasons why the claim was certainly wrong.

After the paper with the exact opposite claim was received at *Nature*, senior editor, Clare Thomas sent it out for review to some of the best people in the world... Not surprisingly, this happened to include a very close colleague of one of the experts who had been on the conference call. You can perhaps imagine the shock. Thomas was quickly appraised of the situation and *Nature* rejected the paper. It was then sent to *Nature Medicine*, where it was soon published.

One author on the paper was not on the conference call: Ian Lipkin. It's not clear how much of the back-story he is aware of. It might be worth giving him a call to ask, in case you feel like investigating. If his co-authors left him in the dark as to what actually happened and he's worried about the possible fallout he may want to help.

I apologize for mailing you without revealing my name (at least for now). I work in the field and have heard this story from two people who were on the initial call with Fauci. I'm not keen to be personally involved, but I find the situation so outrageous, hypocritical, and shameless that I also find I can't keep silent. It doesn't change anything with respect to knowledgeable thinking about the origin of the virus, of course, but it's a pretty ugly situation that I (obviously) think should be exposed.

----- EMAIL REPLY DRAFT -----

Hi Jon,

Here are the facts:

1. In early Feb we had spotted some features in the SARS-CoV-2 genome that at the time appeared unusual - particularly the furin cleavage site and the receptor binding domain.

2. At this stage we thought it was to wise ask for some other expert opinion on this, so a conference call was arranged. There were indeed some coronavirus experts on the call who we chose.

3. Clearly, some people on the call were very strongly of the opinion the possibility of a lab escape was ridiculous and listed reasons why it was unlikely (although there was also some initial confusion about whether we were referring to the crazy HIV origins theory that had just been touted - obviously we were not). Some of those comments we agreed with, others we didn't. There as a long email discussion about what the data said. A take-home message from the call was that we should go away and write something to clearly set-out the background science on the issue.

4. So, we eventually wrote up a paper. Critically, however, drafts of this paper were sent to all the people on the call, including those that have leaked out the information. I've attached here the draft of the document from Feb 7 that was circulated to everyone. As you can see, it is essentially the basis of the document and people on the call commented on it.

5. Very shortly after the call the pangolin data came out. This was critical. As I wrote in an email to everyone on the call on Feb 9th:

"Personally, with the pangolin virus possessing 6/6 key sites in the receptor binding domain, I am in favour of the natural evolution theory."

6. Hence, it is completely and utterly false to claim that we all thought it was a lab escape, we were corrected in our views by the coronavirus experts on the call, and then submitted a Nature paper without anyone else knowing about it. The truth is that we had a range of views among us, our paper included the pangolin data that was not available at the time of the call, and we circulated drafts of our document to everyone.

I also strongly reject the idea that we should not have raised nor discussed the possibility of lab escape: as scientists we have to present all the data and discuss it openly. That's all we did. To have not mentioned the possibility of lab escape would have been negligent. Is the person who emailed you seriously suggesting that we should have not discussed these issues? Wouldn't that be a cover-up? Indeed, the great irony is that 99.9% of the feedback I've had on the paper - including death threats - are people accusing me of dismissing the lab escape theory too quickly!! Can you imagine if we had not mentioned it all?

This is clearly just case of sour grapes based on some half-truths. It's telling that the person who emailed you is anonymous. I've absolutely no problem with people knowing that my views on this issue have evolved as more data have appeared. That's science. Indeed, I've told this to many people: the way see it is that we set-up an hypothesis and then tested it. As far I can tell we are only 'guilty' of following the proper scientific method.

Hope this helps.

Eddie

<Summary.Feb7.pdf>