From: Jeremy Farrar
Sent: Sun, 2 Feb 2020 17:47:36 +0000
To: Michael RYAN;Bernhard Schwartländer;Collins, Francis (NIH/OD) [E];Fauci, Anthony (NIH/NIAID) [E];Dr Tedros
Subject: 2019nC-V

Mike and Bernhard
Thank you for phoning – very helpful, copying in Francis and Tony as well as Tedros.

Fully agree with your summary.

- Best is if this is addressed under the umbrella of WHO
- Has to be framed as 'To understand the source and evolution of the 2019n-CoV"
    - Within that a number of issues to be addressed including – Environmental and animal sampling, human viral genome sequencing and analysis, and more
- Quickest is via a Working Group within an established structure rather than set something new up
- Multiple options for this within WHO
- Mike and Bernhard will work out best approach
- Appreciate the urgency and importance of this issue in midst of a very troubling epidemic
- Gathering interest evident in the science literature and in mainstream and social media to the question of the origin of this virus
- Critical that responsible, respected scientists and agencies get ahead of the science and the narrative of this and are not reacting to reports which could be very damaging.
- I am sure I speak for Francis and Tony when I say we are here and ready to play any constructive role in this
- Do think this is an urgent matter to address (among many we appreciate)
- Fully agree to your comments on the GCM.

Hope that is a reasonable summary

From: Jeremy Farrar
Sent: Sun, 2 Feb 2020 16:28:29 +0000
To: Fauci, Anthony (NIH/NIAID) [E];Collins, Francis (NIH/OD) [E]
Cc: Tabak, Lawrence (NIH/OD) [E]
Subject: Re: Teleconference

Tedros and Bernhard have apparently gone into conclave....they need to decide today in my view. If they do prevaricate, I would appreciate a call with you later tonight or tomorrow to think how we might take forward.

Meanwhile....

https://www.zerohedge.com/geopolitical/coronavirus-contains-hiv-insertions-stoking-fears-over-artificially-created-bioweapon

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From: "Fauci, Anthony (NIH/NIAID) [E]" (b) (6)
Date: Sunday, 2 February 2020 at 15:30
To: Jeremy Farrar (b) (6) Francis Collins (b) (6)
Cc: "Tabak, Lawrence (NIH/OD) [E]" (b) (6)
Subject: RE: Teleconference

Jeremy:
Sorry that I took so long to weigh in on your e-mails with Francis and me. I was on conference calls. I agree that we really cannot take Ron's suggestion about waiting. Like all of us, I do not know how this evolved, but given the concerns of so many people and the threat of further distortions on social media, it is essential that we move quickly. Hopefully, we can get WHO to convene.
Best regards,
Tony

From: Jeremy Farrar (b) (6)
Sent: Sunday, February 2, 2020 7:13 AM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Fauci, Anthony (NIH/NIAID) [E] (b) (6) Tabak, Lawrence (NIH/OD) [E] (b) (6)
Subject: Re: Teleconference

....Really appreciate us thinking through the options.....if Wellcome – I would need 110% support from you all.....it will not be easy!

From: Francis Collins (b) (6)
Date: Sunday, 2 February 2020 at 12:03
To: Jeremy Farrar (b) (6)
Cc: "Fauci, Anthony (NIH/NIAID) [E]" (b) (6), "Tabak, Lawrence (NIH/OD) [E]" (b) (6)
Subject: RE: Teleconference

Hi Jeremy,

Thanks for forwarding these additional reflections from Mike and Bob. I hadn't given much consideration to the idea of lab-based evolution by tissue-culture passage, but that is worth including on the list of options. Waiting a month sounds like a really bad idea. If that's the response from WHO, then another plan will be needed. Would Wellcome be willing to be the host then?

Francis

From: Jeremy Farrar (b) (6)
Sent: Sunday, February 2, 2020 6:53 AM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Fauci, Anthony (NIH/NIAID) [E] (b) (6) Tabak, Lawrence (NIH/OD) [E] (b) (6)
Subject: Re: Teleconference

Thank you

See thoughts overnight from others.

On a spectrum if 0 is nature and 100 is release – I am honestly at 50! My guess is that this will remain grey, unless there is access to the Wuhan lab – and I suspect that is unlikely!

But grey, from a respected group, under the umbrella of let us say WHO, would in itself help!

A question for you – if WHO say, well maybe, let us think, we might do it in a month. What would be our next step?

Jeremy

From Mike Farzan (discoverer of SARS receptor):

1. The RBD didn't look 'engineered' to him - as in, no human would have selected the individual mutations and cloned them into the RBD (I think we all agree)

2. Tissue culture passage can often lead to gain of basic sites - including furin cleavage sites (this is stuff they have seen with human coronaviruses)
3. He is bothered by the furin site and has a hard time explaining that as an event outside the lab (though, there are possible ways in nature, but highly unlikely)
4. Instead of directed engineering, changes in the RBD and acquisition of furin site would be highly compatible with the idea of continued passage of virus in tissue culture
5. Acquisition of furin site would likely destabilize the virus, but would make it disseminate to new tissues

So given above, a likely explanation could be something as simple as passaging SARS-like CoVs in tissue culture on human cell lines (under BSL-2) for an extended period time, accidentally creating a virus that would be primed for rapid transmission between humans via gain of furin site (from tissue culture) and adaptation to human ACE2 receptor via repeated passage.

All of this brings it back to a simple conversation about how this virus might have gained a furin site (but with a stretch and series of coincidences you can find a way to explain others – although very odd all together) and there are ways in which that could occur both in nature and in the lab. Nothing seems to specifically suggest whether this virus was most likely to be "adapted", "evolved", or maybe even "engineered". So I think it becomes a question of how do you put all this together, whether you believe in this series of coincidences, what you know of the lab in Wuhan, how much could be in nature - accidental release or natural event? I am 70:30 or 60:40.

From Bob

Before I left the office for the ball I aligned nCoV with the 96% bat CoV sequenced at WIV. Except for the RBD the S proteins are essentially identical at the amino acid level - well all but the perfect insertion of 12 nucleotides that adds the furin site. S2 is over its whole length essentially identical. I really can't think of a plausible natural scenario where you get from the bat virus or one very similar to it to nCoV where you insert exactly 4 amino acids 12 nucleotide that all have to be added at the exact same time to gain this function- that and you don't change any other amino acid in S2? I just can't figure out how this gets accomplished in nature. Do the alignment of the spikes at the amino acid level - it's stunning. Of course in the lab it would be easy to generate the perfect 12 base insert that you wanted.

Another scenario is that the progenitor of nCoV was a bat virus with the perfect furin cleavage site generated over evolutionary time. In this scenario RaTG13 the wiv virus was generated by a perfect deletion of 12 nucleotides while essentially not changing any other S2 amino acid. Even more implausible imo.

That is the big if.

You were doing gain of function research you would NOT use an existing clone of sars or mersv. These viruses are already human pathogens. What you would do is clone a bat virus they had not yet emerged. Maybe then pass it in human cells for a while to lock in the rbs, then you reclonec and put in the mutations you are interested - one of the first a polybasic cleavage site.

From: Francis Collins [redacted] (b) (6)
Date: Sunday, 2 February 2020 at 10:27
To: Jeremy Farrar [redacted] (b) (6)
Cc: "Fauci, Anthony (NIH/NIAID) [E]" [redacted] (b) (6) "Tabak, Lawrence (NIH/OD) [E]" [redacted] (b) (6)
Subject: RE: Teleconference

Jeremy,

Though the arguments from Ron Fouchier and Christian Drosten are presented with more forcefulness than necessary, I am coming around to the view that a natural origin is more likely. But I share your view that a swift convening of experts in a confidence-inspiring framework (WHO seems really the only option) is needed, or the voices of conspiracy will quickly dominate, doing great potential harm to science and international harmony.

I'm available any time today except 3:15 – 5:45 pm EST (on a plane) for a call to Tedros. Let me know if I can help get through his thicket of protectors.

Francis

From: Jeremy Farrar (b) (6)
Sent: Sunday, February 2, 2020 4:48 AM
To: Andrew Rambaut (b) (6)
Cc: R.A.M. Fouchier (b) (6); Fauci, Anthony (NIH/NIAID) [E] (b) (6)>; Patrick Vallance (b) (6) Drosten, Christian (b) (6)>; M.P.G. Koopmans (b) (6) Eddie Holmes (b) (6) Kristian G. Andersen (b) (6)>; Paul Schreier (b) (6); Ferguson, Mike (b) (6) Collins, Francis (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Josie Golding (b) (6)
Subject: Re: Teleconference

This is a very complex issue.

I will:

- Be in contact with WHO today. I contacted them last night and will speak with them today and set up a broader call with them as soon as possible.
- As discussed on the phone this discussion is not limited to those on this email, it is happening wider in the scientific, social and main stream media.
- I believe the best way forward is for a body like the WHO has to ask or commission a group of scientists from around the world to ask the neutral question "To understand the evolutionary origins of 2019-nCoV, important for this epidemic and for future risk assessment and understanding of animal/human coronaviruses".
- That should be done in an open way and quite quickly so that the world can see it is being done, it can respect the report when it is available and I think that will help with the growing interest of this question.

I suggest we don't get into a further scientific discussion here, but wait for that group to be established.

Jeremy

From: [redacted]
Date: Sunday, 2 February 2020 at 09:38
To: Jeremy Farrar [redacted]
Cc: [redacted] "Fauci, Anthony (NIH/NIAID) [E]" [redacted], Patrick Vallance [redacted], "Drosten, Christian" [redacted], Marion Koopmans [redacted] Edward Holmes [redacted], "Kristian G. Andersen" [redacted], Paul Schreier [redacted] Michael FMedSci [redacted] Francis Collins [redacted], [redacted] Josie Golding <J.Golding@wellcome.ac.uk>
Subject: Re: Teleconference

Dear Jeremey, Ron and all,

Thanks for inviting me on the call yesterday. I am also agnostic on this - I do not have any experience of laboratory virology and don't know what it is likely or not in that context. From a (natural) evolutionary point of view the only thing here that strikes me as unusual is the furin cleavage site. It strongly suggests to me that we are missing something important in the origin of this virus. My inclination would be that it is a missing host species in which this feature arose because it was selected for in that host. We can see this insertion has resulted in an extremely fit virus in humans - we can also deduce that it is not optimal for transmission in bat species.

The alternative is that it arose early in the human outbreak, perhaps during a longer period of hidden transmission and then the current epidemic is the result of this mutation but this seems less likely to me (it didn't happen in SARS for example).

Perhaps this needs to be discussed urgently, not only because of the lurid claims on Twitter but because if it is in a non-human host, pre-adapted, it may threaten control efforts through new zoonotic jumps (although perhaps we are beyond this point now).

The biggest hindrance at the moment (for this and more generally) is the lack of data and information. There have been no genome sequences from Wuhan for cases more recent than the beginning of January and reports, but no information, about virus from non-human animals in Wuhan. If the evolutionary origins of the epidemic were to be discussed, I think the only people with sufficient information or access to samples to address it would be the teams working in Wuhan.

Best,
Andrew

On 2 Feb 2020, at 08:40, Jeremy Farrar [redacted] wrote:

Thanks Ron

My view is completely neutral on this. The evolutionary origins on this virus are clearly important.

I do know these questions are being asked by politicians, starting in the scientific literature, certainly on social and main stream media. If, and I stress if, this does spread further, pressure and tensions rise, j fear these questions will get louder and more polarised and people will start to look who to blame. We live in a polarised world where there is a quick reaction to try and deflect issues by blaming someone somewhere. That may only increase tension and reduce cooperation.

A respected body convening a group now to consider the evolutionary origins of this, with an open mind, neutral, and in a transparent way is I think an approach that may prevent wild claims being made.

Such a group needs the best minds, from around the world, not just US-Europe-Australia. It needs to be transparent and respected.

I am not sure your thoughts on "short time frame". I am concerned if this is not done quite quickly it will be reacting to what may be lurid claims.

Thoughts on that very welcome.

On 2 Feb 2020, at 08:30, R.A.M. Fouchier [redacted] (b) (6) wrote:

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" <r.fouchier@erasmusmc.nl>, Edward Holmes [redacted] Andrew Rambaut [redacted], "Kristian G. Andersen" [redacted], Paul Schreier [redacted] "Ferguson, Mike" [redacted] Francis Collins [redacted], [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] Edward Holmes [redacted] Kristian G. Andersen" [redacted], Paul Schreier [redacted] <rfgarry@tulane.edu>, 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