

## Twitter Thread by [Dr. Angela Rasmussen](#)

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Hard agree. And if this is useful, let me share something that often gets omitted (not by [@kakape](#)).

**Variants always emerge, & are not good or bad, but expected. The challenge is figuring out which variants are bad, and that can't be done with sequence alone.**

Feels like the next thing we're going to need is a ranking system for how concerning "variants of concern" actually are.

A lot of constellations of mutations are concerning, but people are lumping together variants with vastly different levels of evidence that we need to worry.

— Kai Kupferschmidt ([@kakape](#)) [January 15, 2021](#)

You can't just look at a sequence and say, "Aha! A mutation in spike. This must be more transmissible or can evade antibody neutralization." Sure, we can use computational models to try and predict the functional consequence of a given mutation, but models are often wrong.

The virus acquires mutations randomly every time it replicates. Many mutations don't change the virus at all. Others may change it in a way that have no consequences for human transmission or disease. But you can't tell just looking at sequence alone.

In order to determine the functional impact of a mutation, you need to actually do experiments. You can look at some effects in cell culture, but to address questions relating to transmission or disease, you have to use animal models.

The reason people were concerned initially about B.1.1.7 is because of epidemiological evidence showing that it rapidly became dominant in one area. More rapidly that could be explained unless it had some kind of advantage that allowed it to outcompete other circulating variants.

Genomic surveillance/sequencing allowed UK scientists to detect the increased prevalence over a very short time scale, and you need sequencing to identify the variant, but that doesn't tell us much about HOW it outcompeted other circulating variants.

B.1.1.7 contains several mutations that have arisen independently in other lineages and were already on the radar. For example, spike N501Y is in the receptor binding domain and was already being studied because of that. We know it helps increase binding affinity to the receptor ACE2.

But there are other mutations in the variant and we don't know if they are functionally important, or have an additive or synergistic effect with N501Y. And we still don't know the mechanism by which B.1.1.7 is more transmissible.

Could be:

- More viral shedding (infected people produce more virus)
- Increased interval of viral shedding (people are contagious for longer)
- Increased viral fitness (virus can replicate better in infected people)
- Better receptor binding (virus can infect cells more easily)

Could also be:

- Increased environmental stability (virus can remain infectious in the environment for longer)
- Increased ability to evade host defenses (virus can escape innate cellular defenses against infection and thus replicate better)

Could be one, some, or all of the above

What these mutations can't do:

- Render masks or other physical barriers useless
- Make the virus transmissible by a totally different route of infection
- Turn the virus into the infectious equivalent of a smart cruise missile
- Defy the laws of conservation of mass and energy

We won't know why the variants are more transmissible until we do the experiments, & this takes time. This is why in addition to increasing genomic surveillance capacity, we also need to invest in research that allows us to determine the functional consequences of mutation.

What we should NOT do is start reporting breathlessly that things like masks might not work as well, that staying home is futile, or that vaccines will be rendered useless, etc. Most careful science journalists don't report that way, but many others do, including some scientists.

What we SHOULD do is use caution and take every new variant of concern as a reason to be more vigilant about precautions meant to reduce transmission overall. Other variants will emerge. Most of them will not be more worrisome than any other variant.

But variants like B.1.1.7, that are associated with epidemiologic evidence supporting a cause for concern, need rigorous study in the lab before we start speculating about the mechanism for why they are concerning.

We also need more functional virology in general to understand important regions of the genome, which could make it easier to infer function from sequence alone in the future. This is why fundamental, basic research is critically important for preparedness and response.

And while we don't know the WHY of concern, we do know the WHAT we should do in the meantime. Practice additive risk reduction:

- Avoid gatherings/crowds
- Avoid enclosed spaces/shared air
- Masks
- Distancing
- Ventilation if possible
- Wash hands
- Disinfect high-touch surfaces