The vaccine ecosystem

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Towards a stronger Vaccine Ecosystem:

building resilience beyond covid-19

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About this report

"Towards a stronger vaccine ecosystem: building resilience beyond covid-19" is a report by Economist Impact examining the ability of the vaccine ecosystem to meet today's challenges and tomorrow's needs. The protection provided by vaccinations extends beyond individual health to the health of entire communities; therefore investment in this area is an investment in national health, national economic wellbeing and global health security. Our work is not solely focused on the current covid-19 pandemic and the vaccines that have been developed and deployed to address it; our work speaks to the entire ecosystem and all diseases that are amenable to vaccinations. We are committed to an open exchange of ideas and evidence-driven understanding that allows us to better meet the challenges we face and not squander the opportunities to build a dynamic, more equitable, responsive, resilient and robust vaccine ecosystem for the future.

The objective of this report is to present our framework along with insights that we will explore in greater detail in the year ahead as we develop strategies for a strengthened vaccine ecosystem. We have used a structured process to identify successes, gaps and missed opportunities, and to encourage innovations that better support the vaccination ecosystem. A multi-pronged approach was adopted, with a focus on published literature, the work of key multilateral organisations as well as governments, regulatory and industry agencies. To supplement and validate the findings of our literature review, we also conducted in-depth discussions with the experts on our Advisory Council, so that the report incorporates the latest thinking and expertise of those working directly within this arena.

We are truly grateful for the time and commitment of our Advisory Council (in alphabetical order):

- **Mounir Bouazar, MBA,** Covid-19 vaccine Global Logistics Lead, UNICEF Supply Division
- **Thomas Cueni,** Director-General, International Federation of Pharmaceutical Manufacturers and Associations
- **J Peter Figueroa,** OJ, BSc, MBBS, DPH, PhD, FFPH, Professor of Public Health, Epidemiology and HIV/AIDS, University of the West Indies
- **Margaret A Hamburg,** MD, Former Commissioner US Food and Drug Administration
- **Laura H Kahn,** MD, MPH, MPP, Co-founder, One Health Initiative
- **Nigel Lightfoot,** CBE, MBBS, FRCPath, MSc, FFPH, Former Director, Emergency Response and Former Head, Influenza Planning, UK Health Protection Agency
- **Patrick L Osewe,** MD, MPH, Chief, Health Sector Group, Asian Development Bank

In addition, we are grateful to various stakeholders working within the vaccine ecosystem for the many informal conversations and opportunities we have had to share ideas on this subject.

We are excited to be joined on this journey with support from our founding sponsors MSD, a research-intensive biopharmaceutical company and leader in vaccines, and BD (Becton, Dickinson and Company), a leading global medical technology company along with our silver sponsor, Siemens Healthineers. The findings and views expressed do not necessarily reflect the views of the sponsors. Economist Impact bears sole responsibility for the content of this report.

The Economist Group's Vaccine Ecosystem Initiative is led by Dr Mary Bussell. This report was largely compiled in the first nine months of 2021, amid the rapidly evolving situation with the pandemic and the urgent development and deployment of vaccines throughout the world. The report was written by Dr Mary Bussell with contributions and assistance from Dr Vivek Muthu, Dr Alicia White, Marcela Casaca, and Bettina Redway, and edited by Maria Carter.

Executive summary

The Economist Group's Vaccine Ecosystem Initiative

SARS-CoV-2 emerged in 2019 resulting in a pandemic that shattered routine life and global economies around the world. In the early days, no one knew whether this virus was amenable to vaccines. Yet, through the extraordinary collaborative efforts of countless specialists across sectors - virology, vaccinology, engineering, manufacturing, regulatory, logistics, transport, and supply chains - we witnessed the discovery, production and distribution of safe and effective vaccines against covid-19 in an astonishingly short period of time.

The largest immunisation programme in human history was underway less than one year after an announcement from the World Health Organization's China Country Office about the emergence of a pneumonia of unknown origin in the city of Wuhan.[1] Partnerships like the ones that nurtured the covid-19 vaccines require a high degree of cooperation, and considerable financial investment by governments, industry, international agencies and foundations, but success was achieved within just 320 days of the publication of the genetic sequence for SARS-CoV-2. Authorisation was granted for the first covid-19 vaccine for emergency use in the public on 2 December 2020 in the UK followed by the US on 11 December and the European Union (through the European Commission) on 21 December.

It was in this context that The Economist Group launched The Vaccine Ecosystem Initiative. The Initiative envisions a world in which vaccines are used to safeguard good health and wellbeing for the benefit of people of all ages throughout the world. We hope to foster a sustainable vaccine ecosystem, by taking a holistic view of the field, from early laboratory research to the administration of vaccines to members of the public, while also exploring ways to harness the full potential of vaccines for all vaccine-preventable diseases.

Achieving success will require change throughout the entire vaccine ecosystem, from research and development to manufacturing and securing supply chains to maximise system capacity, from improving distribution and logistics systems to increasing public awareness and trust in the value offered by vaccines, as well as enhancing disease surveillance and monitoring systems to reinforce preparedness. Addressing these challenges can only be achieved with a combination of evidence-based insights, cross-sector dialogue and actionable recommendations enhanced by stakeholder collaboration and committed leadership.

We seek to foster innovations that lead to effective and durable improvement across the entire ecosystem. Our ultimate goal is to ensure equitable, comprehensive and effective protection of global populations against all vaccine-preventable diseases. The Vaccine Ecosystem Initiative is based upon a holistic framework that will guide our ongoing analysis and allow us to organise our findings, consider opportunities and eventually make recommendations. Our framework comprises five elements that we call 'pillars' because, collectively, they support the entire vaccine ecosystem. Using the concept of pillars highlights the fact that the vaccine ecosystem is only as strong as its weakest support. Our pillars are: research and development; manufacturing; procurement, pricing and finance; distribution, logistics and supply chain management; and user acceptance and uptake. Our report defines each pillar within the context of our current pandemic, considering the whole vaccine value chain from early discovery to full-scale sustainable programme implementation, while ensuring equitable population protection against vaccine-preventable diseases.

The objective of this report is to present our framework along with insights that we will explore in greater detail in the year ahead as we work to suggest strategies for a strengthened vaccine ecosystem. We have used a structured process to identify successes, gaps and missed opportunities, and to encourage innovations that better support the vaccination ecosystem. A multi-pronged approach was adopted, with a focus on published literature, the work of key multilateral organisations as well as governments, regulatory and industry agencies. To supplement and validate the findings of our literature review, we also conducted in-depth discussions with the experts on our Advisory Council, so that the report incorporates the latest thinking and expertise of those working directly within this arena.

This report was largely compiled in the first nine months of 2021, amid the rapidly evolving situation with the pandemic and the urgent development and deployment of different vaccines throughout the world. New information and evidence constantly emerges and we have done our best to ensure the timely nature of the research we have used in this report and have tried to keep abreast of developments, but we cannot exclude the existence of additional or later evidence of relevance.

Findings for further exploration

Strengthening the vaccine ecosystem is a priority for every country and the global community. Addressing the challenges within each of the five pillars outlined here can facilitate the development of a vaccine ecosystem that is capable of meeting today's challenges and tomorrow's needs.

Having defined the framework of the vaccine ecosystem, in the coming year we will examine each of the pillars in greater detail to maximise the opportunities to ensure a resilient and responsive vaccine ecosystem. The covid-19 pandemic has provided many insights into areas that can be improved in the next stages of this pandemic. Such actions will reinforce our level of preparedness for the emergence of the next public health emergency. In each pillar we have identified key opportunities that we are excited to explore. They include:

Pillar 1: Research and development (R&D)

This pillar includes the vaccine research process from the earliest stages of laboratory research through to Phase III (human) clinical trials. It covers the regulatory oversight necessary for supporting vaccine development and innovations that can improve the characteristics of existing vaccines. It also addresses the R&D that is needed for supporting the delivery of vaccine services, including disease surveillance and monitoring, as well as the enabling policies, infrastructure, investments and partnerships that can promote success.

Key opportunities for further exploration include:

- Investing in vaccine R&D is vital for building upon our current successes and for creating a more robust vaccine ecosystem – one that enables vaccines to be produced more quickly to address future needs. Investment in vaccine R&D facilities and vaccine expertise is likely to improve resilience of the entire ecosystem and encourage R&D innovations that facilitate the production of new and more effective vaccines. Greater investment in vaccine R&D and manufacturing facilities will increase responsiveness to disease outbreaks, and allow technological innovations to be applied to the production of novel vaccines.
- Scanning and surveillance is of paramount importance: pathogens will continue to evolve and evade our best efforts to combat them. Strengthening systems, infrastructure, and policies for sharing data and information on emerging pathogens, including disease surveillance and biological samples, is crucial. Investment is needed to support research and surveillance of novel pathogens with pandemic potential. Timely sharing of data and information on infectious disease pathogens is a vital part of this process and must be encouraged.

- Investing simultaneously in a multiplicity of vaccine technologies increases the likelihood of developing an effective and timely vaccine to combat novel threats. The utilisation of diverse vaccine technologies also has potential to provide complementary approaches, with different manufacturing, supply chain, logistics and cost profiles, which can enhance the response to a disease outbreak.
- Cooperating through diverse modes of collaboration are to be encouraged to allow developers, research institutions and governments to work together to develop vaccines within tight timeframes.
- Opening pathways for expedited authorisation of vaccines while ensuring they meet adequate safety and efficacy standards is an important opportunity for regulatory bodies. However it is essential that science continues to guide the collection of relevant data.
- Enhancing clinical trial design can provide important information that can aid policy-makers and strengthen the vaccine ecosystem in the future. Designing clinical trials carried out by different developers that make use of similarly defined endpoints can produce reliable evidence to better inform decision-making by public health policy-makers. This will also help to improve public perceptions and trust in the rationale and methods used to develop vaccines.

Pillar 2: Manufacturing

The second pillar relates to the factors involved in manufacturing vaccines in a timely fashion, together with regulatory oversight and the use of good manufacturing practices at a scale necessary to meet demand. It covers the infrastructure, human resources and staff training required to manufacture vaccines, and the strict quality control standards that must be met to ensure production of safe and effective vaccines.

Key opportunities for further exploration include:

- Increasing vaccine manufacturing capacity requires a significant amount of forward planning and investment because it can take years to design and build facilities that meet required standards as well as upskill and train the required personnel.
- Collaborating between different vaccine manufacturers can help meet the demand for vaccines. Exploration and mitigation of concerns that can inhibit these collaborations, such as the protection of intellectual property rights, must be actioned.
- Anticipating and avoiding delays due to a lack of manufacturing capacity is vitally important. Building manufacturing facilities carries high financial risk, particularly if the vaccine that it is designed to produce is not authorised, or if demand for the vaccine it produces drops unexpectedly. Consideration should be given to how risks can be mitigated and incentives created to support manufacturing capacity.
- Developing localised manufacturing capacity is a useful option for meeting local demand, but there are significant barriers to overcome, including the need for adequate financing, infrastructure and human resources, as well as guaranteeing the supply of raw materials, and ensuring the continuous operation of these facilities.

- Ensuring that regulatory authorities have the capacity and capability to oversee development and manufacture of vaccines to assure safety and quality.
- Harmonising global regulatory standards to streamline processes can provide system-wide benefits, including reducing strain on the manufacturing supply chain.

Pillar 3: Procurement, pricing and finance

This pillar covers the policies, mechanisms and partnerships involved in the purchasing and pricing of vaccines, and the financing of both vaccine R&D and the implementation of immunisation programmes. It deals with procurement, pricing and finance systems that promote more equitable and faster access to vaccines globally, not only by supporting the development and production of vaccines, but also by meeting global immunisation needs.

Key opportunities for further exploration include:

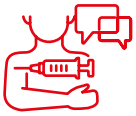
- Safeguarding investment in the vaccine ecosystem with sound financing models across all pillars must be ensured. Supplemental investment may be required to combat short-term public health emergencies to respond to a disease outbreak. Sustainable long-term investment in the vaccine ecosystem is required to meet all aspects of the ecosystem from R&D through to the vaccination programmes that deliver vaccines to the public. The goal is to ensure sufficient financing to sustain the vaccine ecosystem and address the imbalances in access and equity to meet public health needs.
- Ensuring the use of equitable international procurement models that are fit for purpose whether they are required to address endemic disease or public health emergencies.
- Promoting equitable and timely access to vaccines worldwide requires communication and collaboration. Global cooperation is particularly important during public health emergencies. Vaccine nationalism is a real concern, and measures must be taken to alleviate the impact on future vaccine-purchasing schemes.
- Collaborating between countries and regulatory authorities can ease allocation imbalances and promote conservation of the scarce resources required to support every pillar of the vaccine ecosystem.
- Promoting global health security can be addressed by improving equitable access to affordable vaccines and addressing procurement challenges for low- and middle-income countries. Pricing models can be developed to sustainably address inequities around the world.
- Improving procurement and planning can be achieved with better tools to forecast national and global needs.
- Increasing investment can help to rebuild and reinforce routine vaccination programmes that have suffered during the current pandemic, making them more sustainable for the future.

Pillar 4: Distribution, logistics and supply chain management

This pillar relates to the mechanisms that enable safe distribution of vaccines from manufacturing facilities to the sites where the vaccinations are administered. It includes the logistics, infrastructure and systems required to distribute vaccines both within and between countries. It recognises that consistently strong and resilient distribution networks, logistics capabilities and global supply chain management are needed to ensure equitable and rapid worldwide protection of populations against vaccine-preventable diseases.

Key opportunities for further exploration include:

- Improving the synchronisation of manufacturing, including the materials required for packaging and shipping vaccines can ease distribution and logistics steps in the vaccine ecosystem.
- Investing in data systems can improve inventory management of both raw materials and vaccines.
- Improving import and export networks can ensure seamless integration of new suppliers of raw materials, expand the supply of skilled workers, and address vaccine nationalism, which impedes the timely transportation of vaccines.
- Upgrading systems to improve the infrastructure to meet temperature requirements to safeguard temperature-sensitive raw materials and vaccines is needed around the world. Quality control in transportation must be amplified to mitigate the risk of damage to raw materials and vaccines during transit. Countries should be equipped with the right infrastructure to accept and store vaccines, particularly at the start of a vaccination campaign when the first authorised vaccines may have more demanding requirements.
- Maintaining and extending the shelf life of vaccines should be investigated to prevent wastage of scarce resources. Testing a vaccine's ability to be transported and stored for an extended period should be included in the initial investigations of a vaccine.
- Strengthening supply chains by improving distribution channels can help to alleviate bottlenecks.
- Addressing infrastructure requirements necessary to secure the safe storage of vaccines in stockpiles and at vaccination centres.



Pillar 5: User acceptance and uptake

The fifth pillar covers the factors that encourage individuals to choose to be vaccinated and the factors that enable them to get vaccinated easily. It includes health literacy, education and awareness, and the ways in which improvements can be made at each point to improve public trust in vaccines. It examines vaccination programmes and the services that aim to combat these challenges, as well as the reasons for delays in vaccine uptake.

Key opportunities for further exploration include:

- Recognising the role our leaders play in guiding and inspiring confidence in the vaccine ecosystem must not be overlooked. Trusted leaders and influencers have a role in building confidence in their communities about the value and safety of vaccines. They can actively address the issue of vaccine hesitancy – a serious problem during the current pandemic – as well as dispel myths and misinformation and counter anti-vaccine activities that spread fear and mistrust.
- Nurturing the public's trust in vaccines is vitally important to the success of any vaccination programme in terms of rapid uptake of vaccines when they become available. Increasing trust in vaccines allows any infectious disease threat to public health to be handled effectively.
- Investing in health literacy improves public understanding of health-related issues. Trust is necessary to eliminate fear, but it is hard to win and all too easy to lose. Trusting anything or anyone depends on having a thorough understanding, which can only be achieved through the acquisition of knowledge. This is why improving health literacy throughout the world is such an important step. The public must be helped to understand the principles of science and the stepwise nature of scientific inquiry, so that they can feel confident that vaccinations are a safe and effective way to promote health and save lives.
- Communicating with the public must be carefully targeted and be delivered in a consistent way in order to address the concerns of specific groups.
- Providing information grounded in evidence is vital to separate fact from fiction.
- Tackling misinformation requires a strategic approach. Policies and initiatives to alleviate the impact of misinformation can be strengthened by collaborating with mainstream media and social media platforms.
- Integrating vaccination campaigns seamlessly into people's daily lives helps to eliminate the barriers that can delay vaccine uptake even among people who are health literate. Ensuring vaccinations are accessible and convenient improves uptake.

This report provides the framework to The Vaccine Ecosystem Initiative. We have presented the five pillars that support the ecosystem and identified their relevance using the current pandemic to illustrate the relevance of each. But our work does not stop with the current covid-19 pandemic and the vaccines that have been developed and deployed to address it; our work speaks to the entire ecosystem and all diseases that are amenable to vaccinations. While we have identified opportunities for improvement and suggested avenues for further exploration, our work is not complete. As we move into the next phase The Vaccine Ecosystem Initiative will conduct further investigations into wide-ranging perspectives in each of the five pillars to foster and facilitate the development of new and more sustainable vaccination models based upon what we have learned thus far. We are committed to an open exchange of ideas and evidence-driven understanding that allows us to better meet the challenges we face and not squander the opportunities to build a dynamic, more equitable, responsive, resilient and robust vaccine ecosystem for the future.

Section 1: Introduction

The Economist Group's Vaccine Ecosystem Initiative

Approximately 5.38 billion doses of covid-19 vaccines have been administered worldwide and as many as 40.99 million doses were being administered daily as of 1 September 2021.[2] Such numbers were unimaginable when the World Health Organization (WHO) declared that covid-19 was a pandemic on 11 March 2020, two months after the viral pathogen SARS-CoV-2 was first identified in Wuhan, China on 7 January.[3]

The world has experienced many setbacks and successes in the effort to develop and deploy covid-19 vaccines. This report reflects on what we have learned and what we can improve as we continue to confront this virus and maximise opportunities to strengthen the vaccine ecosystem as a whole.

The Economist Group's Vaccine Ecosystem Initiative was established to support the sustainability of this vital component of public health. It aims to break down the critical aspects of the entire arena into more easily understood components using our experience of the covid-19 pandemic as an entry point to discussions. By considering all aspects of the vaccine ecosystem, we will also explore the potential for both radical and incremental changes that will lead to improved global preparedness within health systems and across societies.

We believe there are four overarching thematic areas which we will explore and refine in the years ahead with the ultimate aim of coming up with clear recommendations for actionable change. These underlying and cross-cutting themes around which we can improve the vaccine ecosystem encourage us to:

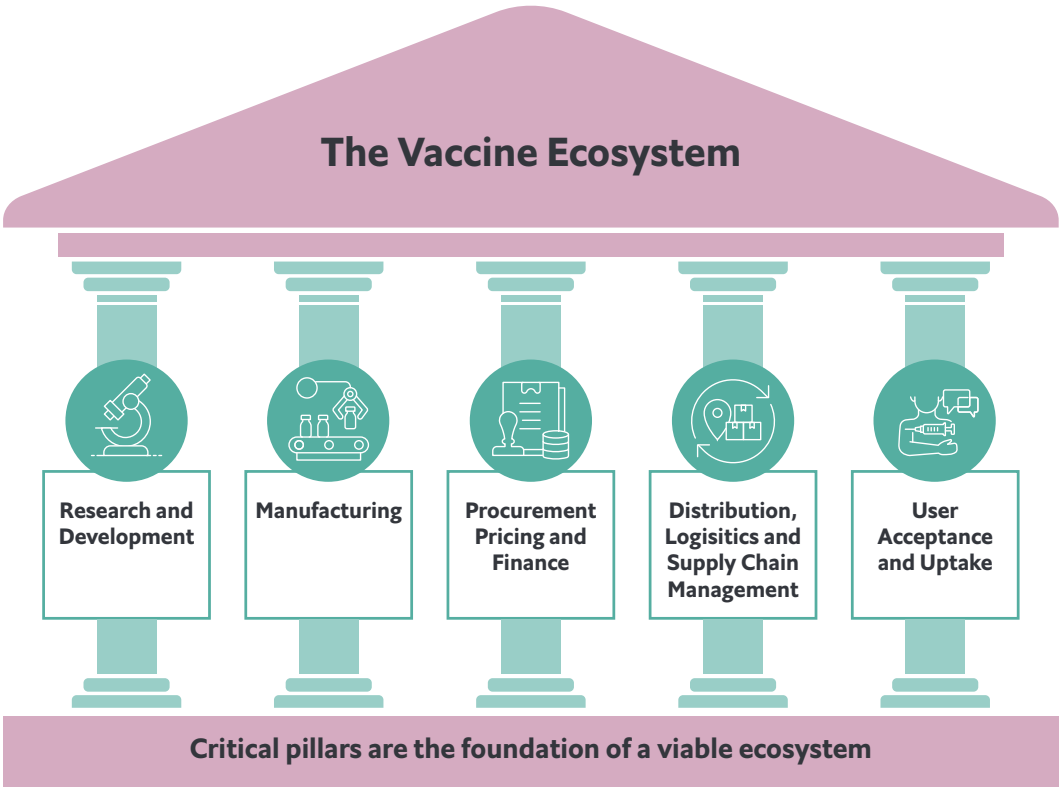
- **Focus on political will**
- **Enhance global leadership and collaboration**
- **Foster and enable vibrant innovation efforts to increase system-wide preparedness**
- **Nurture trust in vaccines**

To operationalise these cross-cutting themes and working with experts in the Initiative's Advisory Council, we identified five key pillars of the vaccine ecosystem. These pillars are: research and development (R&D); manufacturing; procurement, pricing and finance; distribution, logistics and supply chain management; and user acceptance and uptake. The pillars contain the key stages in the life cycle of a vaccine, all the way from inception to administration to individual people. In this report, we examine each pillar individually, but they should not be regarded as siloes because progress or failure in any single pillar has an impact on the others. For example, information gaps in the R&D process can lead to unintended or deliberate misinformation which can influence uptake of the vaccine by the public.

The overarching aims of the Initiative are to engage multiple stakeholders across the vaccine ecosystem and to encourage meaningful dialogue, to spark ideas and to motivate stakeholders to form meaningful collaborations. Stakeholders include virologists, vaccinologists, scientists, engineers, manufacturers, regulators, public health officials, policy-makers, distribution and logistical experts, and many others. The covid-19 pandemic has provided a unique opportunity to stimulate enduring changes that can profoundly improve public health.

Framing the vaccine ecosystem

Five pillars support a successful vaccine ecosystem



The Vaccine Ecosystem Initiative is based upon a holistic framework that will guide our ongoing analysis and allow us to organise our findings, consider opportunities and eventually make recommendations. Our framework comprises five elements that we call 'pillars' because, collectively, they support the entire vaccine ecosystem. Using the concept of pillars highlights the fact that the vaccine ecosystem is only as strong as its weakest support. Below, we describe the five pillars and the aspects of the ecosystem they each impact:

Pillar 1: Research and development (R&D)

The first pillar includes the vaccine research process from the earliest stages of laboratory research through to Phase III (human) clinical trials. It covers the regulatory oversight necessary for supporting vaccine development and innovations that can improve the characteristics of existing vaccines. It also addresses the R&D that is needed for supporting the delivery of vaccine services, including disease surveillance and monitoring, as well as the enabling policies, infrastructure, investments and partnerships that can promote success.

Pillar 2: Manufacturing

The second pillar relates to the factors involved in manufacturing vaccines in a timely fashion, together with regulatory oversight and the use of good manufacturing practices at a scale necessary to meet demand. It covers the infrastructure, human resources and staff training required to manufacture vaccines, and the strict quality control standards that must be met to ensure production of safe and effective vaccines.

Pillar 3: Procurement, pricing and finance

The third pillar covers the policies, mechanisms and partnerships involved in the purchasing and pricing of vaccines, and the financing of both vaccine R&D and the implementation of immunisation programmes. It deals with procurement, pricing and finance systems that promote more equitable and faster access to vaccines globally, not only by supporting the development and production of vaccines, but also by meeting global immunisation needs.

Pillar 4: Distribution, logistics and supply chain management

The fourth pillar relates to the mechanisms that enable safe distribution of vaccines from manufacturing facilities to the sites where the vaccinations are administered. It includes the logistics, infrastructure and systems required to distribute vaccines both within and between countries. It recognises that consistently strong and resilient distribution networks, logistics capabilities and global supply chain management are needed to ensure equitable and rapid worldwide protection of populations against vaccine-preventable diseases.

Pillar 5: User acceptance and uptake

The fifth pillar covers the factors that encourage individuals to choose to be vaccinated and the factors that enable them to get vaccinated easily. It includes health literacy, education and awareness, and the ways in which improvements can be made at each point to improve public trust in vaccines. It examines vaccination programmes and the services that aim to combat these challenges, as well as the reasons for delays in vaccine uptake.

We have reflected on our experience of the current covid-19 pandemic to illustrate achievements in the vaccine ecosystem and to pinpoint areas for improvement in the next stages of the pandemic. We also identify opportunities that will strengthen the vaccine ecosystem as a whole, and with the understanding that the five pillars of the ecosystem are interdependent; any successes and limitations in one of them will eventually impact the others.

Our key objectives for this report

Vaccines must be recognised as investments in health, and drivers of economic growth and development. WHO has acknowledged that vaccines are one of the two public health interventions that have had the greatest impact on the world's health, after clean water.[4] Vaccines strengthen global health security by helping to prevent and limit the spread of communicable diseases.[4] Prioritisation of, and investment in, the vaccine ecosystem must be endorsed by strong leadership across countries and in all sectors around the world.

This report examines the framework of our approach to the vaccine ecosystem within the response to the covid-19 pandemic according to our five pillars of the vaccine ecosystem. We will examine the strengths and weaknesses of the response to the current covid-19 pandemic in order to develop an agenda for further exploration on what we can all do to improve and reinforce the ecosystem to meet future challenges. We are gathering a wide-range of perspectives to facilitate the development of new and more sustainable vaccination models. We are committed to encouraging and ensuring an open exchange of ideas and to developing evidence-driven understanding to enable us to overcome the challenges we face to public health and to avoid wasting any opportunities for improvement.

In the wake of the covid-19 pandemic, there is no time for complacency. We must use what we have learnt – and are still learning – to build a better vaccine ecosystem.

Section 2: Strengthening the Vaccine Ecosystem: opportunities emerging from the covid-19 pandemic

Pillar 1: Vaccine research and development (R&D)

Vaccine research and development (R&D) is typically a long and complex process. In the past it has taken at least a decade to develop a vaccine candidate from preclinical investigations all the way to securing regulatory approval. The unprecedented scale at which covid-19 overwhelmed health systems and stalled global economies, meant that time was precious. To meaningfully address this public health emergency, existing R&D frameworks were reviewed, reconsidered and reoriented. The pandemic response has been characterised by flexibility and agility in vaccine R&D, resulting in early successes in this first pillar of the vaccine ecosystem.

The ultimate aim of our Initiative is to reduce morbidity and mortality from many diseases that can be prevented by vaccines, and it is encouraging to know that research is ongoing on more than 200 vaccine candidates for diseases other than covid-19. Accelerating the pace of this research and supporting the manufacture of both existing and novel vaccines will help eliminate the disparities and inequities that exist between and within countries. However, this means that health policies must be streamlined with the activities of the various regulatory authorities throughout the entire research and manufacturing process.

Greater flexibility aids R&D

The covid-19 pandemic highlights the diversity of vaccine technologies available to vaccinologists; some have been used before and some have emerged as new, untapped resources for the vaccine ecosystem. The novel approaches to vaccine development resulted in the first vaccines to achieve emergency authorisation. These were the messenger RNA (mRNA) vaccines and adenovirus vector vaccines developed using relatively new technologies. mRNA vaccines had not previously been used beyond the earliest stages of clinical trials. Adenovirus vector vaccines were first granted regulatory approval for an Ebola vaccine in China, the US and the EU approximately four years ago.[5]

Box 1: mRNA vaccines

mRNA vaccines were one of the first types of vaccine to secure emergency authorisation for covid-19. mRNA vaccines have two distinct parts – the first is the genetic material (mRNA), which codes for the unique protein of the pathogen, the spike protein of SARS-CoV-2; the second is a lipid nanoparticle (LNP), which is responsible for delivering the mRNA into the recipient's cells. Once in the cell, the mRNA is translated into a unique protein of the virus called an antigen. These antigens are then recognised by the immune system, enabling the recipient's immune system to produce antibodies that confer protection against a natural infection.[6]

mRNA vaccines can be manufactured within weeks, which is a huge advantage during a public health emergency. They can be adjusted relatively quickly to combat variants of the virus when they arise. mRNA vaccines have been tested as therapeutic agents in oncology and their favourable safety profile made the technology appealing for researchers as a vaccine candidate for covid-19.[7]

Box 2: Adenovirus vector vaccines

Adenovirus vector vaccines deliver a section of genetic code from the pathogen into the recipient's cells. However, instead of using an LNP, they use adenovirus vectors as delivery platforms. These viruses are replication-deficient, which means they are designed not to reproduce within recipients.

Manufacturing and stockpiling large quantities of adenovirus-based vaccines can be accomplished inexpensively using relatively simple technologies involving the culture of cells.[6] This has advantages for addressing widespread public health emergencies. The relatively recent approval of this vaccine technology to prevent Ebola and its favourable safety profile, in addition to the clinical trial data obtained from oncology research, suggested their potential for use against covid-19.

Novel approaches to vaccine development were not the only options considered for use against covid-19. Older vaccine technologies utilising older long-established technologies that have been used to vaccinate millions of people to prevent an array of diseases were explored as well.[9,10] This demonstrates the long-term value of investment in vaccine development, in which well-established research, manufacturing and distribution networks can be adapted to meet the challenges presented by new diseases. For covid-19, this group encompasses live-attenuated virus vaccines and protein subunit vaccines.

Box 3: Live-attenuated virus vaccines and protein subunit vaccines

Among the older vaccine technologies used to develop covid-19 vaccines are live-attenuated virus vaccines. These contain inactivated or weakened forms of a disease-causing virus. Many of them have been approved and are in use around the world; they include vaccines for measles, mumps, rubella, vaccinia (smallpox), and varicella zoster (chicken pox and shingles).

Similarly, protein subunit vaccines have been developed against covid-19. They contain specific proteins of the pathogen, rather than the entire virus. Proteins are selected according to their ability to induce a robust immune reaction in the recipient. Protein subunit vaccines in widespread use include those against pertussis, hepatitis B and meningococcal disease.[11]

Both live-attenuated virus and protein subunit vaccines use either a weakened or incomplete version of a pathogen, in combination with an adjuvant. The adjuvant enhances the response of the immune system to the antigen. Developing adjuvants requires long-term data on their safety and efficacy, which is yet another example of the benefits of continued investment in the vaccine ecosystem.[12]

The covid-19 vaccines in current use are administered by subcutaneous injection. Due to the significant ongoing demand for them, there is great interest in producing needle-free vaccines that can be administered nasally, orally or via a skin patch.[13,14,15] They may improve uptake in people who are fearful of needles, as well as ease logistical challenges in the distribution of needles and syringes. These types of vaccines for covid-19 are currently in the early phases of research.

R&D efforts conducted by researchers based in industry, academia, and government laboratories have produced an exciting range of vaccine platform technologies which enabled rapid development of successful options to address covid-19. Each platform has its pros and cons: some are more expensive to manufacture than others and some have more challenging storage requirements. The flexibility and range of options in vaccine R&D improves the likelihood of success, promoting resilience as well as diverse policy options. The vaccine ecosystem will continue to flourish with further support of R&D providing hope for future development of vaccines that can safely and efficaciously address a wider array of diseases both those that are emerging and those that are endemic.

Greater collaboration aids R&D

While collaboration is not new within the vaccine ecosystem, the early months of the pandemic highlighted various ways it could be executed and accelerated within R&D. The cooperation we have seen, such as the sharing of emerging data on SARS-CoV-2 across the scientific community, stimulated the rapid production of the existing vaccines. This type of R&D collaboration can happen between research institutions, vaccine developers and governments.

The diversity of relationships that emerged during the covid-19 pandemic was critical to the speed and success of R&D efforts in general: some large vaccine developers formed alliances with smaller pharmaceutical companies that had insufficient human resources or facilities to carry out robust investigations on a global scale;[16,17] pharmaceutical companies that had never developed vaccines before created partnerships with well-established vaccine-research institutions;[18] some medium-sized companies received assistance from government-run agencies to explore potential vaccines;[19] and some developers established working relationships among themselves, sharing their many years of experience, so that – for instance – one company provided a viral antigen while another provided an adjuvant.[20]

Adaptive regulatory frameworks and processes can aid R&D

Regulatory surveillance encompasses R&D and manufacturing, the second pillar in the vaccine ecosystem. Regulatory oversight is necessary to ensure vaccines attain specific safety and efficacy benchmarks. They also ascertain that the manufacturing process consistently ensures uniformity across batches of vaccines, protecting the public from issues that may negatively impact safety or reduced efficacy. Diligent vaccine oversight is essential during a pandemic in which billions of doses of vaccines must be manufactured within a very short period of time.

Given the urgency of the covid-19 pandemic, regulatory bodies adapted and used atypical approaches to support and encourage vaccine R&D and manufacturing, without compromising safety or efficacy. The pandemic highlighted the importance of open dialogue and technical engagement between developers and regulatory bodies and opened new channels for regulatory bodies to work with developers. The rolling review process has been successful in covid-19 vaccine development, enabling developers to submit important data as they became available, thus allowing for simultaneous review and minimising final review timeframes (Box 4).[21,38]

Due to the pressing need for vaccines and therapeutic agents for covid-19, regulatory bodies enabled the use of emergency authorisations (Box 4). This is rarely done, but it was necessary to allow vaccines and therapeutics to be used beyond the clinical trial setting. In the early 2000s, the US used this approach for the Emergency Use Authorization (EUA) of an anthrax vaccine for certain groups of military and civilian personnel.[22] Considering that this regulatory pathway is not often used, regulatory bodies worldwide had to adapt their existing approval criteria to meet the unprecedented need for an emergency authorisation. As a consequence of the pandemic, more regulators now have experience establishing a pathway for emergency use which will be beneficial in the event of another public health emergency.

Granting emergency authorisation for a vaccine can be risky for both regulators and developers. There must be a trade-off between the need to provide a quick regulatory authorisation pathway to expedite the deployment of vaccines, and the need to ensure that such authorisations are based on sound science and clear demonstrations of safety and efficacy. Emergency authorisations rely upon strong pharmacovigilance and regulatory capacity within a country ensuring that manufacturers continue to collect data after the vaccines have been administered to the public and that they maintain an ongoing dialogue with the regulatory bodies.

To obtain emergency authorisation for covid-19 vaccinations, the developers provided efficacy data for their vaccines collected over a short period of time. The speed of data collection depends on how quickly clinical trials count a specific number of infection events among participants.[23] This data-gathering process can take weeks or months, depending on how high the infection rate is in the community (the higher the rate of infection, the quicker the rate of data collection). Following emergency authorisation, developers continue to collect data on safety and efficacy to maintain the emergency use designation for their vaccines.

Another factor that affects emergency authorisation is the risk of rare adverse events. These may only become apparent over time, when a large proportion of the population has been vaccinated. In fact, we may only learn about very rare side effects when millions of people have received a vaccine. Strengthening the mechanism for monitoring adverse events during emergency use of vaccines is vitally important to the overall vaccine ecosystem. Greater investment in pharmacovigilance is important within and between countries in order to protect public health and strengthen the science for safe and effective vaccines.

Vaccine developers must formally apply to the regulatory authorities to convert an emergency-use designation into full approval for the vaccines they produce (Box 4), and these applications must be supported with six months' of safety and efficacy data along with further details of their manufacturing capabilities to ensure evidence of consistency across batches.

Manufacturing and regulatory challenges will be further discussed in the manufacturing pillar (pillar 2).

Box 4: Regulatory pathways for vaccines during a public health emergency

Rolling review: Vaccine developers can submit sections of a regulatory application for review as they become available, instead of waiting until every part of the application is complete. Usually, regulatory review does not begin until the developer has submitted an entire application.

Emergency use authorization/Emergency use listing: This regulatory process is used to expedite the use of vaccines in the absence of sufficient data for full approval. Vaccine developers must constantly collect data on safety and efficacy of the vaccine to maintain this level of authorisation.

Full Approval: Full approval is only given when robust data about a vaccine is available. In terms of covid-19, vaccine developers must submit data from Phase III trials covering a six-month period, together with real-world data from vaccinated people who were not included in the trials. Detailed information about manufacturing capabilities is also required.

Ways to build stronger R&D

Despite the unprecedented nature of the covid-19 pandemic and the speed with which vaccine development progressed, early lessons can be used to improve the R&D pillar while the pandemic continues. These lessons can be categorised thematically, such as the need for ongoing research and financial investment in the ecosystem, and the need for consistency in the design of clinical trials.

Investing in novel pathogen surveillance enhances vaccine R&D

Between 2002 and 2004, the novel coronavirus SARS-CoV caused an outbreak of severe acute respiratory syndrome (SARS). The disease spread to 29 countries, infected 8,098 people and resulted in 774 deaths before the infection rate dropped.[24] Research to develop a vaccine against it stalled during Phase I clinical trials because the outbreak subsided.

Despite the fact that a vaccine for SARS was not developed, this experience shows the value of research into novel pathogens with pandemic potential.[25] Research conducted during SARS provided valuable insights for vaccine development during our current pandemic. Specifically, it identified the coronavirus spike protein as the most immunogenic part of this type of virus,[25] a vital insight for the development of covid-19 vaccines. Had an efficacious vaccine against SARS been developed and licensed at the time, it would have been a prime candidate for repurposing against covid-19. A vaccine for SARS may have had cross-reactivity with SARS-CoV-2, and that might have slowed the spread of covid-19 in the early stages while more efficacious vaccines were developed. According to a list of SARS vaccine candidates compiled by WHO, only one made it to Phase I trials, with several more in preclinical investigation.[26,27]

Another coronavirus, MERS-CoV causes Middle-East respiratory syndrome (MERS). Since it was first identified in Saudi Arabia in 2012, outbreaks of MERS have occurred in South Korea (in 2015) and Saudi Arabia (in 2018).[28] Currently, there is no authorised vaccine. Only three potential MERS vaccine candidates made it to Phase I trials, with the majority in preclinical investigation stage, according to another WHO list.[26] As with SARS, any vaccine for MERS could have been considered for repurposing during the early stages of the covid-19 pandemic. The SARS-CoV-2 virus shares almost 80% genetic homology with SARS-CoV, and about 50% with MERS-CoV.[29]

A high number of community infections are required to measure efficacy in clinical trials and the clinical trials for SARS and MERS vaccines did not progress because the levels of community infection were not sufficient enough to support the research. As demonstrated by the development of covid-19 vaccines, thousands of volunteers are needed for Phase III trials.[26] However, other investigations into SARS and MERS vaccines could have been possible. For example, there is limited data on the levels of immunogenicity required by a SARS or MERS vaccine for providing protection against their respective viruses. Methods to investigate this issue may have yielded information that could have been very useful in the development of covid-19 vaccines.[30] Determining vaccine efficacy based on immunogenicity is not an unusual surrogate measure of vaccine effectiveness, as this kind of information is typically used to update seasonal influenza vaccines each year.

Investing in R&D to pre-emptively understand novel pathogens, particularly those with pandemic potential, can pay dividends when an unanticipated public health emergency arises. The research conducted into SARS and MERS has been invaluable for researchers investigating SARS-CoV-2.

Enhancing clinical trial designs may improve comparability and inform public health decision-making

In the race to develop a vaccine at the start of the covid-19 pandemic, different phases of clinical research were conducted simultaneously rather than consecutively. This meant that the phases of the clinical trials overlapped. As a consequence, critical data emerged from one phase once the next phase was underway (Box 5). While this relates to the much-needed agility of the R&D pillar, in terms of adjusting to shorter timeframes, it introduces new challenges because the data from the early phases are usually used to prepare the next phase. Moreover, it is very complicated to change research protocols in trials that have already started because it jeopardises consistency and the ability to collect meaningful data.

Box 5: Summary of clinical trial phases in vaccine R&D

Phase I trial: An initial trial that recruits a small number of healthy volunteers aiming to investigate (primarily) the safety of different doses of a new vaccine.

Phase II trial: A subsequent trial that recruits hundreds of healthy volunteers aiming (primarily) to confirm the mechanism of action of a candidate vaccine (how it works, what it is doing). Immunogenicity data is often collected.

Phase III trial: A final large-scale trial that recruits thousands of healthy volunteers. They are divided into two groups; one group receives the candidate vaccine and the other receives a placebo (inactive) vaccine. Data are collected on the number of infection events in the vaccine group relative to those in the placebo group.

In covid-19, once researchers recognised that a single-dose adenovirus vector vaccine failed to stimulate strong immunogenic responses, the ongoing clinical trials had to be redesigned to enable volunteers to receive a second dose.[31] An interval had to be chosen for the second dose, and it was initially set at 4 weeks. However, delays occurred due to manufacturing issues, so some of the second doses were administered up to 12 weeks following the first.[31] This resulted in significant problems in the interpretation of the data later on.

Two-dose vaccines are not unusual. The potential need for a second dose should have been considered when designing the clinical trials, even before full data on immunogenicity had been obtained from an earlier trial.

During early vaccine deployment in January 2021, the UK government decided to allow a 12-week interval between the first and second doses of the adenovirus vector vaccines and they also applied this interval to mRNA vaccines, even though the clinical trial data only related to the former.[32] It was a risk to extend the dosing interval, and all such risks need to be carefully calculated and clearly communicated to the public to avoid unnecessary speculation on the rationale used for policy decisions.

The government's decision was met with widespread criticism, but the longer interval meant that more people in the UK received a first dose, thus giving them some level of protection at a time when vaccine supplies were limited.[33] Indeed, the extended interval between the two doses of mRNA vaccines proved to be beneficial – the longer interval between doses resulted in increased efficacy.[33] In May 2021, the gap between doses in the UK was shortened to eight weeks as a response to the threat posed by the Delta variant, a more potent SARS-CoV-2 variant that was first detected in India.[34]

Another area of inconsistency in the design of clinical trials is the way in which the desired 50% benchmark for efficacy was achieved. The protection rate of a vaccine is determined by the proportion of infection events occurring in the two arms of a trial – the placebo group and the vaccine group.[35] However, clinical trials for the various vaccines under investigation used different designs and different methodologies; they measured infection events at different time points (e.g. at 7 or 14 days

following a second dose); some investigated only moderate-to-severe infections while others included all symptomatic infection events, including mild cases.[36,37] This variability in design for the different vaccine candidates produced data that were difficult to compare. In a few instances, there were even disparities in clinical trials designed for the same vaccine candidate, leading to discordant data, so that a true understanding of that vaccine's efficacy was difficult to obtain.

All of these issues provide insights into the challenges faced by policy-makers who are trying to make informed decisions. Standardising measurements gathered during clinical trials, such as efficacy endpoints, to introduce uniformity across clinical trials of different vaccine candidates can make it easier for public health decision-making. It is obvious that greater consistency across the trials would have made it easier to draw conclusions about the advantages and disadvantages across the range of vaccine candidates.

Historically, clinical trials gather data in order to obtain regulatory approval and the research protocols are designed to reach that goal. These efforts may not always consider what is most important to the patient and may not align with the needs of health systems.

Enhancing clinical trial design can provide important information that can aid policy-makers. For example, all the clinical trials for covid-19 vaccines focused on preventing infections but additional indicators relating to disease transmissibility and severity may have yielded useful data for public health decision-making. Data on a vaccine's ability to reduce transmission of covid-19 would have been highly valuable, as it relates to public health policies on the use of face masks and social distancing to help limit viral spread. Unfortunately these data were not initially collected, so it was not clear whether the first authorised vaccines prevented transmission of the virus from vaccinated people to unvaccinated people.[36] We now understand that vaccinated people can transmit covid-19, but to a lesser extent than unvaccinated people. Having data on transmission at an earlier stage would have been of enormous help to policy-makers.

Historically, clinical trials gather data in order to obtain regulatory approval and the research protocols are designed to reach that goal. These efforts may not always consider what is most important to the patient and may not align with the needs of health systems. Broadening the scope of information gathered in clinical trials to include patient-reported outcomes and impact on health resource utilisation can promote public health decision-making and improve the vaccine ecosystem in the future. In addition, to ease the challenges in distribution and logistics (to be discussed in pillar 4), developers should continue to research ways to improve the storage and transportation capabilities of vaccines as well as improve the opportunity for lengthening the time before expiration.

Anticipating and accounting for the constant evolution of pathogens aids R&D

In the early days of the pandemic, it was not known whether SARS-CoV-2 would be susceptible to vaccines. Regulatory bodies and WHO gave guidance to vaccine developers on the efficacy benchmark required for a vaccine to be considered to secure emergency use authorisation. It was set at 50% and related only to placebo-controlled Phase III trials.[38,39,40] The currently authorised vaccines have met, and in several cases exceeded, this benchmark.

Viruses will continue to evade our immunological defences whether we gain protection from a natural infection or from vaccination. This is why we see the emergence of new SARS-CoV-2 variants, and unfortunately this is entirely unpredictable. There are no reliable indicators for knowing when or where the next variant will appear or what its characteristics and potential for harm will be.

The durability of protection afforded by vaccines can diminish over time, particularly with the emergence of more potent variants. The efficacy rates of covid-19 vaccines that were initially in excess of 94% have dropped over time. While, the degree of reduction in efficacy does not impact the overall usefulness of these vaccines, a similar reduction in efficacy in vaccines with an initial efficacy rate of 50% may be problematic, especially because of the circulation of more virulent variants. What is certain is that an efficacy rate below the 50% benchmark may mean a vaccinated person is at increased risk of becoming infected.

Infections that occur in people who have been vaccinated are called post-vaccination infections. They have been observed more frequently as the number of variants of concern increase in the community. Infections in vaccinated people are generally milder than in those who are unvaccinated. This is because the variants have not completely evaded the protection provided by the current vaccines, which are still effective in preventing hospitalisations.

Any reduction in vaccine efficacy is a liability for countries that are trying to emerge from lockdown. Even a large increase in mild forms of the disease can result in lost productivity in the workforce, and mild infections among vaccinated people can lead to transmission of the virus to unvaccinated people. It is possible that mild forms of the disease can lead to long-term conditions (known as long-term covid or long-covid).[41] Most importantly, any increase in the number of infections in a community provides opportunities for the emergence of new variants.

The unpredictable nature of the evolution of pathogens like SARS-CoV-2 underscores the need for continuous efforts in the area of vaccine development, to ensure that suitable vaccines are always available to safeguard the health of populations.

Greater investment is needed to ensure improved and more consistent surveillance to monitor the appearance and spread of new variants. Even in countries in which this is currently ongoing, the level of monitoring can still be inconsistent.[42] It is critical for countries to make information on the genetic information of all existing and new pathogens widely available to the scientific community – and to do so in a timely manner – to keep abreast of the changing epidemiology of the disease. This is especially important with the new variants.

The unpredictable nature of the evolution of pathogens like SARS-CoV-2 underscores the need for continuous efforts in the area of vaccine development, to ensure that suitable vaccines are always available to safeguard the health of populations.

Key opportunities for strengthening the vaccine ecosystem

Reinforcing and strengthening vaccine R&D is essential for maintaining a resilient and responsive vaccine ecosystem. The covid-19 pandemic has provided many insights into areas that can be improved in the next stages of this pandemic. Such actions will reinforce our level of preparedness for the emergence of the next public health emergency.

Key opportunities for further exploration include:

- Investing in vaccine R&D is vital for building upon our current successes and for creating a more robust vaccine ecosystem – one that enables vaccines to be produced more quickly to address future needs. Investment in vaccine R&D facilities and vaccine expertise is likely to improve resilience of the entire ecosystem and encourage R&D innovations that facilitate the production of new and more effective vaccines. Greater investment in vaccine R&D and manufacturing facilities will increase responsiveness to disease outbreaks, and allow technological innovations to be applied to the production of novel vaccines.

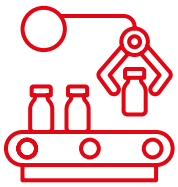
- Scanning and surveillance is of paramount importance: pathogens will continue to evolve and evade our best efforts to combat them. Strengthening systems, infrastructure, and policies for sharing data and information on emerging pathogens, including disease surveillance and biological samples, is crucial. Investment is needed to support research and surveillance of novel pathogens with pandemic potential. Timely sharing of data and information on infectious disease pathogens is a vital part of this process and must be encouraged.

- Investing simultaneously in a multiplicity of vaccine technologies increases the likelihood of developing an effective and timely vaccine to combat novel threats. The utilisation of diverse vaccine technologies also has potential to provide complementary approaches, with different manufacturing, supply chain, logistics and cost profiles, which can enhance the response to a disease outbreak.

- Cooperating through diverse modes of collaboration are to be encouraged to allow developers, research institutions and governments to work together to develop vaccines within tight timeframes.

- Opening pathways for expedited authorisation of vaccines while ensuring they meet adequate safety and efficacy standards is an important opportunity for regulatory bodies. However it is essential that science continues to guide the collection of relevant data.

- Enhancing clinical trial design can provide important information that can aid policy-makers and strengthen the vaccine ecosystem in the future. Designing clinical trials carried out by different developers that make use of similarly defined endpoints can produce reliable evidence to better inform decision-making by public health policy-makers. This will also help to improve public perceptions and trust in the rationale and methods used to develop vaccines.



Pillar 2: Manufacturing

Billions of covid-19 vaccine doses were manufactured by 1 September 2021; indeed over 5 billion doses have been delivered into the arms of the public in 183 countries.[2] This has been an incredible accomplishment given the significant challenges that needed to be overcome to establish sufficient facilities for manufacturing the vaccines, whether they were based on new or older technologies. We cannot be complacent: a significant part of the world has yet to receive any vaccines and there are many areas within the manufacturing sector that require improvement. The second pillar of the vaccine ecosystem examines these challenges, focusing on the urgent need for investment in existing and new manufacturing facilities while working on alleviating delays due to manufacturing issues. A robust manufacturing pillar is necessary to address these demands and ensure equitable access around the world.

Billions of covid-19 vaccine doses were manufactured by 1 September 2021; indeed over 5 billion doses have been delivered into the arms of the public in 183 countries.

Manufacturing is a challenge that requires international attention, investment and collaboration

Many complicated steps illustrate the demanding process of vaccine manufacture, and hint at the logistic burden for developers and governments in establishing new manufacturing facilities, a task that is even more challenging during a global health emergency. The current pandemic has underscored the value of investment in manufacturing facilities.

The advantage of using older, more established vaccine technologies during this pandemic, (such as live-attenuated virus or protein subunit vaccines, Box 3) is that large-scale manufacturing facilities were already operational. However, re-allocating the existing manufacturing infrastructure to meet the demands of covid-19 vaccine production may have had a direct impact on the manufacture of other vaccines. Vaccines based on the newer technologies, like mRNA vaccines, can be produced on a large scale within weeks, but they require precise temperature-controlled conditions and there are only a limited number of manufacturing facilities, so the need for more to be established quickly was clear at an early stage.

Manufacturing resources have been stretched to the limit, and developers have had to collaborate to maximise each other's manufacturing capabilities in order to meet demand. Yet even this exceptional effort has not yet been sufficient to vaccinate the world, and manufacturers face a unique conundrum: their return on investment may be at risk when they share their intellectual property with their competitors.[43] Governments have stepped in to support these collaborations. For instance, in the US, the Biomedical Advanced Research and Development Authority (BARDA) provided US$268 million in funding to support the transfer of technology and help manufacturing sites to bolster their production of covid-19 vaccines researched and developed by firms more usually in competition with each other.[44]

One of the reasons for the establishment of the Covid-19 Vaccines Global Access initiative (COVAX) was to address the challenges faced by covid-19 vaccine manufacturers. COVAX is directed by three organisations: The Global Alliance for Vaccines and Immunizations (GAVI), the Coalition for Epidemic Preparedness and Innovations (CEPI), and WHO. UNICEF is a delivery partner. COVAX initially allocated approximately US$7 billion for market preparation and manufacturing.[45]

Irrespective of the type of vaccine technology utilised, the risk for vaccine manufacturers is that a production facility might be built but not used if their vaccine candidate was found to have a poor safety or efficacy profile. COVAX aims to minimise such risks for manufacturers by investing in manufacturing capacity even before any of the clinical trials generated data on a vaccine candidate. This helps to ensure that vaccine manufacturers can scale up manufacturing processes as soon as a vaccine secures emergency authorisation, thereby avoiding months of delay between authorisation, production and distribution.[45]

COVAX has also invested in R&D, as discussed in pillar 3 on procurement, pricing and finance.

New manufacturing sites require long-term investment in multiple capabilities and capacities

Despite successful collaborations between vaccine manufacturers, additional manufacturing facilities may be required to meet the demand for vaccines so the investment of time and money for building new facilities is worthwhile. Even if it takes several months to build a new manufacturing facility, the increase in capacity for producing a billion additional doses from a baseline of 3 billion has been projected to offset a global economic loss of at least US$576 billion.[46]

Building manufacturing sites in each geographical region of the world can promote greater global manufacturing capacity and prevent over-reliance on any one manufacturing facility. Diversification of the manufacturing base to include local manufacturing, where possible, can promote resilience as long as manufacturing quality standards can be assured. Additionally, expansion of the manufacturing base could ease the demand on logistics and distribution networks, and could result in more countries reducing their dependence on vaccine imports.

At the time of writing, China and the US were the largest producers of covid-19 vaccines in the world, respectively producing 36% and 22% of the global total.[47] India and the EU were the third largest producers, each contributing 17% of all vaccines.[47] India's production helped to meet the needs of low- and middle-income countries[47] who lack local manufacturing facilities. But in early 2021 the country experienced a significant surge of new infections, and news reports explained that the country had to limit its exports to meet the needs within its own borders.[48] Many countries who depended on imported vaccines from India did not receive the shipments they had anticipated. This underlines the importance of having local capacity.

Setting up regional manufacturing hubs in under-served areas could be a step in the right direction. Countries, like Australia, are in discussion with manufacturers to improve local vaccine-manufacturing capability.[49] Unfortunately, this is not practical for many low- to middle-income countries that lack the necessary resources and infrastructure. Some high-income countries have pledged to fund the development of manufacturing facilities on the African continent to enable local production and prevent delays in distribution.[50]

Manufacturing facilities require a consistent supply of raw materials and auxiliary supplies; a manufacturing site is of no use without a reliable supply of these. For example, manufacturing facilities exist in Brazil but, according to news reports, the supply of raw materials has been inconsistent, resulting in delays in vaccine production.[51] Diversification of supply chains and manufacturing facilities can prevent over-reliance on any one supply chain and manufacturing site. Yet too much diversification poses potential risks over the supply of required raw materials and auxiliary equipment.

The challenges relating to raw materials will be discussed further in pillar 4 on distribution, logistics and supply chain management.

Manufacturing facilities cannot sit idle and then be instantly activated with the touch of a button in an emergency, they deteriorate quickly when they are not routinely used and maintained.

Building, establishing or repurposing manufacturing facilities is challenging for both new and old vaccine technologies, and technology transfer requires time and significant forward-planning. Each technology also presents unique challenges. One such challenge is the requirement for highly specialised equipment that must be sourced and installed, and production cannot begin unless there are sufficient experienced vaccine-manufacturing technicians. Furthermore, manufacturers need to monitor production timelines closely, making allowances for output to reach full capacity. On average, it takes 90–120 days to manufacture a single batch of covid-19 vaccine doses, yet despite progress, demand for vaccines continues to outpace supply.[52] Looking ahead, questions rise over how manufacturing sites can be repurposed if and when the demand for covid-19 vaccines subsides. Manufacturing facilities cannot sit idle and then be instantly activated with the touch of a button in an emergency, they deteriorate quickly when they are not routinely used and maintained.

Manufacturing facilities must undergo multiple quality control inspections covering every step of the production process and they must adhere to strict criteria. The standards are even higher for manufacturers of live-attenuated virus vaccines, because they must be capable of safely storing live viruses.

Regulatory authorities approve all of the quality control measures which must be included in manufacturers' dossiers in order to secure and maintain emergency authorisation.[52] Multiple regulatory authorities are involved in quality control, not just in the country where the vaccines are manufactured, but also in the countries where the vaccine is distributed. Manufacturers may have to meet different requirements and benchmarks for different regulatory authorities before their vaccines are authorised for distribution.

Regulatory bodies are involved in both the R&D and manufacturing pillars, and there is additional discussion of their role in pillar 1.

Risk-mitigation strategies are required to avoid manufacturing delays

Vaccine manufacture is complex and requires specialist expertise and processes to ensure and maintain the quality of the vaccines. In mid-2021, some regulatory inspections resulted in negative evaluations of manufacturing facilities for covid-19 vaccines, leading to the rejection of entire batches. In fact, millions of doses of vaccines were discarded because of inconsistencies across batches following manufacturing errors. Such errors underscore the need for risk mitigation, especially when the urgency of a situation threatens manufacturing quality.

Inconsistencies in vaccine manufacturing can lead to delays in obtaining authorisation. Irregularities leading to inadequate adherence to quality control standards can result in a potential risk of harm to vaccine recipients. This was an important rationale behind the decision of Agência Nacional de Vigilância Sanitaria (ANVISA, Brazil's regulatory authority), to reject emergency authorisation for a covid-19 vaccine that was submitted for emergency authorisation.[53]

Other manufacturing problems can impact regulatory authorisation. Possible contamination led to the US Food and Drug Administration (FDA) ordering the destruction of 60 million doses of a covid-19 vaccine.[54] Several problems in the facility were identified by the FDA which led to their decision, including poorly trained staff, a high risk of cross-contamination between different vaccine technologies, a failure to maintain sanitary conditions, and a risk of overcrowding due to the small size of the facility.[55] While this manufacturing site has since reopened, the situation negatively impacted the covid-19 vaccination campaign in the US and other vaccine companies had to compensate for the shortfall.

In addition to being costly and damaging to global vaccine supply, manufacturing errors can undermine public confidence in vaccines and can have a negative effect on vaccine uptake. Nevertheless, these errors were made public, clearly demonstrating that the regulatory bodies are being transparent about the results of their inspections, and this fact has helped to bolster public confidence in the manufacturing process.

Key opportunities for strengthening the vaccine ecosystem

Building and strengthening manufacturing capability and capacity is essential for ensuring a robust and responsive vaccine ecosystem. Several important considerations that apply to the wider vaccine ecosystem have emerged through examination of this pillar.

Key opportunities for further exploration include:

- Increasing vaccine manufacturing capacity requires a significant amount of forward planning and investment because it can take years to design and build facilities that meet required standards as well as upskill and train the required personnel.

- Collaborating between different vaccine manufacturers can help meet the demand for vaccines. Exploration and mitigation of concerns that can inhibit these collaborations, such as the protection of intellectual property rights, must be actioned.

- Anticipating and avoiding delays due to a lack of manufacturing capacity is vitally important. Building manufacturing facilities carries high financial risk, particularly if the vaccine that it is designed to produce is not authorised, or if demand for the vaccine it produces drops unexpectedly. Consideration should be given to how risks can be mitigated and incentives created to support manufacturing capacity.

- Developing localised manufacturing capacity is a useful option for meeting local demand, but there are significant barriers to overcome, including the need for adequate financing, infrastructure and human resources, as well as guaranteeing the supply of raw materials, and ensuring the continuous operation of these facilities.

- Ensuring that regulatory authorities have the capacity and capability to oversee development and manufacture of vaccines to assure safety and quality.

- Harmonising global regulatory standards to streamline processes can provide system-wide benefits, including reducing strain on the manufacturing supply chain.

Pillar 3: Procurement, pricing and finance

The vaccine ecosystem's third pillar – procurement, pricing and finance – has a wide-ranging impact on the four other pillars of the ecosystem, as underscored throughout the covid-19 pandemic. Historically, vaccine developers fund their own R&D or are helped by external funding on the basis that investors will recoup their outlay when the vaccine reaches the market.

Elements of the traditional procurement, pricing and finance models are relevant to the ongoing pandemic. However, new approaches to procurement and financing were used, including push- and pull-funding mechanisms to reduce financial risks associated with scaling up vaccine manufacturing and to create more certainty in the volumes to be purchased.[56] These new approaches may help to promote more equitable access to vaccines and may provide useful insights for the future.

New investment and incentive models are needed to support vaccine R&D

New models of financing R&D have emerged during the covid-19 pandemic, suggesting new ways for securing funding in the future. Operation Warp Speed (OWS) in the US was established with a budget of US$18 billion, of which US$12 billion was specifically dedicated to contracts relating to covid-19 vaccines. This public–private partnership was created between vaccine developers and the US government to speed up the development of potential therapies and vaccines against the disease,[45] decreasing development from years to months. This goal was successfully achieved, and the first covid-19 vaccine was authorised for emergency use on 11 December 2020 in the US (2 December in the UK and 21 December in the EU by the European Commission).

OWS certainly contributed to the speed of the R&D and manufacture of covid-19 vaccines. This US-centric approach was financed by American taxpayers, and the first vaccines manufactured under the scheme were expected to be allocated for use in the US before being made available globally. The perceived politicisation of the initiative led to scepticism towards OWS-financed vaccines during clinical trials, and there were concerns that this scepticism might impact vaccination campaigns in the US. OWS was entirely focused on vaccine development and manufacture; it was never intended to deal with uptake issues.

A global initiative for supporting investment in R&D and manufacturing was created during the covid-19 pandemic through COVAX, as discussed under pillar 2. Vaccine developers who received financial support were placed in the COVAX portfolio and allowed COVAX to secure advanced-purchase agreements when a vaccine was authorised. As of 1 September 2021, more than 236 million vaccine doses were delivered via COVAX to 139 countries, and 1.9 billion doses were forecast to be available by the end of 2021.[57]

In July 2021, COVAX had secured billions of dollars in funding from various sources; its website stated that it required a further US$600 million for continued covid-19 vaccine R&D.[58] Despite facilitating the distribution of vaccines to low- and middle-income countries at the same time as the vaccines are being distributed to high-income countries, challenges faced by COVAX will be discussed later in this pillar.

Box 6: The COVAX principles for prioritising vaccine distribution[59]

1. The country must be prepared to receive the vaccines.
2. Countries that have already initiated a vaccination programme are not included in the first allocation of vaccines from COVAX.
3. For countries that are self-financing, the COVAX vaccine doses must be within the price point of their own (non-COVAX) vaccine doses.
4. Countries must demonstrate a higher risk of infection among their healthcare workers.

Newly established vaccine-funding models such as OWS and COVAX split their budgets across a wide variety of vaccines in order to spread the risk of one or more candidates failing to demonstrate sufficient safety or efficacy during the R&D process. OWS split its funding between six vaccine developers.[60] During clinical trials, manufacturers were preparing to begin large-scale production despite a high risk of not being able to use their facilities for their intended purpose if the vaccine failed to meet the required safety or efficacy standards.

Continuing investment helps to optimise safety and efficacy of vaccines and can help to offset logistical challenges. Some covid-19 vaccine candidates continued to receive OWS funding for R&D even though they faced additional hurdles in authorisation and distribution. For example, some vaccines required a specialised device for administration, increasing regulatory, supply and distribution challenges.[61] Despite these challenges, continued funding was deemed to be justifiable because it was decided that improvements in the mechanism of delivery or other characteristics could be made after authorisation was obtained. For instance, some mRNA vaccines initially presented challenges for low- and middle-income countries in terms of transportation and storage. These obstacles have been addressed incrementally; following their initial authorisation, mRNA vaccines have been authorised for storage at regular refrigeration temperatures and for a longer time than was acceptable initially.

While COVAX and OWS are the most well-known external funding sources for covid-19 vaccine development, some vaccine researchers have chosen to predominantly self-finance their R&D efforts and avoid any direct association with a government. Others have sought funding from the European Investment Bank to support their R&D and large-scale production. After agreeing on a specific loan amount, some lenders distributed the funds in tranches, related to the achievement of pre-agreed milestones in the R&D process.[62] The latter carries more risk for developers than other external funding sources, especially if the candidate vaccine fails to deliver pre-agreed levels of safety and efficacy.

Pooled procurement initiatives and large scale pre-orders play an important role in pandemic response

Before the current pandemic, the manufacturers of newly approved vaccines followed long-established pricing and reimbursement procedures. In the US, this involves the Centers for Medicare and Medicaid Services (CMS) and private insurance companies. In the EU, manufacturers usually negotiate independently with different EU member states, because each country has different reimbursement processes. Governments in high-income countries have traditionally been the primary purchasers of most vaccines, except, perhaps, travel vaccines.

Due to the unprecedented demands of the current pandemic, emergency purchasing through large-scale pre-orders occurred in the US and EU. In the EU, a pooled procurement system emerged over and above the level of the national governments in the member states. This type of purchasing opens a potential new way for developers to market their vaccines in the future.

Many governments placed multiple early orders for covid-19 vaccines while the vaccines were still being studied in clinical trials. Many high-income countries pre-ordered more doses than they required and ordered more than one type of vaccine. Governments did this to reassure their population that they could secure a sufficient supply of vaccines for their own use, while safeguarding against vaccines that might not successfully advance through the R&D and manufacturing processes.

Placing orders early meant that some governments were able to secure lower prices. The UK, for example, ordered around 450 million doses despite having a population of only 66.5 million;[63] while Canada ordered enough doses to vaccinate its population five times over.[64] Governments that did not plan ahead faced longer waiting times for vaccines once they acquired regulatory authorisation, as well as higher prices.

Many governments placed multiple early orders for covid-19 vaccines while the vaccines were still being studied in clinical trials.

While the pre-orders provided financial reassurance for developers to further their R&D and manufacturing investments, the initial prices for covid-19 vaccines were low, despite their high economic and social value. According to pricing and reimbursement experts, these relatively low starting prices create challenges for manufacturers who may seek to increase prices to better reflect the value they feel they are delivering,[65] and to support continuing R&D to address emerging variants or an improvement in pharmacokinetic properties. While some companies producing authorised vaccines have managed to increase their prices to reflect real-world efficacy data, further increases will be difficult.[65]

Another challenge for manufacturers is the emergence of an over-crowded vaccine market, making it harder to demonstrate superiority of their own vaccine. Pricing decisions will depend on increasing competition between vaccines, and therefore profits – based on relatively low vaccine prices – are likely to relate to the volume of orders.[65]

With greater safety and efficacy data on the existing vaccines, questions arise over future contracting procedures and pricing. Some developers have indicated that they plan to increase prices for high-income countries, while keeping prices at their initial levels for low- and middle-income countries,[66] even though the initial prices are already too high for many countries participating in COVAX. The budgetary constraints of low- and middle-income countries make it difficult for them to procure sufficient doses for their populations.

The COVAX Advance Market Commitment (AMC) created a financing mechanism funded through Official Development Assistance (ODA), philanthropic, and private sector donations to assist 92 countries with a per capita gross national income of less than US$4,000 to purchase covid-19 vaccines at low cost.[67] COVAX AMC provides vaccine manufacturers with a commitment to make large purchases of vaccines financed through donors which are made available at a reduced price per dose in these countries.[67] These 92 ODA-eligible countries may be required to contribute to the purchasing of vaccines for their population but they will not have to carry the entire burden. The procurement platform of COVAX, the COVAX Facility, is the mechanism under which global risk is shared, procurement is pooled, and equitable distribution of covid-19 vaccines is assured.[67]

As high-income countries ease their lockdown measures, focus is shifting to the purchase of the next round of covid-19 vaccines. Local reimbursement experts have predicted that future purchasing in the US may revert to traditional purchasing models.[65] New purchases would be used as a third dose following a two-dose vaccine or a second dose following a single-dose vaccine with the intention of improving efficacy against variants of concern.[65] The EU pre-ordered enough doses (1.8 billion) from a single vaccine developer to meet the needs of member states through to 2023. At that point, according to local experts, and depending on how quickly the developer can fill this order, the EU may also revert to traditional reimbursement models.[68]

The current pandemic has brought about new models of joint procurement or coordinated procurement across governments. While this has been useful for covid-19 vaccines, this is not expected to be a long-term option.

Global perspectives are needed to alleviate the impact of vaccine nationalism

Box 7: Definitions of vaccine nationalism and hoarding

Vaccine nationalism: Relates to countries that prioritise vaccines for their own population, even though vaccines are needed more urgently in other countries.

Vaccine hoarding: Relates to countries that pre-order a significant number of vaccines and have more stock than they need to vaccinate their own population.

Viruses do not recognise national borders, thus a concerted global effort is required to control their spread during a pandemic. Despite the extraordinary global need, countries that had early access to vaccine supplies prioritised the vaccination of their own populations above the needs of other countries, even when other countries were confronting more dire circumstances.[69] Vaccine nationalism (Box 4) is not a new phenomenon; in 2009, for example, during the H1N1 influenza pandemic, international access to therapeutic agents only occurred when high-income countries had secured sufficient supplies for their own populations.[70]

The covid-19 pandemic has highlighted the problem of vaccine nationalism, and has demonstrated the importance of addressing it in order to improve the vaccine ecosystem.

When vaccine developers received funding directly from the governments, the pre-ordered vaccines were delivered as soon as they received emergency authorisation, which means that countries with the greatest need may not be the first in line to receive them – a stark demonstration of inequity. But inequity also exists among high-income countries; some received their doses while others had to cope with delays due to manufacturing issues.[71] The European Commission took legal action against developers that failed to meet targets for delivery of vaccines to EU member states.[71]

Viruses do not recognise national borders, thus a concerted global effort is required to control their spread during a pandemic. The covid-19 pandemic has highlighted the problem of vaccine nationalism, and has demonstrated the importance of addressing it in order to improve the vaccine ecosystem.

The mission of COVAX is to ensure all countries have equal access to covid-19 vaccines. It receives financial contributions from countries and philanthropic institutions in order to fund continued vaccine R&D and manufacturing by developers. When a vaccine is authorised, COVAX reviews whether to order doses for the countries that participate in the scheme.[45,72] In order to receive vaccines through COVAX, countries must meet certain criteria (Box 6). COVAX ensures timely access to vaccines for all participating countries; yet there are opportunities for improvement.

The initial wave of COVAX vaccines was allocated to participating countries according to the size of their population, regardless of their level of income; countries were to receive sufficient doses to vaccinate 20% of their population to protect their most vulnerable citizens. Thereafter, each country's specific level of threat and vulnerability was to be taken into account (Box 6).[73] However, this approach was criticised by those who considered that a country's specific level of need should have been taken into account from the start.[74]

Some countries who participated in COVAX also entered into bilateral deals directly with developers to enable them to meet their own vaccine demands.[75] These deals provide vital financing that bolsters vaccine production, and allow countries to obtain additional doses in light of their population's needs, but, unfortunately, they can undermine the COVAX model. Countries that can afford to place orders outside the COVAX model can obtain disproportionately more doses than those that are less well-off, further underscoring issues related to equity of access.

Direct-to-manufacturer deals are a form of vaccine nationalism because the contracts are made beyond the pooled procurement model on which COVAX was developed. While these transactions can give countries earlier access to vaccines, the agreements they make can be problematic. In response to the slow rollout of vaccines and public pressure, for instance, some EU member states made their own agreements with developers outside the EU pooled procurement models.[76] According to news reports, Hungary and Slovakia purchased vaccines before they received EU authorisation (they were either under review or waiting to be submitted for review), but they were purchased outside the scope of the EU so they paid more for them than the European Commission paid in its first round of pre-orders.[76]

Governments attempted to alleviate the challenges of vaccine nationalism before the current pandemic occurred. In response to events during the 2009 H1N1 influenza pandemic, China and India bolstered their pharmaceutical research and manufacturing capabilities, and worked to enhance pathogen surveillance. This led to the creation of WHO's Pandemic Influenza Preparedness Framework.[70]

An obvious way to avoid vaccine nationalism is for each country to have a completely localised vaccine R&D and manufacturing hub, but this is very challenging to achieve, as has been discussed and even more challenging to accomplish in the midst of a global health crisis.

Concerns over vaccine hoarding (Box 7) were raised during the current pandemic when countries pre-ordered more vaccine doses than they required for their population. In response, some high-income countries offered to donate (and have since donated) millions of doses to other nations, after prioritising their own populations.

Ethical dilemmas have arisen over the decision of some countries to broaden their vaccination programmes to a wider cross-section of their population and/or provide additional rounds of vaccinations to populations who had been considered to be fully vaccinated. Experts raised concerns about depleting global supply of vaccines by vaccinating younger age groups when other countries are struggling to vaccinate people who are at much higher risk.[77] For example, in May 2021, the US and EU granted emergency authorisation for administering covid-19 vaccines to people as young as 12 years old,[78,79] before the full threat of the Delta variant in children and young people was completely understood.

According to the American Academy of Pediatrics and Children's Hospital Association, cases of covid-19 in children in the US increased exponentially between early August and early September 2021.[80] In the week of 26 August 2021, they reported that children represented 26.8% of all newly diagnosed cases of covid-19 in the US.[80] On 4 August 2021, the UK announced it would roll out a single dose of mRNA vaccines for all 16- and 17-year-olds, adding to its earlier strategy of providing two doses for high-risk people in this age group.[81] On 13 September 2021, the UK lowered the age of eligibility by extending the roll out of a single dose of mRNA vaccines to all 12- to 15-year-olds.[82]

The emergence of variants, such as Delta, has introduced new incentives for countries with vaccine stockpiles to use them within their own borders to improve vaccine efficacy in their population. On 13 August 2021, the FDA authorised a third dose of mRNA vaccines for people with a compromised immune system.[83] On the same day, Israel lowered the age of people eligible for a third dose to those aged 50 years and over following a surge of infections due to the Delta variant.[83] In Europe, countries like Germany, France and the UK are formulating plans to deploy booster doses in high-risk groups.

Discussions about rolling out a third dose of a two-dose vaccine or a second dose of a single-dose vaccine in high-income countries to address variants of concern have been met with scepticism. The opinion of the experts is that fully vaccinated people are still protected against moderate-to-severe covid-19 with much of the world yet to receive their first vaccinations.[79,84] WHO has called for high-income countries to postpone plans for administering boosters until 2022, because of disparities in vaccine supply between countries, particularly low-income countries.[85] Many people in low- and middle-income countries have yet to receive their first dose of a covid-19 vaccine due to issues related to poor access.

Meanwhile, vaccination uptake is a problem in high-income countries, due to issues related to vaccine hesitancy (discussed further in pillar 5). In the US, the recent spike in new infections related to the Delta variant was mainly driven by unvaccinated members of the population.

The European Commission pre-ordered enough mRNA vaccines to provide up to three doses to all adults, adolescents and children.[86] They report that this includes the potential for re-selling or donating excess doses of vaccines, at the discretion of member states.[86] With the need to ensure that member states are able to provide up to three doses to their populations, it may be some time before the member states decide to redirect their vaccines to other parts of the world. News reports from August 2021 show that the EU has donated 7.9 million doses to date, significantly less than the number of doses donated by the US (59.8 million) and China (24.2 million).[87]

Key opportunities for strengthening the vaccine ecosystem

Strengthening the procurement, pricing and finance pillar provides benefits for the entire vaccine ecosystem. Several important opportunities have been revealed by the current pandemic.

Key opportunities for further exploration include:

- Safeguarding investment in the vaccine ecosystem with sound financing models across all pillars must be ensured. Supplemental investment may be required to combat short-term public health emergencies to respond to a disease outbreak. Sustainable long-term investment in the vaccine ecosystem is required to meet all aspects of the ecosystem from R&D through to the vaccination programmes that deliver vaccines to the public. The goal is to ensure sufficient financing to sustain the vaccine ecosystem and address the imbalances in access and equity to meet public health needs.

- Ensuring the use of equitable international procurement models that are fit for purpose whether they are required to address endemic disease or public health emergencies.

- Promoting equitable and timely access to vaccines worldwide requires communication and collaboration. Global cooperation is particularly important during public health emergencies. Vaccine nationalism is a real concern, and measures must be taken to alleviate the impact on future vaccine-purchasing schemes.

- Collaborating between countries and regulatory authorities can ease allocation imbalances and promote conservation of the scarce resources required to support every pillar of the vaccine ecosystem.

- Promoting global health security can be addressed by improving equitable access to affordable vaccines and addressing procurement challenges for low- and middle-income countries. Pricing models can be developed to sustainably address inequities around the world.

- Improving procurement and planning can be achieved with better tools to forecast national and global needs.

- Increasing investment can help to rebuild and reinforce routine vaccination programmes that have suffered during the current pandemic, making them more sustainable for the future.

Pillar 4: Distribution, logistics and supply chain management

The next critical step in a successful vaccination ecosystem is encompassed by the fourth pillar, distribution, logistics and supply chain management. This pillar covers transportation of raw materials required to manufacture vaccines as well as the logistics required to make sure that vaccine doses maintain their quality. The distribution network comprises a vast array of operators, and the degree to which they were prepared for the pandemic was highly variable. The covid-19 pandemic has drawn attention to many significant challenges in the transport of vaccines.

This pillar will evolve significantly in the coming months as the pandemic continues to unfold. There have been many news reports about vaccines being discarded when they have passed their expiry date in countries in which logistical issues have prevented their timely delivery.[88] But the true impact of the challenges presented by this pandemic in this pillar remains to be seen. The Vaccine Ecosystem Initiative will continue to monitor global progress to identify lessons that can be integrated into this pillar of the ecosystem.

Movement of raw materials and vaccines must be streamlined to prevent delays

Although the existing transportation networks support the movement of raw materials and vaccine products between and within countries, it was acknowledged long before the covid-19 pandemic that they required improvement. With a new focus on these issues, some upgrades have been accelerated.

Every component of a vaccine must be available to manufacturers when it is needed and in the correct quantity. Before the manufacturing process can begin, all of the necessary raw materials and auxiliary supplies (such as needles, vials and syringes) must be obtained from companies that may be based in different corners of the world. Manufacturers need supplies such as bioreactor bags, cell-culture media, filters and sterilisation equipment, each comprised of very specific components.[52] A shortage of any single element can lead to delays in production.

Every component of a vaccine must be available to manufacturers when it is needed and in the correct quantity.

Significant challenges concerning raw materials relate to the accurate estimation of the quantities required as well as export and import barriers.[52] Before the current pandemic, there were only a limited number of suppliers of many of the necessary raw materials. Governments and vaccine developers openly discuss the expansion of manufacturing capacity to address global demand, but these discussions are meaningless if the supply of raw materials cannot satisfy or even reach a growing number of manufacturing facilities around the world. Some countries have established fast-track mechanisms to secure alternative sources of raw materials to address bottlenecks, but

increasing the number of suppliers of raw materials is neither straightforward nor simple, because these suppliers must also undergo quality control inspections to ensure the quality of their raw materials.[89] Furthermore, new suppliers must integrate seamlessly into transportation networks to make sure their materials are moved safely and in a timely manner. There is a significant need for a global approach to strengthening the availability and supply networks of raw materials.

The distribution of vaccines also needs to be streamlined. The World Trade Organization (WTO) developed a checklist for the development and delivery of covid-19 vaccines.[90] Official green lanes (or corridors) were created to facilitate customs clearance at border crossings between EU member states, and it has been possible to submit pre-arrival documents electronically. Import and export declaration forms have been simplified, and business hours have been extended.[91] These approaches have been integrated into other aspects of the vaccine ecosystem to prevent transportation delays. The EU is the main source of vaccine exports for all regions of the world. South Asia and sub-Saharan Africa, for example, import more than two-thirds of their vaccines from the EU, despite the fact that there are several manufacturing sites in low- and middle-income countries in these regions.[91]

Pre-existing export and import highways have facilitated the transport of covid-19 vaccines, but vaccine nationalism has impeded their movement. Italy has local vaccine-manufacturing facilities and used new EU regulations to prevent its vaccines from leaving the country after a developer failed to meet its supply contract with the EU. According to news reports, this prevented around 250,000 doses of vaccine from leaving the country.[92,93] Australia was impacted by import delays so it decided to explore developing its own manufacturing capabilities. In Brazil, deliveries of vaccines were slower than expected, which the country attributed to a surge of covid-19 infections in the manufacturing countries.[94] One solution for preventing transportation bottlenecks like these is to develop localised vaccine manufacturing capability but, as previously mentioned, this is neither straightforward nor simple.

An increasing problem in transportation relates to a shortage of employees to handle the huge quantities of vaccines that need to be shipped. News reports have highlighted the impact of worker shortages on the movement and monitoring of these shipments. Despite efforts to hire new personnel, more staff are urgently required.[95]

Distribution networks require innovations in temperature-control systems

Specific concerns have emerged during the pandemic about the safe transportation and storage of temperature-sensitive vaccines. Even with the right equipment, there is still the potential for damage to temperature-sensitive pharmaceutical products during transit or on arrival at vaccination centres, according to the International Air Transport Association (IATA).[91]

Specific concerns have emerged during the pandemic about the safe transportation and storage of temperature-sensitive vaccines.

Most covid-19 vaccines require precisely controlled environments maintained at cold temperatures (minus 2°C to minus 20°C) or ultra-cold temperatures (minus 70°C). If these optimum conditions are not maintained, vaccines can be damaged and lose potency so that they may no longer be effective. This could result in people not receiving their vaccinations or needing to be revaccinated, placing further strain on limited resources.[96] Refrigerants may be required for transport and storage, and they may be defined as dangerous goods, for which logistics operators must follow stringent rules.[91]

Some countries have upgraded their facilities to cope with, and maintain, cold chain systems,[96] but delivering vaccines to countries without appropriate facilities remains a challenge. Moreover, maintaining cold temperatures is expensive; it accounts for as much as 80% of the vaccination costs for low- and middle-income countries where ambient temperatures are generally higher. Unreliable power supplies and a lack of spare parts for maintaining cold chain facilities are also an issue, particularly in low- to middle-income countries.[96] These are significant challenges and can pose problems for any country regardless of income level, because even some high-income countries lack the infrastructure and facilities to meet the specific storage requirements of these vaccines.[96]

All vaccines have a limited shelf life, and thus have clearly defined expiry dates. For covid-19 vaccines, it is currently six months, but this figure is based on relatively little data, given that the first authorisation for a covid-19 vaccine was received in December 2020.[97] Because of the logistics and distribution challenges in the vaccine ecosystem, six months is a short time for a vaccine to be packaged, shipped around the world, distributed to a vaccination centre, and administered into a waiting arm. Expiry dates must be carefully monitored to avoid wastage and to make sure expired vaccines are not administered to anyone. It is possible for the current shelf life to be extended, but this depends on collection of longer-term data. Based on more recent research, the FDA has extended the expiration date of certain vaccines by several weeks and thus avoided stock from being discarded.

Short expiration dates and the need for highly-regulated storage conditions are challenging for any country, however these challenges are serious in low- and middle-income countries struggling to provide the necessary cold chain conditions to safeguard and distribute vaccines.

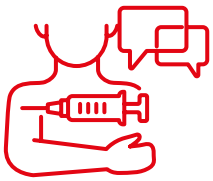
Understandably, the more that can be done to prevent vaccines from being discarded, the better. Further research will be directed at stabilising the existing vaccines to prolong their viability at varying temperatures. The incorporation of specific polymers or sugars may improve a vaccine's ability to remain stable at room temperature or withstand a wider range of temperatures. The composition of a vaccine might be adjusted from liquid to a dry powder that can be reconstituted once delivered to a vaccination centre. Data has already demonstrated that nanoparticle-encapsulated mRNA vaccines can be converted to a powder.[96]

Key opportunities for strengthening the vaccine ecosystem

The safe and secure transportation and distribution of raw materials and prepared vaccines require precise logistical plans and careful supply chain management. This pillar comprises a wide array of operators which will lead to a significant evolution in this area in the coming months.

Key opportunities for further exploration include:

- Improving the synchronisation of manufacturing, including the materials required for packaging and shipping vaccines can ease distribution and logistics steps in the vaccine ecosystem.
- Investing in data systems can improve inventory management of both raw materials and vaccines.
- Improving import and export networks can ensure seamless integration of new suppliers of raw materials, expand the supply of skilled workers, and address vaccine nationalism, which impedes the timely transportation of vaccines.
- Upgrading systems to improve the infrastructure to meet temperature requirements to safeguard temperature-sensitive raw materials and vaccines is needed around the world. Quality control in transportation must be amplified to mitigate the risk of damage to raw materials and vaccines during transit. Countries should be equipped with the right infrastructure to accept and store vaccines, particularly at the start of a vaccination campaign when the first authorised vaccines may have more demanding requirements.
- Maintaining and extending the shelf life of vaccines should be investigated to prevent wastage of scarce resources. Testing a vaccine's ability to be transported and stored for an extended period should be included in the initial investigations of a vaccine.
- Strengthening supply chains by improving distribution channels can help to alleviate bottlenecks.
- Addressing infrastructure requirements necessary to secure the safe storage of vaccines in stockpiles and at vaccination centres.



Pillar 5: User acceptance and uptake

Vaccines are accepted and received by people to varying degrees. Early and enthusiastic adopters are at one end of the spectrum, and those who outright refuse to be vaccinated at the other. Slow adopters lie somewhere between those extremes. They may be well-informed on health matters but prefer to wait before being vaccinated or prefer to receive a specific vaccine when there are several to choose from (Box 8).

The fifth pillar of the vaccine ecosystem discusses the importance of public access to reliable information. The aim of providing better knowledge is to mitigate apprehension and unease that may be felt by some people. Higher levels of health literacy in a population make it easier to understand information and can improve interactions with the health system.[98]

Uptake can also be improved by providing convenient locations for people to obtain their vaccinations during hours that work for them. Vaccination campaigns should be seamlessly integrated into everyday life.

Challenges in user acceptance and uptake are not new, but the covid-19 pandemic has highlighted the importance of not underestimating their vital role in the success of vaccination campaigns and the overarching vaccine ecosystem. There are opportunities for civil society and the private sector to partner with educators, public health professionals, policy-makers and governments at local, national and global levels.

Box 8: Terms used to describe vaccine acceptance and uptake

Early adopters: People who receive a vaccine as soon as it is available and do not need to be persuaded.

Slow adopters: People who intend to receive a vaccine but require reassurance (for covid-19, this includes people who prefer to choose one type of vaccine over another).

Vaccine hesitant: People who delay accepting vaccinations or refuse vaccinations for various reasons, despite having access to vaccines.

Herd immunity: A threshold at which unvaccinated people are protected from infection due to the number of people in the population who have been vaccinated. The calculation depends on the transmissibility of the disease, the vaccine's efficacy and the number of people who receive the vaccine.

Health literacy builds knowledge of and trust in the vaccine ecosystem

Improvements in health literacy and public understanding of the issues surrounding vaccines and vaccination programmes are vitally important. By increasing levels of health literacy, people can be equipped with the tools to understand and act on information and services and make positive health-related decisions.[99]

Health literacy is more than simply having knowledge about health promotion – it includes the person's interactions with the health system and his/her ability to interact with healthcare providers.[100] Investing in health literacy helps to foster trust in the vaccine ecosystem as a whole, and brings other rewards such as improved public engagement with the health system.

Efforts to improve health literacy must be targeted to particular groups of people to deal specifically with their needs and to resolve any previous negative experiences with the health system, concerns regarding systemic racism,[101] and/or concerns rooted in religious beliefs[102] which must be acknowledged, rather than downplayed. There is a disproportionately higher rate of illness in some population groups because of longstanding distrust of health systems.[103] Therefore, communications must be bespoke and delivered to meet their specific needs and information-consumption habits. Various modes of communication approaches must be considered, including delivery channels, the format of the information, and the language used.

Investing in health literacy helps to foster trust in the vaccine ecosystem as a whole, and brings other rewards such as improved public engagement with the health system.

Efforts to improve public communications and, as a consequence, informed decision-making must address the complexities associated with vaccination programmes. Communications that are unclear or incomplete can cause further misunderstanding and can exacerbate mistrust. Some younger people, for example, are slow to get vaccinated because they perceive that their age cohort is less likely to develop severe disease.[104] Delayed uptake has also been found among people who do not trust manufacturing processes or the public health bodies that sanction them.[105] Surveys have shown that concerns about the rapid development of covid-19 vaccines added to delayed acceptance in certain populations.[106]

Actual or perceived differences in the efficacy profiles of the available vaccines can lead to confusion, irrespective of a person's level of health literacy. News reports have shown that some people who are offered an mRNA vaccine prefer to wait for a specific type of mRNA vaccine, made by a specific company.[107] These findings raise concerns because vaccination campaigns can be slowed down, resulting in stocks of vaccines that may be unused and may be wasted.[108]

As the number of vaccinated people in a population increases, more data are generated on the types and frequency of side effects and adverse events. As information emerges, it needs to be clearly communicated to the public. There have been reports of severe adverse events following a second dose of some vaccines which may have impacted the rate of uptake of second doses.[109] Adenovirus vector vaccines have been seen to cause rare adverse events in particular subgroups of the population.[110] News reports have described temporary pauses in clinical trials and the halting of vaccine rollout[111] in some countries.[112] While new vaccine platforms have met regulatory safety and efficacy thresholds, some people remain anxious over unknown long-term effects.

Improved health literacy can bolster vaccination rates, and it is achievable. For example, Israel has carried out one of the most successful covid-19 vaccination campaigns, fully vaccinating 62% of adults by the end of July 2021.[2] This success was directly related to improved health literacy, whereby the government used clear, consistent messaging with the public at every stage of the campaign. They insisted that vaccinated people should continue to use face-coverings and comply with social distancing measures. They used various types of media to tailor their communications to specific population groups to address risk levels and scepticism. The public was also reassured that sufficient doses would be available to vaccinate everyone, which led to widespread trust.[113]

When the process for obtaining a vaccine is cumbersome or challenging to navigate, people might be slow to get vaccinated, irrespective of their knowledge level or willingness to get vaccinated. People need to take time from work or other responsibilities to navigate booking systems to schedule an appointment and must travel to and from vaccination sites; all of these factors can alienate populations to different degrees.

Measures to increase vaccination uptake have involved radical approaches in some countries. In Spring 2021, several states across the US offered free food, alcohol, cash, university tuition, lottery tickets and other tactics to incentivise vaccine uptake.[114] Ohio's Vax-A-Million campaign was open to anyone receiving at least one dose of a covid-19 vaccine.[115] The lottery ran from 26 May to 23 June 2021 rewarding five people with US$1 million and five young people aged 12-17 with full scholarships to any Ohio public university of their choice.[115,116] While the programme cost US$5.6 million, it increased

vaccination rates by 1.5% and prevented approximately US$66 million in healthcare costs related to hospitalisation, but researchers did not factor in the additional benefits stemming from the avoidance of complications stemming from long-term covid and reduced mortality.[115] Researchers report that an increase in vaccination uptake during the programme was found in lower-income counties in Ohio, citing the observation that people living in higher-income counties may have accessed their vaccinations earlier in the year.[116] Other countries have taken similar steps to entice the public at national or local levels, such as Lebanon, the Philippines, Russia, and the UK, as reported in the press.[117,118]

Incentives to increase vaccine uptake need to be handled with care. Sceptics and conspiracy theorists have queried whether these inducements could be viewed as bribes. In addition, while some of these measures have shown success in increasing uptake, ethical issues have been raised about these publicity-generating tactics,[119] particularly when there may be more cost-effective ways to integrate the delivery of vaccinations into people's daily routines.[120]

Causes of vaccine hesitancy need to be addressed

Misinformation is a serious risk to public health: it does not simply threaten physical and mental health, it alienates families, friends and communities. As many news reports have shown, misinformation has led to incidents of harassment and even violence against public health and health professionals, as well as service and transportation workers.[121] It results in confusion, fosters mistrust, injures the health of individuals and destabilises public health efforts.

Vaccine hesitancy arises due to a range of factors, including concerns about side effects, conspiracy theories and political alliances. Interestingly, it was found that people's vaccination status in the US was linked with their voting choices - the single greatest predictor of someone being vaccinated was whether they voted for Joseph Biden or Donald Trump in the 2020 general election.[122]

Refusal to obtain a vaccine is to be expected among a small fraction of the population. Yet without a good level of vaccine acceptance across a population, vaccines are unlikely to adequately control the spread of diseases they have been developed to control and prevent. Vaccine hesitancy is not a new phenomenon; it emerged along with the first vaccine developed by Edward Jenner for smallpox in the 1790s.[123] Vaccination acts in 1840 and 1853 made vaccination compulsory in England and led to anti-vaccination groups charging that the laws violated civil liberties.[124]

While the anti-vaccine movement gained momentum long before the covid-19 pandemic, it has now reached unprecedented levels. One report suggests that much of the anti-vaccine content on social media originates from only a dozen highly influential individuals.[125] They may be small in number, but their online footprint has a significant real-world impact. Overall, social media has had a major role in spreading unsubstantiated concerns over vaccines, however it can also be used to prevent such claims gaining momentum,[126] and some social media companies have attempted to flag vaccine misinformation. More must be done to keep pace with the vast amount of misinformation flooding the internet.

The mainstream media must work to combat misinformation, which is why investment is so important in this area.

The mainstream media must work to combat misinformation, which is why investment is so important in this area. Improved training for those working across all types of media is needed to ensure they are better equipped to tackle misinformation and proactively address the public's need for reliable, evidence-based information. Support should be given to researchers and health professionals to engage with the public.

More can be done at a political level. The US Surgeon General, Dr Vivek Murthy, released his first advisory document on 15 July 2021, *Confronting Health Misinformation: The US Surgeon General's Advisory on Building a Healthy Information Environment.*[127] This seminal report is the latest in a series of what are now commonly known as Surgeon General's Reports which have focused on a range of public health issues since 1964. This report highlights the urgent threat to public health posed by misinformation which all too often stems from fear and lack of knowledge. Misinformation results in confusion, promulgates distrust, injures individual health and destabilises the provision of public health. Addressing this risk to public health can improve public trust in science and inspire confidence in the vaccine ecosystem.

On 10 September 2021, the Secretary-General of the United Nations, António Guterres, held a press conference in which he stated that global action must be taken to promote facts and science and to tackle disinformation and conspiracy theories.[128] In the newly published report, *Our Common Agenda: Report of the Secretary-General*, he framed the covid-19 pandemic and the climate crisis as the greatest challenges in the world since the Second World War.[129] The Secretary-General stated that a global vaccination plan operationalised by an emergency task force must be developed noting that investing US$50 billion in vaccinations now could add an estimated US$9 trillion to the global economy in the next four years.[129] The Secretary-General warned that we must carefully develop strategies to promote a more sustainable, peaceful way forward and in no uncertain terms, he said quite simply, "we must make lying wrong again."[128]

Science and technology move at a fast pace, one innovation quickly follows another, the body of knowledge is always growing. We must strive to overcome all barriers to understanding among the public, by providing access to education and information that promotes and empowers sound

decision-making. Civil society and the private sector have many opportunities to partner with educators, public health professionals, policy-makers and governments to address health literacy at all levels – locally, nationally and globally – to communicate important information that can be easily understood by people across all socioeconomic and educational levels.

Key opportunities for strengthening the vaccine ecosystem

The hesitancy in vaccine uptake witnessed during this pandemic has increased exponentially, in parallel with the growth of social media. More than ever, vaccine acceptance depends on the provision of accurate and reliable information from trustworthy sources. Improving health literacy can help to eliminate misinformation and empower individuals and communities to make well-informed health choices.

Key opportunities for further exploration include:

- Recognising the role our leaders play in guiding and inspiring confidence in the vaccine ecosystem must not be overlooked. Trusted leaders and influencers have a role in building confidence in their communities about the value and safety of vaccines. They can actively address the issue of vaccine hesitancy – a serious problem during the current pandemic – as well as dispel myths and misinformation and counter anti-vaccine activities that spread fear and mistrust.

- Nurturing the public's trust in vaccines is vitally important to the success of any vaccination programme in terms of rapid uptake of vaccines when they become available. Increasing trust in vaccines allows any infectious disease threat to public health to be handled effectively.

- Investing in health literacy improves public understanding of health-related issues. Trust is necessary to eliminate fear, but it is hard to win and all too easy to lose. Trusting anything or anyone depends on having a thorough understanding, which can only be achieved through the acquisition of knowledge. This is why improving health literacy throughout the world is such an important step. The public must be helped to understand the principles of science and the stepwise nature of scientific inquiry, so that they can feel confident that vaccinations are a safe and effective way to promote health and save lives.

- Communicating with the public must be carefully targeted and be delivered in a consistent way in order to address the concerns of specific groups.

- Providing information grounded in evidence is vital to separate fact from fiction.

- Tackling misinformation requires a strategic approach. Policies and initiatives to alleviate the impact of misinformation can be strengthened by collaborating with mainstream media and social media platforms.

- Integrating vaccination campaigns seamlessly into people's daily lives helps to eliminate the barriers can delay vaccine uptake even among people who are health literate. Ensuring vaccinations are accessible and convenient improves uptake.

Section 3: Building a better Vaccine Ecosystem

The Economist Group's Vaccine Ecosystem Initiative seeks to maximise key opportunities to strengthen the vaccine ecosystem. Working with our Advisory Council, we developed a five-pillar framework to understand the different ways we can make the ecosystem more sustainable. This report has examined these pillars within the context of the current covid-19 pandemic, and identified areas for further exploration in the months ahead.

In our intimately interconnected modern world, diseases threaten global security and global development. The protection provided by vaccinations extends beyond individual health to the health of entire communities; therefore investment in this area is an investment in national health, national economic wellbeing and global health security. More must be done to generate the political will to ensure adequate, equitable investment and access to vaccines. Strong leadership is essential for ensuring equitable access to vaccines, irrespective of location, age, socioeconomic status and gender-related factors, and for building public confidence in vaccines. The inequality in access to immunisations across high-, middle- and low-income countries seen during the current pandemic must be addressed as a matter of urgency, and greater effort must be made to inspire impactful global and national leadership capable of eliminating the longstanding inequities that prevent universal access and universal health protection.

We have seen the severe impact of national lockdowns on the economic wellbeing of countries, with far-reaching consequences that cross national borders, extending to international trade, travel and transport. Decision-makers in national governments and in regional and global institutions should work together across public and private sectors to support policies and practices to ensure that vaccines are used to benefit societies throughout the world. Prioritising (and investing in) the vaccine ecosystem must be endorsed worldwide by committed leadership across countries and all sectors.

Throughout the pandemic, we have witnessed that the **research and development (R&D) pillar** is resilient and flexible, offering a range of vaccine technologies and diverse models for collaboration. There are opportunities for further investment into additional approaches for vaccine development and other ways of enhancing collaboration among stakeholders.

Within the first pillar, we were reminded of the value of research into and surveillance of novel pathogens that have the potential to impact global health security. The timely sharing of data and information must be a major point of focus in order to combat the speed of pathogen transmission and evolution of more virulent strains. Furthermore, we are eager to investigate the broadening of the remit of clinical trials beyond investigating safety and efficacy, to address key questions that can inform public health decision-making and positively impact public health policy.

In the **manufacturing pillar** we discussed the need for significant forward planning and investment to establish and adapt vaccine manufacturing facilities. These facilities should be built to support the wider distribution network needed to ensure vaccines are produced and made available to all who can benefit from them. This requires consideration not only of the location of the facilities themselves but must also consider the availability of vaccine components, raw materials and equipment that may be in limited supply. Consideration must also be given to the ability to use or repurpose vaccine manufacturing facilities in the event of a decrease in vaccine demand. Collaboration between vaccine manufacturers has been immensely valuable in meeting vaccine demand, but the impact it potentially holds on sharing intellectual property needs to be addressed.

Regulatory oversight has a major impact on both the R&D and manufacturing pillars. Regulatory channels used during the covid-19 pandemic made it possible to expedite the emergency authorisation of vaccines without compromising safety and efficacy. However, the continued collection of data is of paramount importance and finding ways to communicate the information they yield is vital for helping to alleviate concerns among the public. In terms of vaccine manufacturing, regulatory oversight should allow manufacturers to allocate resources to address regulatory issues appropriately and ensure consistency across vaccine batches. We need to explore opportunities to harmonise regulatory requirements between different bodies to prevent duplication of work and eliminate the complexity of the review process.

In the current pandemic, the **procurement, pricing and finance pillar** has focused on the ways in which country-specific and internationally-focused R&D and manufacturing schemes can work more effectively. While these schemes inspire innovation and alleviate risk to developers and manufacturers, issues surrounding vaccine nationalism remain to be addressed. Vaccination campaigns have to address widespread equity issues, because disease outbreaks resulting in epidemics can lead to pandemics when they are no longer confined within national borders.

In the event of the next public health emergency, we understand that being able to pre-order vaccines from different manufacturers helps to spread the inherent risks confronting all stakeholders. Mechanisms should be enhanced to speed the deployment of vaccines to locations where they are most needed, not just to those countries that have pre-ordered vaccines.

In the **distribution, logistics and supply chain management pillar**, we saw how investment in reliable temperature-control systems to safeguard the cold chain infrastructure is critical for ensuring that all countries can receive and distribute vaccines safely and effectively. This is particularly relevant during health emergencies, when the early-authorised vaccines may require more care during transportation and storage. Identifying ways to extend and maintain the shelf life of vaccines should start as early as possible in the R&D process, because delays in transport and inconsistent environments in storage facilities are always a risk.

In the **user acceptance and uptake pillar**, the importance of investing in bespoke health literacy initiatives was emphasised. Information from each of the other four pillars needs to be communicated clearly and directly to the public to avoid confusion and eliminate knowledge gaps that can be filled by malicious misinformation. Social media has a role in allowing the misrepresentation of vaccines and vaccinations to 'go viral'. However, the same channels can be used effectively, alongside positive engagement with the mainstream media, to prevent false information from being spread. We also identified the need for seamless interweaving of vaccination campaigns into people's everyday lives, because the smallest inconvenience can delay uptake, even among people with good levels of health literacy. There is a need to nurture public trust to ensure increased and rapid uptake of vaccines and we must develop effective strategies to improve access to reliable, evidence-based information, and counter misinformation, to promote decision-making that enhances wellbeing.

As of 1 September 2021, according to Our World in Data, 39.9% of the global population had received one dose of a covid-19 vaccine and 27.2% were fully vaccinated.[2] However, only 1.8% of those living in low-income countries had received one dose.[2] These statistics underscore the fact that while we have made progress since the emergence of SARS-CoV-2, a significant amount of work remains to be done to confront this pandemic. The Vaccine Ecosystem Initiative will follow the progress on a global scale to support the development of more sustainable opportunities to strengthen each of the five pillars of the ecosystem.

This report provides the framework to The Vaccine Ecosystem Initiative. We have presented the five pillars that support the ecosystem and identified their relevance using the current pandemic to illustrate the significance of each. But our work does not stop with covid-19 and the vaccines that have been developed and deployed to address it; our work speaks to the entire ecosystem and all diseases that are amenable to vaccinations. While we have identified opportunities for improvement and suggested avenues for further exploration, our work is not complete. As we move into the next phase The Vaccine Ecosystem Initiative will conduct further investigations into wide-ranging perspectives in each of the five pillars to foster and facilitate the development of new and more sustainable vaccination models. We are committed to an open exchange of ideas and evidence-driven understanding that allows us to address the challenges with which we are confronted and not squander the opportunities we have to build a dynamic, more equitable, responsive, resilient and robust vaccine ecosystem for the future.

Appendices

Appendix 1: Vaccinations save lives

Two decades ago, the US Centers for Disease Control and Prevention (CDC) declared that vaccinations were one of the major public health achievements of the twentieth century, placing it first in its top 10 list.[130]

Humanity has sought to conquer infectious diseases for millennia. Records of disease outbreaks and the devastation wrought on civilisations by these outbreaks fill the history books. Smallpox, a contagious, disfiguring and deadly disease ravaged humans for thousands of years.[131] It is thought to have occurred as long ago as 10,000BC in some of the first human settlements in Africa.[132] Early attempts to protect against smallpox may have been made by Taoist or Buddhist monks around 1000AD, but the earliest documented incident of inoculation to immunise against smallpox (called variolation) was in 1549 in China,[133] and was followed over the years in Africa, Turkey, Europe and the Americas. Edward Jenner is credited with developing the first vaccine for smallpox, following his observations that milkmaids who became infected with cowpox were immune to smallpox in 1796.[123]

It is impressive that all the work carried out prior to the nineteenth century pre-dates the germ theory of disease, which was not published until 1878 by Louis Pasteur. This led to many more advances in medical science, including the field of vaccinology.

Nearly a century after Jenner's discovery, a rabies vaccine was developed by Pasteur in 1885. In subsequent years, vaccines were developed against anthrax, cholera, diphtheria, plague, tetanus, typhoid and tuberculosis (TB). Through the twentieth century, additional vaccines were developed for a wide range of childhood illnesses, including polio, measles, mumps, rubella, meningitis, chicken pox (varicella) and whooping cough. Further innovations led to the development of vaccines for diseases such as seasonal influenza, pneumonia, yellow fever, hepatitis A and B, and human papillomavirus (HPV).

These vaccines have significantly reduced the burden of disease in humans, and lowered rates of morbidity and mortality on a huge scale. The fear generated by many of these diseases has long subsided so by the late-twentieth century, diseases that had been dreaded and deadly no longer induced the same reaction, particularly among people in high-income countries.

Two hundred years after Jenner's discovery, we have successfully eradicated two diseases from the world: smallpox in 1980[134] and rinderpest* in 2011.[135] Today there are 28 vaccine-preventable diseases in humans[136] and many that prevent diseases in animals. Human vaccination has prevented at least 10 million deaths between 2010 and 2015.[136,137]

Innovations in vaccinology have progressed at an exceptional pace since the genetic sequence of the SARS-CoV-2 virus was identified in January 2020. However, much remains to be achieved.

There is no time for complacency.

*Rinderpest resulted in the death of millions of cattle, buffalo, yak, and wild animals, and often led to starvation among humans who raised these animals as livestock.

Appendix 2: Vaccinations are highly cost-effective

The World Health Organization's Decade of Vaccines (2011–2020) ended just as the covid-19 pandemic began. The Global Vaccine Action Plan was endorsed unanimously by WHO member states in May 2012. It acknowledged the important role of vaccines in protecting public health, and called for a world that is free from vaccine-preventable diseases.[138]

Vaccines and vaccinations must be recognised as investments in health, and drivers of economic growth and development. The protection they provide relates to more than just the health of individuals; it encompasses entire communities. Thus any investments are an investment in national health as well as national economic wellbeing and global health security.

Healthy populations are economically productive populations, and open societies are able to support the functioning of businesses. Economic analyses have demonstrated that the return on investment (ROI) for each dollar invested in vaccine development over a decade yields a 16-fold return.[139] This is relevant to both costs of treatment and productivity, as well as the costs of supply chains and service delivery.[139] With respect to the broader economic and societal benefits, the ROI is 44 times greater than the costs of vaccination.[139]

As we have seen – all too well – during the covid-19 pandemic, the economic wellbeing of countries has been severely impacted by national lockdowns. The impact extends beyond national borders and impacts international trade, travel and transport. More must be done to ensure health security experts are aligned with their counterparts in the business and finance sectors, so that sound decision-making leads to maximising the full benefits of vaccinations for populations around the world. The prioritisation of and investment in the vaccine ecosystem must be endorsed by strong leadership across countries and in all sectors around the world.

Appendix 3: Methods

Scope of the report

The objective of this report was to obtain key evidence that allows us to reflect on lessons learned from the covid-19 pandemic thus far in order to provide insights for further exploration as we work to build a more robust vaccine ecosystem. We used a structured process to identify successes, gaps and missed opportunities, and to encourage innovations that better support the vaccination ecosystem.

Our research considers the whole vaccine value chain from early discovery to full-scale sustainable programme implementation, while ensuring equitable population protection against vaccine-preventable diseases.

Within this scope, we asked several key questions:

- How did the vaccine ecosystem facilitate such rapid development of vaccines for covid-19?
- What unexpected obstacles were there to the rapid development of covid-19 vaccines?
- What gaps exist in the vaccine ecosystem hinder more equitable vaccination efforts across the globe?
- Which approaches within the vaccine ecosystem are successful and might be adapted for long-term use to help maintain the structural integrity of the ecosystem?
- Which foundations within the vaccine ecosystem require improvement?

Search approach

A multi-pronged approach was adopted, with a focus on indexed databases such as Medline and EMBASE, the grey literature, and supplemental searching of Google Scholar, Scopus, and other resources. The websites of key organisations were searched for relevant media releases. These included government, regulatory and industry agencies, including WHO, ECDC, CDC, GAVI, CEPI and the Bill and Melinda Gates Foundation.

Given the variety of search terms, and databases, we had no central search taxonomy. Therefore we used a structured triangulation approach across a set list of search terms. The search was conducted and filtered down by three researchers to make sure we captured the most accurate and up-to-date information.

To supplement and validate the findings of our literature review, we also conducted in-depth discussions with experts in diverse areas, so that the report incorporates the latest thinking and expertise of those working directly within the area.

Results

The search produced over 600 relevant results, of which 170 sources were included in the report. Not all of them are cited in this document, but all were reviewed extensively in the creation of this evidence review, and helped us as we moved through our research process.

Limitations and mitigations

The objective of our research was to provide an overview of the key aspects of the covid-19 response from the start of the pandemic, as well as the key components of the entire vaccine ecosystem. This will help to inform further research.

Note that this report was largely compiled in the first nine months of 2021, amid the rapidly evolving situation with the pandemic and the urgent development and roll out of many different vaccines throughout the world. New information and evidence was emerging constantly. We have done our best to ensure the timely nature of the research we have used in this report and have tried to keep abreast of developments, but this is an area of constantly evolving and emerging evidence as the covid-19 pandemic continues.

Our initial research questions were not suitable for conducting a rigid systematic review, which means it is possible that not all of the relevant literature was identified. To mitigate this problem, the literature search was supplemented by expert opinion, as described above.

We also identified a lack of relevant systematic reviews during our searches, which was only to be expected given the broad field and the rapidly changing situation. Reviews of this type would have provided more certainty on many issues and provided a useful sense check of our work.

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ECONOMIST IMPACT

LONDON

20 Cabot Square
London, E14 4QW
United Kingdom
Tel: (44.20) 7576 8000
Fax: (44.20) 7576 8500
Email: london@eiu.com

GENEVA

Rue de l'Athénée 32
1206 Geneva
Switzerland
Tel: (41) 22 566 2470
Fax: (41) 22 346 93 47
Email: geneva@eiu.com

NEW YORK

750 Third Avenue
5th Floor
New York, NY 10017
United States
Tel: (1.212) 554 0600
Fax: (1.212) 586 1181/2
Email: americas@eiu.com

DUBAI

Office 1301a
Aurora Tower
Dubai Media City
Dubai
Tel: (971) 4 433 4202
Fax: (971) 4 438 0224
Email: dubai@eiu.com

HONG KONG

1301
12 Taikoo Wan Road
Taikoo Shing
Hong Kong
Tel: (852) 2585 3888
Fax: (852) 2802 7638
Email: asia@eiu.com

SINGAPORE

8 Cross Street
#23-01 Manulife Tower
Singapore
048424
Tel: (65) 6534 5177
Fax: (65) 6534 5077
Email: asia@eiu.com