A review of leading COVID-19 vaccines, the quest for immune protection, and its key challenges

Part 4: Global Covid-19 vaccination campaign – supply and distribution logistical requirements and challenges

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Summary

Rationale

- Rapid manufacturing and effective distribution of sufficient quantities of vaccines is paramount to launch a successful vaccination campaign that will successfully achieve herd immunity to interrupt the pandemic crisis.
- The fundamental objective driving COVID-19 vaccine deployment is to ensure that all people have fair access to safe and effective COVID-19 vaccines.
- The purpose of Part 4 of this series is to highlight the logistical and ethical challenges of the supply and distribution chain of COVID-19 vaccines.

Key points

- All phases of the COVID-19 vaccination campaign merits strong consideration from an ethical and logistical perspective.
- Vaccines must be authorised by regulatory authorities before use.
- Governmental implementation bottlenecks are the cause of the inability to vaccinate at-risk populations rapidly.
- Productivity and manufacturing of mRNA-based vaccines remain low, and ultra-cold chain requirements impose significant storage and distribution challenges.
- Viral vector-based vaccines are based on proven technology and expected to yield significantly higher annual volumes.
- Recombinant protein subunit vaccines can be easily scaled up, are reasonably stable and easier to manage, but development is currently running months behind schedule.
- Live attenuated and whole inactivated virus vaccines require regulatory-approved biosafety level 3 (BSL-3) facilities for development and manufacturing, thus have more safety hurdles, are more complicated and slower to develop, and therefore unpredictable to manufacture.
- An effective vaccination campaign requires adequate procurement of vaccines and political will.
- Health care workers and elderly adults are the highest priorities for vaccination.
- Exposing vaccine distribution and implementation plans to scrutiny is critical.
- Allocation of limited vaccines should be prioritised and based on the ethical principles of maximising benefits, minimising harms, fair and equal access, transparency, informed consent and trust.
- Public trust can only be ensured through transparent communications and consistently applied allocation of safe, effective, and fair vaccines to everyone.
- Safety and public trust are critical considerations in vaccine acceptance.
- Health care professionals are the most trusted source of information.

Public health implications

- Access to vaccines for global distribution before the end of 2021 will be a task of unprecedented proportions.
- Experts recommend that governments invest in a more expansive and diversified portfolio of vaccines.
- Many countries are under-resourced with vulnerable high-risk communities.

- Multiple stakeholders are driving a global approach to equitable access.
- Public distrust, anti-vaccine messaging, and vaccine hesitancy are a significant concern to vaccine campaign efficacy to contain the pandemic.

Introduction

Rapid manufacturing and effective distribution of sufficient quantities of vaccines are essential to launching a successful vaccination campaign to achieve herd immunity to interrupt the pandemic crisis successfully.[1] A successful vaccination strategy needs a system that meets the six “rights” of supply and distribution chain management: the right product, right amount, the right conditions (cold chain), right place, right time and the right cost.[2] The ‘right product’ refers to the vaccine's selection considerations that will meet regulatory safety and efficacy requirements. Key challenges relating to the ‘right customer’ include identifying and prioritising target groups for vaccination and increasing vaccine acceptance. ‘Right quantity’ is critical for manufacturers and governments to ensure sufficient vaccines are available for required dosages and prevent wastage. ‘Right conditions’ refers to cold chain supply, shipment, and storage requirements are met to maintain stability of vaccines. ‘Right place’ refers to logistical considerations to ensure that vaccines arrive at their required destination, and that appropriate tracking systems and storage facilities are in place. ‘Right time’ is an essential factor considering the urgency of delivering vaccines as quickly as possible. ‘Right cost’ (affordability) is critical because procurement and purchases have to meet budget requirements. All abovementioned essential elements of the supply and distribution chain have their unique challenges to meet end-to-end logistic solutions required to guarantee safe and effective storage, handling, tracking, and inventory management of vaccines, the need to trace doses and individuals receiving vaccines, and rapid identification of safety and efficacy issues.

Manufacturing and distributing vaccines effectively require that the people and organisations with expertise in manufacturing, warehousing, transportation, supply chains, conserving the cold chain along the supply chain, and last-mile distribution must be positioned to direct efforts, to manage the distribution of approximated 10

billion doses of vaccines globally as quick as possible to establish herd immunity.[1,3] Furthermore, appropriate registration systems, vaccinators, support documenting staff, adequate supplies such as syringes, needles and swabs, cold storage and tracking systems need to be in place to ensure effective roll-out of the vaccination campaign.[4]

Historical lessons learned from past pandemics and vaccine campaigns with the objective to achieve herd immunity, suggest that governments and health care authorities need to invest in an effective vaccine deployment strategy that is based on (i) procurement of adequate supply effective and safe vaccines, (ii) promoting vaccine acceptance, (i) rapid distribution where it is needed, (iii) fair and equitable vaccine allocation, and (v) verification and tracking of immunised individuals.[1]

Purpose

The purpose of this 4-part series is to enhance private and public health care practitioners, as well as policymakers, knowledge and understanding of the what, why, and how COVID-19 vaccines are emerging and being deployed, their key challenges, and their impact on immune protection against COVID-19.

Part 1 explores the emerging leading COVID-19 vaccine landscape, vaccine platforms and the current status of global COVID-19 vaccination campaigns.

Part 2 provides an overview and summarises the evidence-based research from relevant interim published results from phase 1/2/3 clinical trials supporting the tolerability, safety and efficacy of current leading vaccines approved for emergency use.

Part 3 investigates the scientific considerations related to critical challenges associated with COVID-19 vaccines and immune protection.

Part 4 highlights the logistical and ethical challenges of the supply and distribution chain of COVID-19 vaccines.

Literature search methodology

Emerging literature on COVID-19 vaccines is scattered over various sources, characterised by lack of, or incomplete or uncontested evidence-based data and by a plurality of voices within the health care, academic, research, and pharmaceutical,

community as well as health care, regulatory and governmental organisations. The pandemic and emerging SARS-CoV-2 variants and their implications is rapidly evolving, making it difficult to clearly and rapidly synthesise and articulate scientific evidence. There is a need for timely and accurate evidence to inform and update private and public health care practitioners and policy decision-makers on the developing status of COVID-19 vaccines.

A comprehensive literature search of multiple bibliographic databases was conducted, including Medline, Embase, the Cochrane Collaboration and Google Scholar. COVID-19 repositories with lists of grey literature sources (e.g., LitCOVID, COVID-END and WHO-COVID-19) and preprint servers or repositories for biological and medical sciences (e.g., med$R_x$iv, bio$R_x$iv) were also included in the search strategy. Preprints are initial reports of research work that have not been subjected to peer review. Information derived from preprints thus have to be interpreted with caution. Studies and reviews in all languages were considered for inclusion. Search keywords used in this review include COVID-19, coronavirus, SARS-CoV-2, vaccines, manufacturing, production, vaccination campaign, availability, accessibility, allocation, acceptance, storage, distribution, management, logistics, procurement, ethical principles, equitable distribution, supply chain, distribution chain, verification, tracking, vaccine hesitation. Electronic databases were searched to March 31, 2021.

Strategic management requirements for an effective vaccine delivery campaign

The Effective Vaccine Management (EVM) initiative from the World Health Organization [5] provides the required support systems for Governments and non-Governmental Organisations (NGOs) to forecast the need for vaccines and supplies accurately, monitor, assess, and improve the performance of their vaccine supply and distribution chains, to avoid equipment breakdown, and to reduce waste.

Governments and NGOs have to collaborate with manufacturers and logistic services to ensure that the right amount of doses will be distributed to the right place at the right time, under the right conditions as soon as the vaccine becomes

available. Vaccines and requirements for use must be approved by regulatory authorities. The regulatory authority for medicines and vaccines in South Africa is the South African Health Products Regulatory Authority (SAHPRA).
Considering the speed of COVID-19 vaccine development, it is likely that the time plan for the roll-out of the COVID-19 vaccine campaign will also be placed under severe pressure. Implementation bottlenecks have frequently been cited in past pandemics as the primary cause for not vaccinating at-risk population fast enough.[1]

Internationally, countries are collaborating internationally, to scale-up manufacturing capacity to produce sufficient doses, addressing barriers to access vaccines, and pooling risks and costs. It is unlikely that any country will develop and manufacture a single successful vaccine at sufficient speed and scale for global use.[7] It should also be noted that pharmaceutical companies are competing with each other, which is understandable, given the financial stakes and the prestige involved, the latter particularly for academic collaborators.[7] As in all global public health matters, there are multiple stakeholders with many competing interests trying to balance the challenge of national and global interests.[7] This is not a time for nationalist or business politics. Global cooperation around COVID-19 vaccines is already being obstructed by nationalistic and political tendencies. If this continues, ineffective vaccine delivery strategies will play out, much like those still being experienced in distributing personal protective equipment, testing, and COVID-19 treatments.[1]

To ensure that COVID-19 vaccines lead to widespread vaccination and that 60-70 per cent of the population has immunity, governments, companies and public health leaders need to prepare transparent, evidence-based strategies to promote COVID-19 vaccine acceptance, and implement equitable and effective vaccine delivery.[4]
The urgency and speed required to distribute vaccines effectively, has forced improved performance of distribution strategies and cold-chain supply teams using integrated technology.

Phased immunisation campaigns of priority groups such as health care workers, elderly, care homes, individuals with co-morbidities, essential workers in many countries are being implemented.[4] Only through investment in such interconnected

and evidence-informed strategies will COVID-19 vaccines protect individuals, suppress transmission, and minimise disruption of health services and livelihoods.

Development and production

Producing the required number of doses for a global immunization campaign will be a big challenge for all vaccine manufacturers[6] (Table 1), especially for the new ones, such as mRNA or viral vector-based vaccines, that have never before been manufactured on a large scale.[7] Extraordinary amounts of money are being invested at risk by investors, institutions, and governments, to accelerate the scale-up of vaccine development and production. Multiple COVID-19 vaccines are being developed at unprecedented speed, with the primary focus on the safety and efficacy to ensure rapid regulatory approval for their use. Several countries have secured millions of vaccine doses pre-imptively from pharmaceutical companies without any evidence that they will be safe and effective, and prior to being approved for use.[8]

Diverse vaccine platforms are both desirable and economically necessary to achieve global immunisation targets.[7] Manufacturers must ensure adequate warehousing infrastructure and shipment of doses in the proper conditions. Shipment by air is preferred as this reduces time wasted due to distances covered and unloading points, mainly because of strict temperature requisites. (**Table 1**)

mRNA-based vaccines (e.g. Pfizer BioNTech, Moderna, Curevac) have the best potential for speed of scale-up. These vaccines can be manufactured quickly because they use synthetic processes. However, knowledge and experience on mRNA vaccines are limited and have not previously been registered for commercial use. Furthermore, lipid nanoparticles (LNP) technology required to stabilize mRNA is a complicated process. mRNA-based vaccines are naturally unstable and need to be formulated in LNPs and stored at ultra-cold temperature levels to maintain their stability. (Moderna's vaccine needs to be kept at -20°C, whereas Pfizer/BioNTech vaccine needs to be at -70°C).[7] Practical concerns about mass roll-out of mRNA-based vaccines, given their thermal instability, is securing ultra-cold shipping and storage for clinical use, especially in the developing world.[7] Currently manufacturing

productivity of mRNA-based vaccines remain low, therefore the cost can be expected to be significantly higher.[7,9,10] (**Table 1**)

The development of viral vector-based vaccines are comparable to gene therapy technology, a modality where plenty of experience and proven technology are generally scalable and expected to yield significantly higher annual volumes. However, specific vector platforms have thermal stability limitations.[7] Pre-validated adenovirus vector vaccine formats developed by AstraZeneca /Oxford University (ChAdOx1; adenovirus serotype 6 vector) and Johnson & Johnson (Ad26 vector) can be engineered rapidly and scaled up quickly to produce large quantities of vaccine doses at a relatively affordable price.[7]

The infrastructure for developing, manufacturing, supply and distribution chains for recombinant-subunit protein-based vaccines are well established, and are widely used as vaccines throughout the world.[7] They are relatively inexpensive to develop and to manufacture, can be easily scaled up to produce large quantities, and are reasonably stable and easier to manage for global shipping and distribution.[7] It is therefore reasonable to predict that the annual manufacturing capacity of protein-based vaccines may achieve greater volume yields to meet the needs a larger fraction of the world's population.[7] However, subunit protein-based vaccines are currently running about six months behind the vector- and mRNA-based leading vaccines because their development and manufacturing is slower due to dependency on biological processes.[7] With the manufacturing of subunit proteins, epitopes and the integrity of the antigens must be verified to ensure that the required quality, efficacy and safety standards are met.[11]

Whole inactivated- and live-attenuated virus-based vaccines, primarily developed in China, are older generation approaches, well understood, and generally effective vaccines.[7] However, these vaccines have not yet been scaled to large enough volumes suitable for global manufacturing and distribution because regulatory approved live virus biosafety level 3 (BSL-3) containment facilities are required for their manufacturing.[7] Approved BSL-3 manufacturing facilities worldwide are limited.

Vast quantities of contagious virus must be treated in BSL-3 facilities to produce whole inactivated or live attenuated virus for use in vaccines. Developing a live-attenuated virus-based vaccines (LAV) is typically protracted to find the right level of attenuation while maintaining sufficient immunogenicity and has many more safety hurdles than protein- viral vector- or mRNA/DNA-based vaccines.[7] For these reasons, there are few whole inactivated or LAV's vaccines currently in development.[7] Concerns relating to whole inactivated- and LAV vaccines are low levels of manufacturing yields, potentially lower immunogenicity in the elderly, challenging and complex manufacturing requirements and putative concerns over safety due to reversion to virulence.[7]

LAV and whole inactivated virus vaccines are older generation approaches that are now being replaced by high-end, cutting edge, highly flexible vaccine platform technologies that are more controllable, predictable, safer and easier and faster to manufacture in large quantities.[7]

Procurement and optimisation of vaccine allocation

Experts predict that first generation vaccines will be inadequate and not effective enough to end the pandemic on their own, and therefore recommend that governments invest in a broader, more diversified portfolio of vaccines for national vaccination campaigns.[12]

Assuming safe and effective vaccines are developed, having an adequate supply of vaccines is only the first step in ensuring that vaccines are procured and get delivered to the right people at the right time. Assuming that demand can be generated for COVID-19 vaccines, the question remains about who should be in line first to receive them. Unfortunately, scarce resources too often go to the most privileged/wealthy countries or individuals. Decisions about how to allocate and inform prioritisation of the limited supply of vaccine doses should be based on the principles of maximizing the interruption of SARS-CoV-2 transmission, minimising COVID-19 disease burden (morbidity and mortality), and optimising societal benefit and functioning.[1]

To allocate vaccines on an equitable basis, qualified organisations and expert coalitions must be allowed to determine evidence-based vaccination approaches and generate the political will to ensure local and national governments' cooperation.[1] The WHO and other stakeholders have formed the ACT (Access to COVID-19 Tool) Accelerator, a collaboration to facilitate equitable access to COVID-19 tests, treatments, and vaccines at global level.[5] COVAX, led by the WHO, GAVI, the Vaccine Alliance, and the Coalition for Epidemic Preparedness and Innovations, is a global mechanism under the ACT Accelerator, to accelerate the development and manufacturing of COVID-19 vaccines, to guarantee fair and equitable global access to these vaccines, and to maximise global impact.[13] To reduce mortality and protect health care workers, the WHO also released a Global Allocation Framework for COVID-19 products recommending that health care workers, elderly adults, and other high-risk groups be the highest priorities for vaccination.[14]

As all nations will face an initially scarce vaccine supply, a global allocation mechanism will be vital to efficiently and effectively decrease transmission to stop the pandemic. Despite this evidence-based guidance, COVID-19 pandemic preparedness has been obstructed for months by politics, including vaccine nationalism, as some countries are procuring vast quantities of doses even before the completion of clinical trials.[1] As of December 2020, the WHO and nearly 190 countries had put their diplomatic weight behind the COVAX initiative to pool investment and promote global vaccine access.[15] However, the United States and Russia have opted out of this plan. ACT- Accelerator donor funding commitments to date total US$ 6 billion with an additional US$ 4 billion in projected funding. Irrespective, the ACT-Accelerator still faces a US$ 27.2 billion funding gap, indicating a gap in the availability of vaccines for under-resourced countries

Vaccine shortages will likely occur, even in the most optimistic scenarios. Research found that using an age-stratified mathematical model, a vaccine with an effectiveness equal to or greater than 50% effectiveness, and provided that a high percentage of the population is optimally vaccinated, would be adequate to substantially mitigate the ongoing pandemic.[17] It is suggested that when minimising deaths with low effectiveness vaccines, an optimal result can be achieved to allocate vaccines to high-risk older age groups first. Optimisation in minimizing disease

severity, hospitalization and deaths can be achieved through allocating low effectiveness vaccines to high-risk elderly groups.
In contrast, it is recommended that greater optimisation can be achieved by allocating vaccines with a higher effectiveness to high transmission risk younger age groups.[17]

Various Governments and institutions have formulated recommendations for the prioritization and allocation of limited availability of COVID-19 vaccines.[18.19] In South Africa, the Department of Health, in collaboration with the Ministerial Advisory Committee on COVID-19 Vaccines, has published a framework and roll-out strategy for COVID-19 vaccines.[18] The Department of Health has introduced a phased approach for vaccine introduction based on the availability of vaccines. Phase I, with a constrained supply of vaccine doses, targeted frontline healthcare workers (Target population: 1,250,000). Phase II, when a more significant number of doses become available, (i.e. COVAX facility), vaccination will be targeted to include other essential workers (2,500,000), people in congregate settings (i.e. nursing homes, teachers, police, retail food, banking, municipal services and detention centres) (1,100,100), people > 60 years (5,000,000), and people older than 18 years with co-morbidities (8,000,000). Phase III will shift to a routine strategy of continued vaccination of all other individuals older than 18 years (22,500,000) as supply of vaccine becomes available through contracted manufacturers.[18]

It is critical that vaccine distribution and implementation plans are transparent and should not be shrouded in secrecy and designed by those who have never done it before, as too much depends on getting it right the first time.[4] Therefore, all phases of the COVID-19 vaccination campaign merits strong consideration from an ethical perspective.

Ethical principles for allocating limited supply of COVOD-19 vaccines

Fundamental ethical principles help steer and support decisions around prioritising and optimising the allocation of limited vaccines in an equitable manner so that everyone has access to safe and effective vaccines.[24,25]

- **Maximising benefits (beneficence) and minimising harms (Non-Maleficence)**

The fundamental ethical principles relating to the allocation of safe and effective vaccines are beneficence (doing good or maximising benefits) and non-maleficence (do no harm or minimising risks) to both individual recipients and the overall population.[19,26] Maximising benefits included reducing transmission SARS-CoV-2 infections, decreasing COVID-19 associated disease, hospitalisations and deaths , lessening the strain and the burden on health care facilities, protection of essential services and preservation of overall societal welfare and functioning.[19]

Individual groups or populations at highest risk (e.g. elderly and those with comorbidities), or those that play essential roles in society (e.g. frontline health care workers) should be identified, prioritized and targeted for vaccine allocation. [19] COVID-19 vaccine allocation guidelines during constrained supply indicate overwhelming consensus that frontline health care workers should be prioritized for vaccination to protect the health care system.[19,20,21,22,23] The ability of essential workers, including health care workers and other essential non-healthcare workers, to remain healthy has a multiplier effect, potentially resulting in minimising the burden on the health care system and other essential services, help to protect the health of others, and to minimise societal and economic disruption.[19,26]

- **Promote justice and mitigate health inequities**

It is anticipated initially that demand for vaccines will be far greater than supply. It is already evident that the race is on between countries, making deals with manufacturers to secure adequate vaccine doses for their population. Those countries that cannot afford deals with manufactures will be pushed back in the row, leaving vulnerable and maginalised groups unprotected. Every country needs to ensure through collaboration processes, that adequate resources are made available to get fair access to vaccines to frontline health care workers and most vulnerable groups.

Inherent in the fundamental ethical principle of justice is taking into account existing health inequalities and barriers and the obligation to protect and promote fair access and equal opportunity for all people to be vaccinated, including those that are vulnerable, disproportionately affected or marginalized groups, to enjoy optimal health and well-being.[19] It is essential that obstacles and barriers to receiving the COVID-19 vaccines should be identified and removed through input and collaboration from a range of entities in the public and private sectors and community representatives is essential to ensure that the roll-out of vaccines is a fair and equitable process.[19]

To address this challenge, the WHO together with its public, private and philanthropic partners, have launched COVAX a global initiative that aims to provide an end-to-end solution to vaccine development, manufacture, supply of COVID-19 vaccines, as a solution that will deliver vaccines on a fair, equitable and necessary access, on a global scale.[7] All countries participating in COVAX, of all income levels, will get doses for at least 20% of their populations, which is expected to cover at least those most at risk, including health workers, older people, and adults with co-morbidities. [7]

- **Promote transparency (Autonomy)**

The fundamental ethical principle of and autonomy is based on promoting transparency, public trust and informed consent during vaccine program planning and implementation.[19] Transparent vaccination campaigns, must be evidence-based, clear, understandable, and publicly available. Individuals cannot make an informed decision to vaccinate or not if they do not have access to information. Transparency includes being clear about the safety and efficacy levels of certainty in the available evidence, and the need to communicate new information that might change vaccine recommendations.[19] Public trust can only be ensured through transparent and consistently applied allocation of vaccines that are safe, effective and fair to everyone.[27]

Promoting vaccine acceptance and generating demand

Studies suggest that vaccine safety concerns play a critical role in individual choices whether or not to accept the vaccine.[28,29,30] Vaccine hesitancy and anti-vaccine messaging have led to distrust resulting in many individuals becoming doubtful and reluctant to being vaccinated.
It is reported that a significant portion of the global population may experience vaccine hesitancy.[31] This is an increasing concern since exposure to a infectious poses dangers to both the individuals and communities, at risk. Individuals are far more likely to spread the COVID-19 disease to others if they are not vaccinated.[31] Because vaccination campaigns require healthy people to seek an intervention, such campaigns require generating demand. Humanity will fail to reach herd immunity and contain the COVID-19 pandemic if not enough people accept a vaccine.[1]

To generate demand, there must be an understanding of the roots of hesitancy, involvement of trusted sources of authority in the advocacy for vaccination, and commitment to longitudinal engagement with communities.[1] The WHO's Increasing Vaccination Model acknowledges that people's views and thoughts about vaccines, including their perceived safety concerns, risks, confidence, and trust, can affect their willingness to get vaccinated.[32] Vaccine hesitancy remains a barrier to full population inoculation[29] and cited in 2019 as one of the top ten threats to global health.[32,33] Strategies to promote vaccine acceptance and stimulate COVID-19 vaccine demand must be based on perceptions, attitudes, and public trust.[1]
Engaging influencers in promoting vaccine acceptance and demand include health care workers, grassroots and local leadership, vaccine industry leaders, and the global community. Health authorities aiming to achieve a high vaccine acceptancy, should be focusing on informing the public about the safety of a forthcoming COVID-19 vaccine.[29] Public opinion polls have clearly shown that safety is a crucial consideration in people's decisions regarding vaccination and that doctors or other health care professionals are the most trusted source of information about vaccine safety.[30]

Storage, supply chain distribution and tracking of vaccines

One of the toughest challenges associated with the storage and distribution of COVID-19 vaccines is managing temperature stability. There is no available historical stability data to support decision-making because vaccines on this scale are being developed and deployed in real-time. Stability data are being generated for the regulating authorities as the vaccine implementation process proceeds. For the vaccines stable at 2-8°C, such as adenoviral vector and adjuvanted protein subunit vaccines, this will be somewhat easier; however, those vaccines subject to prone to thermal fragility, such as mRNA-based vaccines, require ultra-cold storage, will therefore need very well thought-through deployment strategy to maintain vaccine stability throughout the supply and distribution chain.

Each leading COVID-19 vaccines comes with different storage requirements. (**Table 1**) mRNA- based vaccine, in particular, is vulnerable to degradation by enzymes. Hence vaccine developers modify their mRNA, using lipid nanoparticles (LNP) to contain the mRNA to enhance stability. mRNA-based vaccines require an ultra-low temperature (-20°C to -70°C) protection from the manufacture site to their final distribution. (Dry ice storage containers that maintain a temperature of -70°C through transportation can be used for up to 10 days.) Very few pharmacies and clinics, especially in rural regions, have ultra-low freezing equipment for storage and dispensing mRNA-based and other vaccines requiring very low temperatures storage for extended periods. Also, experts have stated that there will likely be an insufficient supply of vials, stoppers, and other necessary products to package, transport and deliver the vaccine and the necessary medical supplies (syringes and needle) required for the vaccination.[34]

Supply-chain and distribution strategies must also be backed by digital technology to plan, track, and monitor vaccine delivery and have appropriate training facilities in place for the delivery of vaccines. Verifying that the appropriate people and populations have received a COVID-19 vaccine will be critical for informing allocation, tailoring strategies to generate demand among the appropriate priority groups and populations, and tracking global effectiveness and progress toward herd immunity.[1] The number of required doses and follow-up for second doses will play a

vital role in the logistic management of vaccines. To verify vaccine coverage, mobile, secure, and interoperable vaccination tracking systems must be developed and implemented. Immunisation information system or centralised registries can play an important role in vaccine coverage verification for the pandemic response.

Conclusion

Rapid manufacturing, procurement, promoting acceptance of vaccines, effective and fair distribution of sufficient quantities of vaccines, combined with the verification and tracking of immunised individuals, are essential to launching a successful vaccination campaign that will successfully achieve herd immunity interrupt the pandemic crisis. Governments, NGOs, and public health leaders have to collaborate with manufacturers and suppliers of vaccines, regulatory authorities, and logistical services to ensure consistent commitment, speed, and transparency to reduce bottlenecks and promote an effective vaccination strategy.

Multiple COVID-19 vaccine platforms are being developed at unprecedented quantities and speed to ensure global economic efficacy and allow rapid global distribution. Availability, costs, and cold-chain requirements to ensure vaccines' stability will impose significant challenges for mass roll-out campaigns.

Procurement of a diverse portfolio and ensuring that an adequate supply of safe and effective vaccines are available at the national level, is the first critical step towards an immunisation campaign. The COVAX program, led by the WHO, aims to optimise fair and equitable access and allocation to these vaccines.

All phases of a COVID-19 vaccination campaign merits strong consideration from an ethical perspective as this helps steering, prioritising and optimising the allocation of limited vaccines fairly and equitably. Ethical principles are fundamental for stewardship of limited vaccine supply, and when vaccines are widely available, to ensure effective, fair and equitable access to all individuals.

There is a concern that a significant part of the global population may experience vaccine hesitancy, thus failing to contain the pandemic. Promoting vaccine acceptance should primarily focus on safety issues to gain people's trust. Health care professionals are generally considered the most trusted sources of information about vaccine safety.

Critical challenges associated with supply chain and distribution logistics include managing temperature at recommended levels to secure stability and quality of vaccines and access to digital immunisation information systems to plan, track and monitor vaccine delivery.

In conclusion, we hope that the insights provided by the 4-part series will enhance clinician's understanding of the current vaccine landscape, safety and efficacy data, and critical scientific, logistical and ethical challenges associated with COVID-19 vaccines supply and distribution chain, immune protection, and herd immunity.

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Table legends

Table 1: Leading COVID-19 vaccine manufacture projections, shipping and storage, dosage requirements, and estimated cost per dose

Table 1: Leading COVID-19 vaccine manufacture projections, shipping and storage, dosage requirements, and estimated cost per dose

Developer	Platform	Vaccine name	Manufacture projections/yr [4]	Shipping & storage	Dosage	Estimated cost /dose [1,2]
Sinopharm Beijing (China)	Inactivated virus	BBIBP-CorV	1 billion	Refrigeration 2°C - 8°C	2	$145 /2 doses
Sinopharm Wuhan (China)	Inactivated virus	WIBP/BIBP	600 million	Refrigeration 2°C - 8°C	2	$145/2 doses
Sinovac Biotech (Brazil)	Inactivated virus	Coronavac	600 million	Refrigeration 2°C - 8°C	2	$30

Bharat Biotech (India)	Inactivated virus	Covaxin BBV152	700 million	Refrigeration $2^{\circ}C$ - $8^{\circ}C$	2	$4
University Oxford/ Astrazeneca (U.K./India)	Viral vector	ChAdOx1/ AZD1222	3 billion	Refrigeration $2^{\circ}C$ - $8^{\circ}C$	2	$4
Jansen /Johnson& Johnson Pharmaceuticals (USA)	Viral vector	JNJ78436735 Ad26.CoV.S	1 billion	Refrigeration $2^{\circ}C$ - $8^{\circ}C$	1 or 2	$10
Cansino Biologics (Canada & China)	Viral vector	Ad5-nCoV	Pending	Refrigeration $2^{\circ}C$ - $8^{\circ}C$ or Freezing $15^{\circ}C$ -$25^{\circ}C$	1 or 2	$30
Gamaleya (Russia)	Viral vector	AD5-nCoV	1 billion	Refrigeration $2^{\circ}C$ - $8^{\circ}C$ or Freezing max -$18^{\circ}C$	2 (Prime Ad26,Boost AD5) 21 days apart	$10
Moderna (USA)	m-RNA	mRNA-1273	1 billion	Refrigeration 2-$8^{\circ}C$ for up to 30 days or Frozen -15° -$25^{\circ}C$ for long-term storage freezer -$20^{\circ}C$	2 (1 month apart)	$25-37
BioNTech/Pfizer (USA)	mRNA	BNT162b2	1.3 billion	Ultra-cold -$60^{\circ}C$ to -$80^{\circ}C$ 5 days in refrigerator, 30 days in dry ice chest and 6 months in ultracold freezer (-$94^{\circ}C$	2 (21 days apart)	$20
Novavax (USA)	Protein subunit	NVX-CoV23	2 billion	Refrigeration 2-$8^{\circ}C$ (6 months) 24 hrs at room temperature	2 (21 days apart)	$16