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Towards Herd Immunity: Valuation of COVID-19 Vaccines

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Insights

- As of February 19, 2021, 11 COVID-19 vaccines have been approved by at least 1 country.
- Vaccines can help achieve herd immunity as they prevent a virus from spreading - when a virus keeps encountering individuals who have been already protected against infection, the chain of transmission is broken.
- Phase 3 trials have shown promising results for several vaccines (e.g., the Moderna: mRNA-1273 and Pfizer/BioNTech: BNT162b2 vaccines), while phase 3 results are still impending for few vaccines (e.g., the FBRI: EpiVacCorona and Bharat Biotech: Covaxin vaccines) that have already been approved by some countries.
- COVID-19 vaccines not only have unique production and deployment challenges, but many of them are simply unaffordable for low- and middle-income countries.
- Many high income countries have pre-purchased large proportions of vaccines, which raises serious allocation concerns for the rest of the world.
- Herd immunity will not be achieved by only vaccinating selected populations given the transient nature of the spread of SARS-CoV-2 that knows no borders - a COVID-19 outbreak anywhere is an outbreak everywhere in the world.
- Investment in equitable and sustainable vaccine strategies at the global scale will be the only way to win the battle against this pandemic.

> "Billions of individuals around the world might not have access to COVID-19 vaccines in 2021, which could prolong the pandemic and raise the risk of further mutations of the virus emerging, possibly undermining the efficacy of existing vaccines."
>
> **Wouters et al (2021) (1)**

After a year of the COVID-19 pandemic being characterized by chaos and uncertainty, there is finally some hope on the horizon with the emergence of some successful vaccines. While safe and effective vaccines do indeed hold much promise for curbing this global health crisis, there are currently many factors that prevent vaccines from reaching their true protective potential. It is not enough to have successful vaccines – people have to be willing to take them and they have to be delivered to people in a timely manner. This has not been an easy goal to achieve as vaccine hesitancy for COVID-19 has been on the rise (see our OE Insight "**Vaccine Hesitancy: A Top 10 Threat to Global Health**"). Different vaccines using different platforms have been approved in different countries – which come with their own unique manufacturing and distribution challenges and may become available to their respective populations at different times. Furthermore, the lack of equity has been a prominent challenge since the beginning of the pandemic (see our OE Insight "A Vexing Virus and The Valuation of Vaccines" for details) which continues till today – with high income countries securing large proportions of vaccines in advance and leaving a far smaller share for low- and middle-income countries (LMICs). Not only does vaccine availability vary by country, but the rollout strategies are also very different across different settings – leading to different proportions of the populations in these countries receiving the vaccine, with direct implications for achieving herd immunity against COVID-19. As these system level barriers prevail, SARS-CoV-2 continues to run its course in an ever-evolving manner. There are now new SARS-CoV-2 variants of concern, with a lack of conclusive evidence regarding whether currently approved vaccines are indeed effective in providing protection against the new variants (see our OE Original "**COVID-19 Variants of Concern: Will There Be A Third Wave?**"). Despite this dire context, global travel has not been restricted and SARS-CoV-2 and its emerging regional variants continue to spread across borders, highlighting the truly global nature of this crisis that calls for a comprehensive action plan. Achieving herd immunity for COVID-19 does not only require customized local strategies, but also investment in global strategies that are committed to vaccinating everyone regardless of where they live.

> "As long as vaccines are fragile, expensive and difficult to distribute, the pandemic will continue."
>
> "But by far the most important issue, Altmann (Dr. Danny Altmann, Immunologist, Imperial College London) says, is "durability": how long people remain immune after vaccination. If a vaccine confers immunity for only a few months rather than many years, little progress will have been made in six months. By then we could be faced with more virulent forms of the disease swirling around the globe."
>
> **Aymes (2020) (2)**

First Things First: Status of Current Vaccines

As of February 19, 2021, there were 11 vaccines approved by at least 1 country, 20 vaccines in phase 3 trials, 39 vaccines in phase 2 trials, and 27 vaccines in phase 1 trial (3). Exhibit 1 summarizes the 11 approved vaccines, emphasizing key characteristics of their production, affordability, allocation, and deployment – all of which have direct implications for how fast vaccines get to people around the world and how fast we achieve herd immunity in different populations. In summary, vaccines that are expensive and require additional infrastructure for deployment will be more easily accessed by high income countries. Many high income countries have already pre-purchased large volumes of vaccines.

Exhibit 1: Key characteristics of COVID-19 vaccines approved in different countries as of February 19, 2021 (1,3,4)

Vaccine	Platform	Countries With Approval	Efficacy in	Estimated production capacity of 2021	Lowest price offered (US$ per course)	% of doses pre-purchased by high income countries for 2021
FBRI: EpiVacCorona	Protein subunit	1	--	--	--	--
Moderna: mRNA-1273	mRNA	38	94%	1 bn	$31	97%
Pfizer/BioNTech: BNT162b2	mRNA	60	95%	2 bn	$14	77%
CanSino: Ad5-nCoV	Non replicating viral vector	3	65.70%	320 m	--	0%
Gamaleya: Sputnik V	Non replicating viral vector	26	92%	1 bn	$6	0.40%
Oxford/AstraZeneca: AZD1222	Non replicating viral vector	48	62%*	3 bn	$5	27%
Serum Institute of India: Covishield	Non replicating viral vector	11	--	--	--	--
Bharat Biotech: Covaxin	Inactivated	1	--	700 m	$6	0%
Sinopharm (Beijing): BBIBP-CorV	Inactivated	14	79%**	1 bn	$62	8%
Sinopharm (Wuhan): Inactivated	Inactivated	2	--	600 m	$62	8%
Sinovac: CoronaVac	Inactivated	7		1 bn	$21	18%

No phase 3 trials underway for EpiVacCorona; Covishield is the manufactured in India version of AZD1222 – currently there is a phase 2/3 trial underway for Covishield; Phase 3 trial results for Covaxin have not been published yet; †Clinical trial designs, as well as efficacy endpoints, differed for the different vaccines – the efficacy figures may not be perfectly comparable; *Result based on main efficacy analysis for participants receiving two standard doses, as specified in the protocol. The result in the out-of-protocol arm (a half dose followed by a standard dose) was 90%; **These are interim phase 3 results – these have not been published in peer-reviewed journals; these results were retrieved from press releases by companies or researchers conducting the clinical trials; ††Sinovac and its research partners have reported a range of efficacy levels based on phase 3 trials in Brazil (50%), Indonesia (65%), Turkey (91%), and the United Arab Emirates (86%), but none of these results have been published in peer-reviewed journals. bn=billion; m=million. (Exhibit 1 has been adapted from **here**)

“WHO supports achieving 'herd immunity' through vaccination, not by allowing a disease to spread through any segment of the population, as this would result in unnecessary cases and deaths”

World Health Organization (2020) (5)

“Herd immunity happens when a virus can't spread because it keeps encountering people who are protected against infection.”
“High levels of vaccination-induced immunity in the population benefits those who can't receive or sufficiently respond to a vaccine, such as people with compromised immune systems. Many medical professionals hate the term herd immunity, and prefer to call it “herd protection”… That's because the phenomenon doesn't actually confer immunity to the virus itself — it only reduces the risk that vulnerable people will come into contact with the pathogen.”

“Estimates of the (herd immunity) threshold for SARS-CoV-2 range from 10% to 70% or even more. But models that calculate numbers at the lower end of that range rely on assumptions about how people interact in social networks that might not hold true…Low-end estimates imagine that people with many contacts will get infected first, and that because they have a large number of contacts, they will spread the virus to more people. As these 'superspreaders' gain immunity to the virus, the transmission chains among those who are still susceptible are greatly reduced. And “as a result of that, you very quickly get to the herd-immunity threshold” (Dr. Samuel Scarpino, Network Scientist, Northeastern University). But if it turns out that anybody could become a superspreader, then “those assumptions that people are relying on to get the estimates down to around 20% or 30% are just not accurate” (Dr. Scarpino)”.

Aschwanden (2020) (6)

> "If vaccines were to prove notably less effective against a (new SARS-CoV-2) variant, it would require vaccinating an even greater portion of the population or updating existing vaccines to make them more effective…scientists are still studying the situation, and worry about further mutations."
>
> **Choi & Ghosal (2021) (7)**

A Primer on Herd Immunity: Looking at the Nuances

Before we can fully appreciate the complex process for achieving herd immunity for COVID-19, it is important for us to review some basic concepts about this phenomenon. A detailed discussion on herd immunity, as well as the advantages and disadvantages of achieving herd immunity using vaccines or through natural disease transmission has been discussed in a previous **OE Insight.** Below is an overview of the basic concepts about **herd immunity**:

- World Health Organization (WHO) definition: "The indirect protection from an infectious disease that happens when a population is immune either through vaccination or immunity developed through previous infection".
- Herd immunity occurs when those who are vaccinated or those who have developed immunity to a disease through exposure extend an "umbrella of immunity" to those who have not.
- When a substantial proportion of a population achieves immunity, disease transmission is limited to a small proportion of the population.
- Herd immunity threshold: The proportion of the population that must be vaccinated to achieve herd immunity.
    - Factors influencing herd immunity threshold:
        - Reproduction number of viruses (R0 or R-naught): The higher the reproduction number, the higher the herd immunity threshold.
        - Effectiveness of vaccines: The higher the effectiveness of vaccines, the lower the herd immunity threshold.

In reality, calculating herd immunity is not as easy as plugging in numbers in a formula and deriving a threshold that can be expected to remain constant over time. Instead, epidemiologists recommend that it is more appropriate to think of herd immunity as a gradient rather than a steady state (6). This is precisely due to the fact that R0 assumes that everyone is susceptible to the virus – but this changes through the course of an epidemic, where some people become infected and develop immunity (6).

There has been some research on the herd immunity threshold for COVID-19, but there is still no consensus on this number (8,9). One of the biggest limitations of this research is that the estimates of this threshold are built on assumptions that may not reflect real life (6). For example, these models do not account for interventions or behavioural changes that can alter the spread of the virus (6). Most of these models show COVID-19 herd immunity threshold to be closer to 60-70%, however, given the highly infectious nature of SARS-CoV-2, it has been also proposed that the required herd immunity threshold could be much higher (10).

> "It is also conceivable that "the best" COVID-19 vaccine could not exist at all, as vaccines developed on distinct technological platforms could induce different forms of immunity, each of them appropriate in different environmental and human contexts. The polio vaccine provides an interesting example. The injectable killed Salk vaccine is turning out to be appropriate for the industrialized world: it is safe and effective in areas of the world where polio no longer exists. By contrast, the attenuated Sabin vaccine, more effective and easier to be administered orally, is appropriate for the developing world where the wild virus is still circulating."
>
> "Thus, the evolution of the pandemic could make some vaccines more appropriate in different geographic contexts or for different clusters (e.g., infants, elderly) of the human population. It is quite possible that the sequential arrival of subsequent wages of vaccines could increase and make more appropriate the protection initially induced by the first vaccines."
>
> Forni & Mantovani 2021 (11)

> "Dr. Walter Orenstein (Professor and Associate Director, Emory Vaccine Center) notes vaccination levels and other factors that affect spread could differ even within a city. In India, for instance, scientists believe that more people will need to be protected in densely populated cities, where the virus spreads faster, than in its vast countryside."
>
> Choi C & Ghosal 2021 (7)

Multidimensional Threats to Herd Immunity

Beyond characteristics of the virus itself and the vaccines for COVID-19, many other factors have been identified as important determinants of herd immunity for this disease. It has been hypothesized that COVID-19 herd immunity will also vary by the differences between communities, populations prioritized for vaccines, in addition to a wide range of system level barriers (5). Exhibit 2 provides a detailed summary of all these factors, illustrating the many pieces of the puzzle that must come together in order to achieve herd immunity for this new disease. One key takeaway message from our analysis of these factors is that given the different efficacies of vaccines from different companies and their varying expected availability and acceptability in the respective countries where these vaccines have been approved, the process of achieving herd immunity will be very different depending on where we are looking in the world.

Exhibit 2: Factors influencing COVID-19 herd immunity (1,11,12)

Virus	New SARS-CoV-2 variants of concern	● Current research findings are inconclusive regarding the effectiveness of existing vaccines against new variants.

	Affordability	• Some companies (e.g., AstraZeneca and Johnson Johnson) will leverage public-sector investment and sell vaccines at low prices. • Some companies will sell their vaccines at considerably higher prices. • Some companies are planning to sell vaccines at premium private markets in Bangladesh, India, and Brazil. • LMICs have been historically charged vaccine prices that are not adjusted to income levels – which will be a near impossible challenge to overcome during the COVID-19 pandemic when their economies are already suffering.
	Allocation	• Vaccine scarcity is compounded by high income countries making large volumes of pre-orders for vaccines. • Billions living in LMICs may not have access to vaccines in 2021. • The COVID-19 Vaccine Global Access (COVAX) Facility has been established to ensure an equitable global vaccine allocation mechanism. The premise of COVAX is to ensure no country is able to vaccinate more than 20% of its population until all countries have been able to vaccinate 20% of its population. However, as of February 2021, this initiative is already underfunded and its global vaccine rollout plans are unclear.
	Deployment	• There is not enough time to prepare effective vaccine rollout programs (e.g., identifying risk groups, delivering vaccines to risk groups which may require special arrangements, ensuring second doses are given on time). • LMICs simply do not have the infrastructure to administer vaccine programs at the scale required for COVID-19 – which includes lack of immunization registries, storage, delivery, and waste management systems.

Vaccine	Research	● There are still many unknowns that only population data collected over time can clarify. For example, it is presently not known how long protection from the vaccines lasts and how frequently booster injections are required to maintain full protection. It is also not clear the extent to which vaccines prevent vaccinated individuals from passing the virus to others. ● Some countries have approved vaccines without results from phase 3 trials. For example, Russia and India have approved EpiVacCorona and Covaxin, respectively, without results from phase 3 trials. Not only is there incomplete evidence regarding the effectiveness of these vaccines, any potential negative implications of this approval based on inadequate evidence can place the health of millions at risk. ● Current phase 3 trials have largely focused on healthy populations. Vaccines that are proven to be effective on this population may not be effective on other at-risk populations (e.g., pregnant women, individuals with obesity, individuals with diabetes).
	Production	● Companies with leading vaccine candidates have different supply capabilities by the end of 2021. ● There is no single company that can supply all countries. ● There was no pre-existing network of manufactures equipped to produce vaccines that use novel technologies, including those using the mRNA platforms. ● Global demand for vaccines and supporting supplies (including glass vials, syringes, and stabilizing agents) is unprecedented and production capacity is largely limited.

Context	Population	● Vaccine hesitancy is observed around the world in high income countries and LMICs alike. Findings of a global survey show vaccine hesitancy ranges between 2% (in Vietnam) to 62% (in Serbia). ● The virus will spread faster in densely populated regions than regions that are less populated.
	Public health interventions	● Places with more restrictive measures that promote rigorous sanitary practices, social distancing, and travel bans will slow down the spread of the virus.

"Dr. Maria Van Kerkhove (WHO's technical lead of COVID-19) noted that during the summer, COVID-19 cases were down to single digits in most countries across Europe. "We lost the battle because we changed our mixing patterns over the summer, into the fall and especially around Christmas and the new year," she said, explaining that many people had multiple contacts with family and friends over the holidays. "That has had a direct impact on the exponential growth that you have seen in many countries," she said, describing the case count increase in some places as "vertical."

Cheng & Keaton 2021 (10)

"Differences in vaccination levels among countries are also why many experts believe the virus will never be completely stamped out."

Choi & Ghosal 2021 (7)

"However, because it is unclear which vaccines will be distributed to which countries at what time, it is challenging for governments reliant on COVAX to plan vaccination programmes. Similarly, uncertainty about COVAX supply complicates governments' decisions about how to acquire the best vaccine portfolios for their populations, including doses beyond those covered by COVAX."

"The success and approval of the first COVID-19 vaccines should not detract from the enthusiasm and practical possibility of planning new studies leading to the development and production of second and third-generation vaccines as well as the design of different types of clinical trials. Indeed, COVID-19 eradication is going to be a long and winding road that will not finish once we have the first vaccine available."

Forni & Mantovani 2021 (11)

2020 and Beyond

Even after significant investment in developing vaccines and the necessary infrastructure to produce and deploy them around the world, one of the most difficult realities to accept is that COVID-19 is here to stay for the long haul. Since the beginning of the pandemic, epidemiologists have been developing many models based on different assumptions to make short- and long-term projections regarding the spread of SARS-CoV-2. Despite the differences between these models, epidemiologists agree that the future of the pandemic depends on many unknowns – which includes whether people will develop long-term immunity to SARS-CoV-2, whether seasonality will affect its spread overtime, the timing of the introduction a new virus, the cross-reactions between the coronaviruses themselves, as well as the decisions made by governments and individuals (13,14). Vaccines can indeed be the magic bullet for eradicating the pandemic by achieving herd immunity globally. However, when vaccines are administered under circumstances, which influence their effectiveness, that are constantly in flux, herd immunity becomes an extremely difficult goal to achieve.

Finish Line is Much Further than We Think

Reflecting on the current state of the pandemic and vaccines, we have identified some key challenges for achieving herd immunity (Exhibit 3), which requires many factors to operate effectively in tandem.

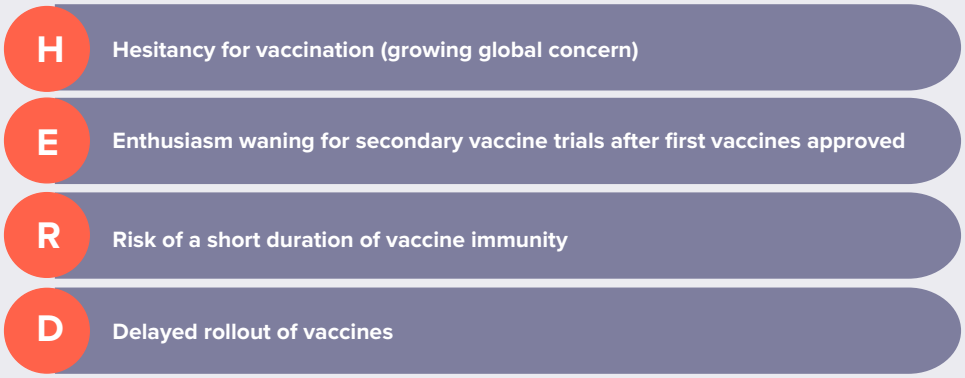

Exhibit 3: Challenges for achieving herd immunity

It is undeniable that each country will have their own set of challenges to tackle to disseminate the vaccines, however, LMICs will require a significant amount of support to protect their populations. There may be some unknowns about the current vaccines and there will likely be the need for new vaccines as we move through the future. Yet, the first step towards achieving herd immunity would be administering the vaccines in the first place, and subsequently avoid unnecessary illness, hospitalizations, and deaths. In the words of Dr. Zain Chagla, an infectious disease physician from Hamilton, Canada, “the best vaccine is the one that's administered” – reminding us that a pragmatic approach may be the best one to combat one of the biggest pandemics of our time (15).

Contributors

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