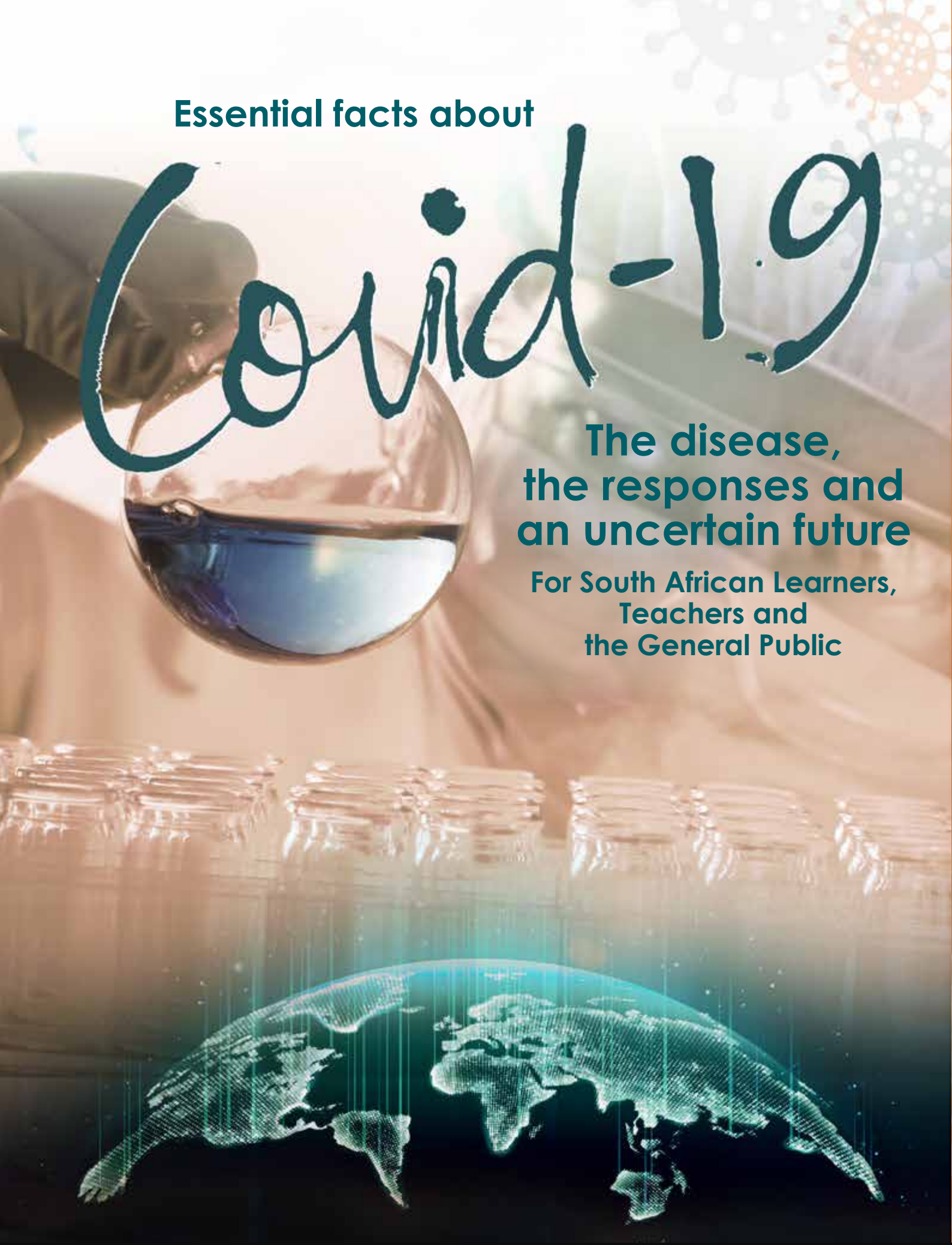
Essential facts about

Covid-19

The disease, the responses and an uncertain future

For South African Learners, Teachers and the General Public



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The **Academy of Science of South Africa** (ASSAf) was inaugurated in May 1996. It was formed in response to the need for an Academy of Science consonant with the dawn of democracy in South Africa: **activist** in its mission of using science and scholarship for the **benefit of society**, with a mandate encompassing all scholarly disciplines that use an **open-minded** and **evidence-based** approach to build **knowledge**. ASSAf thus adopted in its name the term 'science' in the singular as reflecting a common way of enquiring rather than an aggregation of different disciplines. Its Members are elected on the basis of a combination of two principal criteria, **academic excellence** and **significant contributions to society**.

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CHAPTER **8**

Anti-Viral Drugs and Vaccines

In this pandemic we have the advantage of the lessons from former pandemics and modern medicine. However, SARS-CoV-2 is a new virus only distantly related to the original SARS-CoV family. This put the whole world on a back foot, and the medical world soon informed us that the only solution for prevention of infection (besides behavioural changes) would be the development of a vaccine. It was estimated that vaccine development would take time. Some countries hoped that a rapid and widespread infection would provide populations with herd immunity but that was risky. The alternative, while a vaccine was being sought, was to try different combinations of known drugs for those who became very ill. Drugs that interfered with viral RNA replication were of choice, amongst others. Happily, a number of effective vaccines have been developed, and the challenge has become to deploy them wider.

How can drugs stop the spread of viruses?

The development of antiviral chemotherapies has been one of the success stories of the last forty or so years, with a huge expansion in the availability of effective drugs that can limit virus replication and even cure disease.

If one understands in detail the various and often very diverse mechanisms viruses employ to enter our cells, to express and replicate their genomes once within, and to disperse themselves again, it is possible to develop drugs targeted at one or more of these processes. Possibilities include: (1) to interfere with entry of viruses into cells; (2) to prevent release of virus components inside the cell; (3) to target specific viral-encoded enzymes essential to expression and processing of viral proteins; (4) to block the machinery the virus uses to make copies of their own genomes. All this can be attempted, hopefully without adversely affecting the essential work of the host cell.

Why can't one use antibiotics against viruses?

Antibiotics target a number of bacterial- or fungal-specific functions, which occur in the cells of these organisms, removed from the essential functions of the host organisms or their cells. One can specifically interfere in bacterial cell wall biosynthesis (as the antibiotic penicillin does) without affecting the host organism. One can use ciprofloxacin, which specifically targets the DNA gyrase in bacteria to stop DNA replication, but also does not affect the animal host.

Viruses use the host cell's own machinery to make the components for replicating themselves, from regulatory proteins to structural components to their own nucleic acids

The main problem here is that viruses take over the cells they infect in a way bacteria do not. Viruses use the host cell's own machinery to make the components for replicating themselves, from regulatory proteins to structural components to their own nucleic acids, whereas bacteria have their own protein-synthesising machinery and DNA and RNA-processing enzymes. Interfering with these virus processes, therefore, could mean adversely affecting the processes of the host cell. It is, consequently, much harder to precisely target virus-specific processes compared to bacterial processes because the virus often uses host processes. This means that nearly all antibiotics are useless against viruses.

Sadly, all too often, doctors prescribe antibiotics for illnesses that are actually caused by viruses. The best example of this is doctors that prescribe antibiotics for the common cold, an infection caused exclusively by viruses. Unfortunately, huge collateral damage is done by giving a person an antibiotic who does not need one. The truth is that we humans live in an exquisitely important symbiotic relationship with

The accelerated development for Covid-19 vaccines was in part made possible by the fact that many of the developers had already been working with related coronavirus vaccine candidates.

bacteria. In fact, there are over 10 times more bacterial cells in and on our body than there are human cells. In our gut alone there are 100,000,000,000,000 (10^{14} bacteria)! These bacteria play critical roles in keeping us healthy, including protecting the gut surface from pathogens (think of bouncers stopping people getting into a club), helping us digest food and vitamins, and critically playing an important role in our immune system. Every time we give someone an antibiotic, large numbers of these beneficial bacteria in the gut and elsewhere are killed, leaving us vulnerable and damaging our health. Use of antibiotics in infancy has been associated with later obesity, and changes in the bacterial composition of the gut due to antibiotics has been associated with many diseases from inflammatory bowel diseases like Crohn's disease to neuropsychiatric illnesses. Furthermore, indiscriminate use of antibiotics increases bacteria that are resistant to those drugs, damaging our ability to treat people with bacterial infections. Antibiotic resistance presents a global public health crisis that threatens modern medicine as we know it.

What are the ways to interfere with viral replication?

Viruses have the most varied genomes, or nucleic acid components, of all organisms. Moreover, while all cellular organisms (bacteria, archaea, fungi, plants and animals) have only double-stranded DNA as their genetic material, and all replicate their DNA in similar ways, viruses have seven different types of genetic material, based on both structure and how they replicate their genomes. Virus particles may have double- or single-stranded DNA replicating via DNA intermediate, or double-stranded RNA replicating via single-stranded RNA, or single-stranded RNA of positive or negative sense that replicates via double-stranded RNA, or single-stranded RNA or double-stranded DNA that replicates via reverse transcription from RNA to DNA and back again, or the converse mechanism. All of these, save some of the first, have virus-specific enzymes that mediate the process, meaning that it is possible, with knowledge of the structures of the proteins, to develop drugs that can specifically jam up different types of proteins. For example, a drug known as acyclovir specifically inhibits a human herpesvirus enzyme called thymidine kinase that is vital for virus replication. The drug cidofovir, a nucleoside analogue that interferes in DNA replication, is also a potent agent for treatment of poxvirus infections, probably because the viruses do not use cell nuclear machinery for replication of their DNA.

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Other drugs target the replication machinery of RNA viruses, a function that is not present in host cells: thus, chronic infections of hepatitis C may be effectively treated using a variety of drugs that target components of the viral replication complex, or stop RNA chain elongation. In fact, it is now possible to cure chronic hepatitis C

infections, something the Egyptian government embarked upon as a national strategy recently.

A drug called remdesivir was developed as a broad-spectrum antiviral drug that interferes with RNA virus replication and was used with some success to treat Ebola virus infections. Remdesivir was recently re-purposed to treat COVID-19 patients and was used mainly in serious cases, for which it seemed to shorten the period of illness. A later, bigger study did not confirm this however, showing how slowly we acquire reliable knowledge in science.

Why is fighting a virus like shooting at a moving target?
Viral evolution and natural selection.

Apart from viruses with big DNA genomes-poxviruses, adenoviruses, herpesviruses, iridoviruses–most virus genomes are far more susceptible to mutagenic change than the host cell DNA. This is especially true for most RNA viruses, and is due to the fact that RNA viruses generally do not have a 'proof reading' capability in their replication machinery, meaning that they mutate at a much faster rate than cellular DNA does. Consequently, natural selection operates far faster among the virus than their host cells. Influenza viruses, for example, mutate fast enough that they can 'drift' away fast enough from being recognised by host immune systems. Strains circulating a couple of years down the road may be different enough to re-infect you despite previous exposure. HIV and other retroviruses are even worse. The rate at which their genomes accumulate mutations is such that every single one of the billion or so HIV genomes made in the course of a single day in a single infected individual will have at least one difference to every other one. Such rapid evolution can lead to 'escape phenotypes', where viruses can be isolated that are resistant to previously successful chemotherapies. This occurs distressingly often with the HIV virus.

This sort of variation has its limits. Although mutations may occur at a high rate, this depends to some extent on the size of the viral genome–bigger viruses code for more functions and can tolerate fewer mutations that may impair their viability, so their nucleic acid repair mechanisms are more effective. Virus evolution does not, therefore, necessarily proceed at the same rate in the case of different viruses. For example, while HIV-1 and HIV-2 are as different from one another in terms of genetic sequence as any two randomly-picked animal descendants of the Cambrian Explosion over 500 million years ago, they are far more similar to one another in terms of structure, morphology and gene order than crayfish and humans, for example. Viruses like measles and mumps - both RNA viruses - also only have one 'serotype', despite infecting and being selected for variation in humans for centuries. This is because their surface proteins are under a strong constraint not to mutate, so as to preserve functions essential for infection of host cells.

HIV drugs: A case study

The explosion of research sparked by the discovery and characterisation of HIV-1 and HIV-2 in the 1980s led to an unparalleled expansion of our understanding of host immunology, virus-coded structures, and how to develop drugs that targeted different stages in the virus lifecycle. This was in fact probably the spur that led to the successful development of drugs to target hepatitis C and B viruses, because so much expert attention was being focused on retroviruses, and how to interfere with their replication and spread.

If one divides the virus lifecycle into entrance, entertainment, and exit - a useful tool for remembering the essential stages in the process - then it is possible to differentiate entry inhibitors, replication and expression inhibitors/antagonists, and inhibitors of viral particle dissemination. HIV-1 and -2 are retroviruses, which are viruses that replicate via conversion of RNA to DNA incorporated into the host chromosomes, and back again. Retroviruses have replication and expression machinery (reverse transcriptase, integrase) that are specific to retroviruses and dissimilar to machinery of the host cell. Retroviruses also have membranes around their particles derived from host cells, but containing additional envelope proteins whose function is to fuse the virus particle with cell membranes in order to deliver the virus genome and replication machinery into the cell. Regulation of the expression of the viral DNA phase relies on virus-encoded proteins, and the virus proteins need to be processed by a virus-encoded protease for proper assembly of particles within the cell and for those particles to reach their final form to be infectious. All of these stages can be targeted with drugs that exploit knowledge of the molecular mechanisms that make them work. Developing such drugs took a long time and a great deal of research. But it is now safe to say we understand the life cycle and structures of HIV-1, and its expression and replication machinery better than just about any other organism on this planet.

Influenza viruses, for example, mutate fast enough that they can 'drift' away fast enough from being recognised by host immune systems.

A wide variety of drugs are given to people with HIV infections to keep their viral loads low, or even as pre-exposure prophylactics. Drugs that block virus particles from attaching to cells are known as attachment inhibitors. These include very expensive monoclonal antibodies (mAbs), which block CD4 receptors on cells, compounds such as fostemsavir (FTR, FDA licenced in 2020), which binds to the viral gp120 and blocks its binding to cell-surface CD4 protein as the first stage of entry, and other drugs that bind to and block viral attachment to the second of two cell proteins vital for viral entry. Post-attachment inhibitors, or fusion inhibitors, work at the next stage of infection and block the virus from entering the cell after binding to the CD4 and CCR5 proteins by fusing membranes.

Drugs that specifically interfere with the replication machinery of the virus are nucleoside analogues and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs, respectively). Other drugs interfere with the virus protease that is vital for proper processing of virus proteins. Integrase inhibitors block the action of the viral integrase enzyme, which is necessary for the HIV DNA form to integrate into host chromosomes.

South Africa presently has nearly 8 million people living with HIV-1 and, with over 4 million on treatment, has about 20% of the world's total number of people who are on HIV therapeutics. The initial or first-line therapy regimens for previously untreated patients in 2017 were chosen from among the following combinations:

- A mixture of the NRTIs TDF and FTC or 3TC, plus the NNTRI EFV
- NRTIs TDF + FTC/3TC plus integrase inhibitor DTG
- TDF + FTC/3TC plus NNTRI RPV (if viral load > 100 000 copies/mL)
- Second-line regimens–given when first-line treatment is not working–preferably include two NRTIs and a RTV-boosted protease inhibitor: this involves using low-dose RTV, which inhibits the breakdown of the added inhibitor.

In 2019, South Africa introduced an advanced therapy regime consisting of three drugs in a single pill known as TLD, to be taken daily. This contains the integrase inhibitor Dolutegravir (DTG), as well as NRTIs 3TC and TDF. DTG is the drug of choice for people living with HIV in high-income countries as it has fewer side effects and fewer negative interactions with tuberculosis medicines, which is a bonus given the very high rate of co-infection of people in South Africa with HIV and TB.

What has been the success of existing anti-viral drugs against Covid-19?

Given the burgeoning in recent years of the antiviral drug field, it was natural for researchers to turn to tried and proven agents successful against other viruses to attempt to treat Covid-19, the disease caused by the newly-emerging betacoronavirus SARS-CoV-2. This is a single-stranded RNA virus that replicates similarly to hepatitis C virus (HCV). However, the viruses are sufficiently different from one another that therapies targeting HCV have no guarantee of being effective against SARS-CoV-2.

Early, small observational studies of chloroquine and hydroxychloroquine (CQ and HCQ) looked promising. Both are cheap drugs with a well proven safety record in humans. They are known to act to prevent the acidification of internal vesicles in cells of the type that SARS-CoV-2 can fuse with and, thus, allowing its genome to enter. However, while both these drugs worked in cell culture experiments against both SARS-CoV-2 and the related MERS-CoV, early studies in Covid-19 patients,

which were often coupled with the macrolide antibiotic azithromycin for its anti-inflammatory actions, remained inconclusive. The same was true for the antiretroviral combination lopinavir/ritonavir. More recently, however, the UK's adaptive multi-armed randomised controlled trial, RECOVERY, proved that neither HCQ nor lopinavir/ritonavir had any effect in reducing mortality in Covid-19. They are no longer used. The WHO's multi-country SOLIDARITY trial also failed to show benefit.

However, a breakthrough in treatment of Covid-19 came from the RECOVERY trial, which demonstrated that dexamethasone reduced mortality in patients admitted to hospital requiring supplemental oxygen. Patients requiring ventilation had a 33% reduction in death, with those requiring lesser oxygen support having a reduced mortality of 20%. No benefit was observed in patients admitted to hospital but not requiring supplemental oxygen. Dexamethasone or its equivalent, e.g., prednisone, is now standard of care for severe, hospitalised Covid-19 patients worldwide.

Hopes for remdesivir, a re-purposed antiviral nucleoside analogue first used in Ebola patients, were also high following a US study that showed that it significantly reduced recovery time if people were treated early (11 days vs. 15 for untreated), but was less effective in severely ill patients. This was not confirmed in a much larger, later study. Furthermore, the RECOVERY trial proved that remdesivir had no effect on mortality in severe Covid-19.

There have also been reports of success in reducing the death rate among severely ill patients by use of infused convalescent plasma, which prompted the FDA in the USA to issue an "emergency use authorisation (EUA)" to allow hospitals to try it. Monoclonal antibodies are also under study. Bamlanivimab, for example, has had some success in treatment of non-hospitalised patients at risk of progressing to severe disease, and REGN-COV2, a cocktail of two monoclonal antibodies, is also in late stage trials.

IL-6 receptor inhibitors, such as tocilizumab, also gained traction in the early phase of the pandemic, with putative effect on the cytokine storm seen in severe COVID-19. Although IL-6 inhibitors reduced inflammatory responses in patients with extensive lung involvement, and who had elevated IL-6 concentrations, tocilizumab has yet to show any effect on short term mortality, but may reduce the risk of mechanical ventilation in hospitalised COVID-19 patients.

How do vaccines work? Training the body's immune system

A vaccine may be defined as a substance that produces an immune reaction, subsequently leading to an acquired immunity against a natural micro-organism. The advent of vaccines ranks among the most important developments in medical and veterinary science of the last three hundred years. The term vaccine covers a wide range of agents, including attenuated live bacteria and viruses, killed whole-cell or

whole-virus-particle vaccines, isolated components of disease agents, recombinant proteins made in cell cultures, parts of viruses expressed in other live vaccines, and synthetic compounds such as bacterial carbohydrates.

Whatever its form, the simple requirements for a vaccine are that it be safe and that it work. Unlike therapeutics given to people having a disease, vaccines are administered to healthy people, and generally to children. Consequently, there is a stringent requirement to prove their safety beyond the requirement that they prevent disease.

Vaccines work by eliciting adaptive immune responses in their recipients that will protect them against disease caused by the selected agent. They do this by exposing the immune systems of the vaccines either to parts of the actual pathogen–in the form of subunits, or synthetic or killed vaccines–or to a whole organism that does not cause disease. For example, the original smallpox vaccine–later called vaccinia virus–was derived either from a horse-pox virus that infected a cow, or from an actual cowpox virus. This was an agent similar enough to the actual smallpox virus to elicit the right immune response, but it did not cause severe disease. Its use allowed the complete eradication of the human disease in the late 1970s. This was the first human disease ever to have been eradicated. This feat was followed in 2011 by eradication of the rinderpest virus of cattle and wild animals as the result of a live vaccine campaign over many years. The modern measles, mumps, and rubella vaccine consists of viruses that were derived from the original virulent viruses via extensive culture and selection, and which now do not cause disease. There are both live and killed polio virus vaccines, which are derived by extensive tissue culture selection, in the first case, and by chemically inactivating live, virulent polio viruses. in the second case.

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Subunit vaccines are not a modern idea. The diphtheria and tetanus vaccines are both inactivated toxins derived from cultured live bacteria. Moreover, recombinant virus protein vaccines produced via genetic engineering by bacteria, yeasts or insect cells are now well established in human medicine. These include hepatitis B virus-like particles (VLPs) produced in yeast cells, and human papillomavirus VLPs produced in yeast or insect cells.

How have vaccines helped to reduce infant mortality?

It is reliably estimated that over 3 million children's lives are saved every year worldwide by use of vaccines that are included in the Expanded Programme on Immunisation (EPI), established by the World Health Organisation (WHO) in 1977.

The first diseases targeted were diphtheria, whooping cough, tetanus, measles, poliomyelitis, and tuberculosis. This list has since been expanded quite considerably, although implementation is subject to individual country policies and abilities.

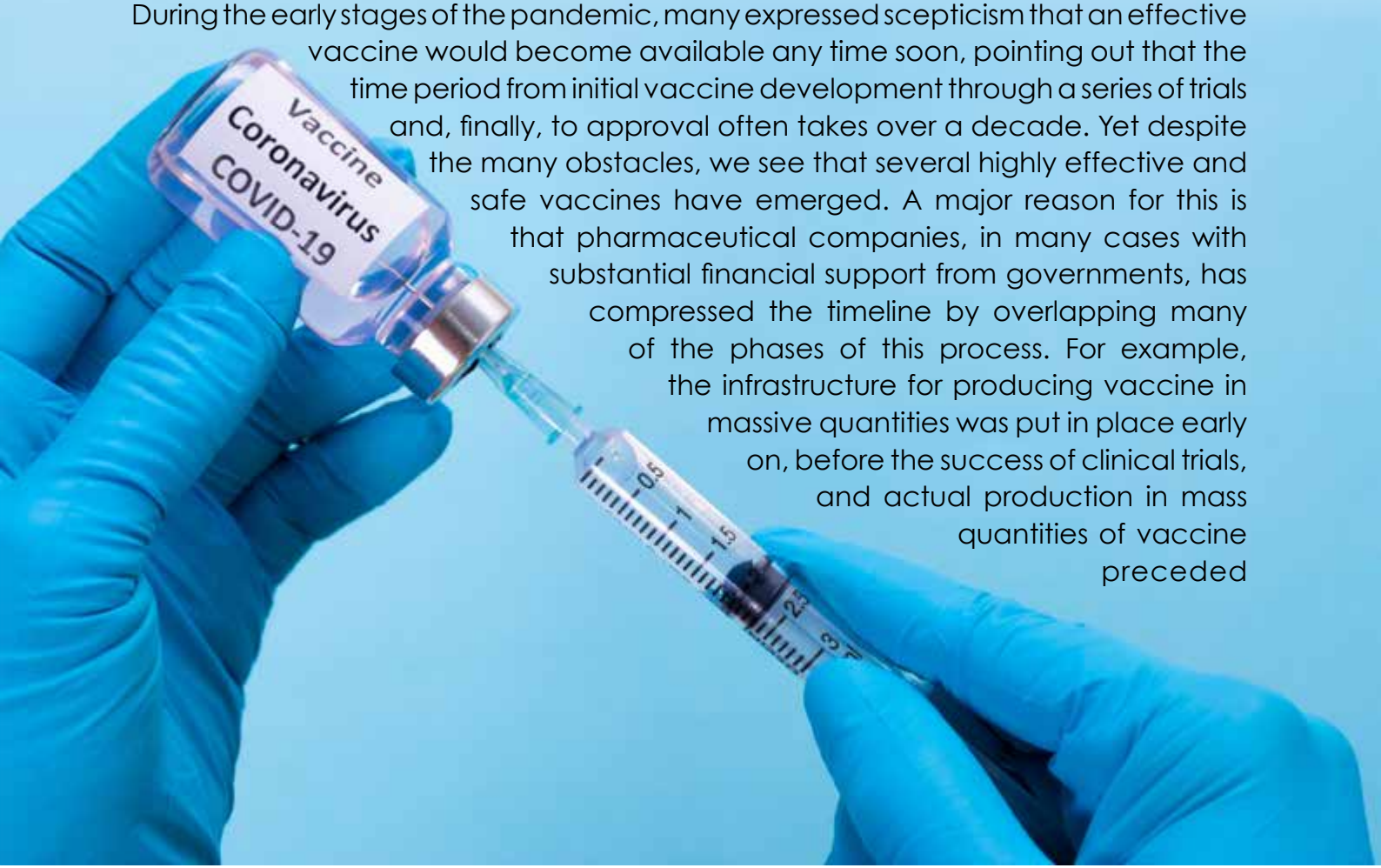
South Africa presently targets three diseases for eradication: poliomyelitis, measles, and neonatal tetanus. A further seven diseases targeted by the programme are diphtheria, pertussis, tuberculosis, hepatitis B, Haemophilus influenzae type B (Hib), rotavirus, and pneumococcal infections. Poliomyelitis has effectively been eradicated in South Africa, and wild-type polio has been eradicated in Africa as of 2020.

How safe are vaccines?

Any vaccine that has received regulatory body approval has passed extremely stringent conditions for its release and has been proven to be safe and efficacious in large, and usually international, Phase III clinical trials and subsequent observational studies. Although this does not completely eliminate the possibility of rare adverse events, vaccines that are used in the EPI programmes worldwide are among the safest medicines ever made, and the benefits have been shown to greatly outweigh the small risk of rare adverse events.

What has been the process leading to the emergence of several effective vaccines against Covid-19?

During the early stages of the pandemic, many expressed scepticism that an effective vaccine would become available any time soon, pointing out that the time period from initial vaccine development through a series of trials and, finally, to approval often takes over a decade. Yet despite the many obstacles, we see that several highly effective and safe vaccines have emerged. A major reason for this is that pharmaceutical companies, in many cases with substantial financial support from governments, has compressed the timeline by overlapping many of the phases of this process. For example, the infrastructure for producing vaccine in massive quantities was put in place early on, before the success of clinical trials, and actual production in mass quantities of vaccine preceded



approval and in some cases the final results of clinical trials. From a financial point of view, such a compressed timeline entails considerable extra risk, in case the vaccine fails. But many governments were willing to subsidise these risks given the considerable losses that result from a continuation of the pandemic.

The accelerated development for Covid-19 vaccines was in part made possible by the fact that many of the developers had already been working either with related coronavirus vaccine candidates, for the Middle Eastern respiratory syndrome coronavirus (MERS-CoV) or the original severe acute respiratory syndrome virus (SARS-CoV)–and could simply swap in SARS-CoV-2 genes or proteins, or had well-developed vaccine 'backbones' like measles and VSV, making it easy to adapt them for Covid-19. These factors, and the willingness to collapse the clinical testing regime, so as to allow concurrent Phase 1/2 and 2/3 testing, means that development time could be reduced to as little as ten months to a year.

There is a stringent requirement to prove their safety beyond the requirement that they prevent disease.

Of the over 150 vaccines development efforts to date, ten vaccines have already succeeded and been approved under "emergency use authorisation" in at least one country, and this number can be expected to grow.

Covid-19 vaccines fall into the follow general categories:

- Genetic vaccines, consisting only of RNA or DNA encoding the spike protein, or the main virus particle outer protein;
- 'Killed' or inactivated whole virus particle vaccines;
- Subunit, or nanoparticle, vaccines, which consist only of the spike protein made in a recombinant expression system;
- Live virus vaccines, such as several different kinds of adenoviruses or measles vaccine or vesicular stomatitis virus (VSV, also used for Ebola) that carry the gene for the spike protein

Attenuated vaccines, with the live SARS-CoV-2 virus itself.

The Pfizer-BioNTech and Moderna vaccines are of the category of the genetic vaccines, using messenger RNA encoding the spike protein. The Oxford Astra-Zeneca, Johnson and Johnson, Sputnik V and Chinese Ad5-nCoV vaccines use an adenovirus vector to deliver the spike protein in order to provoke an immune response. The Chinese BBIBP-CorV and CoronaVac vaccines, as well as the Russian Covivac vaccine and Indian Covaxin vaccine, on the other hand, are inactivated virus vaccines. The EpiVacCorona and RBD-Dimer vaccines are subunit vaccines.

Once a Covid-19 vaccine has been proven safe and effective, what challenges will remain in distributing it widely and making sure that a sufficient number of people are vaccinated so that life can return to the previous normal?

Although developing, testing, and licensing a vaccine involves many formidable challenges, once these challenges have been overcome the story is not over. We now have several vaccines that have been proven both safe and efficacious, but large-scale manufacture and distribution poses new, equally formidable challenges. Manufacture is a major challenge for certain types of vaccines. Those merely requiring a live virus to be grown, such as the adenovirus-based candidates, are probably the easiest to produce, as the volume of material to be produced would be much less than for subunit vaccines, which typically require much more material to be made and purified, as they are not infectious. Killed vaccines are one of the quickest ways to make the product, but this requires that a very large amount of live, virulent SARS-CoV-2 be grown. This is problematic due to the stringent safety requirements imposed when working with live, unmodified virus. The production volumes required for the non-live vaccines are such that the world may simply not have the capacity to make the required amounts in less than a couple of years.

As this booklet goes to print (July 2021), a small fraction of the world's population has been vaccinated, even in the affluent, developed countries.

Distribution is also potentially a problem, as certain of the vaccines require refrigeration to as low as -80° C for storage and transport, which may pose a serious obstacle for rolling these out to remote locations in underdeveloped countries.

As this booklet goes to print (July 2021), a small fraction of the world's population has been vaccinated. While many in affluent countries have been vaccinated,only a small fraction of those in developing countries have been so fortunate. The fraction of people having been fully vaccinated in the US, Europe, and the UK are 56%, 48%, and 49%, respectively. The comparable fraction for South Africa is 4.8%.

It remains to be seen how manufacturing capacity is scaled up and the geopolitical issues of vaccine distribution are handled.

As we write there are several vaccines in circulation around the world. The well-known ones are Pfizer-BioNTech, Moderna, Johnson and Johnson, Oxford Astrazeneca and NovaVax, and a few others. Their use depends on their availability in different countries. There is a rush in many of the rich countries to vaccinate a huge number of people to reach herd immunity, a point of safety in which the vaccination of a certain percentage of people will slow or stop the virus from spreading to those who are not vaccinated.

Poorer countries like South Africa have been slow in their vaccination roll-out. We initially procured one million Oxford Astrazeneca vaccines and did not use them because it showed low efficacy against the Beta variant (B.1.351 or 501Y.V2) in South Africa. The Johnson and Johnson vaccine is currently the preferred choice and is now being used to vaccinate our healthcare workers. Anti-Covid-19 is a developing story worldwide.

While the vaccines presently being used worldwide do not protect vaccinees completely against infection, they do appear to protect vaccinated people against severe disease and hospitalisation, whichever variant (Alpha, Beta, Delta or the new Gamma) they have been infected with.

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PO Box 72135, Lynnwood Ridge, Pretoria, South Africa, 0040
Tel: +27 12 349 6600 • Fax: +27 86 576 9520
E-mail: admin@assaf.org.za

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