February 6th, 2020

Robert Garry 19:09
You can also synthesize bits of the genes de novo with perfect precision then add them back in without a trace.

And, excellent responses Andrew! You're doing much better than I would.

Andrew Rambaut 19:22
True (but you are still going to get the sequence from somewhere - unless it is very short).

Robert Garry 19:24
I'm thinking mostly about the PRRA to generate the furin site. Relatively easy to drop 12 bases in.

The proline is the hang-up - why add that? Makes me think the cell culture passage scenario is possible/probably assuming this has in fact been observed before by Farzan and Fouchier.

Andrew Rambaut 19:34
Yes. I am quite convinced it has been put there by evolution (whether natural selection or artificial).

I haven't got the paper yet. Killing me.

> **Kristian Andersen**
> Oh boy... what's the name??
>
> And for Don - I gotta say, he pretty much nailed it. Let's not tell him
>
> Posted in paper-2020-nature_medicine-proximal_origin | Feb 6th, 2020

Apparently the manuscript is still being finalised. It will be preprinted and sent to the WHO at the same time.

> **Eddie Holmes**
> Can't believe that the ICTV did not preprint their paper.
> Posted in paper-2020-nature_medicine-proximal_origin | Feb 6th, 2020

Robert Garry 19:44
I've known Don for 30 years. First time my work made the front page of NYTimes. I saw him at Trop Med meeting a few months ago. Very smart man - don't quite know wher he is going to go with this - curious as to the high in the USG is.

his source. It would be prudent to continue to pre-think responses.

I do like Wuhan snake flu virus for the name BTW.

Too bad they didn't test turtle codon usage.

Then it could be Wuhan Turtle Flu virus - WTFV

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Eddie Holmes 19:49
Nailed it.

Andrew - thanks! Important typo.

Kristian Andersen 20:28
My drafted reply to Don. I'll chew on it a bit more, but lemme know if you have any suggestions.

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Dear Don,

It's good to hear from you, and yes I of course remember our great conversations about Zika and Ebola. It's an interesting question you're asking, but I'm afraid I might not be the best
person to answer, as we are mostly looking at what's going on during the epidemic (not before). Mostly, unless the virus was a really obvious recombinant virus, I'm not quite sure what a
virus from culture vs an intermediate host would look like - I think they'd probably be indistinguishable.

A couple of things I can say based on the data so far though:

1. A lot of the conspiracy theories are talking about this being either a lab strain that had previously been produced (Nature Medicine paper) or some new recombinant. These rumours are
demostratively false - we would have been able to easily pick that up if that were the case, however it is not.

2. The virus is highly related to bat SARS-like coronaviruses so we can with strong evidence say that the reservoir host is also a bat. Likely there was an amplifying host involved before the
virus got into humans, but we don't yet know what it might be. I'm sure there's a lot of investigations going on addressing that exact question.

3. As you mention, we can clearly see from the sequence data produced so far that the introduction into the human population was a single event. This could either be from a single infected
host to a single human, or a small cluster of hosts into a small cluster of people. The virus has then been spreading human to human ever since.

4. While the RaTG13 bat sequence is interesting, it still too divergent from nCoV to have anything to do with the current epidemic - the genetic distance is simply too great.

5. From a genomics perspective, the theories Richard Ebright lay out I expect would look the same - there would be no way to distingush between them.

I hope some of these answers were helpful.

Best,
Kristian
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Robert Garry 20:31
PItch pergect responses.As I'm sure you'll know Ebright is the guy who thinks Yoshi and the of GOF researc should be locked up with the key thrown away. A little knowledge being the most danger ous thing. I suspect Ebright [i'm working with a bit of historical experience] is going to flat-out say this is for sure a lab escape - not unlike the underbelly article. Reporters aside I do not think any of this is going away.

Kristian Andersen 20:37
Agreed - this'll amplify over the next couple of weeks. I just wish there was a way to conclusively say one or the other, but without that intermediate host or very earlier cases, there's just no telling IMO. Which all means it's back to opinions - and honestly, for this type of question I don't think opinions are helpful - unless they have some damn strong science behind them.

Robert Garry 20:40
"So, he argued, it could have entered humans from the cave in Yunnan or another cave, or a wet market. Or, alternatively, it could have escaped into a human from the lab"

Three hypotheses here.

1. not likely a bat virus right into a human - could have happen long ago but not so likely.

2. Wet market -ok maybe an intermediate host. I think pangolin viruses sequences still too far afield but could be part of an animal circulation that generated the virus.

3. lab passage I'm open to and can't discount - that just because I don't know the data and few others do. Either furin sites have been generated or they haven't. If they have I'm suspicious of lab escape, but not conclusive evidence. If furin sites have not been generated on cell culture passive, then were looking at either a long circulation or a very intense circulation in either humans or animals.