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Public health surveillance of infectious diseases: beyond point mutations

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The COVID-19 pandemic has once again brought the concept of viral mutations into the spotlight. The latest impetus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) N501Y, associated with an increase in case numbers in parts of the UK[1] and bringing concerning images of packed platforms at London train stations. This comes on the heels of the Y453F variant, which gained tremendous media attention as it was proposed to evade the long-awaited vaccine; accompanied in this case by disturbing images of mink being hurriedly culled and purportedly rising from their graves. Likewise, other point mutations have been in the limelight in recent months, notably D614G. Grubaugh and colleagues addressed the effect of this mutation,[2] elegantly stating that D614G "is the pandemic"—ie, this mutation did not have an effect on a large diverse human population and did not radically change the course of the pandemic—it was essentially absorbed by it. In other words, D614G, or any other SARS-CoV-2 point mutant, has not to date been transformative, despite initial claims.

Viral genomic surveillance has certainly helped illuminate the spread of outbreaks, notably for Ebola in 2014.[3] Tracking mutations gave temporal context to the events that led to the outbreak and also confirmed that spread was human–human and not from the natural reservoir, providing crucial information for disease management. In contrast, a retrospective study[4] revealed that the 2019 resurgence of dengue after Zika declined was due to low level endemic transmission of multiple lineages. Despite initial claims, Brito and colleagues argue that increased host susceptibility due to waning cross-protection from Zika was to blame, rather than viral mutations (or even environmental change).

The question is, can a point mutation be transformative, as we are often led to believe? The answer is, occasionally yes—and this must always be kept in mind—but this is rare. One prominent example is chikungunya, for which a single substitution (E1-A226V) was attributed to a change in the mosquito vector species, with a dramatic effect on global distribution.[5] However, mechanisms of viral emergence are typically not this simple and usually involve multiple factors, including co-evolution of pathogens and receptors over long time-scales.[6]

The recently emerged mink-associated SARS-CoV-2 variants have shown that there was in reality a group of human infections with a concerning grouping of mutations (so-called cluster 5). The variant that is more widespread (Y453F) certainly has some concerning in-vitro data related to antibody escape, but no evidence of effects on morbidity or mortality.[7] Yes, the mink outbreaks are concerning for both human and animal health, but mainly because of the sheer numbers of animals concentrated together.

We need to go "beyond point mutations" and look at variation across genomes, as has been done with foodborne bacterial surveillance and outbreak response for more than 5 years.[8] What are some lessons we can learn from bacterial genomes, which are around 100 times bigger than viruses and carry dispensable sets of genes? First, sequencing data needs to be interpreted in the context of relevant epidemiological data. Second, mutations occur not just in genes encoding attachment proteins, but across the genome. Looking at the totality of variations between strains not only provides robust support for outbreak response but also points us in the direction of where to look for outbreaks before they are recognised. This happens more quickly with bacteria owing to the greater resolving power of bigger and more complex genomes, but for sustained viral outbreaks we can still gain important information, either in real time or in retrospect.

How do we do this in a useful way? Integrating genomic sequence data with clinical and laboratory studies is crucial, as there are often compensatory mutations that balance each other out.[9] We should always remember that mutations (whether point or cluster) are part of the natural process of virus evolution, and not an inherently problematic attribute for disease outcome. N501Y—more accurately referred to as VOC-202012/01 or lineage B.1.1.7—deserves vigilance and further study, as in reality it comprises 17 changes spanning the virus genome, some of which have arisen independently.[1]

Virus evolution will undoubtably continue to play a central role in the COVID-19 pandemic. It is now three decades since the term emerging virus was coined; we have certainly learned a lot in this time, and our technological resources have advanced dramatically. However, as commented on by Holland in the now-classic text by Stephen Morse,[10] the direction of viral evolution is probabilistic and difficult to predict, and the over-reliance on deterministic outcomes, especially concerning point mutations, is uncertain and should not be prejudicated.

We declare no competing interests.

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