How Vaccines Drive Covid Variants

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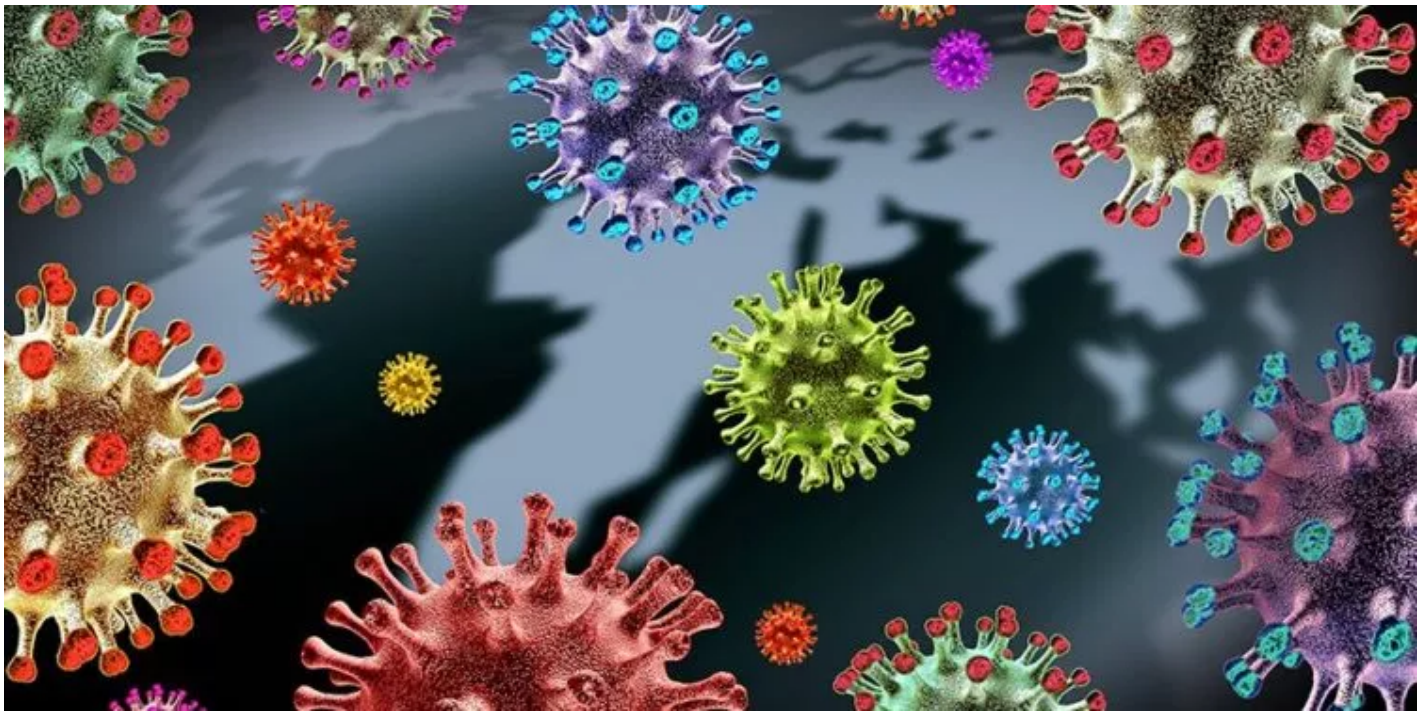

Variants have been one of the hallmarks of this pandemic, with ever more infectious forms of the virus apparently mutating themselves into existence at regular intervals. However. it is easy to forget that prior to 2021 variants were a rarity and the only sign of our variant ridden future was the emergence of the scarily named Kent variant (later renamed Alpha) late in 2020. The UKHSA Vaccine Surveillance Report started mentioning variants in May of 2021, but only in passing. However, as 2021 wore on new variants started appearing more frequently, and in recent reports there are 10 times more references to 'variants' compared to their debut. (To be fair, there used to be an entirely different vaccine report devoted to 'variants of concern', the Technical Briefings.)

But 'variants' weren't simply a natural process of viral evolution – not when there were people to blame. By summer 2022 there had been multiple articles published explaining that it was the unvaccinated that created

these variants, adding to the cries for (mandated) universal vaccination. I believe that the idea that it was the unvaccinated that were causing the problem arose due to a misunderstanding of the role of the mechanisms that drive viral evolution. While it is true that for many vaccines the main source of vaccine escape variants is the unvaccinated, this is only true for sterilising vaccines (which stop any viral load on infection), and isn't the case for non-sterilising vaccines such as the COVID-19 ones. To explain this effect further we need to delve into the evolutionary process.

Evolution is a natural process that explains how organisms become better at surviving within a given environment. It occurs when certain differences between otherwise similar organisms are favoured for some reason, resulting in that particular difference becoming more prevalent in the organism's population. Evolution requires two things to occur – a population of the organism with heritable diversity and selective pressure. The 'population' part refers to how many of the organisms in question exist; selective pressure refers to the 'strength' of the drive of the evolutionary process, which might be described as 'survival of the fittest', i.e., those specific organisms that happen to be better at surviving and reproducing will be more likely to pass on their genes to future generations, thus on average making the future species better at surviving and reproducing.

At first glance the 'population' part appears obvious as clearly there can't be evolution without anything to evolve. However, it is a little more complex than this. When it comes to cuddly mammals it is generally fairly easy to see what 'population' means (you can count them). However, when it comes to viruses there are two factors: the viral load in any given infected host and the incidence of infection across a population. Evolution 'cares' about both factors, and it is important to consider these two 'populations' in the discussion that follows.

Most vaccines given to humans are fairly sterilising, that is, they stop any meaningful quantity of the virus developing in a vaccinated individual. Thus it is clear that by vaccinating a very high proportion of the population with a sterilising vaccine the evolution of that particular virus can be slowed to a crawl. No one vaccinated will have any meaningful viral load, and there will be only few in the population where evolution could occur (the unvaccinated). Note that there is still selective pressure for the virus to evolve to escape the vaccine-derived immunity – as soon as a viral mutation emerges that offers the virus a better chance of thriving within a vaccinated individual or infecting other vaccinated individuals it will soon take over as the predominant viral variant even in a largely vaccinated population. Indeed, the very fact that large numbers of people are vaccinated will become the predominant selective pressure for that virus – if the main thing 'holding back' the virus from thriving is vaccine derived immunity then that's what evolution will 'try to overcome'. However, with sterilising vaccines the only people with meaningful viral loads are the unvaccinated, and thus evolution towards vaccine escape largely occurs within the unvaccinated population. Moreover, because there is no selective pressure within unvaccinated individuals for vaccine escape (there is no vaccine-derived immunity in these individuals), the evolution towards vaccine escape will be muted.

However, the Covid vaccines aren't sterilising: vaccinated people can still get infected and will have high viral loads when this occurs. We didn't know this, way back in December 2020 when vaccination started. Arguably this should have been identified before the vaccines were approved, but it was considered a public emergency and normal vaccine development processes weren't followed. However, it soon became clear that this was going to be a problem – I first became aware of the potential for trouble in March 2021 with the publication of a paper out of Israel. This team found far higher viral loads than expected in the vaccinated-and-infected; certainly

enough viral load to allow viral evolution towards vaccine escape. Unfortunately, our authorities ignored this and other emerging evidence and continued to jab their populations indiscriminately.

At the point that it was clear the vaccines weren't sterilising, the theory behind what might be the 'correct' level of vaccination changes completely. With non-sterilising vaccines, 'herd immunity' becomes impossible and this goal should have been dropped immediately. But worse than that, the fact that the vaccines weren't sterilising meant there was a large selective pressure for evolution and a sufficiently high viral 'population' in vaccinated individuals, and so this also meant that the virus could more effectively evolve vaccine escape.

Also note that viral evolution to 'get around' vaccine protection in non-sterilising vaccines isn't as simple as the vaccines ceasing to offer protection. There are instances of so-called 'leaky vaccines' that have evolved increased pathogenicity (severity) as a result of their evolutionary journey to escape vaccine protection. Perhaps the most famous example of a vaccine driving increased pathogen virulence is the vaccine for Marek's disease. Marek's disease was an inconvenience for the poultry industry when the vaccine for it was introduced into chicken farms in the early 1970s. From that point it has evolved to become significantly more pathogenic, requiring widespread vaccination to protect against the disease. The virus responsible for Marek's disease continues to evolve vaccine escape and the risk of future problems is very real. Fortunately, there's little evidence that this has occurred with Covid; hopefully this will remain the case.

Another relevant aspect of Covid evolution is the matter of how mutations appear to target the spike protein. Mutations in the viral RNA occur at random during each viral replication, and there is little preference in the RNA of the virus where mutations might occur. However, the proteins that they encode aren't equally able to remain viable after a mutation in the RNA that encodes them. This means that while a mutation in the part of the viral RNA that encodes a given protein is as likely as anywhere else, the virus won't survive a mutation in an unfavoured location and thus that particular mutation won't even have a chance to exist. On the other hand, the Covid spike protein happens to be very tolerant of mutations in the RNA that encodes it, remaining viable even with relatively large numbers of mutations. As mutations in the spike protein change its shape and make-up slightly, this makes it look slightly different to antibodies that have been created by the body's immune system to neutralise it, resulting in a reduced ability of the body's immune system to deal with an infection. It is likely that through vaccination we exposed the immune systems of many millions of people worldwide to an identical spike protein, and the virus has responded by evolving rapidly through the introduction of changes in its spike protein which has allowed it to thrive in this new highly-vaccinated world.

There's also a complication of viral evolution that you don't find in evolution in most plants and animals, namely that the selective pressure that drives evolution in viruses occurs both *between* infected individuals and *within* infected individuals, and this is particularly relevant for vaccine escape. With normal vaccines there is no meaningful viral presence in vaccinated individuals, thus mutations occur within unvaccinated individuals. Sometimes these mutations happen to lead to partial escape of vaccine protection, but before evolution can select for this mutation it has to leave the unvaccinated individual and try to infect a vaccinated person – it is only then that the mutation is 'tested'. However, if the vaccine escape mutation offers no selective advantage in an unvaccinated individual it won't thrive before it gets a chance to try its higher infectivity in other, vaccinated individuals. The fact that the virus 'doesn't know' if a given mutation that occurs in an unvaccinated

individual actually achieves vaccine escape until the virus is transmitted to a vaccinated individual slows down the effective rate of viral evolution towards vaccine escape significantly.

On the plus side, as the virus has had such a very strong selective pressure to overcome the immunity offered by antibodies to the original (Wuhan) spike protein, this could have made it less likely to mutate to overcome the diverse range of antibodies (and other immune responses) generated after natural infection (i.e., after exposure to all of the proteins in the whole Covid virus).

There's an additional nuance to this effect. The interplay between mutations and viral fitness is complex, and it is possible that a mutation might result in a virus that achieves some escape of vaccine-derived immunity (positive for the virus) but which also has a slightly inferior ability to infect upper respiratory tract cells (negative for the virus) compared with the variant then prevalent in the population. In a community with low vaccination levels the fact that the mutation resulted in an inferior infectivity would probably result in that mutation dying out, because the vaccine escape mutation wouldn't offer much benefit if few individuals were vaccinated. However, if a community has high vaccination levels then the escape of vaccine derived immunity will give the mutated virus a selective advantage even with lower infectivity in non-vaccinated individuals and the mutated variant could take over as the dominant variant in that outbreak. Furthermore, once that mutation has become established it might be possible for a further mutation to occur that regained the original virus's infectivity, so that it has both high infectivity and vaccine escape. It is for this reason that it can in some circumstances be advantageous to only vaccinate the most vulnerable in circumstances where sterilising immunity is not obtained and where the vaccine targets mutable parts of the virus's genetic code (particularly for RNA viruses, which mutate much faster than DNA viruses). Too late for that now, though.

One more minor point of note about the Covid variants. Back in 2021, the World Health Organisation decided that it should name each new variant using the Greek alphabet. It is likely that this response arose due to media news organisations being keen on naming variants from the area of the world where they were first discovered. The WHO had enough problems insisting that people didn't refer to Covid as the 'Chinese Virus', although it is a bit weird that it was so passionate about this relatively irrelevant aspect of a worldwide public health emergency. (To be fair, the avoidance of 'stigmatising' names for new diseases has been WHO policy since 2015.) The strange thing is, there have been no more Covid variants named by the WHO since Omicron came along. Omicron is rather highly mutated compared with the original Wuhan strain and all prior variants. Indeed, there is an argument that the Omicron variant really should have been called COVID-21 given the evolutionary distance from and clinical differences with COVID-19. All of the major subvariants of Omicron are at least as valid as 'new variants' as the variants that came prior to Omicron, and so the WHO stopping at Omicron is odd. Then again, if the WHO had continued to name new variants it would probably have run out of Greek letters by summer 2022 (they were even two short, as they decided to not use Nu or Xi for some strange reason). Anyway, I imagine that the succession of complex named variants (XBB!, BA2.75.2! etc.) suggests to many that the evolution of Covid has become a scientific curiosity and doesn't reflect an ever increasing rate of viral mutation compared with the Greek letters of 2021. Perhaps this is of convenience to some parties.

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