STRAINS AND MUTATIONS:

THE EMERGING THREAT

Is the evolution of **SARS-CoV-2** and the **emerging variants** going to effect attempts to **inoculate against the virus?** We look at the issues.

The deteriorating COVID-19 situation in the UK since November has been driven by one key factor – the B117 variation, which has allowed the virus to spread more easily.

Also known as Variant of Concern 202012/01, B117 was first spotted in September in Kent. Though known as the "UK variant", its point of origin is probably elsewhere, possibly Spain back in the summer. It was detected in the UK simply because so much COVID genome sequencing is being done here.

B117 was identified by COVID-19 Genomics UK (COG-UK), a partnership of public health agencies, the Wellcome Sanger Institute and numerous universities, which has randomly sequenced 140,000 virus genomes since April 2020.

While the press greeted news of B117 with alarm, scientists were more sanguine about the mutations – it's just what viruses do. "The original SARS-CoV-2 virus came about because of a mutation in the bat virus, so further mutations were likely to happen," says Dr Sarah Pitt, from the School of Pharmacy and Biomolecular Science at the University of Brighton.

Dr Anthony Fooks, Head of Virology at the Animal and Plant Health Agency, adds: "Mutations in SARS-CoV-2 were anticipated. It is not possible to prevent the virus from evolving through genetic divergence and adapting to new animal reservoirs."

Once the virus forces its way inside human cells, it quickly begins to replicate,

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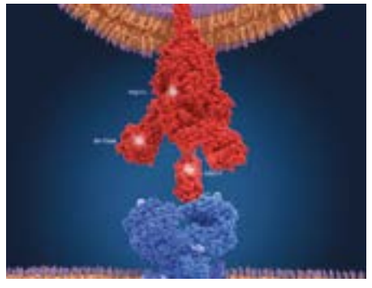
grow and divide, and that's when the mutations start. "It's happening so fast that mistakes begin to creep in," says Sarah Pitt. "The SARS-CoV-2 genetic material is RNA, so unlike DNA, which has mechanisms for noticing mistakes and correcting them because it's important, the errors are not spotted and put right. The virus is dividing so quickly these mutations will appear frequently, though more often than not they make no difference either way to the integrity of the virus."

The spike protein

COG-UK found that the genome of the B117 variant had 17 mutations. Though most were indeed insignificant, one of them caught the attention of the analysts – named N501Y, this mutation had altered the spike protein that the virus uses to bind to the ACE2 receptor in human cells. The spike protein is the key offensive weapon in the SARS-CoV-2 armoury, so any changes here could be significant.

"Single-point mutations at the nucleotide level of the viral genome often result in changes to the amino-acid composition of the viral proteins, including the virus surface spike protein, leading to new viral variants that are genetically 'fitter'," says Anthony Fooks.

It was also found that the B117 variant showed up in the routine COVID-19 test in a very distinctive way: while picking up the other usual gene indicators, the one for the spike protein is missing. So by mid-December it was clear that B117 was responsible for around 80% of all COVID-19 cases in London and the surrounding areas, and with it the implication that the mutation had indeed caused the virus to become more infectious. "There is sort of a competition between the different strains," says Sarah Pitt, "and if one of them turns out to be more robust, it will win and become the dominant strain in a particular area. Then people travel to that area and bring it back as a sort of souvenir of their holiday."



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Anthony Fooks says that high mutation rates that create a broad "variant spectrum" of descendent viruses is an evolutionary trait that potentially increases the ability of the virus to be more transmissible. "This improves the chances of viral infectivity in the host with a lower dose of virus being required to establish infection. It is also likely that any viral variant may have an increased viral load in an infected person, escalating the amount of virus shedding, thereby improving the ability of the virus to establish and infect a naïve host."

The implications

According to a preliminary report issued by the Wellcome Sanger Institute and the European Bioinformatics Institute, the rise of B117 "indicates a strong transmissibility advantage over previous circulating lineages". Their analysis showed "a consistently higher R value for B117 by a factor of 1.47 at any given time".

While there is nothing to suggest this variant is any more damaging to the health of any given individual, its rapid spread all around the UK inevitably means more people getting sick, which is why the numbers of infections soared during January, causing more deaths and putting enormous pressure on the NHS.

The other big question that B117 poses is what its effect will be on the vaccines and inoculation programme that has begun in haste and with such hopes? The vaccine scientists knew enough about the potential problem to factor it into their plans, despite the enormous challenges of developing vaccines so quickly.

Meredith Wadman, author of the book *The Vaccine Race*, says that earlier work to understand and develop vaccines against COVID-19's more deadly but less contagious cousins, SARS and MERS, meant that developers weren't starting from scratch.

"We're lucky that SARS-CoV-2 resembles these two viruses in, for instance, being studded with a spike protein that the viruses use to invade host cells. That gave vaccine developers a starting target, and indeed most COVID-19 vaccines attack the spike protein. What's more, companies have for several years been developing the vaccine technologies that are being deployed against SARS-COV-2, such as mRNA vaccines and adenovirus-vectored vaccines, to try to develop vaccines against viral diseases like Zika, influenza and Ebola. So while it may look like these vaccines were developed in 10 months, they actually stand on the shoulders of work that preceded them over the last two decades."

Sarah Pitt says the developers will have looked at parts of the genetic material that are more prone to change. "They would have concentrated on the spike protein in the design of the vaccine. To overcome the vaccine, the virus is going to have to do a lot more mutating. I think the feeling is that there wouldn't be enough changes in one go to get round the vaccine."

The vaccines

Research from the US suggests that B117 has not mutated sufficiently to challenge the effectiveness of the vaccines, concluding that in the overwhelming majority of cases B117 wouldn't be able to evade the vaccine-generated antibodies. But the South African variant, known as B1351, is looking like a greater cause for concern. The evidence so far suggests that it is more infectious than B117 and that the E484K mutation may even give it some resistance against the vaccines. PHE is closely monitoring the situation.

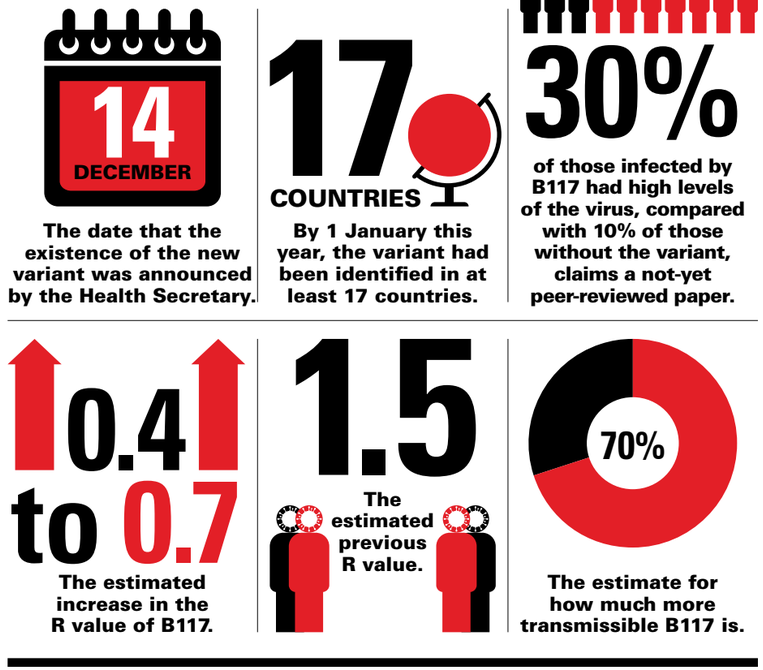
"What I am hearing from scientists is that if vaccine-resistant strains of the virus evolve, this is going to be a gradual evolution that can be addressed as we go, with vaccines reengineered accordingly," says Meredith Wadman. "Bear in mind, too, that the vaccines prompt production of many antibodies against many viral targets, so it will likely take the accumulation of several mutations in a single strain to have a significant impact blunting a vaccine's effectiveness."

Sarah Pitt is also confident that the vaccines are going to work, in the short term, at least. "These are good vaccines and should help to bring the virus under control, but even if the virus changes to the extent that they become less effective, there are other vaccines coming through, such as the one being developed by Valneva."

This vaccine, based on more traditional techniques, is currently undergoing clinical trials and should appear later in 2021. "These sorts of vaccines help the body respond to all parts of the virus and not just the spike protein, so they are potentially a bit more of a well-rounded response. This is also the basis of the seasonal flu vaccine."

While the impact of the variants on the vaccines won't become clear for some time yet, what is certain is that the virus will continue to mutate. "Whether these mutations will be functionally significant, for instance making the virus more transmissible, as strain B117 clearly is, or deadlier when it does infect people – or

THE B117 STRAIN IN NUMBERS



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Vaccines are just one of the tools. We will still need to keep testing

the opposite – remains to be seen," says Meredith Wadman. "What reassures me to some degree is that countless scientists are surveying these mutations in real time, probing their impact and flagging those that could be problematic."

Continual mutation

Only ongoing studies will eventually confirm whether the mutations in the UK and South African variants have resulted in an enhanced evolutionary fitness, says Anthony Fooks. "All viruses are continually mutating, and this virus is no different. Viral genome mutations are the building blocks of evolution, which generate diversity at the genomic level upon which natural selection can act."

However, once the immunisation programmes are well under way, they could begin to dictate the trajectory of the virus and the way it reacts to the vaccines. "With the introduction of vaccines, it will be more difficult for the virus to transmit, as the number of susceptible people in the population is dramatically reduced," says Anthony Fooks. "This will force the virus to 'escape' from the herd immunity through mutating its genome. This occurs for any virus for which vaccines are available. As SARS-CoV-2 does not have a segmented genome, nor does there appear to be multiple animal reservoirs, it is unlikely that new vaccines will be required annually."

There is also a potential end point, where the virus and human population begin to live in something resembling harmony. "SARS-CoV-2 will eventually adapt to its 'obligatory' host species environment, resulting in the reduction of the viral mutation rate to minimal levels," says Fooks.

SEQUENCING CAPACITY

WHO is closely monitoring emerging SARS-CoV-2 variants and their potential impact on diagnostics, treatments and vaccines. It has also noted the vital role genomic sequencing has played in identifying and responding to variants, and has made it a research priority to increasing sequencing capacity across the world. "Our collective goal is to get ahead of the game and have a global mechanism to quickly identify and study variants of concern and understand their implications for disease control efforts," says WHO's Dr Ana Maria Henao Restrepo.

"Although the virus has established itself in the human population and is likely to remain, it can be predicted that the virus might adapt to a low level of morbidity and mortality and high transmissibility, no different to the seasonal common cold, which circulates globally."

That scenario may be some way off, but, in a fine touch of irony, reported cases of seasonal cold and influenza are well below what they would normally be. That's likely a by-product of ongoing social distancing, mask-wearing and hand-washing, but serves to show just how effective these measures can be at resisting the spread of viruses. Along with the vaccines, they could become features of everyday life for the foreseeable future.

The next year

For now, though, 2021 has started in as uncertain a fashion as 2020. But taking vaccines, mutations, viral variations and other variables into account, what might the situation look like in 12 months time?

"I hope we'll have only smaller outbreaks of COVID-19 that can be brought under control through testing and contact tracing," says Sarah Pitt. "At the moment, there are so many cases that it's difficult to keep a track of everybody, which is why we need the vaccine. But vaccines are just one of the tools. We will still need to keep testing, we'll need to keep quarantining people, and we will need to keep social distancing and wearing masks for some time. I think I was hoping that we might be relaxing by Easter, but I'm less confident about that now."

Meredith Wadman's hope is that substantial proportions of people in many countries will have been vaccinated. "We are focused on the constrained supply. We shouldn't lose sight of several promising vaccines that are not so far from delivering results in pivotal phase 3 trials that, in the best case, will lead to their speedy authorisations by regulators. If even a few more companies can gain marketing authorisations and begin distributing millions of doses of vaccines, the current picture will grow less bleak. That said, I fear that for less-developed nations the wait for adequate supplies of vaccine may stretch well past 2021."

The development and deployment of the vaccines takes centre stage for Anthony Fooks: "Intrinsically, vaccine development has been the single most important technological advancement in the 20th century, and likely to also be in the 21st century. The efficacy and rapid licensing of COVID-19 vaccines will undoubtedly prove to be another major achievement of humankind." BMS