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Lessons learnt from COVID-19 to reduce mortality and morbidity in the Global South: addressing global vaccine equity for future pandemics

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ABSTRACT

COVID-19, which killed more than 6 million people, will not be the last pandemic. Vaccines are key to preventing and ending pandemics. Therefore, it is critical to move now, before the next pandemic, towards global vaccine equity with shared goals, intermediate steps and long-term advocacy goals. Scientific integrity, ethical development, transparency, accountability and communication are critical. Countries can draw on lessons learnt from their response to the HIV pandemics, which has been at the vanguard of ensuring equitable access to rights-based services, to create shared goals and engage communities to increase access to and delivery of safe, quality vaccines. Access can be increased by: fostering the spread of mRNA intellectual property (IP) rights, with mRNA vaccine manufacturing on more continents; creating price transparency for vaccines; creating easily understandable, accessible and transparent data on vaccines; creating demand for a new international legal framework that allows IP rights to be waived quickly once a global pandemic is identified; and drawing on scientific expertise from around the world. Delivery can be improved by: creating strong public health systems that can deliver vaccines through the lifespan; creating or strengthening national regulatory agencies and independent national scientific advisory committees for vaccines; disseminating information from reliable, transparent national and subnational surveillance systems; improving global understanding that as more scientific data become available, this may result in changes to public health guidance; prioritising access to vaccines based on scientific criteria during an epidemic; and developing strategies to vaccinate those at highest risk with available vaccines.

Summary box

⇒ We need to prepare for the next pandemic by taking actions now to strengthen global vaccine equity.
⇒ Principles of scientific integrity, transparency, accountability and working with communities, together with global goals, are key, learning lessons from HIV and COVID.
⇒ We propose that access to vaccines can be increased by establishing mRNA vaccine production in multiple continents, ensuring price transparency, creating a new international intellectual property legal framework, creating easily accessible data on COVID vaccines and drawing on scientific expertise from around the world.
⇒ We propose that delivery of vaccines can be strengthened by creating strong public health systems for all ages, vaccinating those at highest risk with available vaccines, creating and/or strengthening national regulatory agencies, prioritising access based on public health criteria, fostering clinical and mortality surveillance systems, creating or strengthening independent national scientific advisory committees to disseminate scientific-based information and improving communication that as more scientific data are available, public health guidance may change.

INTRODUCTION

As of 3 January 2023, COVID-19 has been a leading cause of morbidity and mortality globally, resulting in over 660 million infections and almost 7 million deaths.[1] Given the widespread lack of diagnostic test availability,[2] cases went undetected, and therefore the number of deaths from COVID was likely higher. Unknown in 2019, by 2020, COVID-19 became the third leading cause of death globally.[3] Individuals who are not vaccinated against COVID-19 are more likely to report Long COVID symptoms,[4] with increased mortality.[5] Vaccines, while not the only tool, have been essential in reducing morbidity and mortality.[6] Given that all COVID vaccines currently require additional doses to protect against new variants,[7] additional doses are needed globally to reduce mortality and to prevent future pandemics with COVID-19.

Because COVID-19 impacted all countries, every country scrambled to access COVID-19 vaccines to prevent high mortality rates and reduce the burden on overwhelmed health systems and healthcare professionals. As with

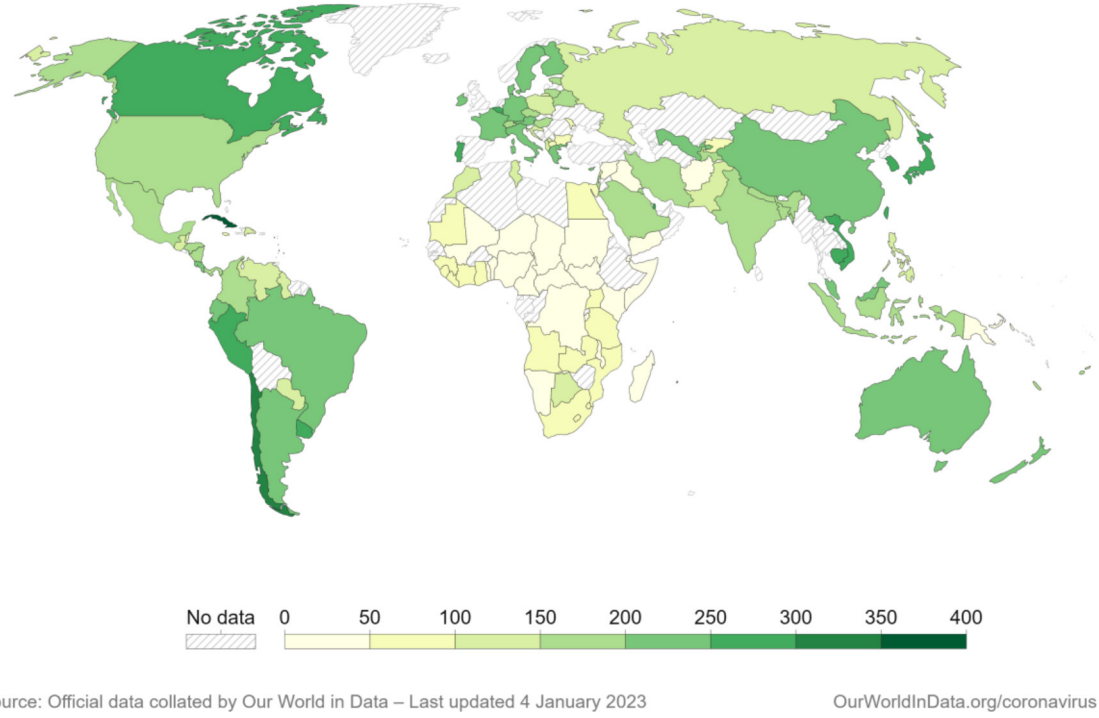

Figure 1 Total COVID-19 vaccine doses administrated per 100 people, 3 January 2023, based on Mathieu *et al*.[9] All doses, including boosters, are counted individually.

H1N1 influenza,[8] the most effective vaccines largely went to countries in the Global North early on in the COVID-19 pandemic, with vaccine inequity a salient feature (see figure 1,[9] table 1[10 11] and figure 2[12]).Vaccine effectiveness varies by type of vaccine; the number of doses and interval between; the dose volume; which virus variant is circulating at what time in which country; how transmissible the virus variant is; and host factors such as age, health risks and immune status.[13] Vaccines made with mRNA (Pfizer/Moderna) have been found to be more effective at preventing mortality than other vaccine modalities.[14] Scientists in Hong Kong concluded that individuals who received CoronaVac, an inactivated virus vaccine made in China, would require boosters with mRNA vaccines to be effectively protected against the Omicron variant.[15] The Africa region represents one-fifth of the global population, but in 2021 it received just 3% of all COVID-19 doses.[16] While the number and types of vaccines delivered to the Global South have increased over time, countries in the Global South have been the most disadvantaged in obtaining access to the most effective vaccines.[17] Prices for some vaccines were sometimes higher in the Global South than in the Global North (see table 1).

Vaccine equity could be considered across two central dimensions:

- Access: Are the vaccines a country has the most effective vaccines available? Are the prices for the vaccines affordable for the country?
- Delivery of vaccines: Does the country have a quality healthcare system, supply chain and workforce to deliver the vaccines?

Also, within a country, vaccines have often been distributed unequally, with the most vulnerable in the Global South last.[18] Inequities in access to vaccines have been noted in all countries. Examples include people with disabilities, homeless populations, refugees, as well as those in prisons, crowded living conditions and with precarious work conditions.[19–23] In addition, those living with HIV who are not virally suppressed are at high risk of COVID mortality.[24] Over 25 million of the total world population of over 38 million of those living with HIV are in Africa,[25] which has among the lowest rates of COVID vaccination. While public health dictates that those at highest risk should be the highest priority to be vaccinated, one reason this did not occur is that individuals who had resources or were in positions of power were vaccinated first.[26] Global vaccine inequity has persisted despite the recognition that without effective COVID vaccines for the majority of the world's population, mutations have and can arise which in turn puts everyone everywhere at risk of new variants of the virus that may not respond to the current arsenal of vaccines or treatment.[27]

When COVID-19 emerged as a global pandemic, many global health bodies and scientists issued guidance and recommendations and wrote scientific articles on what should be done differently for a future pandemic to ensure increased global vaccine equity, as was done in 2010 after the H1N1 pandemic. However, these guidance reports and articles had as their primary audience other scientists,[28] the US government,[29] the WHO,[30] or they had a wider scope, such as focusing on the origins of COVID-19 pandemic.[21] What can countries in the Global South, with civil society organisations (CSOs),

Table 1 Unequal pricing of COVID vaccines based on Fiolet *et al* + (WHO) the MI4A COVID-19 vaccine purchase database (for COVAX)[10 11]

Name of vaccine	Global North		Global South									
	Price in the USA	Price in European Union	Price in Brazil	Price in African Union	Price in Botswana	Price in China	Price in Senegal	Price in Pakistan	Price in India	COVAX	Price in Ukraine	Price in Hungary
Pfizer/BioNTech	$19.50	$19.50	$10	$6.75						$7.00		
Moderna	$15.00	$25.50			$28.80					$10.00		
AstraZeneca/ University of Oxford	$4.00	$2.15								$4.00		
Johnson & Johnson	$10	$8.50		$10						$7.50		
CanSino								$27.20				
Sinovac Biotech			$10.30			$29.75					$18	
Covaxin			$15.00		$16				$3–$5			
Sinopharm						$30	$18.60					$36

COVAX, COVID-19 Vaccines Global Access.

do now to prepare for the next pandemic by promoting global vaccine equity? This article focuses on distilling policy-level recommendations and actions that can be considered by leaders in countries in the Global South, including ministries of health, ministries of finance, parliamentarians and CSOs. Many scientists and human rights activists, among others, have called on pharmaceutical companies and countries in the Global North to promote global vaccine equity. Given how little progress has been made to date, in an effort to 'decolonize' global health,[26] countries in the Global South and CSOs may want to consider what actions to take now that will not solely depend on the goodwill of the Global North.[31]

OUR PROPOSAL

Actions need to be taken now by the leadership of countries in the Global South and CSOs (which includes community groups) to improve global vaccine equity through increasing access and pathways for delivery.

Increasing access

Decentralise the production of vaccines,[32] *fostering the increased production of mRNA vaccines on many continents rather than relying on donations.* The WHO, the Medicines Patent Pool, Africa Centres for Disease Control and Prevention, Afrigen, the South African Medical Research Council and Biovac partnered to set up an mRNA vaccine manufacturing centre in South Africa, which succeeded in reproducing Moderna's mRNA vaccine based on publicly available information.[33] To date, mRNA vaccine manufacturers have facilities located in 15 middle-income countries.[32–35] WHO, donors and universities in the Global North and Global South could develop a transparent, web-based system to monitor the raw materials supply chain that supports developers and manufacturers of vaccines.[34] Countries of the Global South can continue to develop their capacities and expertise to scale up vaccine trials, with scientific integrity and transparency that is independent of political pressures.[35]

Donations of vaccines from the Global North are a short-term, not perfect solution that creates a dependency on donors.[36 37] In addition, the Global North did not donate their excess vaccines in a timely manner, so many countries received vaccines with a short expiration date, rendering many doses unused and having to be destroyed.[32] Additionally, donations of vaccines from the Global North may have other risks or unintended consequences. For example, Denmark discontinued vaccinating with AstraZeneca on the basis of reports of the risks of blood clotting. While AstraZeneca donated vaccines to COVID-19 Vaccines Global Access (COVAX) for use in the Global South, communities in the Global South expressed concerns about being offered vaccines rejected by those in the Global North.[32]

Create a system of price transparency for vaccines. COVAX is a public–private partnership founded specifically to deliver COVID vaccines globally. The countries of the

Figure 2: Vaccine effectiveness of Pfizer compared to SinoVac (12)

Vaccine effectiveness (95% CI) against COVID-19-related mortality after two doses of BNT162b2 (Pfizer) and CoronaVac (SinoVac)

Age	BNT162b2 (Pfizer)	CoronaVac (SinoVac)
≥65	90.7%	74.8%
50–64	87.6%	80.7%
18–50.	86.6%	82.7%

Vaccine effectiveness (95% CI) against severe complications after two doses of BNT162b2 (Pfizer) and CoronaVac (SinoVac)

Age	BNT162b2 (Pfizer)	CoronaVac (SinoVac)
≥65	90.7%	74.8%
50–64	87.6%	80.7%
18–50.	86.6%	82.7%

Figure 2 Vaccine effectiveness of Pfizer compared with Sinovac.

Global South and CSOs were not meaningfully engaged in the creation of COVAX.[38] COVAX also does not require technology transfer for vaccine development. COVAX did not have transparent contracts, with published prices paid.[39] Some information has emerged on pricing,[10] with Dr Ghebreyesus, Director-General of WHO, noting that wealthier countries sometimes paid less for vaccines than countries in the Global South[40] (see table 1). Few countries in the Global South purchased their preferred vaccine due to high costs and availability.[41] Transparency of pricing could be a way to obtain the lowest prices for low-income countries in the Global South,[42] following the model established by UNICEF for childhood vaccines.[43]

We propose that WHO, donors and/or universities in the Global South and/or Global North collect easily understandable, accessible and transparent data on COVID vaccines. As a matter of transparency, a website with the following information would be useful to develop: (1) what is the effectiveness of different vaccines against which variant to prevent mortality? (2) where are the different vaccines available? (3) where is a particular vaccine useful given a country's infrastructure? (4) safety profile of the different vaccines and (5) cost per dose of vaccine in each country. While WHO[11] has provided some cost information, it is not complete nor easily understandable. While it is difficult to assemble all this information during the earliest stages of a pandemic, the existence of a website asking for this information will help vaccine developers, distributors and manufacturers focus on the data they should collect that would be shared.

Create demand for a new international legal framework that allows intellectual property (IP) rights to be waived quickly once a global pandemic is identified. The most effective vaccines with the fewest side effects were the mRNA vaccines developed by Pfizer and Moderna, with important scientific input from the US National Institutes of Health (NIH) and NIH-funded grantees. But US law (Bayh-Dole) encourages grantees to protect their findings as IP which is then sold to pharmaceutical companies to develop into products. Pharmaceutical companies are unlikely to undertake this development unless they are guaranteed the profits.[44] Some have argued that the USA could invoke the Defense Production Act to compel technology sharing.[45] Changing these laws in the USA is unlikely in the immediate future but international advocacy may help, as in the example of lowering the price of life-saving antiretroviral therapy drugs for HIV. An ongoing global advocacy strategy by Global South governments, CSOs and multilateral and bilateral organisations pressuring the Global North to engage in improved global vaccine equity is needed. CSOs in the Global South, such as People's Vaccine Alliance, and the Vaccine Advocacy Accelerator have started to mobilise.[46 47] A model for global vaccine advocacy could be based on what has been accomplished for HIV. One of the lessons from the global AIDS pandemic is that public advocacy leads to results. Effective HIV triple drug treatment was available in the Global North starting in 1996 but it took until 2003 for serious efforts to address HIV in the Global South, with public pressure from scientists, such as Dr Paul Farmer, and activists globally contributing to commuting HIV from a death sentence to a chronic disease. The HIV response has often been at the vanguard in establishing models for ensuring equitable access to rights-based services and serving the most vulnerable.[48]

The World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights is the most comprehensive multilateral agreement on IP and ensures protection globally of pharmaceutical patents for different vaccines.[49] The Doha Declaration clarifies that public health exigencies legitimately qualify as a national emergency where a nation may issue a compulsory licence for IP. But licences issued under Doha are subject to judicial review and are terminated at the conclusion of the emergency.[50] With the current system in place, the Global South never retains control of any vaccine and may lose any investment made to manufacture a vaccine on an emergency basis. Countries have yet to successfully reform the Doha mechanism.[51] There is no international legal instrument for COVID-19 vaccines.[52] However, 171 countries have legally binding obligations under the International Covenant on Economic, Social and Cultural Rights to the right to enjoy the benefits of scientific research without discrimination[53]; this obligation has not been heeded. Private companies may consider equitable access only after the wealthiest nations have secured their supplies.[54] Some have argued that pharmaceutical companies would be willing to share technology if only the company could get assurances about liabilities, risks and other factors.[55] Voluntary technology transfer would be faster.[31] While some have been sceptical that anything short of revising Doha to make waiving IP rights less onerous,[53] it may be useful for countries, working together, to see what could be obtained from pharmaceutical companies through negotiation. We recommend that countries work simultaneously to both build their own mRNA vaccine production, supply and expertise as well as negotiating with pharmaceutical companies.

Draw on the expertise of scientists in pharmaceutical companies around the world and other expert scientists globally who are willing to share and collaborate. The Medicines Patent Pool (MPP) has developed an important alternative to assist the Global South in voluntary licence management with transparency a key feature although concerns are still raised regarding voluntary licensing.[56] The MPP has assisted Afrigen with licensing.[57]

Some institutions and scientists have freely shared their expertise. Since mRNA vaccines are a new technology but with potentially wide applicability to numerous diseases, access to this kind of expertise is challenging, but Afrigen scientists received training from the Vaccine Research Center at the US NIH.[58] In another US example, Dr Barton Haynes of Duke University has shared with South Africa and Thailand how to conduct manufacturing in accord with good manufacturing practices (GMP), along with protocols, standard operating procedures (SOPs)

and other valuable scientific information, regarding how to make an mRNA vaccine without infringing on IP and pharmaceutical company trade secrets. Vaccine manufacturing is hampered by lack of knowledge of how to use the appropriate technology, along with established SOPs, rather than just by patents; this knowledge can be shared by US scientists working in academia, for the US government and non-profit organisations.

While many US pharmaceutical companies operate under the Bayh-Dole legislation and are unlikely to share their expertise in vaccine manufacturing, some pharmaceutical companies outside the USA may be useful resources for their expertise. For example, the British-Swedish multinational pharmaceutical company, AstraZeneca, shared their expertise with the Brazilian Bio-Manguinhos, a public laboratory linked to Brazil's Ministry of Health.[59]

It is critical to verify the credentials of experts and WHO could develop agreed upon criteria for the qualifications needed for those engaged in capacity building and sharing of expertise.

Improving delivery

Create or strengthen public health systems that can deliver vaccines and other healthcare services throughout the lifespan that will lead to a reduction in morbidity and mortality. Strong public health systems have been correlated with COVID-19 vaccine distribution and uptake.[60] Many public health systems are focused on maternal child health and are inadequate to provide country-wide vaccinations for adults and the elderly. Public health systems could be designed to vaccinate all members of a family together. For example, many countries in Latin and South America have created special vaccination days to reach children, adolescents and adults within the same timeframe.

There is an ongoing need to create an adequate cadre of health workers, with sufficient remuneration and with the resources needed to succeed. From 2014 to 2019 in Africa, there were just three physicians and just under 13 nurses and midwives for every 10 000 people.[61] Specific laws to provide fair working conditions may need to be enacted to protect healthcare workers, including community health workers, from stigma and violence.

Donors could foster improved outcomes by ensuring that health programmes they support be delivered in a community are more inclusive by investing in creating community demand and decision-making,[62] along with health systems,[63] creating synergies across health services. In some contexts, vertically funded health programmes have been faulted for increasing inequalities and deviating health workers away from providing comprehensive health services.[64] There is an opportunity for increased synergies among vertically delivered health programmes, such as between vaccination and malaria prevention strategies. One of the strengths of the US President's Emergency Plan for AIDS Relief (PEPFAR) programme was that while focused on HIV outcomes, PEPFAR worked to strengthen the public health system within a country.[65]

While focused on ending HIV, tuberculosis (TB) and malaria epidemics, the Global Fund for HIV, AIDS, TB and Malaria has invested in improvements in health security, laboratory systems and public health and clinical workforces.[66] The Global Fund has also invested in medical countermeasures, including personal protective equipment, diagnostics and their implementation, hospital services such as oxygen, national and subnational disease surveillance and community-led and community-based responses.[67] One practical goal for pandemic preparedness is the recently introduced 7-1-7 target for detection, notification and response, with preservice education for health workers.[68 69] This would require at the primary care level 7 days to assess a suspected outbreak, 1 day to notify public health authorities who initiate a response and 7 days to implement effective responses. A retrospective study in Brazil, Ethiopia, Liberia, Nigeria and Uganda found that this framework helped identify how to improve responses of a public health system and how to prioritise national planning.[70]

Vaccinate strategically, vaccinating as many as possible, particularly those at highest risk, with available vaccines to reduce mortality. Early on in the pandemic, the effectiveness of different vaccines was not known, and it was critical to vaccinate as many individuals at risk as possible. Providing any vaccines (see figure 2) did provide some level of protection. Additional shots (ie, boosters) of many vaccines are important to close immunity gaps. Use of non-pharmaceutical interventions, such as lockdowns, social isolation and/or masking, is best deployed in advance of vaccination campaigns, as Vietnam did. Vietnam also deployed massive diffusion of information through all media, including TikTok, with dance tunes by youth, until Vietnam gained access to vaccines. Starting vaccination on 8 March 2021, Vietnam had administered more than 272 doses per 100 population by 5 January 2023. By comparison, the USA has administered less than 200 doses per 100 population, with a first vaccination start date of 14 December 2020. Vietnam had a rate of 44.37 deaths from COVID per 100 000, while the USA had a rate of 327 deaths per 100 000.[71]

Based on public health criteria, create an equitable system of prioritisation for gaining access to vaccines. In order to ensure a functional health system, it is critical that healthcare workers and providers be among the first to gain access to life-saving vaccines, in addition to public safety officials. Criteria for prioritisation should be transparently conducted based on the evidence of those at highest risk of infection or death. Other criteria will depend on the pathogen and the pandemic; in the case of COVID, the elderly, the immunocompromised and those who are most at risk need to gain access to vaccines prior to those who are younger, richer or with political power.[72]

We recommend to either create and/or strengthen national regulatory agencies (NRAs) in order to be able to appropriately regulate vaccines, ensuring that any manufacturing of vaccines meets GMP standards. Countries need NRAs which can transparently and effectively evaluate the safety and

efficacy of any vaccine product.[73] NRAs are important in the successful delivery of quality vaccines; for example, in Brazil, the NRA worked closely with both AstraZeneca and BioM to adapt procedures to support vaccine production, with rolling submissions and constant communication to resolve technical issues and was fundamental to streamlining production.[59] Some countries may not have their own NRA but can draw on regional regulatory systems, such as the Caribbean Regulatory System, which serves as the regulatory unit for 15 countries in the Caribbean. WHO assists countries in strengthening their NRAs as only 26% of member states have functioning NRAs.[74] Afrigen is working to ensure regulatory compliance, working closely with the NRA in South Africa.[57]

Identify credible, trusted sources of health information, promote health literacy and create a national scientific advisory committee to disseminate accurate and reliable information during a pandemic. The Netherlands Institute for Public Health and the Environment (RIVM) was empowered to speak directly to media, with scientific independence while simultaneously advising government. The Dutch government, by law, did not tell RIVM what to say or do. RIVM engaged on a regular basis with the government to advise on the public health implications based on the most recent rigorous science. In addition, it is critical to protect these bodies, with laws, against death threats to scientists and public health officials. The media relied on RIVM for their expertise, reliability and independence.[75] Improving health literacy fosters understanding that as more scientific data are available, this may result in changes to public health guidance.[76] It is important for governments and scientists to disseminate data and information, through all platforms, including radio, mass media and digital media, that can be interactive, trusted and transparent while listening to the needs and concerns of the population.[77] There is a need for governments to create and/or strengthen ways to counter misinformation and disinformation. Social media, such as Facebook, can be a useful tool to spread vaccine information, but has also been shown to be a major purveyor of vaccine misinformation or disinformation.[78] How to best ensure that social media does not spread misinformation or disinformation that is not scientifically validated while not engaging in censorship is an ongoing challenge.[79] Where rights are violated and scientific misinformation or disinformation is spread by social media, these companies should be held to account. Gathering information on sources of vaccine hesitancy and how to overcome these barriers could be important in reducing mortality.

Foster transparent surveillance systems. Improving registrations of births and deaths and making these data available as part of improved civil registration and vital statistics to inform accurate numbers of deaths in a country can provide critical information during a pandemic, as well as identify emerging pandemics. Providing access to these data to health officials in an available format can increase transparency and accountability. A recent assessment by WHO found that almost 40% of the world's deaths are not registered. In 2021, modelling of excess deaths suggested that 50–75% of COVID-19 deaths were not recorded as such, particularly in the Global South and in areas of conflict and humanitarian emergencies.[80] COVID can be transmitted asymptomatically and depending on numerous factors, can either have minimal impact on a person's health or result in death. Therefore, measuring mortality is a key component of a national surveillance programme, and transparent data on mortality in real time are critical during a pandemic,[81] but lacking globally. As of the end of December 2022, Our World in Data stated it no longer had accurate information on COVID-19-related deaths in China. In another example, research by a student in Pakistan found that government officials did not want to provide data on COVID mortality and hospitalisations.

Wastewater can be used for surveillance,[82] although this may be more challenging in countries where the majority of the most vulnerable live in slums or rural areas without sewage systems. Countries could provide digital phones to community health workers to gather incidence and mortality data. Additionally, other surveillance data are needed, such as a surveillance system that tracks the best matched vaccine against a particular variant.[83] Finally, tracking of clinical care outcomes is needed to understand the cause of death—however, when patients die without any contact with the medical system, this will be less useful.

CONCLUSIONS

According to the US National Academy of Sciences, as well as Dr Fauci, there 'is near certain agreement that this will not be the last time a novel pathogen emerges and affects the world…'.[84] A number of the interventions suggested as a way forward to move towards global vaccine equity may take varying lengths of time to institute, so therefore, it is critical to start now to take action for the future. Both from a moral ethical standpoint and from the standpoint of reducing preventable mortality globally, it is vital to have the long-term goal of vaccine equity with practical intermediate steps and long-term advocacy goals. Scientific integrity, transparency, accountability and clear communication will be key.

Those committed to global vaccine equity can draw on recent history. Change for those living with HIV shows that progress in achieving equity is possible. In 1996, triple antiretroviral therapy became available only in the Global North. By 2004, most deaths from HIV were in the Global South. WHO guidelines for HIV between 1996 and 2013 enshrined inequality between the Global North and Global South by recommending that only monotherapy, such as azidothymidine (AZT), the first antiretroviral medication for HIV, or duo therapy be used,[85] despite the fact that more effective antiretroviral therapy was widely used in the Global North. But shared goals for HIV to treat every person—90% diagnosed, 90% on treatment and 90% virally suppressed—were ultimately adopted by

governments, civil society and global agencies,[86] creating accountability. Now, HIV is no longer a death sentence in most parts of the world. A similar global goal is needed for vaccine equity. It is hoped that promoting many of the solutions proposed here may lead to global vaccine equity, with reduced mortality and morbidity in future pandemics.

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