Pandemics and the illumination of "hidden things"

Lessons from South Africa on the global response to Covid-19

A. Gray

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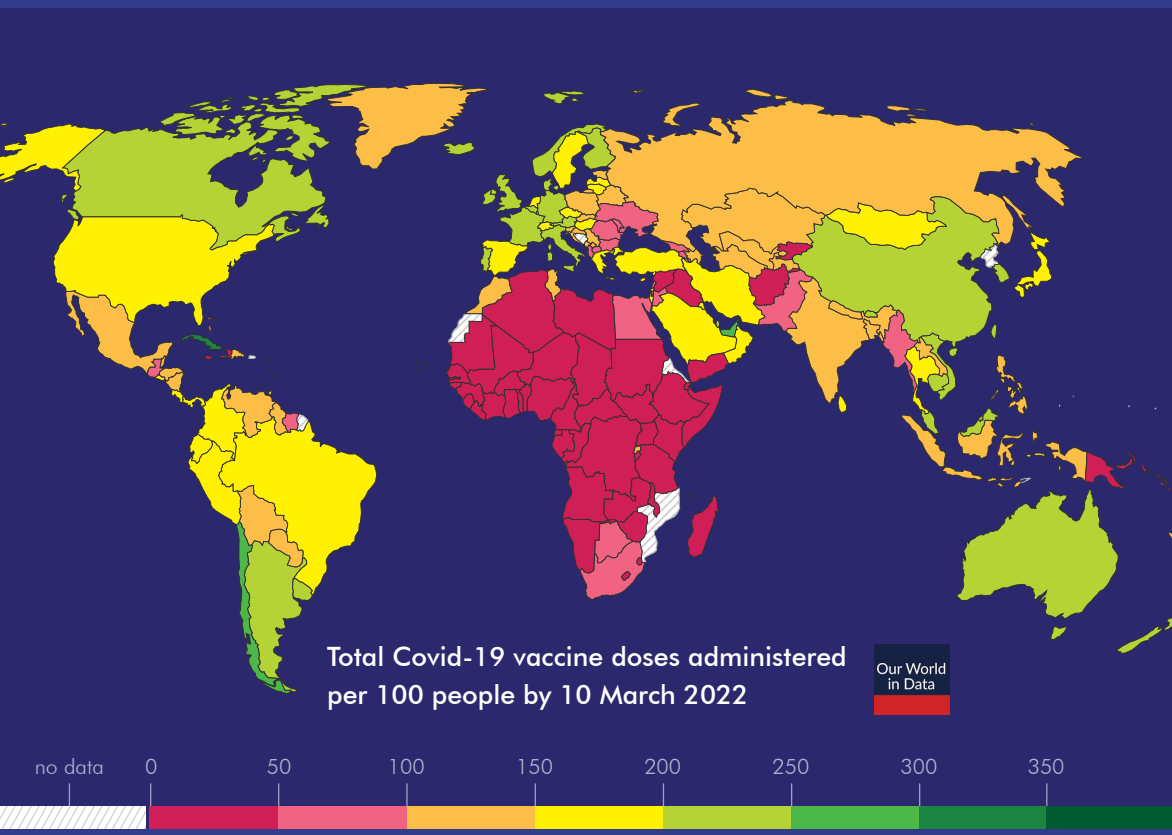

HEALTH JUSTICE INITIATIVE

Suggested citation: Health Justice Initiative *Pandemics and the illumination of "hidden things" – Lessons from South Africa on the global response to Covid-19*. Edited Volume. June 2023.

Editor: Laura Lopez Gonzalez
Project Lead: Marlise Richter
Proofreader: Sigwabusuku Mafu
Lay-out & Design: Jaywalk Design
Funding: The Health Justice Initiative is grateful to all its organisational and individual donors for funding and supporting its work. We would like to acknowledge the contributions of the Rockefeller Brothers Fund, the Joffe Trust and the Claude Leon Foundation towards funding this Compendium in particular.

Credit front-page image:

Adaption of *World in Data*. Image shows Total Covid-19 vaccine doses administered per 100 people, as of 11 March 2022 (two years since the WHO declared Covid-19 a "pandemic").

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World Health Organization
Our World in Data
The Lancet

Regulatory approval in a public health emergency: Lessons from Covid-19 vaccines

Andy Gray

One of the Covid-19 pandemic's defining features has been the speed with which a wide variety of vaccines were developed, appraised and approved by national and regional regulatory authorities and the WHO, procured by governments and then, finally, administered to more than two-thirds of the world's population (Mathieu, 2023). Understandably, there has also been keen interest internationally in the adverse events associated with the use of the different vaccines given their novelty.

However, as always, aggregated data hide all manner of inequities. In low-income countries, as discussed in several chapters here, less than a quarter of the population had been fully vaccinated by February 2023 (Mathieu, 2023). Regulatory decision-making has varied between countries and the extent to which safety data have been gathered, analysed and shared publicly has also differed between settings.

This chapter briefly reviews the evolution of regulatory approaches towards Covid-19 vaccines globally, including how

national medicine regulatory agencies balanced gaps in data with the need to address a rapidly moving public health emergency. Next, it describes processes in SA to streamline approvals and ways in which the country monitored and reported adverse events following immunisation. Lastly, it argues that SA made important strides in transparency regarding medicine regulation that bode well for continent-wide efforts to harmonise regulation but that entrenching these ways of working will be key moving forward.

Covid-19 vaccines – a long time coming

The perception that Covid-19 vaccines were developed from scratch after the identification of SARS-CoV-2 ignores a long process of technological refinement. Those Covid-19 vaccines that contain attenuated or weakened forms of the novel coronavirus relied on a well-developed process. Still, of the 11 vaccines that had received WHO emergency use listing or prequalification by November 2022, only three relied on a traditional development approach (WHO, 2022). Of these, two were developed in China and one in India. As shown in Table 2, two vaccines were based on recombinant spike proteins, four used viral vectors to deliver spike protein antigens, and two used mRNA. India has become an important source of vaccines, particularly for low and middle-income countries. Indian companies also produced a viral vector vaccine, under licence from a developer in a high-income country, and a recombinant spike protein vaccine.

Vaccine	Vaccine Type	Manufacturer
Comirnaty, including original and subsequent versions for omicron sub-variants	mRNA	BioNTech Manufacturing GmbH
Vaxzevria, previously the Oxford / AstraZeneca vaccine	Viral vector	AstraZeneca
Covishield	Viral vector	Serum Institute of India (licensed from AstraZeneca)
Covid-19 Vaccine Janssen (Ad26.COV2-S [recombinant])	Viral vector	Janssen–Cilag International
Spikevax	mRNA	Moderna Biotech
Sinopharm	Inactivated virus_	Beijing Institute of Biological Products
CoronaVac	Inactivated virus	Sinovac Life Sciences
Covaxin	Inactivated virus	Bharat Biotech International
Covovax	Recombinant spike protein	Serum Institute of India
Nuvaxovid	Recombinant spike protein	Novavax
Convidecia	Viral vector	CanSino Biologics Inc.

Table 2: List of WHO emergency use listed/prequalified Covid-19 vaccines as of November 2022.

It is the last of these technologies, mRNA Hub, that had never been used in a vaccine outside of clinical trials. However, it could also be considered a maturing technology, having been the subject of intensive research and development efforts over many years (Fauci, 2022). The basic science work around mRNA immunisations was partially based on the immense efforts to develop an HIV vaccine, but was also behind the development of other as-yet experimental vaccines, such as that for respiratory syncytial virus (RSV), which causes lung and respiratory tract infections (Graham, 2020).

Data dilemmas: Regulatory challenges within a public health emergency

Despite somewhat long histories, Covid-19 vaccines initially posed significant challenges for national medicines regulatory agencies which approve vaccines for use in countries. During the pandemic's early years, agencies were expected to take decisions quickly given mounting Covid-19 cases and deaths. Different regulatory agencies took diverse routes to vaccine approvals, some based on early phase immunological data rather than placebo-controlled efficacy studies.

Immunological data rely on the detection and quantification of an antibody response to vaccination, with the assumption that the detected antibodies will be protective. Still, these studies are not designed to prove whether a vaccine works to reduce the risk of a disease, in part because sometimes there is no controlled comparison group, that is, a number of people who did not receive a vaccine, received a "dummy" vaccine containing no active ingredients or received another vaccine without an effect on Covid-19.

Conversely, randomised placebo-controlled efficacy studies are considered the "gold standard" for clinical trials and are designed to prove whether a medicine or vaccine is effective. In these studies, people are randomly assigned to receive a vaccine or a placebo. Next, results are compared between these two groups. Randomisation ensures that any trait among participants that could affect results is equally distributed among groups and so cannot affect results.

Chinese authorities, for example, approved locally developed vaccines without randomised efficacy clinical trials and, instead, relied on immunological data. Manufacturers did, however, conduct subsequent randomised efficacy studies outside of China. Similarly, Russia's domestically produced vaccine — which has yet to receive WHO approval — was also reportedly deployed prior to completion of randomised controlled efficacy studies.

A careful balance of rigour and agility

The International Coalition of Medicines Regulatory Authorities (ICMRA) is a voluntary association of nearly 40 national medicine regulators, including the South African Health Products Regulatory

Authority (SAHPRA). Together, these regulators — with the WHO as an observer — work to enhance collaboration, communication and approaches to common challenges.

Early in the pandemic, ICMRA and WHO recognised the need for a co-ordinated approach to assessing Covid-19 vaccine efficacy and safety data (ICMRA/WHO, 2020). In a joint November 2020 statement, the ICMRA and WHO emphasised regulatory authorities' obligation, warning that Covid-19 vaccines and treatments could only be rapidly approved if applications were supported by robust and sound scientific evidence that allowed medicine regulators to conclude that products were effective enough to outweigh any potential risks associated with their use.

But they also stated a clear preference for the kind of evidence that should support Covid-19 vaccine approvals: "Robust and reliable data on efficacy and safety to support market approval of medicines and vaccines are best collected through randomised controlled clinical trials which control for bias, meet Good Clinical Practice standards, respect the rights, autonomy and safety of clinical trial participants, and can be audited."

While highlighting the need for "regulatory agility", the ICMRA and WHO also called for "full transparency of clinical trial results to support regulatory decisions", and cited the need to safeguard the public's trust in authorities and vaccines. In the statement, both organisations pledged to monitor Covid-19 vaccines following approvals to identify, communicate and mitigate any possible safety or efficacy issues. Lastly, they recognised the need to "reduce the risks associated with unproven treatments, potentially fraudulent and false claims which endanger patients' lives".

Building consensus: Setting the benchmarks for new vaccines

Subsequently, in May 2021, the ICMRA developed consensus documents to guide Phase 1, first-in-human trials for Covid-19 vaccines, but most critically, it set the global standard for Phase 3 vaccine efficacy studies in June 2020 (ICMRA, 2020).

Although expressed as a desirable level, not an absolute minimum,

vaccine efficacy of at least 50% was required, as measured in a placebo-controlled randomised trial that enrolled sufficient participants, which the ICMRA and WHO advised was "generally, at least 10,000 and usually about 30,000" people and included the elderly.

Efficacy was carefully defined: "Clinical trials should show that a candidate vaccine very significantly reduces Covid-19 in people who are vaccinated, compared to a control group of people who do not receive the vaccine, through a reduction in numbers of laboratory confirmed SARS-CoV-2 infections."

The ICMRA and WHO also produced a series of statements to provide healthcare professionals with the needed confidence in Covid-19 vaccines. The most recent of these, issued in May 2022, has updated the approach to assessing efficacy, allowing for "appropriately designed" immuno-bridging studies (ICMRA/WHO, 2022).

After a vaccine has been proven to be effective, immuno-bridging studies allow scientists to use existing efficacy data to infer how well a vaccine would work in different circumstances, for instance, if it was given to different population groups or alongside other immunisations. These kinds of studies are most often done to supply regulatory authorities with additional data to approve vaccines for wider use or to allow extension to age groups not initially included in the efficacy studies.

Recent work may also help pave the way for more immuno-bridging studies as recent work claims to have found a *de facto* correlate of protection for Covid-19 vaccines, in the form of target levels of neutralising antibodies (Gilbert et al., 2022). Correlates of protection define the immune response, via a vaccine or natural infection, needed to protect one from future infection. Once scientists confirm a correlate of protection, it may become a measure by which future vaccines are tested.

Local regulatory decision-making in SA

Covid-19 struck SA just *two years* after SAHPRA replaced the country's previous regulator, the Medicines Control Council (MCC) in 2018.

SAHPRA's immediate priority then had been to address the backlog in applications for registration of medicines that it inherited from the MCC. That backlog has finally been cleared, but only when using the definition initially applied: "Applications submitted prior to February 2018" (SAHPRA, 2022).

Meanwhile, a new backlog was being generated, with the majority of uncompleted reviews being for generic medicines. While considerable resources were devoted to addressing SAHPRA's inherited backlog, less attention was paid to revising what were termed "business-as-usual" processes.

Nonetheless, SA's decision-making model for regulatory approvals faced a major change in the transition between the two bodies (Gray, 2018).

Previously, under the MCC, technical reviews of dossiers submitted for registration were considered by a series of committees, which then presented proposals for decision. In the interests of continuity, the identity and composition of these technical advisory committees has been left largely untouched in the transition to SAHPRA. Under SAHPRA's new model, however, the final decision now rests with SAHPRA staff, nominally with the chief executive officer.

Read literally and simplistically, SA's medicines legislation (RSA, 1965; Minister of Health, 2017) does not contemplate the submission of an incomplete application for registration, nor does it enable an emergency or conditional registration of a medicine, including a vaccine. A complete dossier is assessed and either rejected or accepted, with conditions attached to every registration. There is, nonetheless, a process for enabling access to unregistered medicines for individual patients or groups of patients, via an electronic portal. This process, allowed for under section 21 of the country's medicines legislation, was initially adapted during Covid-19 to allow for the prompt initial approval for importation of the first Covid-19 vaccine, AstraZeneca. Thereafter, registration with specific conditions was relied upon.

By June 2021, SAHPRA had approved the AstraZeneca, Pfizer and Janssen (Johnson & Johnson) vaccines, and was considering applications for the Sinovac and Gamaleya vaccines.

SA and a more agile regulator

More importantly, SAHPRA adopted one of the "agility" mechanisms promoted by the ICMRA — rolling reviews — during Covid-19. In a rolling review, data are presented to the regulator as they become available, shortening the time to reach a decision, once the "full" dataset is presented. Equally importantly, the conditions to registration included obligations to submit missing data that would traditionally be required before a full-fledged dossier could be accepted, such as longer-term safety data or data on particular sub-populations, such as children and adolescents.

During Covid-19's initial years, there were internal debates about whether to rely on the section 21 pathway or use conditions to registration as a form of conditional approval to expedite access to vaccines. As a result, SAHPRA developed a guideline on enabling availability of medicines for use in a public health emergency (SAHPRA, 2022a). Under the guideline, SAHPRA envisages two scenarios: one in which the unregistered medicine needed has already been authorised or registered for use under comparable circumstances by a national medicine regulator recognised by SAHPRA and a second instance, where no such authorisation exists.

In the first case, a section 21 application would be possible; in the second, a rolling submission of an application for registration — in terms of section 15 of the same legislation — would be required.

In every rolling review, technical appraisal of the evidence is still needed, drawing on the capacity of SAHPRA's multiple committees, which must co-ordinate to consider evidence of quality, efficacy, and safety while also developing an appropriate risk management plan. In the case of the Covid-19 vaccines, a dedicated working group was also created to address the complete set of evidence. The decision-making power, however, remains vested in SAHPRA's chief executive officer and her staff.

Safety monitoring and public reporting in an emergency

Regulatory decisions are based on consideration of the available evidence for product quality, efficacy and safety. In the case of the Covid-19 vaccines, as the Phase 3 trials were powered to deliver a prespecified number of endpoints in terms of laboratory-confirmed infections, the available safety data were limited. The ICMRA and WHO listed the many ways in which this evidence gap could be addressed by regulators, health systems and manufacturers (ICMRA/WHO, 2022). These included:

- reviewing and analysing adverse events reported by healthcare professionals and consumers;
- actively sharing emergent information, among regulators and researchers;
- requiring manufacturers to continue safety surveillance from their ongoing clinical trials; and
- requiring manufacturers to develop and implement risk management plans, in some cases with additional post-authorisation safety studies.

Such requirements could be included as conditions to registration or appended to section 21 approval.

In SA, there has traditionally been a degree of separation between the monitoring of adverse events following immunisation and adverse events associated with the use of other medicines. Although the routine, passive surveillance pharmacovigilance systems did not specifically exclude reporting on vaccine safety, the Expanded Programme on Immunisation gathered reports on adverse events, which were then considered by the National Immunisation Safety Expert Committee (NISEC).

NISEC is specifically enjoined to assess causality, using a standardised method. SAHPRA's pharmacovigilance unit staff contribute to the NISEC process. Although the national Covid-19 vaccination programme was not initially entrusted to the usual advisory structure (the National Advisory Group on Immunisation), NISEC was assigned the task of assessing Covid-19 adverse events following immunisation for causality (NDH, 2021).

Communication about vaccine safety issues was, nonetheless, managed by SAHPRA. A dedicated micro-site which gathered together all Covid-19 adverse events following immunisation materials in an easily accessible format was created (SAHPRA, 2022b). Apart from definitions and explanations of the terms used, the site provided links to various ways in which adverse events following immunisation could be reported. Data on the number of Covid-19 vaccine doses administered were linked with a dedicated Covid-19 NDH website. Graphic representations of aggregated data on the adverse events following immunisation reported were provided, as shown in Figure 2.

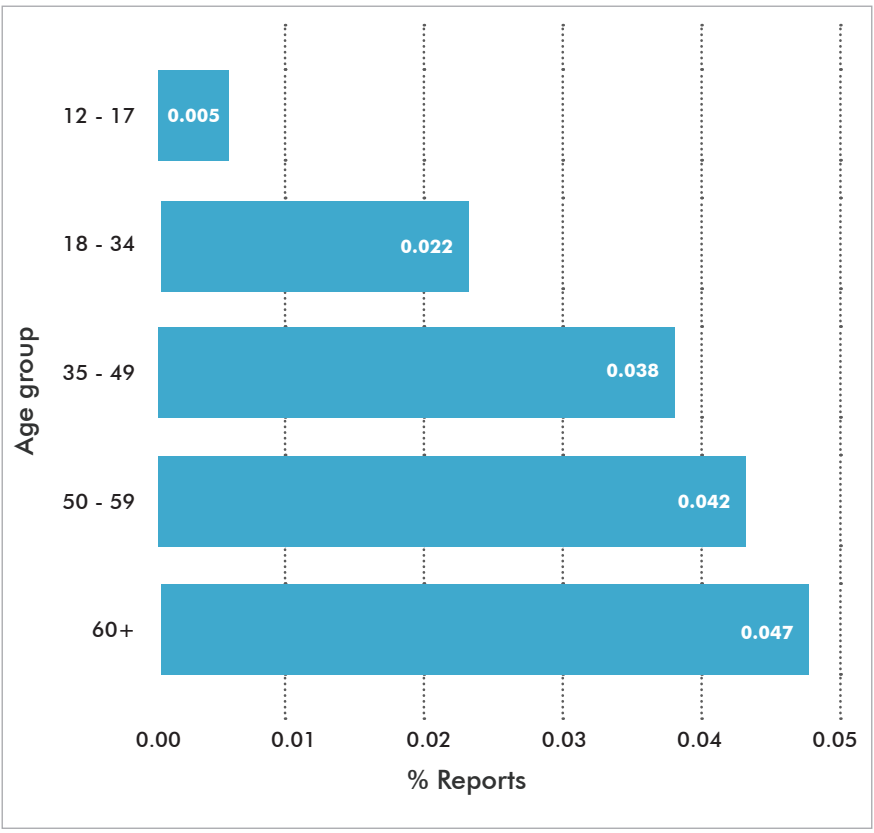

Figure 2: Total number of adverse events following immunisation reports by age group as a percentage of total vaccinations as of 7 March 2023, reproduced from SAHPRA's dedicated website.

By 31 October 2022, a total of 7,009 reports had been received and about 37 million Covid-19 doses had been administered. Data were presented separately for the two vaccines used in the national programme, Pfizer-BioNTech's Comirnaty and Janssen's Covid-19 vaccines, and the 10 most frequently reported adverse events following immunisation were summarised (see Figure 3).

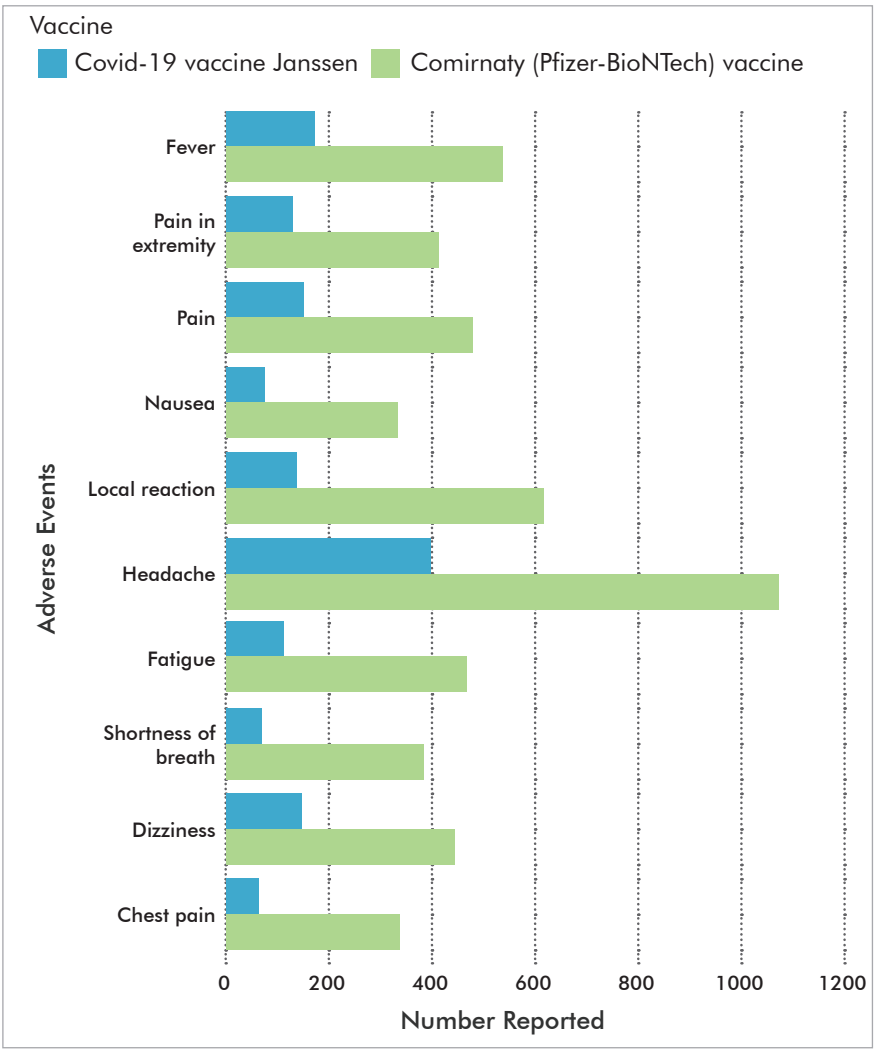

Figure 3: The 10 most frequent adverse events following immunisation reported by vaccine type as of 7 March 2023, reproduced from SAHPRA's reporting website.

Separately, a brief summary of serious adverse events following immunisation was provided, as well as the outcome of causality assessments conducted by NISEC. SAHPRA defines serious adverse events following immunisation, including those that are life-threatening, requiring hospitalisation or prolonging an existing hospitalisation, causing a congenital anomaly or birth defect, and/or that result in death.

By 31 October 2022, SAHPRA and NISEC had received 217 reports of deaths of people who had received Covid-19 vaccines. Of these, 194 had been investigated and causality had been assessed and 38 were under investigation. The outcomes were:

- 30 cases were unclassifiable, as the available information was inadequate;
- 162 cases were assessed as coincidental; and
- 2 cases were causally linked to the use of the vaccine.

The SAHPRA micro-site also provided a description of the causality assessment process.

In addition, SAHPRA issued brief media statements on the two fatal cases of the rare Guillain-Barré Syndrome, in which the immune system attacks a person's nerves, that were reported and causally linked to administration of the Janssen vaccine (SAHPRA, 2022c; SAHPRA, 2022d).

Early in the process, a webinar on vaccine safety was arranged in March 2022, which was addressed by the NISEC chairperson, the chairperson of SAHPRA's pharmacovigilance advisory committee and SAHPRA's pharmacovigilance manager.

In her seminal 2020 book, *Stuck*, American anthropologist and the founding director of the Vaccine Confidence Project, Heidi Larson, notes that "vaccination, from its start, has always walked a tense line between personal choice and public health, between autonomy and cooperation, and those waving the libertarian flag find a welcoming home in broader movements against government control" (Larson, 2020: 22).

"Vaccination campaigns and trials in different corners of the world have been stalled or suspended because individuals and groups feel as if they were not consulted and their views not respected," she

continues. “Immunisation has become a profound test of our ability to cooperate.”

Although SAHPRA has expanded access to safety data in an unprecedented way, the extent to which the general public or public interest groups have been engaged, in a meaningful manner, is less evident. Communications have been largely driven by the regulator and health authorities, and ultimately in a unidirectional fashion.

SA’s “secrecy clause” and regulatory transparency

In May 2021, the ICMRA and WHO issued a joint statement calling for maximum transparency and data integrity in relation to Covid-19 medicines and vaccines (ICMRA/WHO, 2021). The statement was directed at the pharmaceutical industry: “ICMRA and WHO call on the pharmaceutical industry to provide wide access to clinical data for all new medicines and vaccines (whether full or conditional approval, under emergency use, or rejected).”

However, the statement also included this line: “Regulators are opening their decisions to public scrutiny demonstrating confidence in their work.” It was claimed that “the first benefit is public trust”.

Despite still labouring under the restrictions of an outdated “secrecy clause” in SA law, SAHPRA did communicate more openly than usual about which applications for registration of Covid-19 vaccines had been received and how the rolling reviews were progressing (Vawda and Gray, 2017; SAHPRA, 2021).

The “secrecy clause” is contained within section 34 of SA’s Medicines and Related Substances Act and has been interpreted as prohibiting the sharing of almost all information about deliberations and decisions taken by the SAHPRA — other than the final registration of medicines and vaccines. Advisory committee meetings are closed, their documents marked as confidential, and the advice they offer to the SAHPRA staff is not disclosed.

Meanwhile, other regulators are committed to increasing transparency in relation to their regulatory decisions. Still, unlike more mature regulators — notably the European Medicines Agency and the Australian Therapeutic Goods Administration — SAHPRA does not yet publish public assessment reports, so does not detail

the reasoning behind its regulatory decisions in a publicly accessible format.

The Covid-19 vaccine experience meanwhile has demonstrated SAHPRA's ability to increase transparency, despite the "secrecy clause".

Of note, SAHPRA communicated in detail about its concerns with the safety of the Gamaleya Sputnik V vaccine and the reasons for refusing its section 21 approval. It has also shared more information about Covid-19 serious adverse events following immunisations than it had ever done before for other vaccines or for medicines in general. The data are accessible; however, they are not shared proactively with the public and in ways that are more easily understandable. SAHPRA communications are not exclusively aimed at health professionals, but neither are they deliberately crafted for a lay audience.

At the time of writing, it was unclear whether SAHPRA will be asked to approve adapted or bivalent vaccines, which are specifically aimed at protecting against variants with immune escape mutations. Although such vaccines are now being deployed in high-income settings, no applications for their registration have yet been received as of January 2023, and no indication has been offered by the government that they are considered necessary.

Covid-19 spurred new, more agile regulation and transparency, but will they live on?

Covid-19 vaccines have been a truly critical component of the global response, enabling the development of hybrid immunity which has protected millions of people and enabled a lessening of restrictions. Public health and social measures such as mask-wearing in specific contexts remain important, and ongoing booster vaccination may prove to be necessary.

A commentary in early 2023 in The Lancet proposed that Covid-19 vaccines could exert a positive influence on global disease prevention, by drawing attention to the need for greater use of available adult vaccines (Agus, 2023). There is already some

evidence — from both global and local regulatory practice — that the need for agility, transparency and improved public engagement in relation to Covid-19 vaccines has shaken up entrenched assumptions and processes. SAHPRA has shown that it can interpret its existing statute and mandate in ways that enable flexibility and transparency. The challenge remains to entrench those new ways of working, to resist the effects of entropy and habit. The trend towards greater harmonisation, reliance and co-operative regulatory practice augurs well for the nascent African Medicines Agency, which looks to increase harmonisation and to which SA is seemingly committed.

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Covid-19 vaccines explained

The Covid-19 pandemic saw the first use of an mRNA vaccine outside of clinical trials. Still, mRNA technology had been years in the making, benefiting from intensive efforts to develop vaccines for HIV, Hepatitis B and respiratory syncytial virus (RSV), for example. Here are the four major types of Covid-19 vaccines.

1. **Whole virus vaccines:** Use either weakened (also called attenuated) or dead viruses that cannot reproduce. These kinds of viruses would not make a person sick, but they do jump-start the body's immune response to provide future protection against a disease. These are the earliest forms of vaccines.

   Some attenuated vaccines may not be recommended for some people with underlying health issues such as HIV or who are on cancer treatment because even a weak virus may cause some illness in people with already compromised immune systems.

2. **Subunit, recombinant, polysaccharide, and conjugate vaccines**: Rely on pieces from viruses, like bits of protein, to trigger an immune response. Often, this is done with the help of adjuvants — substances used to super-charge vaccines and help them work better. Sometimes, these adjuvanted vaccines can cause more swelling or redness in your arm after a jab, or flu-like symptoms than immunisations without this super boost, but these symptoms pass quickly.

   These vaccines can be used on almost everyone who needs them, including people with weakened immune systems and long-term health problems. However, since vaccines contain only a small fragment of the antigen, people usually have to take more than one dose to develop memory cells that last for a long period.

3. **Nucleic acid vaccines:** Use pieces of a virus' genetic material — either DNA or messenger RNA (mRNA) — to give our cells the recipe to produce proteins that look like virus components, but are not. These look-alikes trick our immune system into thinking it is under attack and mounting a defence, leaving it ready to respond when our body meets the real baddies.

   DNA vaccines are largely confined to animal use, but more companies are looking to explore these in humans.

   In the case of mRNA Covid-19 vaccines, these vaccines give a person's cells instructions for how to make the spike protein found on the surface of SARS-CoV-2. After vaccination, cells begin making spike protein pieces and displaying them on cell surfaces, prompting the body to create antibodies. Once these vaccines have passed along these instructions to a cell, the mRNA breaks down and disappears. Still, the antigen-like proteins your cells churn out are enough to prompt an immune response.

   Because mRNA vaccines are in some ways faster to make than traditional vaccines, African countries began to invest in this kind of vaccine development and production during the Covid-19 pandemic.

   4. Viral vector vaccines: Use one of several harmless and common viruses like delivery trucks, carrying into cells a genetic code to produce proteins that look like virus components but are not, prompting an immune response.

How are vaccines developed safely?

Before any vaccine reaches a local health centre, it goes through years of testing and re-testing to make sure it works to protect you (also called efficacy), and whether it is safe to use. Then, vaccines must be approved for use by national regulators, bodies of local scientists, and other experts. Many countries also require the WHO to approve vaccines before they roll them out locally, especially if they rely on donors like the vaccine alliance, GAVI or UNICEF to buy them.

Once vaccines are introduced publicly, the work does not stop there. Scientists also conduct further studies to determine how well a vaccine works in the real world, outside of controlled clinical studies. Here, they look at how well it reduces the rates of disease in broader communities once it is introduced.

How do clinical trials work?

Vaccine trials begin in laboratories, where scientists often spend years testing out early versions against diseases without any humans involved. If these tests show promise, vaccines may next be tested in animals like mice, rabbits or monkeys. Each of these steps can involve many different studies as scientists double-check results.

If experimental vaccines are safe and show promise after all these steps, only then do researchers begin to test them in humans as part of clinical trials.

Before any clinical trial can proceed, scientists must submit an ethics proposal to an independent ethics review board. As part of this, researchers must show that studies have been designed to minimise risks to potential participants and that they have put in place every reasonable measure to protect participants from harm. Scientists must show that they have done this before ethics review bodies give their approvals to allow studies to go ahead.

Ethics proposals must also explain why the trial is important and how aspects such as randomisation and participant recruitment will be conducted ethically. Importantly, the review must show that the potential benefit of a clinical trial balances out the risks to participants.

Ethics committees monitor clinical trials after they start and until they finish. Scientists also provide ethics committees with regular reports on safety and side effects, for instance, that allow committees to protect participants' rights and safety.

Clinical trial steps: A ladder of evidence

Clinical trials happen in a series of steps, or phases, to test for safety and how well they work to protect people from infection in a controlled setting — what scientists call "efficacy."

Efficacy is the degree to which a vaccine prevents disease, and possibly also transmission, under ideal and controlled circumstances — comparing a vaccinated group with a placebo group.

Effectiveness, meanwhile, refers to how well a vaccine performs in the real world.

Most vaccine trials regardless of the phase should be designed as randomised controlled clinical trials.

What are randomised controlled clinical trials? In clinical trials, participants are often randomly assigned to different groups, or arms, of a study. When this happens, trials are known as randomised clinical trials, and they are the gold standard in clinical trial research.

Trial participants are randomised to either receive an experimental vaccine or a dummy vaccine, also known as a placebo. When this happens, it means that any characteristic — like a chronic illness — that could potentially influence the study's outcome is randomly and equally distributed among these two groups.

Comparing results from the two groups suggests whether

changes in the test group result from the vaccine or occur by chance. In many trials, no one actively in the trial — not even the research team — knows who gets the vaccine or the placebo. This reduces the chances of treating people differently depending on the study group they are in. When participants, their family members, and staff are all "blind" to the treatment while the study is underway, the study is called a "double-blind, placebo-controlled" clinical trial.

The phases of vaccine clinical trial testing

Phase I: The vaccine is tested among a very small number of healthy people who are at a low risk for the relevant disease. For their protection, people who want to fall pregnant are excluded from studies like these because scientists still are not sure at this stage whether a vaccine might cause complications in pregnant people.

Scientists are not yet looking to test how well the vaccine works to fend off infection. Instead, they are making sure that the vaccine is safe to use**.** Plus, they find out more about how it works in the body.

Phase II: If phase I trials show a vaccine is safe, it moves on to phase II. Here, scientists continue to evaluate an experimental vaccine's safety and whether it works. In particular, scientists will be looking at whether or not the vaccine kick-starts the body into producing what are called "memory cells" as part of the immune system. Also known as B-cells and T-cells, memory cells work against specific germs — and they are relatively long-lived so they "remember" how to fight their enemies for a long time.

In Phase IIa trials, an experimental vaccine is tried among hundreds of people at a natural risk of the disease because they live in areas of the world where the relevant disease is prevalent. Additionally, researchers are also looking to test how many doses a vaccine will need to be effective.

Sometimes Phase II research can also include "proof of

concept" trials. These studies are meant to determine if the vaccine being tested *might* work. Proof of concept studies can be conducted among several hundred to thousands of people, depending on how prevalent the disease is. It is not designed to tell if a particular vaccine works; instead, it helps scientists figure out if they should move forward with testing in bigger groups of people.

Phase III: If a vaccine's safety and potential signs of efficacy have been satisfactory in Phase II studies, it progresses to Phase III trials. Usually conducted among 10,000 or more people, these studies tell us whether an experimental vaccine works. This trial phase also gathers additional information on rare side effects, as the number of people included is in the thousands.

Phase IIIb: This kind of study can occur after a vaccine is considered to be safe and elicits an immune system response, but before it has been registered for use in a country by a national regulator. The goal of Phase IIIb studies is usually to provide additional data to guide the policymaking and launch of a vaccine in a country.

Phase IV: Phase IV studies are done when a drug or vaccine has already been proven safe and effective and approved for use. These studies may track side effects over decades.

Phase IV research can also involve what is called implementation studies. In this instance, they can be used to learn more about how to best use these new tools in real life. Why? Because countries have different healthcare systems and face different levels of disease.

Collecting data on vaccines in the real world can help policymakers decide, for example, whether they can afford to introduce a vaccine or how it should be given (for example, in schools or at clinics).

How long does it take to develop a vaccine?

On average, it can take at least a decade to develop a new vaccine, from the time it is first discovered until it has passed clinical trials and is available to the public.

Many vaccines will never pass all three initial phases of clinical trials.

Still, scientists were able to produce initial Covid-19 vaccines in less than a year — how? Many Covid-19 vaccines relied on long-used, traditional approaches to immunisation. Even mRNA vaccines — which had not been used outside of clinical trials until Covid-19 — had been in the works for at least a decade.

And the world threw everything it had towards developing Covid-19 vaccines.

Scientists and the people who work to oversee trials knew the world was facing an emergency. Countries invested large amounts of public, taxpayer money in finding vaccines to help deal with the crisis. Scientists who were working on other diseases — like HIV, TB or cancer — also shifted to try to discover a Covid-19 vaccine.

They worked together to allow some of these phases of research to run at the same time, but only after vaccines had been shown to be safe. They also put in longer hours to review clinical trial applications faster.

This section has been adapted from Lopez Gonzalez, Laura. Vaccines: A guide for African activists from science to access. African Alliance, 2021. (In publication)

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