Vaccine Preventable Disease and Vaccine Hesitancy

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KEYWORDS

• Vaccine • Immunization • Vaccine acceptance • Vaccine hesitancy • Antiscience • Antivaccine

KEY POINTS

- The success of COVID-19 vaccines in saving greater than 3 million lives in North America points to the promise of accelerating new vaccine technologies.
- Several new vaccines for emerging infectious diseases, including respiratory syncytial virus, norovirus, enteric bacteria, influenza, herpes simplex virus, shingles, dengue, malaria, and Chagas disease, may become available over the next 5 years.
- New vaccines for cancer and other noncommunicable diseases are also in development.
- Successful uptake and delivery of these vaccines will require expanded efforts to communicate vaccine safety and efficacy and maintain commitments to vaccine equity and diplomacy.
- This will also require heightened efforts to counter rising antivaccine activism.

INTRODUCTION: IMPACT OF COVID-19 IMMUNIZATIONS

Since 2000, an estimated 50 million deaths have been averted through global immunization programs,[1] including many pediatric lives saved through the actions of Gavi, the Vaccine Alliance of international partners.[2] Some estimates project that up to 100 million deaths could be averted before the close of this decade.[1]

Arguably such vaccination activities comprise the most impactful public health programs in modern human history. Developing and distributing vaccines also represents the top priority in preventing current and future pandemics. There were not many public health victories in the COVID-19 pandemic of 2019 to 2023, but (not surprisingly) among them was the impact of COVID-19 vaccinations in North America, especially in the United States and Canada. Through Operation Warp Speed in the United States, and advance purchase arrangements with the multinational vaccine producers, literally millions of lives were saved by delivering highly effective messenger

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RNA (mRNA), adenovirus-vector, nanoparticle, and other COVID-19 vaccines. For example, in the Unites States alone, as the first vaccines rolled out in December 2020 and until March 2022, one estimate finds that COVID-19 immunizations averted almost 2.3 million deaths and prevented 17 million hospitalizations.[3] Moreover, the economic impact of COVID-19 vaccinations on the United States economy was profound with almost one trillion dollars saved in direct and indirect health care costs.[3] An update of those numbers extended through November 2022 indicates that the US COVID-19 vaccination program prevented 3.2 million deaths, 18.5 million hospitalizations, and $1.15 trillion in medical costs, as well as 120 million COVID-19 infections.[4]

In 2023, the fourth year of the COVID-19 pandemic, the goalposts have shifted in terms of the number of immunizations required to prevent hospitalizations and deaths. During the deadly delta variant wave in 2021 in North America, 2 mRNA vaccine doses constituted a full immunization course required to prevent more than 90% of the COVID-19 deaths.[5,6] However, as the virus evolved into omicron immune escape subvariants, it became essential to boost the population with a third or even fourth vaccine dose to maintain similar levels of protection.[7] In addition, a new bivalent booster was required to cross-neutralize the newest omicron immune escape variants, such as BQ.1.1 or XBB.1.5, that accelerated in early 2023.[8] However, in North America, only Canada exhibited consistently high boosting rates, with many nations, including the world's low- and middle-income countries (LMICs), left mostly unboosted. In the presence of circulating omicron immune escape variants, new vulnerabilities may arise owing to such low boosting rates accompanied by waning herd immunity. For example, this phenomenon led a catastrophic wave of COVID-19 deaths in China during the last quarter of 2022 and first quarter of 2023.[9] This reality led to calls for expanding bivalent booster access as the newest means to achieve equity.[10] Therefore, success in defeating COVID-19 may depend on renewed efforts to encourage bivalent booster shots, both in North America and globally.

BUILDING ON THE STRENGTHS OF COVID-19 IMMUNIZATIONS

The pandemic provided proof-of-concept that it was possible to accelerate both new vaccine production and clinical testing, with only a 1-year timeframe between the time Western scientists first learned about the virus emergence until the delivery of the first mRNA vaccines.[11] However, it is important to highlight how COVID-19 vaccine development built on almost 2 decades of coronavirus vaccine work to produce vaccines for severe acute respiratory virus and Middle Eastern respiratory virus.[12] That early work first demonstrated why the spike protein, including its receptor-binding domain, was a promising vaccine target, in addition to the steps required to minimize or prevent vaccine-induced immune enhancement.[12] Nevertheless, the rapid development and testing of COVID-19 vaccines were an impressive achievement, which facilitated the immunization of North American and European populations by early 2021.[13] A parallel success story was the advances in regulatory science by national regulatory bodies in North America, the United Kingdom, and Europe that streamlined the structure of clinical trials and data sharing, or their interpretation.

One major downside of this unprecedented speed and level of innovation was how the new technology mRNA, adenovirus-vector, and nanoparticle failed to reach the world's LMICs, such as those in South Asia or Southern Africa, in time to prevent the emergence of the delta and omicron variants, respectively. Therefore, there must be improvements in vaccine technology equity, even though countries such as India and Indonesia ultimately showed an extraordinary resilience in building their own indigenous vaccines.[14] For the most part, these vaccines used more traditional

technologies, including recombinant protein-derived vaccines, with levels of virus neutralizing antibodies comparable to the newer technologies from big pharma.[15–18] This included unique vaccine development partnerships between the Texas Children's Hospital Center for Vaccine Development and vaccine producers in India and Indonesia.[14–18] Now, there are efforts to develop bivalent versions of all of these COVID-19 vaccines to target new omicron immune escape variants and their spin-off subvariants.[10]

For the mRNA vaccine technology, there are several exciting new vaccines under development for both neglected and emerging pathogens.[19] These include new mRNA vaccines for malaria, tuberculosis, and neglected tropical diseases.[19,20] BioNTech (Germany) with Pfizer is advancing the development of new mRNA vaccines for influenza,[19] and there are some prospects for a new universal influenza mRNA vaccine.[21] Moderna (United States) is also advancing new mRNA vaccines for shingles and herpes simplex virus infection.[19] This work will undoubtedly benefit from the regulatory precedents set by having COVID-19 mRNA vaccines already pass through detailed review in the United States and Europe, in addition to prequalification by the World Health Organization (WHO).

Outside of the mRNA platform, for low-income countries there are 2 new recombinant protein-based vaccines for malaria from GSK and the Serum Institute of India (SII), respectively,[22] in addition to new vaccines in clinical trials for enteric or diarrheal bacterial pathogens, such as Shigella and enterotoxigenic *Escherichia coli*, and anthelminthic vaccines for hookworm infection and schistosomiasis.[23] Because bacterial diarrheas and worm infections can exacerbate malnutrition, these enteric vaccines might help reduce global hunger now emerging owing to a food security crisis in East Africa and elsewhere. For both LMICs, there are also several different dengue virus vaccines expected soon,[24,25] including a tetravalent live-attenuated dengue vaccine from Takeda that builds on a dengue serotype-2 virus backbone.[26] A new Chagas disease vaccine is in development and expected to enter clinical testing in Mexico.[27] Takeda also has a viruslike particle vaccine for norovirus in development, while other vaccine producers are advancing their own norovirus vaccines.[28,29] From GlaxoSmithKline (GSK) and Pfizer, several new respiratory syncytial virus (RSV) vaccines are expected to be licensed or authorized in 2023 for either older adults or pregnant women (to prevent RSV infection in newborns).[30,31] Finally, active efforts are underway to explore new mucosal delivery routes for the major vaccines highlighted above, including new intranasal, sublingual (under the tongue), and oral vaccines.[32] The new mRNA, adenovirus, and nanoparticle technologies may also accelerate the development of new vaccines for noncommunicable illnesses, including cancer vaccines.[33] Several mRNA vaccines targeting melanoma, lung cancer, and blood cancers are advancing through the pipeline.[34]

VACCINE DIPLOMACY

Ensuring that these new vaccines or vaccine technologies reach all populations and achieve the requirements for vaccine equity will remain a great challenge in the 2020s (**Fig. 1**). In the first 2 years of the COVID-19 pandemic, it was learned that true equity does not depend exclusively on the multinational pharma companies or waiting for new mRNA, adenovirus, or nanoparticle vaccine technologies to filter from pharma to LMIC vaccine producers. Although the multinational companies can have an important role, true vaccine diplomacy will require active engagement between governments and LMIC vaccine manufacturers to produce vaccines locally.[35] This was a rationale for the Texas Children's Center for Vaccine Development entering

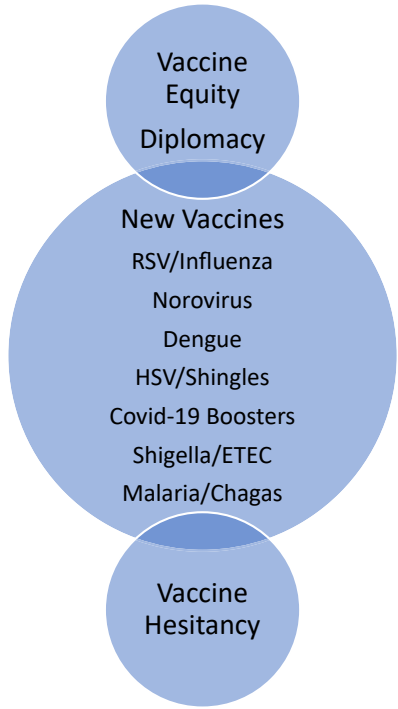

Fig. 1. Introducing new vaccines: the pull and tug of vaccine equity or diplomacy versus hesitancy growing antivaccine activism. ETEC, enterotoxigenic *Escherichia coli*; HSV, herpes simplex virus.

into partnerships with a vaccine producer in India (Biological E) and Indonesia (Bio-Farma) to produce, test, and deliver Corbevax and IndoVac, respectively.[15,16,35] Almost 100 million doses of these vaccines have been administered since 2022. AstraZeneca and Oxford University also collaborated to accelerate its adenovirus-based COVID-19 vaccine with the SII leading to the production of CoviShield for India and elsewhere.[35] Lessons learned from these experiences will be crucial for developing and introducing the new vaccines highlighted above. Potentially they could serve as a model for new LMIC vaccine producers on the African continent, the Middle East, or in Latin America.

After the pediatric *Haemophilus influenzae type b* (Hib) vaccine was introduced in the United States during the 1980s, it was rapidly adopted by pediatricians and accepted by parents. This acceptance almost immediately resulted in dramatic declines in Hib-related illnesses.[36] By the 1990s, invasive Hib illness was largely eliminated from North America.

In contrast, since 2000, the introduction of other new vaccines in North America has not always met with the same levels of enthusiasm or uptake. For instance, the Food and Drug Administration approved the first human papillomavirus (HPV) vaccine in 2006 to prevent HPV strains linked to cervical cancer and other cancers.[37] Currently, Merck's Gardasil 9 is the only vaccine for HPV available in the United States. These HPV vaccines produced significant declines in the prevalence of the HPV strains that were targeted by the first version of the Gardasil vaccine, particularly for women in their 20s.[37] However, HPV vaccine uptake and acceptance remain low in some

areas of the United States, especially in Southern states, such as Mississippi, Oklahoma, and Tennessee, or in the Mountain West states of Idaho, Utah, and Wyoming, where the estimated vaccine coverage for adolescents is less than 46% to 47%.[37] In only 5 states—Hawaii, Maryland, Massachusetts, North Dakota, and Rhode Island—is the HPV vaccination higher than 64% among adolescents 13 to 17 years.[37] This low uptake remains in stark contrast to other high-income countries. For example, far higher HPV vaccination coverage in adolescents has been achieved in Canada, Australia, and several European countries, and even in some LMICs.[38] Since 2017, 80% of Australian adolescents have received a 3-dose immunization course, through a national, school-based program.[38] Now, Australia's federal government has made commitments to eliminate cervical cancer through accelerated HPV immunizations and other measures.[39]

The factors underlying low HPV vaccine uptake in the United States relative to other high-income countries remain under active investigations. At first glance, it appears that repairing such efforts must be linked to improvements in communicating the risks of remaining unvaccinated,[40] together with information showing that HPV-vaccinated adolescents are no more likely to engage in sexual activity than those who are unvaccinated.[41] However, a reality has set in that the factors discouraging HPV vaccine acceptance represent just one aspect of a larger antivaccine ecosystem in the United States, and one that has since spread to neighboring Canada and even LMICs.[42]

Antivaccine activism in North America accelerated in the 2000s following a report published in 1998 claiming that an immunization with the measles-mumps-rubella (MMR) vaccine for infants could lead to pervasive developmental disorder (autism).[43] Despite the publication of several well-conducted and peer-reviewed studies showing that there was no MMR-autism link, antivaccine activists took advantage of the growing public access to social media by promoting unwarranted fears about this vaccine. Later, the activists would switch up the basis for their concerns regarding childhood immunizations. For example, after initially blaming the MMR vaccine, they subsequently claimed the thimerosal preservative in some infant vaccines caused autism.[43] Then they shifted again, insisting that vaccines were spaced too close together, and that somehow this overwhelmed the immune system to cause autism, or that an alum adjuvant was responsible.[43] However, each time the scientific community debunked these assertions through carefully conducted epidemiologic studies or experimental work performed in laboratory animals.

Eventually, the antivaccine community began pivoting away from autism in order to shift to the introduction of new vaccines. This new tactic began with the HPV vaccine, as antivaccine activists falsely claimed that it might cause infertility, autoimmunity, or other chronic conditions.[44] This was not only true in North America—in 2013, the Japanese Ministry of Health, Labor, and Welfare suspended its HPV vaccine program and recommendations, although the program was allowed to resume in 2021.[45] However, a dangerous precedent was set that antivaccine activists had the power, organization, and bandwidth to disrupt the introduction of a new vaccine.

During the COVID-19 pandemic, resistance to a new vaccine introduction reached a new level. Although more than 3 million lives were saved in the United States through new COVID-19 vaccinations based on mRNA, adenovirus, and nanoparticle platforms,[3] many Americans also died needlessly because they refused a COVID-19 immunization even after vaccines had become widely available by May 2021. In Texas, for example, an estimated 40,000 people lost their lives because of COVID-19 vaccine refusal, mostly during the delta variant wave in the last half of 2021, and the early BA.1 omicron wave during the winter of 2022.[46] As many as 200,000 unvaccinated Americans may have also died needlessly during this period.[47] Beyond the resistance to

new vaccine introduction during the COVID-19 pandemic was the increasing politicization of vaccines.[48] Through "health freedom" propaganda promoted by elected leaders on the far right and conservative news channels,[49,50] especially Fox News,[51] vaccine refusal became a type of badge of political allegiance. Americans living in Southern states refused vaccines because they were gaslighted into believing that the COVID-19 vaccines were either ineffective or unsafe, or that they represented tools of oppression.[47–52] This was especially true in Texas and other states where the health freedom movement began during the 2010s.[53] During the second half of 2021 and into 2022, disproportionately the COVID-19 deaths occurred among the unvaccinated in conservative or "red" states, so much so that *The New York Times* simply labeled this phenomenon as "red Covid."[47,52,54] This phenomenon extended into Canada around the "freedom convoy" antivaccine protests of 2022.

AVERTING A VACCINE CATASTROPHE

A major concern for national governments and international health agencies, including the WHO, is how antivaccine activism might now spill over into other vaccination programs.[42] This might have a role in promoting resistance to the introduction of new malaria or other vaccines intended specifically for LMICs.[22] A globalizing antivaccine movement could also extend to all routine childhood immunizations and hasten the reemergence of measles, pertussis, or even polio globally. In 2022, the WHO announced that the "COVID-19 pandemic fuels largest continued backslide in vaccinations in three decades,"[55] with much of that due to the social disruptions from the pandemic, but now even as the pandemic wanes, antivaccine activism could prevent a return to baseline immunization rates. An ensuing decline in herd immunity and a return of measles, pertussis, or other ancient scourges would have catastrophic consequence for global child health, and possibly even begin to reverse many of the successes over the past 20 years through the Gavi Alliance and other international vaccination campaigns. It could also derail efforts to introduce new and important vaccines for RSV, norovirus, dengue, and other major infectious pathogens highlighted above.

Therefore, it is imperative that the major partners of the Gavi Alliance, including the WHO, UNICEF, the Gates Foundation, and stakeholder governments, recognize the dangers of a globalized and politically empowered antivaccine movement. Antivaccine activism has already derailed cervical cancer elimination efforts in the United States and Japan and precipitated the untimely COVID-19 deaths of hundreds of thousands of people in North America—that might otherwise have been prevented. Antivaccine activism has emerged as a potent killing force, and one that requires new and innovative solutions. Because in North America the antivaccine movement now aligns to a political infrastructure, its dissolution may also depend on political interventions, or at least those that might fall outside the traditional health sector.[47] Failing to do so could erode vaccine confidence worldwide.

DISCLOSURE

Prof. P.J. Hotez is a coinventor on vaccine patents for neglected tropical diseases owned by Baylor College of Medicine (BCM). He is also a coinventor of a COVID-19 recombinant protein vaccine technology owned by BCM that was recently licensed by Baylor Ventures nonexclusively and with no patent restrictions to several companies committed to advance vaccines for low- and middle-income countries. These include Biological E (India), BioFarma (Indonesia), Incepta (Bangladesh), and ImmunityBio (United States with partnerships is the African Continent, including Botswana

and South Africa). The coinventors have no involvement in license negotiations conducted by BCM. Similar to other research universities, a long-standing BCM policy provides its faculty and staff, who make discoveries and that result in a commercial license, a share of any royalty income. Any such distribution will be undertaken in accordance with BCM policy. In addition, Dr P.J. Hotez is also the author of several books published by academic presses (ASM–Wiley and Johns Hopkins University Press), and he receives modest royalty income from this activity.

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