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Review Article

The future of COVID-19: A vaccine review

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ABSTRACT

The COVID-19 pandemic has impacted individuals, families, and communities for well over a year, and has brought light to how a broad range of social, economic, and historically relevant factors take massive tolls on the health and well-being of underserved communities around the world. This literature review aims to bring light to the current landscape of vaccines, disparities that exist in COVID-19 response, the historical relevance of the ongoing pandemic, and what needs to be accomplished for a more prepared response to potential future pandemics. It will be shown that as the world continues become more interconnected, amplification of international cooperation and well-funded response organizations are imperative to provide more equitable care in future health crises. The synthesis of current research will be helpful to researchers analyzing historical trends in the COVID-19 pandemic and individuals interested in better understanding and advocating for underserved communities across the globe.

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Introduction

In December 2019, the World Health Organization (WHO) China Country Office was informed of a group of cases of pneumonia of unknown etiology identified in Wuhan City, Hubei Province, China [1]. By early January 2020, Chinese authorities identified the cause of these pneumonia cases as a new coronavirus. This novel coronavirus was later named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and its infectious syndrome was named by the WHO, Coronavirus Disease 2019 (COVID-19). Even with significant measures taken to contain the virus, SARS-

CoV-2 rapidly spread across Eastern and Southeastern Asia, and then on to every continent in the world. To date, after over a year and a half of lockdowns, strict travel restrictions, and 3.7 billion vaccines administered, SARS-CoV-2 has claimed the lives of over 4.1 million people worldwide [2]. While the exact efficacy of vaccines preventing transmission of SARS-CoV-2 is still unclear, there is strong evidence demonstrating the protective nature of the major vaccines in use against severe symptomatic COVID-19 [3–5]. With the potential of vaccinated individuals to asymptotically acquire COVID-19 and transmit it on to those around them, herd immunity will require close to the entire population receiving vaccines. Unfortunately, government responses and access to vaccination vary drastically country to country; this inequity opens the door to long term socioeconomic, and health disparities that could create further inequity between various communities across the world.

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This literature review aims to bring light to the current landscape of vaccines, disparities that exist in COVID-19 response, the historical relevance of the global pandemic, and what needs to be accomplished for a more prepared response to potential future pandemics.

Vaccine protection and efficacy

Candidate vaccines primarily act against infection, disease, or transmission: a vaccine capable of reducing any of these factors would be valuable in contributing to the control of COVID-19 spread [6]. In this regard, many vaccines have demonstrated a strong case for implementation and a variety of vaccines are already in use including: Pfizer-BioNTech, Moderna, AstraZeneca-University of Oxford, Johnson & Johnson (J&J) Janssen, Russia's Sputnik, Sinovac Life Sciences, and Novavax (Table 1). However upon development of each of these vaccines, public perception heavily focused on published efficacy rates especially with the Pfizer-BioNTech mRNA vaccine leading the way with 95% efficacy in preventing COVID-19 infection. That number can be misleading to the general public, especially when compared to other vaccines such as the J&J vaccine that reported ~70% efficacy rate [7]. In calculating the Pfizer vaccine's efficacy, it is important to note that Pfizer did not test respiratory specimen of their subjects until after they demonstrated at least one of the following symptoms: fever, new/increased cough, new/increased shortness of breath, chills, new/increased muscle pain, loss of taste or smell, sore throat, diarrhea, or vomiting [4]. This exception is noteworthy because Pfizer's vaccine may not necessarily prevent 95% of patients from becoming infected or transmitting COVID-19: the data simply speaks to the vaccine's ability to minimize symptoms and severe cases [4]. Unlike some other vaccines, Pfizer's initial vaccine data was heavily based off of subjects living in the United States with 130 of their 152 vaccination/testing sites based in the United States [4]. These limitations suggest that other vaccines with low efficacy rates could potentially be comparably useful depending on the context. Additionally, it highlights that every vaccine manufacturer had its own process of determining vaccine efficacy. The raw efficacy scores published by different manufacturers may not all translate to real world use in the same ways. It has been well documented that the genome of SARS-CoV-2 is highly susceptible to mutations that result in genetic drift and different strains seen across the world [8]. This variability means any of the vaccines in use could be highly efficacious for certain strains of SARS-CoV-2 and not for others.

A comparison of clinical endpoints between vaccinated and unvaccinated groups through randomized controlled trials would be the most efficient study design for demonstrating vaccine efficacy. Unfortunately, all the accepted vaccines in use rely on natural exposure to SARS-CoV-2 or laboratory identification of neutralizing antibodies in titer experiments for identifying vaccine efficacy: such a reliance creates an emphasis on the test subjects' demographics, and the region of the world the subjects live in. While large enough sample sizes can account for differences in age (e.g. older volunteers may pre-emptively be more carefully quarantining), profession (e.g. healthcare workers may have heavier exposures than other professions), and other demographic risk factors (e.g. comorbidities, lifestyle, etc.), the rise of regional SARS-CoV-2 variants poses a significant hurdle for the scientific community as larger variants of the spike protein could escape vaccine-induced antibodies [20]. Head-to-head comparisons of different vaccines' efficacy becomes increasingly difficult given each was developed and tested at different periods of the epidemic (different rates of infection), with different populations of experimental subjects, and are represented with efficacies that are calculated differently. Evidence is still limited regarding how efficacious the available COVID-19 vaccines will be compared to each other against different variants.

Studies directly comparing the health outcomes of large but related populations of people will be required to have confirmatory comparisons between the various vaccines. In the meantime, each of the vaccines significantly reduces the rate of hospitalizations and death from COVID-19 [3–5,7,9,10,17]. This suggests that for communities struggling to gain access to the more expensive vaccines with higher published efficacy rates, vaccines with lower published efficacy rates will provide better protection than having access to no vaccines at all. Many low- and middle-income countries (LMIC) face this dilemma and logically continue to procure vaccines that have a lower published efficacy rate.

Beyond efficacy standards, it is important to highlight the differences that exist between the major vaccines as they are. The SARS-CoV-2 vaccine development platforms include live attenuated vaccines (LAV), inactivated virus vaccines, sub-unit vaccines, viral vector-based vaccines, DNA vaccines, and RNA vaccines [21]. Each platform for vaccine production provides various benefits and drawbacks but notably, after 30 years of research and development efforts, this is the first instance of the mRNA platform being licensed for use in humans. Notable for its ability to be rapidly developed without exposing the patient to the pathogen, the mRNA platform used by Pfizer and Moderna will be watched closely as a potential model for future emergency vaccine responses.

Vaccination vs population acceptance

Another important consideration regarding world vaccination is the issue of vaccine hesitancy. If significant proportions of the population are hesitant or refuse to take vaccines that are made available, the pandemic will continue to ravage lives around the world. Unfortunately, along with the fastest turn around in vaccine development history has come a significant level of skepticism surrounding vaccine efficacy and safety. This global rise in vaccine hesitancy that has largely been correlated with political misinformation is directly related with an increase in social media use due to adults and children staying home from work and/or school [22]. In fact, children staying home from school around the world has not only been found to be marginally effective at reducing transmission, but also poses generational threats of deepening social, economic, and health inequities in LMIC and reduced trust in government information sources [23]. Global acceptance of COVID-19 vaccines vary directly with levels of trust in government information sources, with acceptance rates ranging from as high as 90% in China to as low as 55% in Russia [24]. Any factor that potentially decreases the trust in government information regarding vaccines could potentially magnify the COVID-19-related impact in affected communities. Thus, if an underserved community faces lengthened periods of dangerously high transmission rates requiring adults and children to stay at home, longer term negative impacts could create further generational inequities as compared to well-resourced communities. The WHO has emphasized that up-to-date scientific information paired with enabling environments, positive social influences, and motivation are key in increasing vaccine uptake [25]. Whether or not these strategies have impacted vaccine uptake is still yet to be seen, but researchers from the Mayo Clinic developed evidence-based strategies for COVID-19 vaccine uptake that largely mirror the plans set forth by the WHO, but at policy, organizational, interpersonal, and individual levels [26]. Continued dedication to such initiatives and messaging goals could significantly impact infection and mortality rates in countries around the world.

Vaccination and economic implications

Research identifies the highest COVID-19 risk populations as individuals with underlying health conditions, communities in

Table 1
An overview of major vaccine information [3–5,7,9–17].

Vaccine	Type	Doses; days between doses	Price per dose USD	Published efficacy	Effectiveness vs variants	Additional information
Pfizer-BioNTech	mRNA	2; 21 days	\$19.50	95% [4]	Effective against Alpha, and Beta variants in real world; neutralizing antibodies identified for Delta, and Lambda variants [18]	- Must be stored between –80 °C and –60 °C which limits its use to well-funded areas
Moderna	mRNA	2; 28 days	\$32–37	95% [3]	Neutralizing antibodies identified against Alpha, Beta, Delta, Gamma, Eta, and Kappa variants [16]	- Must be stored between –25 °C and –15 °C - \$15/dose for the US, \$18/dose EU. Vaccine to be sold for \$32–37/dose elsewhere
AstraZeneca-University of Oxford	Adenovirus-based	2; 28–84 days	\$2.15–\$5.25	70% [5]	Neutralizing antibodies identified against Alpha, Beta, Gamma, Delta, and Kappa variants [5]	- Can be stored, transported, and handled at normal refrigerated conditions, and administered within existing healthcare settings. - Will provide vaccines at cost “in perpetuity” to low- and middle-income countries in the developing world. - Member of COVAX, a global initiative aiming to distribute 2 billion vaccine doses to 92 low- and middle-income countries at no more than \$3 a dose. Neither Pfizer nor Moderna has joined the initiative.
Johnson & Johnson	Adenovirus-based	1	\$10	64–72% [7]	Neutralizing antibodies identified against Alpha, Beta, Delta, Gamma, Epsilon, and Kappa variants [19]	- Costing the EU \$8.50, with each dose going twice as far as the other brands
Russia's Sputnik V Vaccine	Adenovirus-based	2; 21 days	\$10	91.60% [9]	Limited efficacy results published	- Used in 43 predominantly LMIC countries.
Sinovac Biotech	Inactivated SARS-CoV-2 virus	2; 28 days	\$29.75	50.38–91.25% [10]	Limited efficacy results published	- Demonstrating dramatically varying efficacy rate, but consistent protection against severe cases
Novavax	Protein-based vaccine	2; 21 days	\$16	89.70% [17]	Effective against Alpha and Beta variants [17]	- Stable from 2 °C to –8 °C and shipped in a ready-to-use liquid formulation.

densely populated areas, and LMIC with limited ability to respond to larger outbreaks: such example populations include African nations with high HIV acquired immunodeficiency syndrome (AIDS) prevalence or small island nations with high diabetes prevalence [27]. Unfortunately the trend of vaccine distribution has not followed this concept. Similarly to the 2009 influenza A (H1N1) pandemic where high income countries (HIC) monopolized the vaccine supply leaving LMIC to wait until later in the pandemic for fewer doses, HIC have already acted in their self-interest [28]. By mid-August 2020, the United States and United Kingdom had both secured close to 5 doses per capita meanwhile, as of publication, many LMIC still are unable to shore-up even a single dose per capita [2]. Through a combination of private negotiations that involved vaccine development funding and large bundled purchases during clinical trials, HIC have already secured 6 billion doses of the vaccines with the highest published efficacy rates being produced in Western HIC [29]. The combination of the secrecy of these agreements and the lack of financial assets make world-wide equitable access to the highest efficacy vaccines being developed close impossible for LMIC [30]. In fact, the lack of vaccine supply in LMIC has even triggered the opening of clinics where wealthier citizens can pay high fees to receive high efficacy vaccines from abroad: opening the door for further socioeconomic status-related disparities in healthcare outcomes across the globe and fraudulent, harmful “vaccines” being used to exploit desperate communities [31,32]. As a result of limited supply, many LMIC have turned to any vaccine option they can access. For example, Brazil ordered the material for the AstraZeneca vaccine as its primary vaccination tool, but faced limited supply. As a result, Brazilian leadership turned to Sinovac Biotech’s “Coronovac” which, alongside the Sputnik vaccine, has faced concern that trials were not subject to the same scrutiny and levels of transparency as their Western counterparts [33]. Coronovac was found to be 50.38% effective in Brazilian clinical trials after the second dose, 65.3% effective in Indonesian clinical tri-

als after the second dose, and 91.25% effective in Turkish clinical trials after the second dose: these variations are attributed to different trial sizes, patient criteria, observation time, and prevalence of COVID at each of the sites. As mentioned previously, efficacy rates do not provide the entire picture as varying strains, times, and calculation methodologies all play into different reported values. Given the uncertainty surrounding long-term variant efficacy and financial barriers to vaccines with the highest published efficacy rates, it is in the best interest of LMIC around the world to secure any WHO approved vaccine regardless of efficacy to reduce mortality and transmission rates. However, it is important to consider that if vaccines with lower efficacy rates do in fact provide less protection than the more expensive mRNA vaccines produced by Pfizer and Moderna (that also require expensive storage at very low temperatures), LMIC dependent on the more affordable vaccines could face significantly worse long-term outcomes, increased healthcare costs, and untold socioeconomic impacts. In such a scenario, there would be a prolonged period of elevated infection rates among communities using less effective vaccines as compared to the nations using vaccines with higher true efficacies. Such a gap in vaccine access poses the risk of further jeopardizing at-risk LMIC, potentially creating an extended disadvantage for growth moving forward.

An analysis of vaccine hoarding in which citizens of HIC are vaccinated years ahead of those in LMIC shows that the global economy would lose \$9.2 trillion US, predominantly due to decreased exports from HIC [34]. This implies that beyond humanitarian reasons, it is in the best interest of HIC to focus on vaccinating the global community just as much as its own citizens. Additionally, when SARS-CoV-2 transmission is uncontrolled, the virus has a greater opportunity to mutate and further complicate its control: a new variant outbreak in one region of the world can become an outbreak across the world very quickly. For example, the surge in delta variant cases and deaths during late April 2021 in India not only posed

devastating burdens on Indian families, communities, and leadership, but also quickly spread across the rest of the world [35]. Future COVID-19 mutations could potentially lead to vaccine-resistant variants. The delta variant has demonstrated reduced sensitivity to vaccine-elicited antibodies and by early May 2021 had already spread to over 40 countries [35]. Increased cooperation between HIC and LMIC to bring more vaccines to communities struggling to obtain access would help accelerate the end of the pandemic. The COVID-19 Vaccine Global Access Facility (COVAX) was formed for this reason. COVAX aims to vaccinate 1 billion people by the end of 2021 through a full two-dose regimen and overcome vaccine hoarding/“vaccine nationalism” by encouraging HIC to participate even while they conduct bilateral deals with vaccine manufacturers [36,37]. A study commissioned by the International Chamber of Commerce demonstrated that HIC would reap significant benefits if the full \$27 billion funding requirement of the COVAX initiative was met to vaccinate populations of developing nations [11,34]. Unfortunately, to date the full funding of the COVAX initiative is far from being met; ultimately countries continue to adopt policies that benefit their own public health needs at the cost of others. As of late June 2021, the United States has pledged a donation of 500 million Pfizer-BioNTech mRNA vaccines to be delivered through the first half of 2022. Large donations such as these still will not account for the needs of all LMIC. This dichotomy raises the need for international dialogue and contractually fixed contribution agreements to better serve the world's population moving forward. Creating such an international agreement would be undoubtedly difficult but considering the continued suffering and variant strains still affecting HIC over a year and half since the start of major outbreaks, HIC should have internal motivation to begin working alongside LMIC preemptively.

Past vs present: COVID-19 outbreak

In order to better understand what lays ahead for the global community in the wake of COVID-19, looking back to previous health crises is invaluable. As it stands, the COVID-19 pandemic shares similarities with the severe acute respiratory syndrome associated coronavirus (SARS-CoV) epidemic, the 1918 Influenza (colloquially called the “Spanish Flu”), and the AIDS epidemic.

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In February 2003, SARS-CoV was first reported in Eastern Asia and within a few months had spread to two dozen countries across North America, South America, and Europe [38]. In what retrospectively seems like a prequel to the SARS-CoV-2 pandemic, what made the spread of SARS-CoV different from previous epidemic infectious diseases was its explosive spread which caught health and hospital authorities ill-prepared: insufficient communication led to weakened public cooperation and inadequate epidemiological information hampered prompt application of control measures [38]. The SARS epidemic had immediate sociological, psychological, and economic repercussions globally and especially so in harder hit cities like Hong Kong [38]. This impact is notable given the SARS epidemic only affected 8422 patients worldwide with 919 deaths; COVID-19 has surpassed this footprint by leaps and bounds.

As a direct correlate to size and potential devastation, media outlets have repeatedly compared the ongoing pandemic to that of

the 1918 influenza. While such comparisons are valid, the Spanish Flu heralds the famed history of being the worst pandemic in modern history [39]. It is approximated that one third of the world's population (~500 million) were infected with a 2.5% case-fatality rate, compared to a <0.1% fatality rate in other influenza pandemics. The death toll between 1918 and 1919 is estimated to have been between 50 and 100 million people [39]. The 1928 influenza was so impactful it is often referred to as the “mother” of all pandemics in part due to the fact that all influenza A pandemics since that time have been resultant from descendants of the 1918 influenza [39]. Additionally, researchers have shown that the 1918 influenza had significant social impacts, directly causing a long-term decline in social trust as a result of the social disruption and generalized mistrust of the pandemic period. Further, it has been shown that this decline in trust was passed on generationally to the descendants of survivors; this trust has in turn been directly related to economic development, meaning harder hit communities faced residual socioeconomic effects the 1918 influenza decades after the pandemic's resolution [39]. With levels of social media misinformation and vaccine hesitancy rising today, it is reasonable to raise concern over growing lack of trust between communities and governments and the long term social and economic impact of the ongoing pandemic.

Unlike the SARS and 1918 epidemics, the AIDS epidemic stands apart in its ongoing nature. As a result, the AIDS epidemic provides an example of how unresolved health crises disproportionately affect socioeconomically disadvantaged communities both in developed and developing nations. In developing countries around the world, the AIDS epidemic left millions of children orphaned, disrupted community life, and continues to contribute to the erosion of civil order and economic growth [40]. In developed countries such as the United States, communities of color, in which the poor, the undereducated, and those without regular access to health services are overrepresented, are at a higher risk of infection [40]. More than two decades after it was first clinically reported in the United States in 1981, AIDS-related healthcare costs accounted for more than a third of government health spending in Ethiopia, more than half by Kenya, and nearly two thirds in Zimbabwe [40].

The SARS, 1918, and AIDS epidemics each share different qualities with the ongoing COVID-19 pandemic, and each of these similarities provides us with stark warnings of potential long term impacts vulnerable communities across the globe face in the oncoming years and decades. Comparable epidemics have caused generational social, psychological and economic impact to communities across the globe. As compared with the periods of time in which all three aforementioned epidemics took place, the modern world provides us with a much stronger influence of technology and the opportunity for much quicker turn around and recovery. Notably, a wide array of potential vaccines produced in large quantities are available to many countries around the world. If disseminated equitably, these vaccines have the potential to significantly reduce death and transmission rates globally while also helping the world avoid many of the long term affects seen from the SARS, 1918, and AIDS epidemics. With this access to modern technology and industrialization, it is of utmost importance that the global community works together to ensure adequate vaccines are made available to the most vulnerable global citizens and dedicated resources are provided to communities of higher risk to minimize the impact of post-COVID-19 repercussions.

Conclusion

With COVID-19 having affected individuals, families, and communities for well over a year and a half, we have seen the development of a broad range of social, economic, and historically relevant factors already taking massive tolls on the health and

well-being of underserved communities around the world. While many questions do remain regarding the future of the COVID-19 pandemic, the current progression of world-wide infection rates and vaccination inequity raise many concerns. The wide range of vaccines available to individuals and communities world-wide have no in-depth studies comparing their real-world efficacies under a standardized metric. Wealthier nations could be receiving significantly more effective vaccines, or those same nations may be wasting resources in prioritizing more fragile mRNA vaccines when they could instead utilize the extra funding to assist under-resourced communities beyond their borders. On the other end of the spectrum, LMIC could be on track to face dire repercussions as seen in major epidemics of the past as a result of vaccine nationalism on the part of HIC and slow global response to disease. This could be accentuated if the more readily available vaccines with lower published efficacy rates do not provide the same protection against severe disease long term as compared to the mRNA vaccines being more prominently used in HIC. Current community health safety and international leadership standards have failed to prevent continued virus transmission and death. Inequitable vaccine deployment, vaccine hesitancy, variable vaccine efficacy, and poor international cooperation all directly put LMIC at greater risk for long-term economic challenges, health disparities, and stunted growth and development.

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