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COVID-19 vaccines and the pandemic: lessons learnt for other neglected diseases and future threats

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ABSTRACT

Through the experiences gained by accelerating new vaccines for both Ebola virus infection and COVID-19 in a public health emergency, vaccine development has benefited from a 'multiple shots on goal' approach to new vaccine targets. This approach embraces simultaneous development of candidates with differing technologies, including, when feasible, vesicular stomatitis virus or adenovirus vectors, messenger RNA (mRNA), whole inactivated virus, nanoparticle and recombinant protein technologies, which led to multiple effective COVID-19 vaccines. The challenge of COVID-19 vaccine inequity, as COVID-19 spread globally, created a situation where cutting-edge mRNA technologies were preferentially supplied by multinational pharmaceutical companies to high-income countries while low and middle-income countries (LMICs) were pushed to the back of the queue and relied more heavily on adenoviral vector, inactivated virus and recombinant protein vaccines. To prevent this from occurring in future pandemics, it is essential to expand the scale-up capacity for both traditional and new vaccine technologies at individual or simultaneous hubs in LMICs. In parallel, a process of tech transfer of new technologies to LMIC producers needs to be facilitated and funded, while building LMIC national regulatory capacity, with the aim of several reaching 'stringent regulator' status. Access to doses is an essential start but is not sufficient, as healthcare infrastructure for vaccination and combating dangerous antivaccine programmes both require support. Finally, there is urgency to establish an international framework through a United Nations Pandemic Treaty to promote, support and harmonise a more robust, coordinated and effective global response.

SUMMARY BOX

- ⇒ Based on the recent track record of successes for new Ebola and COVID-19 vaccines, accelerating next generation global health and pandemic threat vaccines will require a multidimensional approach that advances several vaccine technologies—messenger RNA, adenovirus, inactivated virus, nanoparticle and protein vaccines—simultaneously.
- ⇒ Low and middle-income country (LMIC) vaccine producers must be prioritised for financial and technical support early on, along with the multinational pharma companies.
- ⇒ These LMIC vaccine producers must be encouraged to pursue vaccines based on their existing capabilities, but also afforded opportunities to produce new technology vaccines along with support for rapid scale-up of production.
- ⇒ The system of stringent regulatory authorities must be extended to national regulatory authorities (NRAs) in Asia, Latin America and Africa.
- ⇒ Capacity building for regulatory science in LMICs is paramount.
- ⇒ A United Nations (UN) Pandemic Treaty and Group of 20 (G20) nations, especially the large middle-income G20 countries, should support LMIC vaccine producers and NRAs through better organised and funded initiatives.
- ⇒ In parallel, the UN Pandemic Treaty, G20 nations and civil societies must acknowledge the threat of rising antivaccine disinformation and its evolution into a wide-ranging and dangerous ecosystem, and seek solutions through international cooperation to combat it while maintaining or restoring trust among their populations.

INTRODUCTION

A 4-year-long COVID-19 pandemic that began in late 2019 and continues into 2023 dramatically altered how scientific communities think about vaccine development, manufacturing, clinical testing and ultimately emergency use release, licensure and global distribution. The COVID-19 vaccines that were licensed and delivered further affected public perceptions about scientific and medical research and the timelines required to have access to life-saving interventions. At the same time vaccine supply tended to benefit wealthy nations at the expense of low and middle-income countries (LMICs). Here we summarise both the positive and negative aspects of the COVID-19 vaccine ecosystem and how we might consider this experience as relevant for future vaccines for pandemic threats and global health inequities.

FIRING MULTIPLE 'SHOTS ON GOAL'

The COVID-19 pandemic emerged on the heels of lesser known public health successes following the emergence of the Ebola Zaire outbreak in West Africa in 2014–2015.[1] Through the support of funds from the US government and then Obama White House, together with the Group of 7 (G7) nations, several promising Ebola vaccines were developed. They included a replication-competent vesicular stomatitis virus-based Ebola virus (VSV-EBOV) vaccine, together with replication-defective adenovirus-5 (Ad5), Ad26, and chimpanzee adenovirus-3-vectored vaccines, modified vaccinia Ankara (MVA) vaccines and DNA vaccines, each proposed as a stand-alone technology or combined in prime-boost approaches.[1] Only the VSV-EBOV vaccine advanced to efficacy trials in 2015, inducing protection against Ebola infection and disease that exceeded 90%.[2] Subsequently, an Ad26/MVA combination from Johnson & Johnson and Bavarian Nordic, respectively,[3] also attained WHO prequalification status. Ultimately, the Ebola vaccination strategy in the next outbreak in the Democratic Republic of the Congo (DRC) in 2019 helped confine the spread of this highly lethal disease and possibly prevented a widespread epidemic regionally. Now, a new Sudan strain of Ebola threatens Uganda, with the hope and expectation that a new or modified vaccine will emerge.[4]

One takeaway from the DRC Ebola outbreak and the triumph of vaccine development in this instance was the importance of having available multiple vaccine technologies tested against a single disease target in the expectation that at least one might advance in terms of proven efficacy, scale-up and delivery. A similar philosophy was used for the COVID-19 vaccine programme in the USA known as Operation Warp Speed (OWS),[5] together with a broad portfolio of common candidates through the Coalition for Epidemic Preparedness Innovations (CEPI), the governments of the UK, China and India and the Access to COVID-19 Tools Accelerator and its COVID-19 Vaccines Global Access (COVAX) sharing facility.[6] Through OWS US government contracts and procurement, pharma companies in the USA and Europe gained substantial financial and regulatory incentives to test and produce multiple vaccine candidates using innovative and novel messenger RNA (mRNA), VSV, adenovirus, DNA and protein platforms.[5 7–10] Together, the UK government, CEPI, COVAX or other organisations helped support both overlapping and unique vaccine technologies including the AstraZeneca-Oxford adenovirus-vectored vaccine. It should be noted how these technologies built on almost two decades of earlier research on coronavirus vaccines that began following the initial emergence of severe acute respiratory syndrome in 2002.[11 12]

From these activities, multiple COVID-19 vaccines were developed, tested, manufactured 'at risk' (meaning their production started before completing the clinical trials) and approved. Over 11 billion doses have been delivered globally, with estimates that such vaccines may have saved millions of lives. This includes estimates of more than 300 000 lives saved in Brazil during its first year of COVID-19 immunisations,[13] and at least 2–3 million in the USA from 2020 to 2022,[14] as examples. However, across the LMICs in Africa, Asia and parts of Latin America, many more lives might have been saved if high-quality vaccines were made widely available in 2021 (during the Alpha and Delta variant waves) or early 2022 (during the BA.1 Omicron variant wave) or if COVAX targets set by WHO were achieved over this period.[15]

Nevertheless, from both the Ebola epidemic of 2019 and now COVID-19 we therefore have proof of concept that successes in slowing these scourges rely on a portfolio approach using multiple different vaccine technologies. It is not possible to predict which particular vaccine technology might prove to be successful (notably the VSV platform of Merck, which succeeded in Ebola, was unsuccessful for COVID-19) but shaping a vaccine ecosystem in which multiple different approaches are attempted in parallel should remain a priority for future pandemic threats. However, this portfolio-based approach must also remain a priority for new vaccines to combat long-standing infections for global health including HIV/AIDS, tuberculosis, malaria and neglected tropical diseases. The acceleration and scale-up production of the new technologies for COVID-19 might further help to facilitate vaccines for these more complicated targets. Therefore, the innovations leading to mRNA, adenovirus and particle vaccines, and their ability to produce them at scale, might eventually spill over to global health vaccines more broadly. In addition to the technologies, critical to the future success of this endeavour will be the ability for LMICs to establish vaccination programmes with sufficient immunisers and an adequate infrastructure including engagement of affected communities, ensuring reliable cold or freezer chain capabilities, and new administration mechanisms (eg, microneedle patch or low-cost single-dose non-reusable vaccine syringes, if proven effective), which are compatible with local health systems to get shots in arms.[16 17]

ACCELERATING VACCINE PRODUCTION AND REGULATORY SCIENCE IN LMICS

The successes in vaccine development highlighted above tell an incomplete story. More than 2 years after COVID-19 vaccines were first released, overwhelmingly they have been secured for high-income countries (HICs) in the northern hemisphere. Tragically, over this timeframe, vaccine inequalities accelerated across the LMICs on the African continent as well as the impoverished countries of Southeast Asia, Central and South America and the Caribbean (eg, Haiti and Jamaica). For example, almost 80% of the population of the USA and Canada has received at least a single dose of COVID-19 vaccine compared with only 20% in many African countries.[18] This translated to catastrophic and unnecessary losses in life and productivity.[15]

The reasons for such global vaccine inequalities are further explored in the other papers for this series,[16 17] but among them was the overemphasis on G7 nation support for the multinational companies to produce new technology vaccines such as mRNA vaccines. As a new technology, it became impossible to scale enough doses to vaccinate the world in a rapid timeframe. Despite a well-designed COVAX sharing facility, both Moderna and Pfizer-BioNTech initially sold most of their doses to HICs that could both support higher prices for the new technology and had the capacity to support the cold chain requirements. Therefore, while there is no question that the mRNA nanolipid particle approach is an exciting one, a reality is how the majority of doses were prioritised initially in high-income and some upper middle-income countries. Moreover, even when mRNA vaccines or other technologies did become available later in the pandemic, they were not always immediately accepted in part due to national resentment due to this 'too little, too late' approach. Equally important and devastating was a dearth of G7 or G20 support for local or indigenous vaccine technologies for LMIC producers.

Vaccine equity suffered from the absence of a multipronged approach that included G7 prioritisation to provide mRNA doses to LMICs, with simultaneous support for technology transfer of mRNA vaccine (and other new cutting-edge vaccine technologies) manufacturing to LMIC vaccine producers.

Thus, an important lesson learnt is the requirement to shape innovations to make vaccines that use new technologies available to LMICs, while simultaneously making appropriate vaccine technologies available widely to LMIC vaccine producers, mostly belonging to a Developing Countries Vaccine Manufacturers Network (www.DCVMN.org). The term 'appropriate' in this instance refers to the reality that the ability to both make and 'fill and finish' vaccines at a scale suitable for large populations is already in place.[19] For example, a large number of countries including Argentina, Brazil and Cuba in Latin America, and Bangladesh, India, Indonesia, Thailand, China and Vietnam in Asia produce their own recombinant hepatitis B vaccine through microbial fermentation in yeast. Therefore, it would have made sense to provide global or large-scale financial support to vaccine producers in these countries in order to mass produce a COVID-19 vaccine using both new and traditional approaches.[20] Regarding the latter, this did eventually happen through a partnership between the Texas Children's Hospital Center for Vaccine Development and several developing country vaccine manufacturers. In India, this led to the production of CORBEVAX that was released for emergency use authorisation in adults and children,[9 21] while in Indonesia it led to the release of INDOVAC, with almost 100 million doses of both vaccines administered so far. However, this approach could potentially have been accelerated and applied more widely with additional G7 support.

A parallel and alternative approach that also demonstrated some levels of success was to work on accelerating the transfer of new technologies for DCVMN members. For instance, together the UK government, CEPI and later COVAX supported the AstraZeneca vaccine, which early on made commitments to technology transfer for LMIC vaccine producers in Brazil, India and Thailand, while also supporting additional upstream technologies from Australia, China, South Korea and the USA.[22] In addition, strong efforts were made towards supporting Indian manufacturers to produce the Novavax protein particle vaccine and the Johnson & Johnson adenovirus-vectored vaccines,[23 24] while similar arrangements were made between Johnson & Johnson and Aspen Pharmacare in South Africa.[25] Beyond these examples, could there have also been much faster technology transfer of mRNA and other approaches to LMIC or DCVMN vaccine producers? In the second year of the pandemic, WHO made a commitment to facilitate mRNA technology transfer to six countries in Africa, including Egypt, Kenya, Nigeria, Senegal, South Africa and Tunisia, while the US-based Moderna made a commitment to build manufacturing capacity in Kenya[26] and BioNTech in Rwanda. A new Partnerships for African Vaccine Manufacturing in collaboration with the Africa Centres for Disease Control and Prevention and the African Union has developed a framework for regional production of most of Africa's vaccines by 2040.[27 28]

A key aspirational goal is the urgency to continue empowering DCVMN and LMIC vaccine producers rather than the current model that relies predominantly on the multinational companies in the hopes that something eventually filters through or trickles down. Experience with other vaccines suggests that the years ordinarily required before a new vaccine technology is available in LMICs could now be greatly reduced.[29] With a global pandemic increasing the speed of manufacturing technology dispersal will increase manufacturing volume, improving access to vaccines in LMICs. Among the possible approaches to consider is the possibility of further decentralisation of global fund or donor initiatives to the Global South, including the Indian subcontinent, Indonesia or the African continent. This approach embraces accelerating new and sustainable regional manufacturing hubs linked to LMIC and DCVMN vaccine producers.[30] Doing so and making such commitments over an aggressive timeframe might help reshape the current model and better address global vaccine inequalities, while also highlighting the potential contributions of LMICs to vaccine innovation in the true spirit of vaccine diplomacy.[18 24]

Still another aspect deserving of consideration is the recognition that WHO currently lists only a select group of HICs as the ones hosting 'stringent' national regulatory authorities for subsequent global distribution. While WHO will consider other LMIC regulatory authorities for global emergency use if they have attained so-called Maturity Level 3 (ML-3) status,[31] market authorisation

holders must still go through WHO prequalification mechanisms for global distribution, whereas approval by a stringent regulator can almost function as a surrogate by rapidly expediting this process. Therefore, we face a situation in which the LMIC vaccine producers must pass the gauntlet of either WHO prequalification or HIC stringent regulators that focus on problems predominantly in the 'Global North'. This is in spite of the extraordinary track record of India vaccine producers to achieve WHO prequalification of more than a dozen global vaccines and their commitment to provide vaccines for LMICs globally.[23] Moreover, we have no stringent national regulatory authority with expertise to evaluate fully vaccines for diseases that are of regional importance to particular LMICs, as opposed to global health threats, for example, a Buruli ulcer vaccine for West Africa, or a Chagas disease vaccine for Latin America.

A programme of regulatory science capacity building and strengthening is needed. This might include building capacity for LMIC regulatory authorities to become listed as stringent by WHO, while bringing others to ML-3 regulatory status, which will allow vaccines approved by that national regulatory authority to be considered by WHO for emergency use listing (EUL) or prequalification. Such regulatory strengthening will further benefit vaccines developed for neglected diseases because multinational vaccine manufacturers are not incentivised to make low-cost vaccines for problems found predominantly in LMICs. There are some nascent beginnings in this regard,[32] but more comprehensive schemes are required.

Still another consideration is whether to emphasise capacity building at the individual country level versus international platforms of open technology, data and regulatory sharing. While open sharing and mutual acceptance of regulatory approvals are certainly desirable attributes, a reality is that national pride in local life science industries has been an important driver for nations, including LMICs, with a strong track record of success.

COMBATING ANTIVACCINE AGGRESSION AND SPILLOVER

Still another consideration is the realisation that the antivaccine movement in its modern form, which began in England more than 20 years ago before it accelerated in the USA, is now a global enterprise.[33] Antivaccine propaganda and disinformation is widespread across the African continent and LMICs in Asia, and there is an urgency to identify new means to counteract it.[34] Although antivaccine activities accelerated in the COVID-19 pandemic, they may also threaten critical progress made in childhood vaccination through the work of Gavi, the Vaccine Alliance, UNICEF and WHO.[33] In parallel, is the threat of a more general erosion of trust and urgency in vaccinating the world's children. Creating a task force or committee that spans across the different agencies of the United Nations (UN) would acknowledge how the antivaccine movement has globalised and its complexity that reaches beyond the traditional health sector. In the USA, antivaccine aggression is now tightly enmeshed in American politics, becoming a major killer of young and middle-aged adults who refused COVID-19 vaccines even after they became widely available.[35] We must recognise that the forces that caused so many Americans to shun vaccines have now expanded into Canada, Australia, Western Europe, Africa and Asia with predictable, unnecessary, vaccine-preventable deaths.[33]

BRING IN THE G20 AND OTHER CONSIDERATIONS

The COVID-19 pandemic has revealed the geopolitical complexities of vaccine research, development, production, manufacture and distribution. By now the world recognises how both infectious diseases and antivaccine activities represent threats to economic attainment and national and international security, and public health. Therefore, we should not rely on the health sector alone to correct past deficiencies. More than 20 million people have perished in the COVID-19 pandemic.[36] Averting future losses in human life from pandemics means we must consider responses systematically—including diagnostics, therapeutics, vaccines and personal protective equipment—and give it the same status as other imminent threats including global conflicts, cyberattacks and other forms of terrorism.

Efforts are in progress to elevate international cooperation during a pandemic beyond WHO or its International Health Regulations (2005) and bring this to the level of the UN General Assembly through an international pandemic treaty.[37] Vaccine equity must be the front and centre of this activity. Therefore, the UN member states through a pandemic treaty, together with the G20 and their DCVMN and LMIC partners, need to address the lessons learnt, creating more robust, coordinated and effective pandemic response. We must also rely on civil society and grass-roots efforts, thus both top-down and bottom-up. Otherwise, we risk repeating failures of the past. Moving forward, we must consider a new level of financial investments, coordinated by the G20, but potentially from multiple funding sources and with input and advice from CEPI and Biomedical Advanced Research and Development Authority (BARDA).[4 6] At the 2021 G20 Summit in Rome, the G20 Leaders' Declaration specifically emphasised some of these elements including mRNA hubs for COVID-19 vaccines in South Africa, Brazil and Argentina with a goal to broaden the list of COVID-19 vaccines authorised for EUL.[38] These activities must now be generalised to include vaccines for major global health infections that include neglected diseases and potential pandemic threats. Beyond funding for vaccine development and production is the urgency to enhance the quality and capabilities of LMIC national regulatory authorities and to recognise this constitutes a fundamental element of health system strengthening. Decolonising the vaccine ecosystem to develop future

vaccines will be long and difficult and not without bumps and dead ends, but the lessons learnt from COVID-19 pandemic make this essential.

CONCLUSION

We offer the following summary recommendations for future consideration to combat global infections that cover both neglected diseases—HIV/AIDS, malaria, tuberculosis and neglected tropical and other poverty-related diseases—and pandemic threats.

- Continue the 'multiple shots on goal' approach to new vaccine targets that embraces simultaneous technologies to include, when feasible, VSV, adenovirus, mRNA, whole inactivated virus, particle and recombinant protein technologies.
- Expand scale-up capacity for each of these technologies, potentially at individual or simultaneous hubs.
- Encourage and support the development of indigenous and appropriate vaccine technologies already in place for DCVMN vaccine producers. For example, many of the DCVMN organisations already have existing strengths in recombinant protein-based vaccines.
- In parallel, support the transfer of new technologies to DCVMN producers, and emphasise this aspect of vaccine equity through a new UN Pandemic Treaty.
- Build capacity for LMIC national regulatory authorities, with an emphasis on designating several as stringent regulators.
- Take a more aggressive approach to combating antivaccine misinformation, especially now that the antivaccine movement permeates many LMICs. The antivaccine ecosystem is costing hundreds of thousands of lives; it is serious enough to warrant combating it through new international cooperation, including the proposed UN Pandemic Treaty.
- Establish a G20 framework for DCVMN and LMIC partners to promote, support and, in some cases, harmonise a more robust, coordinated and effective pandemic response. Potentially, these aspects could be pursued through a UN Pandemic Treaty.
- Encourage and embrace feedback from civil society and grass-roots in-country organisations. This may include establishing local infrastructure and capacity, including a 'warm base', in order to rapidly introduce, distribute and communicate the importance of new vaccines. Without such infrastructure, both vaccine producers and public health officials will struggle to immunise large populations.

A sobering reality is that developing COVID-19 vaccines with an established spike protein target was a relatively straightforward proposition in terms of producing a successful vaccine compared with far more complicated eukaryotic parasite and bacterial targets. We must therefore get a running start on to accelerate these activities as quickly as possible and be especially mindful about engaging country stakeholders and health systems for efficient and timely vaccine delivery.

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