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Covid-19: variants and vaccination

We have the tools to track variants and adapt vaccines as required

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SARS-CoV-2 has been in the human population for more than a year now, causing severe disease in some and resulting in a pandemic that continues to put severe strain on economies and healthcare infrastructures worldwide.[1] In the UK, the first three vaccines have emergency use authorisation, and a national rollout is in progress. Many other countries are also instigating large scale vaccination programmes. These vaccines express the spike glycoprotein, the major target of neutralising antibodies in a natural infection. The vaccines protect against disease,[2-4] and preliminary data suggest that transmission is also decreased after vaccination.[5]

Current vaccines are based on a version of the spike glycoprotein from the start of the outbreak, however, and central questions remain around the ability of an old version of the spike glycoprotein to generate protective antibodies against newer emerging variants. The linked paper by Challen and colleagues (doi:10.1136/bmj.n579) suggesting that variant of concern B.1.1.7 might be associated with increased mortality adds urgency to these questions.[6]

SARS-CoV-2 infections can be established by multiple virus genotypes within the same person,[7] and together with new rounds of virus replication, provide the raw material for natural selection. The extent of genetic diversity in a viral population is critical to natural selection for growth advantages such as better binding to the receptor, faster replication, and more effective suppression or avoidance of the host immune response.

A popular misconception, currently receding, is that SARS-CoV-2 mutates more slowly than other viruses. Genome sequencing of SARS-CoV-2 shows a nucleotide substitution rate of roughly 1×10^{-3} substitutions per year[8]—similar to that of Ebola virus (1.42×10^{-3}).[9] SARS-CoV-2 (and coronaviruses in general) throw up variants all the time, and they do this through single point mutations, recombination, insertions, and deletions.[10] These changes can lead to altered pathogenesis, and tracking them is vital.

The value of real time viral genomic sequencing was a major lesson from the Ebola virus disease outbreak in west Africa.[11 12] Sequencing of SARS-CoV-2 occurs worldwide, but particularly in the UK, through the efforts of the COVID-19 Genomics UK (COG-UK) consortium. By conducting a continuous nationwide surveillance programme, almost in real time, the likely origin and spread of SARS-CoV-2 variants can be identified.

Considerable attention has been paid to changes in the spike glycoprotein and how these influence transmission dynamics and risk of immune escape. All the current variants of concern (lineages B.1.351, B.1.1.7, and P1) have multiple differences from the original Wuhan variant that affect the function of the spike glycoprotein and other SARS-CoV-2 proteins. Mutations in the spike can alter interaction with receptor hACE2.[13]

For example, compared with the Wuhan reference sequence, all current variants of concern have the N501Y substitution, and all these lineages can carry the E484K substitution in the spike glycoprotein. Additionally, both B.1.351 (first identified in South Africa) and P1 lineages (first identified in Brazil) have a K417T substitution, whereas B.1.1.7 (first identified in Kent, UK) and P1 share the same 11288:9 deletion (source https://cov-lineages.org/). That these mutations seem to be associated with greater transmission suggests that spike variants should be monitored carefully as part of routine genomic surveillance, and also shows the need for studies to characterise the threat posed by potential mutations of concern.

Variants of concern might be associated with changes in both morbidity and mortality. Worse outcomes might be due to higher viral loads in infected individuals, altered transmission dynamics, or suppression of the host immune response. Some variants with deletions in viral genes that suppress the innate response are associated with milder infections,[14] but Challen and colleagues report evidence that a B.1.1.7 variant might be associated with an increase in mortality.[6] This is consistent with animal studies showing increased weight loss in Syrian hamsters infected with a B.1.1.7 lineage, compared with controls infected with a previously circulating strain.[15]

Protecting the future

Some countries will be slower than others to vaccinate their populations. SARS-CoV-2 and its variants will be around for some time, and concerns around the protection afforded by current vaccines will continue. The risk of immune escape is hard to predict long term, but we do know from experience with avian coronavirus that vaccines against one variant will protect against similar variants but not always against highly divergent variants.

Currently available vaccines will likely offer protection against prevailing variants of SARS-CoV-2. However, multivalent vaccines might be more robust in the longer term. Multivalent vaccines would probably include the viral nucleoprotein, which has less selection pressure than the spike glycoprotein, due to critical functions in binding the viral genome.

Vaccines against SARS-CoV-2 will be needed for many years, and those vaccines will change as variants become too divergent, similar to vaccines against

influenza. National and global surveillance, together with well controlled assays to rapidly identify and characterise variants of concern, will allow us to move from current reactive approach to something much more proactive.

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