ISSUES IN PUBLIC HEALTH

Viruses, variants and vaccines

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The current SARS-CoV-2 pandemic has brought a number of major global clinical, sociological and economic issues into sharp focus. We address some of these issues, focusing on short-term factors such as virus mutations and vaccine efficacy, and also considering the longer-term implications of the current pandemic. We discuss societal responses to the presence of a pathogen that will probably remain in circulation for decades or longer, and to future new emergent viruses.

S Afr Med J. Published online 1 March 2021. https://doi.org/10.7196/SAMJ.2021.v111i5.15578

Like diamonds, most viruses are *forever*. The ability to adapt by mutation of their genomes may change a virus and its behaviour over time, but 'once a virus, always a virus'.

Viruses have been evolving with life on this planet for several billion years. Most infect the dominant cellular organisms – prokaryotes such as bacteria and archaea – and only a very small subset infect mammalian hosts. Many of these are 'orphan' viruses, causing transient or asymptomatic infections that are of little concern. However, a few that are highly infectious and virulent may have serious health and/or economic impacts, and are of considerable concern. The global human population is currently focused on one particular coronavirus, SARS-CoV-2, which emerged unexpectedly to become highly infectious to humans, and which has swept the planet.

Viruses may become more or less infectious over time, and symptoms from the diseases they cause may become milder or more severe. As new viruses enter the human population immunity levels will increase, and antiviral prophylaxis, including vaccines, is likely to become the norm, but most viruses still live on. There has been some, but limited, success in eradicating disease-causing viruses: smallpox was widespread in Europe a thousand years ago,[1] but was declared to have been eradicated by the World Health Organization in 1980. As a result of a concerted vaccine campaign over decades, wild-type poliovirus type 1 – one of the three that were common – is now only present in two south-east Asian countries, while poliovirus types 2 and 3 have been eradicated in their 'wild' forms. The deadly rinderpest virus, once a scourge of cattle and wildlife, was also eradicated, in 2011, as a result of sustained vaccination campaigns. Conversely, other viruses, such as the rhinoviruses, coronaviruses and adenoviruses that cause the common cold, as well as influenza viruses, are permanent residents in the global human population, re-emerging annually as seasonal epidemics.

Not all viruses infecting humans or animals are harmful, and some have evolved with their hosts over millions of years: many human papillomaviruses, for example, seem to be harmless commensals of the skin, even though they have distant relatives that can cause serious diseases such as cervical, anal, and head and neck cancers. Evidence of past retroviral infections can be found as integrated DNA sequences in all animal genomes: up to 10% of the human genome is composed of degraded retrovirus genomes, and the evolution of many animal lineages can be tracked according to which integrated retroviral genomes they share. Indeed, ancient retroviruses have shaped the evolution of many mammalian and human cellular and developmental pathways.[2,3]

On the other hand, most of the viruses that do pose threats to the health of humans and their livestock have emerged in relatively recent times and result almost exclusively from zoonotic transmission: HIV-1 and HIV-2 crossed into humans in West Africa from chimpanzees and sooty mangabeys, respectively, as long ago as the early 1900s. Both the deadly Ebola and the related Marburg viruses were unknown prior to the late 1960s, and emerged as a result of human encroachment into wilderness areas. The mosquito-transmitted yellow fever and dengue and West Nile and Zika viruses have spread from Africa around the world as a result of human activity. Coronaviruses have been increasingly important more recently, with emergence into the human population of severe acute respiratory syndrome virus (SARS-CoV) in 2002, Middle East respiratory syndrome virus (MERS-CoV) in 2012, and what is now known as SARS-CoV-2 in 2019. While the first two viruses were fortunately limited in their spread, given that their case fatality rates were nearly 10% and over 30%, respectively, it is worth noting that the four coronaviruses that cause the common cold also emerged in humans over a period of several hundred years, and may originally have caused much more severe disease.

SARS-CoV-2 is therefore just the most recent coronavirus to emerge from obscure origins to cause widespread human disease. However, the core issue is not whether SARS-CoV-2 is here to stay, like

its common cold-causing relatives, but how we as the human race will deal with it in the medium to long term. How will human behaviour and lifestyles 'normalise' in a 'post-COVID pandemic' world?

At the time of writing, the approval and distribution of a small (but rapidly increasing) number of effective anti-COVID-19 vaccines has offered hope to the global human population[4] that, through 2021, the current pandemic will be contained. It is highly likely, however, given the evidence of previous coronavirus 'domestication', that COVID-19 will not disappear (i.e. will not be fully eradicated).

Life after vaccines

As vaccines are becoming available at a hitherto unprecedented rate, the medical responses to COVID-19 are transitioning from non-pharmaceutical interventions such as hygiene, social distancing and lockdowns to national and international vaccination programmes. There is no doubt that immunisation of the majority of the global community is a key requirement for controlling COVID-19. However, the limitations of vaccine production capacity globally, and in particular the issue of affordability by low- to middle-income countries (LMICs), are constraining the pace of vaccination programmes. The constraints on vaccine production and access bring with them a host of social and political issues, and equity is one of these.[5] High-income countries' governments have 'bought up' large proportions of the available vaccines, so-called vaccine nationalism, leaving the LMICs, which account for the majority of the global population, in the disadvantaged position of not being able to vaccinate their vulnerable (and often poverty-stricken) communities, even where financial provision has been made.

It is possible that in the short term, requirements for SARS-CoV-2 vaccination certification will become a norm for international travel, as they already are for travel to several countries for yellow fever virus: this has the potential to exacerbate the divide between countries able to provide vaccinations and those not yet in a position to do so. In turn, it will impact on many national travel and tourism industries. It could also result in a thriving black market in fake certificates, as already occurs with yellow fever and for PCR results for SARS-CoV-2.

Until vaccination programmes have been extensively implemented and enough people have acquired immunity to SARS-CoV-2, governments and communities will need to continue to rely on non-pharmaceutical interventions to contain the spread of the virus. These regulations bring another set of concerns, including a heavy impact on national and regional economies and an increase in socioeconomic hardship.

In some cases, restrictions are being imposed without clarity of purpose, with misguided intentions and even with the intention of effecting political or personal agenda-driven goals. In many poverty-ridden communities, compliance with lockdown restrictions is almost impossible, for various social and economic reasons. The consequence is that infections are surging, and at the same time unemployment is increasing, with the wave of viral infection being closely followed by secondary effects, including a substantial rise in mental ill health.

The essential consideration in respect of these social and economic impacts is that it is likely to be some years before the global community has developed sufficient immunity to overcome the COVID-19 pandemic, and national and international agendas will need to take this into account.

New viral variants

RNA viruses naturally mutate faster than DNA viruses and host DNA. The incidence of mutation may increase as environmental pressures increase. A lineage containing a limited number of new mutations is generally referred to as a new *variant* (not a new *strain*). Mutations are often functionally neutral (do not affect the viral phenotype), but are occasionally functionally important. Over the period around Christmas 2020, scientists identified two new SARS-CoV-2 variants, one in the UK (B.1.1.7)[6] and one in South Africa (SA) (B.1.351).[7] Both had acquired a number of point mutations (nucleotide changes leading to amino acid changes or deletions), a few of which have occurred in the viral spike (S) protein that binds to the host ACE2 receptor protein to initiate host cell infection. These mutations have resulted in a significant increase in viral infectivity, meaning that these new variants tend to spread more rapidly within the host (human) population. These new variants are responsible for the very rapid second-wave infection rates that have now been recorded in many countries, including the UK and SA.

Widespread concern has been expressed that some of the currently available vaccines being distributed across the globe may be less effective against the B.1.351 variant, since the viral spike protein contains the antigens chosen for vaccine development. However, expert opinion has been mostly reassuring: 'both vaccines and natural infections lead to a broad immune response that targets many parts of the virus',[7] and changes in a limited number of viral protein structures are unlikely to affect the efficacy of current (and future) vaccines, unless significantly more of these changes are concentrated in the S protein. We now know that at least one vaccine does have reduced efficacy against the SA variant virus (at least, in young people with mild infections), while a second appears to retain its efficacy in all age groups.

Many SARS-CoV-2 variants now exist across the world, and there are probably many more that have not yet been detected because of absent or inefficient surveillance programmes. Additional SARS-CoV-2 variants will continue to emerge in the future – we can be sure of this as long as the pandemic continues – although maybe at a slower rate as immunity (natural and acquired) becomes the norm in the global human population. Moreover, transmission to farmed animals such as mink could select for a different spectrum of variants to those that occur in humans – and these may readily be transmitted back to humans, as happened with the H1N1 2009pdm influenza virus. Some variants will show changes in functional properties, like the UK VOC 202012/01 and SA B.1.351 variants, that may be significantly more transmissible than wild-type viruses, and some of these changes may additionally influence the virulence of the virus (although this does not generally appear to have been the case to date).

There is little we can do to prepare ourselves for these possibilities, other than to ensure that we continue to maintain a robust level of surveillance, in particular whole-genome virus sequence surveillance. We can have some confidence, however, that the current anti-COVID-19 vaccines, and the many more to follow, will very probably retain their efficacy, given the much lower rate of mutation for SARS-CoV-2 relative to influenza viruses and the lack of evidence for immune escape in existing variants. It is also a fact that the new vaccine technologies being applied to the COVID-19 problem – the various adenovirus vectors (e.g. Astra-Zeneca, Johnson & Johnson, Gamaleya Center, CanSino Biologics), mRNA (Moderna, Pfizer-BioNtech) and subunit vaccines (Novavax, Medicago) – make it relatively quick and easy to adapt the vaccines to accommodate new mutations in emerging variants, thereby ensuring that vaccines remain highly effective. There is a very real possibility that annual booster vaccines will become the routine in years to come, as happens for seasonal influenza. Reassuringly, Pfizer-BioNtech announced that the efficacy of their vaccine is not affected by the mutations in the UK and SA variants,[8] and new data released by the US Food and Drug

Administration on the Johnson & Johnson product show that the vaccine is also highly effective against both variants.

The post-COVID-19 world

How will the world adjust, once the COVID-19 pandemic has subsided? In addition to investing in continuous rapid development and testing of vaccines, we will need to ensure that everyone is equipped to manage 'normal' (working) life in an increasingly infectious environment.

One key to managing future virus epidemics is through broad, meaningful community-based education, driven by heightened awareness that compliance will come from everyone being provided with relevant information, which must be available, understandable and accurate. While medical scientists will continue their endeavours to understand viral diseases and find therapies, people from all disciplines will need to work in integrated, collaborative ways to provide information and educate communities. Moreover, leadership in science communication will be as important as leadership in science itself.

The next viral pandemic

COVID-19 is just the latest in a series of severe viral diseases circulating in the human population. In addition, an ever-increasing number of coronaviruses are being discovered in mammalian hosts (particularly bats and primates), which may have the potential to drive the next viral pandemic. While some have argued that a critical priority is therefore to invest in increased pan-viral genomic surveillance to facilitate the early identification of potential new viral pathogens, the reality is that this is a shotgun approach that will be exorbitantly expensive, and can only identify *potential* pathogens. A more directed approach that surveys diseased animals and humans is far more likely to yield important information at a far lower cost: a current example is the seroepidemiological and genomic surveys of stock animals in SA for viruses associated with encephalitic disease. In addition, there needs to be a substantial investment in the development of a stock of antiviral compounds including pan-family drugs that have already progressed through preclinical trials, and that can rapidly be deployed against emerging viral pathogens, in parallel with the development of effective vaccines.

African vaccine production capacity

It is perhaps not widely known that SA currently manufactures just one component of one paediatric combination vaccine: the country effectively has no significant human vaccine manufacturing capacity. We were therefore unable to respond to the 2009 H1N1 influenza virus pandemic, and in fact had to wait until 2011 for deployment of vaccines to the general population. While the government of the time made declarations of intent about establishing influenza virus manufacturing capacity, nothing was done in this regard. The same is true for the whole of Africa: while Nigeria, Tunisia, Senegal and Egypt do manufacture human vaccines, capacity and variety are severely limited, with only BCG, yellow fever, cholera and DTP vaccines currently being commercially available, and usually only for domestic use.[9] There is therefore effectively no emergency-response vaccine manufacturing capacity in a continent that is home to over 1 billion people: this is in stark contrast to China, India, Russia and Brazil, all of which have significant capacity, and all of which are involved in the global COVID-19 vaccine response. This MUST change, or Africa will always be at the end of the global queue for emerging disease vaccines – and the next pandemic could well be far worse than the present one.

Conclusions

What is important at this stage, and looking ahead, is that we prepare ourselves for a future where mutant variants of known viruses, and indeed entirely new viruses, will emerge; further pandemics will sweep across the world, and we will need better ways to respond. A more severe disease agent than the present one would test most of the world – and Africa potentially more than anywhere else. Viruses are with us forever! However, the diseases they cause need not be.

Recommendations

- Establish and expand existing surveillance of pathogens causing severe diseases in humans and animals to identify novel and emerging pathogens: this should be linked to pathogenomic surveillance programmes where these already exist and the establishment of new programmes where they do not.
- Increase drug repurposing and discovery platforms and programmes aimed at existing pathogens, in anticipation of novel future pathogens.
- Expand pharmaceutical production capacity to provide localised supply pipelines of affordable therapeutics and vaccines, together with associated primary healthcare infrastructure to support mass vaccination initiatives.
- Promote equity in terms of access to medications and vaccines and implement strategies that mitigate against hoarding by higher-income countries to the detriment of LMICs.
- Finally, and very importantly, increase educational and awareness programmes and provide scientifically sound and accessible information to the general public, in part to mitigate the infodemic that erodes public trust in vaccine and other preventive (non-pharmaceutical) programmes.

Declaration. None.

Acknowledgements. The authors thank the University of Pretoria (DAC, SGB, MSP), Rhodes University (RAD) and the University of Cape Town (EPR, A-LW) for institutional support, and the South African Medical Research Council (MSP, RAD) and the National Research Foundation for financial support.

Author contributions. All authors contributed equally.

Funding. None.

Conflicts of interest. None.

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Accepted 25 February 2021.