White Paper

Vaccines, Today and Tomorrow
A review of the global vaccine ecosystem and the path to vaccine equity
A note from the CEO

Vaccines are widely considered the most effective healthcare innovation in history. Over the last century they have revolutionised global healthcare. Vaccines have slashed child mortality rates, extended life expectancy, protected billions from disability and death, eradicated smallpox, and — at least in high income countries — made once common diseases like polio, diphtheria and cholera little more than vague folk memories among the general public.

The 20th century was the first age of vaccines. It witnessed the development of dozens of viral and bacterial vaccines and the first widespread adoption of vaccination programmes as public health tools.

In the 21st century we now have the potential to build on that legacy and become the great age of vaccines. But turning potential into reality will require the collaborative and coordinated efforts of the whole spectrum of vaccine stakeholders; including international and supranational bodies, national governments, industry, donors and not-for-profit organisations.

The COVID-19 pandemic has certainly refocused the world’s attention on vaccines once again, and reminded us of the importance of those fundamentals. It also reinforced the importance of global cooperation and solidarity in facilitating broad access to vaccines. The global response to the pandemic has demonstrated what can be achieved when those fundamentals are applied, funding is available, and stakeholders collaborate.

The inaugural Hilleman Vaccines & Biologics Symposium held in Singapore in February 2022 brought together many thought leaders from the global vaccine ecosystem, several of whom have contributed to this paper — for which I am most grateful. The broad consensus among the participants at the symposium was that the COVID-19 pandemic has brought us to an inflection point and presented us with an opportunity for change. COVID-19 has taught us valuable lessons and we should use the experience from this crisis to address unmet needs for vaccination. We need to act now and seize the opportunity to change the current global vaccine inequity into vaccine equity for all.

Dr Raman Rao

Chief Executive Officer
Hilleman Laboratories
Vaccines and vaccination programmes have been one of the most impactful medical advancements in history; they save millions of lives every year [1]. They have given us the ability to prevent and control many infectious diseases that were once common scourges, effectively eradicating smallpox, one of the worst.

Vaccines are vital for global health security; a fact the current pandemic has demonstrated to a world that had almost forgotten the critical role vaccines play in containing outbreaks of infectious diseases.

Additionally, around 7% of infectious diseases in developed countries and 10% in developing countries are nosocomial infections, also known as healthcare-associated infections (HAI) because they are contracted by patients while in hospital or under medical care [4]. And these could be vaccine preventable as well.

Ironically, their very success has led to some people no longer fully appreciating the importance of vaccines for public health. Two or three generations of people in the developed world have become adults with no direct experience of diseases like polio, smallpox and diphtheria, beyond being vaccinated as children and taking their own children to be vaccinated. Until COVID-19 arrived, safe water, better housing, improved nutrition, modern waste management, antibiotics, and vaccines had made the dangers of infectious diseases little more than a distant memory for the developed world.

But that has never been the case for the people living in low- and middle-income countries (LMICs). There, many of the infectious diseases that were eradicated in high-income countries (HICs) in the last century have continued to claim lives and impoverish communities; 94% of all global deaths from infectious diseases occur in the LMICs, more than half of them from vaccine-preventable disease [2,3].

“For public health, what really matters is where you’re born and into which stratum of society, because that is going to determine what happens to your health, economic and educational prospects”

- Professor Gagandeep Kang (Wellcome Trust Research Laboratory), Hilleman Vaccines & Biologics Symposium, 23 Feb 2022

Additionally, around 7% of infectious diseases in developed countries and 10% in developing countries are nosocomial infections, also known as healthcare-associated infections (HAI) because they are contracted by patients while in hospital or under medical care [4]. And these could be vaccine preventable as well.

Thanks to remarkable technological advances in the last 20 years, we now have more vaccines for more diseases and better forms of vaccines than ever before. But there are still many diseases for which we don’t have vaccines — half of infectious diseases deaths in LMICs are from diseases for which we have no vaccines.

The other half of infectious disease deaths in LMICs are from diseases which can be substantially prevented by existing vaccines, which are not available to all populations in need of them. Many factors impact the accessibility and uptake of vaccines, including cost, lack of local infrastructure, government priorities, conflicts, and local culture.

We will look at how some of these situations have come about and what we can and should be doing to change them.
A review of the vaccine industry and wider ecosystem
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The 20th century was the first age of vaccines. It witnessed the development of dozens of viral and bacterial vaccines and the widespread adoption of vaccination programmes as public health tools. Widely considered the most effective healthcare innovation in history, vaccines have revolutionised global healthcare. They have slashed child mortality rates, extended life expectancy, protected billions from disability and death, eradicated smallpox, and — at least in HICs — made once common diseases like polio, cholera and diphtheria little more than vague folk memories among the general public.

The 21st century has the potential to become the great age of vaccines but turning potential into reality will require the collaborative and coordinated efforts of the whole spectrum of vaccine stakeholders including supranational bodies, national governments, industry, donors and not-for-profit organisations (NPOs).

“The immunization is a key component of primary health care and an indisputable human right.”

- Vaccines and immunizations, World Health Organization

The origin of vaccines

The origins of modern vaccine science, including the name ‘vaccine’, date back to the late 18th century and Edward Jenner’s work inoculating people with cowpox virus vaccinia to prevent them from contracting smallpox. Although, Jenner probably only used the word ‘vaccine’ as an adjective, and it was his friend and colleague Richard Dunning who actually coined the use of ‘vaccination’ as a noun to refer to the practice [5,6].

The public health benefits of vaccination were quickly recognised and widely adopted with mass, and sometimes compulsory, programmes implemented around the world. When Thomas Jefferson became President of the United States of America in 1801, he declared smallpox vaccination a public health priority [7].

In 1853, the British government made it compulsory for babies to be vaccinated within three months of birth. By the mid-1860s two-thirds of babies were vaccinated, resulting in a dramatic fall in deaths from smallpox [8].

But from their beginning vaccination programmes had their sceptics. Within months of the passing of the 1853 Act, the Anti-Vaccination League (AVL) was formed in London to object to it as an infringement of personal and religious liberties. The AVL and similar organisations questioned the science behind vaccination, and the motives of those introducing it [9].

Originally only associated with smallpox prevention, the use of the words vaccine and vaccination was extended to refer to any treatment containing live, attenuated, or killed bacteria or viruses, given to produce immunity against a specific infectious disease, after Louis Pasteur called his rabies treatment a ‘rabies vaccine’; although technically it was an antitoxin. Later, Pasteur did discover the first live, attenuated vaccine while working on chicken cholera [6].
The first modern vaccines

Late 19th century advances in microscope design and the development of germ theory led to scientists in many countries experimenting with materials that could induce immunity in humans and animals. This in turn spawned further scientific advances in the first half of the 20th century and an explosion of vaccines, including those against whooping cough (1914), tuberculosis (1921), diphtheria (1926), tetanus (1938), influenza (1945) and mumps (1948) [10,11].

However, the adoption of these vaccines was far from swift or universal, as the slow adoption of the anti-tuberculosis vaccine BCG (Bacille Calmette–Guérin) demonstrated. Tuberculosis is thought to have killed more people than any other infectious disease in history, probably more than a billion in just the last two centuries, and it is still killing in excess of two million people a year [11,12].

The BCG vaccine was first demonstrated to be effective in 1921 [11]. By the end of the 1920s, it was being used in the Scandinavian countries, France, Spain, Germany, and a variant in parts of the United States but it took another quarter century before Britain adopted it in 1953 [11,12].

The impact of war

World War II (WWII) was a turning point in vaccine development and adoption as public health tools. After World War I (WWI) many governments and militaries were concerned that another war could generate new threats from both the natural and intentional spread of disease.

During WWI outbreaks of pneumonia, typhoid and typhus fever, as well as various louse-borne diseases had been common in the trenches as well as the towns and cities where troops were billeted or sent on leave [13]. The 1918 influenza pandemic had claimed tens of millions of lives worldwide and had hit military populations hard. Some estimate that almost 80% of the US Army’s casualties during World War I were caused by influenza [14].

Fearing a repeat during WWII, the United States committed its vast resources to R&D programmes for vaccines and many other medical and technological innovations.

The United States Surgeon General’s Office (SGO) and the Office of Scientific Research and Development (OSRD) funded vaccine development programmes that brought together academia, industry and military end users.

The programmes contributed to the development of new or significantly improved vaccines for 10 of the 28 vaccine-preventable diseases identified in the 20th century [15]. These included the first licenced vaccines for influenza, pneumococcal pneumonia, and plague, an entirely new typhus vaccine, and the first Japanese encephalitis vaccine.

Maurice Hilleman, who would go on to be one of the most important vaccine innovators of the 20th century, worked on the Japanese encephalitis vaccine at Squibb in 1944 [16]. The programmes also produced yellow fever, cholera, smallpox, and tetanus vaccines. The improved smallpox and tetanus vaccines were widely used for the general population after the war, making a significant contribution to public health [15].
In many cases, the groundwork and basic understanding of how to develop these new vaccines had been developed years before. But without the organisational structures and demand, they had not been brought to fruition. The WWII vaccine programmes benefitted from governance structures with defined development goals and they effectively drafted scientists from academia, industry and the military and government agencies to drive the projects forward. The project managers drove innovation by bringing together different disciplines including epidemiology, pathology, immunology, bacteriology, and virology, and even bioprocess engineering to develop, test, scale up, and manufacture specified vaccines [15].

This system allowed the rapid integration and application of existing knowledge to vaccine production and also accelerated technology transfer. The successes of these programmes were due less to novel scientific breakthroughs than their ability to pool, distil and apply existing knowledge and expertise [15].

The urgent need for vaccines for troops being deployed to Africa and the Pacific meant some clinical trial steps were skipped, their widespread use in military populations providing de facto evidence of their safety and efficacy. This was the case with the tetanus vaccine which demonstrated such high rates of safety and presumed efficacy among troops, that in 1944 the American Pediatric Association recommended it for use in the general population, despite the lack of formal clinical trials [15].

Safety and efficacy were not enough to guarantee post-war success for all the vaccines developed by these programmes. Those for Japanese encephalitis and yellow fever were vital to deploy troops to the Pacific theatre but after the war, there was no commercial demand for them in western civilian markets as their incidence in North America and Europe was so low.

An unmet need did not guarantee market success either. Pneumococcal infections were common in the West but in the 1940s and early 1950s, most civilian doctors were using antibiotics to treat them, rather than trying to prevent them with Squibb’s wartime pneumococcal vaccine. Faced with no demand for its product, Squibb closed the vaccine plant in 1954. In the 1970s, growing evidence of antibiotic resistance made pneumococcal vaccines commercially viable but too late for Squibb to benefit [15].

The WWII vaccine development programmes demonstrated that vaccine development requires the cooperation of multiple stakeholders. Without the funding and the pooled talent provided by the programmes, industry would not have had the capabilities or commercial incentives to rapidly develop so many vaccines.

### The first three post-war decades

Vaccine development continued to benefit from the work of the wartime programmes for some years after the war with the first influenza vaccine in 1946 and the first combined DTP (diphtheria, tetanus, and pertussis) vaccine in 1948, but as the participants moved on and funding dried up, the vaccine ecosystem reverted to its former fragmented nature.

Even so, the three decades after the war were a remarkable period in vaccine history; both for the discovery of new vaccines and the dramatic increase in global vaccination rates. Today, the threats of polio, measles and rubella are drastically lowered thanks to vaccines developed to protect against them; polio in 1955, measles in 1963 and rubella, developed by Maurice Hilleman, in 1969.

The story of the development of two polio vaccines in the 1950s is the best known among stories about vaccines. In part because of the unprecedented amount of media coverage of the rivalry between the principal developers, Dr Jonas Salk and Dr Alfred Sabin, and in part because of the huge impact the vaccines made.

Within six years of Salk’s injected, inactivated poliovirus vaccine (IPV) being licenced in the US in 1955, and a nationwide children’s vaccination campaign, recorded polio cases dropped from 35,000 to just 161 [17,18].

In the 1960s, the US and much of the world switched to using Sabin’s orally administered, live attenuated vaccine (OPV) as it was better suited to mass vaccination campaigns and because it provided both humoral immunity and cell-mediated immunity, and thus longer-lasting overall immunity than IPV [19].

Interestingly, both Salk and Sabin were alumni of the SGO and OSRD wartime projects. During WWII Sabin served in the US Army Medical Corps and worked on vaccines for insect-borne encephalitis and dengue. Salk also worked on an OSRD project with his long-term mentor Thomas Francis Junior; they successfully developed an inactivated flu vaccine in 1943. Francis later oversaw the large-scale trials of Salk’s IPV [20].
In the closing days of WWII, diplomats from 50 nations attended the United Nations Conference on International Organization. The conference resulted in the creation of the United Nations (UN), which officially came into existence on October 24, 1945. From its inception the UN recognised the need for an organisation focused on global health, and within three years the UN council had ratified the constitution of the World Health Organization (WHO). Among its initial priorities were combating malaria, tuberculosis and other communicable diseases. Its duties included collating member states’ reports of outbreaks of contagious diseases including plague, cholera and yellow fever [21].

Probably the WHO’s first significant impact on vaccine usage was an early report praising the freeze-dried smallpox vaccine produced by the Vaccine Institute of Paris (VIP). The VIP had developed the technique at the end of the WWI, but curiously, the manufacturing method had not been widely adopted, even though it was suitable for large-scale production and the resulting vaccine could be transported and stored in tropical conditions without the need for refrigeration. The WHO report brought it to global attention and it was soon widely adopted [22]. This and other new manufacturing techniques allowed vaccine production to be scaled up by the late 1940s; a prerequisite for the global vaccination and disease eradication efforts to come.

The tuberculosis campaign

The first major international disease control and research activity instigated by the WHO post-WWII, and at the time the largest public health campaign ever attempted, was the International Tuberculosis Campaign from 1947 to 1951. The campaign tested 37 million people, mainly children and adolescents, for tuberculosis, and administered more than 16 million BCG vaccines [23].

In their ‘Prospectus of Research in Mass BCG Vaccination’ which was presented to UNICEF and WHO in late 1948, the drivers of the campaign, Rajchman, Holm, Debrie, Hilleboe, Palmer outlined three goals: “research on the details of techniques, procedures, and results of tuberculin testing and immunisation; basic epidemiological research on tuberculosis infection and disease; and evaluations of the BCG programme in the prevention of tuberculosis morbidity and mortality,” hence, establishing research as an important aspect of any vaccination programme [24].

The programme’s first director Dr Johannes Holm, Former Chief of the Tuberculosis Division of Denmark’s State Serum Institute in Copenhagen, understood that local buy-in and participation would be essential for the campaign to succeed. He built on the Danish Red Cross’s experience in Poland, where the recruitment and training of hundreds of Polish doctors, nurses and senior medical students had significantly expedited the rollout of their vaccination campaign.

He built tuberculosis-focused laboratories and created an international institute to train doctors, nurses and laboratory technicians from participating countries in antituberculosis work. Then he returned them to their own countries to assist with, and eventually take over, their nations’ tuberculosis vaccination programmes [24].

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Dr. Maurice Hilleman was the first person to combine different viral vaccines into one shot with the measles, mumps and rubella (MMR) vaccine and played a primary role in the research and development of numerous vaccines including:

- Measles
- Mumps
- Rubella
- Japanese encephalitis (JE)
- Hepatitis A
- Hepatitis B (two versions)
- Influenza
- Chickenpox
- Adenovirus
- Meningococcus
- Haemophilus influenzae type b (Hib)
- Pneumococcus
- Marek’s disease (MDV) – veterinary vaccine

References:
As the campaign rolled out internationally it became apparent that success depended on winning the support of local doctors, healthcare practitioners (HCPs), civic authorities, various national organisations, and influential individuals by sharing information and soliciting cooperation. This included extensive and localised public education on the purpose and nature of the vaccination programme via newspapers, films, and leaflets. In non-literate societies, trucks were equipped with speakers broadcasting the information around testing and vaccination site neighbourhoods [24].

The pioneering International Tuberculosis Campaign developed the basic template still used for running international public health campaigns:

- Find and collaborate/partner with existing experts and programmes
- Train local HCPs to support and eventually lead and take over national programmes
- Run research in parallel with service provision
- Inform and work with local government, grassroots and religious leaders
- Overcome hesitancy and secure the buy-in of the local population with public education

More than 70 years later the battle against tuberculosis has still not been won, making support for the ongoing search for an effective vaccine to prevent the development of disease in adult carriers an imperative for global health security. But the lessons learnt from that first international campaign helped to make subsequent ones more successful, such as those against smallpox and polio.

Smallpox

Smallpox was the first and so far, the only human disease to have ever been officially eradicated according to WHO. There is hope that polio too may soon be declared eradicated (See section on polio on page 20). In the mid-1960s, many argued that categorical eradication programmes were costly and futile, and compromised existing health programmes, especially in LMICs where they were sometimes seen as taking money away from the development of basic healthcare systems; a debate which continues in some forms today. However, eradicationists believe global programmes are the only practical approach to the prevention of some important diseases.

"The world and all its peoples have won freedom from smallpox".

- World Health Assembly, May 8, 1980
The success of the smallpox programme spawned several new programmes. Two of the more successful are the campaigns to eradicate poliomyelitis and Guinea worm disease. Although they have already missed their targeted completion dates by a decade or more, both have come tantalisingly close, only to be stalled on the brink of success by civil conflict, and in the case of polio, the cynical demonising of the vaccination programme for political purposes [26].

Programmes focusing solely on the eradication of a single disease may be becoming outdated as vaccination programmes are increasingly combined with other healthcare services. More countries and organisations are now shifting their focus from sporadic vaccination drives, and the old, centralised, acute care facilities model of healthcare to focus more on delivering primary and preventative healthcare services to rural populations. District nurses visiting villages for paediatric and post-natal check-ups, and offering vitamin A, mosquito netting, and crucial health education, provide a basic infrastructure for regular and emergence vaccination programmes [26]. More regular contact of this sort with medical teams also helps to combat vaccine hesitancy and disinformation.

### Polio today

In the 1970s, multiple surveys found that polio was prevalent in many developing countries, prompting the World Health Assembly of 1974 to include polio, amongst other diseases, in an Expanded Programme on Immunization. As a result, many more countries had introduced Sabin oral polio vaccines (OPV) to their national immunisation programmes by the end of the 1970s.

In 1985, Rotary International launched the PolioPlus international vaccination drive, which at the time was the largest private-sector support of an international public health initiative. Inspired by Rotary International’s programme, WHO, UNICEF and the US Centers for Disease Control and Prevention (CDC) joined with them in 1988 to create the Global Polio Eradication Initiative (GPEI), with the goal of eradicating polio by the year 2000 [27].

Wild polio has three individual and immunologically distinct strains: wild poliovirus type 1 (WPV1), wild poliovirus type 2 (WPV2) and wild poliovirus type 3 (WPV3). All three strains can cause irreversible paralysis or even death but the genetic and virologic differences are great enough that they are three separate viruses that must each be eradicated before polio can be considered fully eradicated [28].

In 1988, there were an estimated 350,000 new cases of polio. It was present in dozens of countries around the world and paralysed more than 1,000 children every day. Since then, more than 2.5 billion children have been vaccinated in over 200 countries [29].

By 2020, wild poliovirus had been eradicated in all continents except Asia, and today only Afghanistan and Pakistan are still classified as having endemic polio [30,31].

Only 140 WPV1 cases were reported in 2020, a 99.96% reduction from 1988’s estimated 350,000 cases. All the recorded wild-virus cases since 2019 have been WPV1. The other two wild-virus types have been declared eradicated; WPV2 in 2015 and WPV3 in 2019. Unfortunately, OPV vaccines against each of the three wild strains of polio have given rise to strains of vaccine-derived poliovirus (VDPVs) and these are now the most prevalent source of polio cases, having caused 1,112 cases in 2020; the majority in Afghanistan, Pakistan and Nigeria [28]. VDPVs arise when genetic reversion events in the Sabin OPV increase their otherwise attenuated transmissibility and neurovirulence [32].

Until all forms of the virus are eradicated globally, outbreaks are possible almost anywhere. In the first half of 2022 the United Kingdom (UK), Israel and the US all detected traces of a type 2 VDPV (VDPV2) variant in sewage. All three countries had switched from attenuated oral poliovirus vaccines (OPVs) to an inactivated polio vaccine (IPV) administered by injection some years previously, because the inactivated virus cannot revert and become a VDPV. Therefore, the virus detected in their sewage must have originated in one of the many LMICs still using oral vaccines [33].

All three countries have stepped up vaccination efforts, particularly among unvaccinated and under-vaccinated communities. At the time of writing, no actual cases of VDPV2 have been identified in the UK or Israel but in the US one young man has presented with acute flaccid paralysis caused by VDPV2.
A single case of paralysis in New York might not sound that alarming but it actually indicates the virus has been in circulation for months and that there could be hundreds or even thousands of unidentified cases. Less than 1% of all polio infections in children result in flaccid paralysis [34]. Depending on the strain involved, it may occur in less than 0.1% of cases. The majority, roughly 70% of polio infections in children are asymptomatic but they can transmit the virus to others via virus shed in nasopharyngeal secretions and stool for several days or weeks. About 24% of cases will have a mild illness similar to the flu but without clinical or laboratory evidence of central nervous system invasion. Between 1% to 5% of polio infections result in nonparalytic aseptic meningitis. Patients report stiffness and pain in the neck, back, or legs, and sometimes headache and vomiting but make a full recovery [34].

The solution to the problem of VDPV2 may already be available in the form of a novel type 2 OPV (nOPV2) which has been genetically engineered to reduce the risk of the genetic reversion events. The nOPV2 received an emergency use listing from the WHO in November 2020 [36] and has already been used in vaccination campaigns in West Africa and other VDPV2 hotspots. The key Phase III licensure trial of the nOPV2 was carried out in The Gambia in 2022 [36,37]. If the new vaccine can soon replace all other type 2 OPV vaccines and prevent future VDPV2 outbreaks it will bring us one step closer to the total eradication of polio.

The Expanded Programme on Immunization

The WHO established the Expanded Programme on Immunization (EPI) in 1974 to develop and expand immunisation programmes globally and in particular, in developing countries. An initial vaccination schedule that included immunisation against diphtheria, pertussis, tetanus, poliomyelitis, measles and tuberculosis and ‘general programme policies’ was approved by resolution in 1977, as was the stated objective of making the six core vaccines available to every child in the world by 1990 [38].

Because it was universally recommended, the WHO used the combined diphtheria-tetanus-pertussis vaccines (DTP3) as a standardised marker of the overall EPI immunisation programme performance across countries and progress was slow in the first few years. By 1980, only about 20% of children around the world were receiving all three doses of DTP3 and the rollout was uneven, with coverage much higher at 20% in HICs while some LMICs only reached 5% coverage.

To address the inequity, WHO and UNICEF established the Universal Childhood Immunization (UCI) initiative in 1984 with the aim of increasing DTP3 coverage to 80% globally by 1990. UCI very nearly achieved its goal, increasing DTP3 coverage in LMICs from 5% in 1980 to 62% and global coverage to 75% by 1990 [39].

In 1984, a standardised vaccination schedule was established for the original EPI vaccines and over the years additional vaccines have been added to the schedule as they became available. Of these, five are routinely recommended by WHO for inclusion in all countries’ national immunisation programmes (NIPs). These include hepatitis B (HepB) recombinant vaccine, Haemophilus influenzae type b conjugate vaccine (HibCV), pneumococcal conjugate vaccine (PCV), rotavirus vaccines (RotaV) and human papillomavirus vaccine (HPV).

In its first decade, EPI had considerable success with many developing countries agreeing to set up NIPs and administer the six vaccines on the original schedule [40].

“Building on the momentum of the smallpox eradication effort, the Expanded Programme on Immunization (EPI) was launched in 1974 to ensure that all children, in all countries, benefited from life-saving vaccines. Today every country in the world has a national immunization programme.”

- World Health Organization, July 22, 2021

The PATH story

Now one of the world’s largest healthcare-focused NPOs operating in over 40 countries, PATH (originally Program for Appropriate Technology in Health) was founded by three researchers in Seattle, US in 1977. At first focused on family planning, it now covers pharmaceuticals, diagnostics, devices, system and service innovations, and vaccines. PATH focuses on building collaborative partnerships to develop and support novel technologies with funding, technical advice, and assistance with scaling up production to bring them to market.

The PATH Center for Vaccine Innovation and Access (CVIA) is active in vaccine research, development, and introduction as well as technical supply chain and delivery solutions such as the vaccine vial monitor, a small, heat-sensitive sticker intended for use on vaccine vials, which may be used beyond the cold chain. The sticker is a square with a circle of a different colour inside which changes colour if exposed to heat to indicate the vaccine is no longer usable [1]. The WHO has credited the stickers with playing a crucial role in polio programmes [2].

References:
In the beginning, the EPIs struggled to start National Immunisation Programmes (NIPs) in countries lacking the relevant experience and infrastructure. Personnel had to be trained and NIP systems established to deliver and monitor the immunisation efforts, while national and international funding and resources had to be secured to support them. Despite the challenges, EPI managed to secure the commitment of more than 90 countries to their goals within just a few years [41].

Among the early challenges were a lack of public and governmental awareness of the scope and seriousness of the target diseases, ineffective programme management, inadequate equipment and skills for vaccine storage and handling. Even their successes were a challenge as they lacked the means to monitor the impact of increasing immunisation coverage levels and decreasing the incidence of the target diseases [42].

The EPI was — and is — one of the largest and most successful global health programmes in history [41]. Despite all the challenges EPI faced, UNICEF estimated that by the end of 1991, 80% of the world’s infants were receiving BCG, measles, DTP (diphtheria and tetanus toxoids and pertussis vaccine), and oral polio vaccines (OPV) [43]. However, as the newer and more expensive vaccines were added to the schedule, many developing countries struggled to afford them and some felt they could not add them to their own NIP schedules [40]. By the end of the 1980s there was a growing realisation that more needed to be done. There were still many unmet vaccine needs and every year the number of children needing vaccines was growing as the global population increased.

1990 to 2019, The current vaccine ecosystem

The Children’s Vaccine Initiative – WHO

To try and address some of those issues, the Children’s Vaccine Initiative (CVI) was launched after the World Summit for Children in New York City in 1990. An international and multistakeholder initiative, it was founded by the Rockefeller Foundation, United Nations Development Program (UNDP), UNICEF, the World Bank and WHO. Later contributors included the European Community, Japan, the Netherlands, Rotary International and the US.

The CVI’s focus was on vaccine development and production efforts with a long-term objective to ensure adequate supply of vaccines for children in the developing world, and simplify the complex logistics of vaccine delivery.

The activities of the CVI were carried out primarily through product development groups and task forces that examined strategic, logistic, and policy issues relevant to the development and introduction of CVI vaccine products. A new task force was proposed to plan, coordinate, and implement a global effort to ensure the development and supply of quality diphtheria and tetanus toxoids and pertussis vaccine to developing countries.

In collaboration with the international scientific community, public health organisations, governments, and local vaccine manufacturers, IVI strives to develop and deliver affordable vaccines and sustainable programmes. The institute’s first WHO-licensed and approved product was the bivalent inactivated oral cholera vaccine, and they are also working on vaccines for VI-DT typhoid conjugate (approved by the Korean Ministry of Food and Drug Safety, WHO Prequalification pending), MERS (GeneOne), Schistosomiasis (SM-p80), non-typhoidal salmonella (NTS), hepatitis A, hepatitis E, Shigella, group A Streptococcus, and tuberculosis.

References:
Gavi

Gavi was created in 2000 at the World Economic Forum (WEF) in Davos, Switzerland to succeed the CVI, with the objective of improving child health in the poorest countries by extending the reach of the EPI. Gavi is an international public and private coalition but the main initial financial contribution, a US$750 million five-year pledge, came from the Bill & Melinda Gates Foundation [45].

“Economically, epidemiologically and morally, it is in all countries’ best interest to use the latest available data to make lifesaving vaccines available to all.”
- World Health Organization, July 22, 2021

The CVI hoped to make vaccination programmes easier to run for LMICs by developing combination vaccines that would immunise against multiple diseases with single temperature-stable dose (preferably oral) that could be given to infants shortly after birth, eliminating the need for cold chain logistics and multiple shots at different stages of infant development [41]. Vaccines incorporating some or all of these characteristics would be able to protect more of the world’s children against a larger number of diseases at a lower cost per child or per disease prevented [41].

In 2006, in response to the challenges of a rapidly changing and increasingly interdependent world, WHO and UNICEF jointly drafted a global immunisation vision and strategy for the years 2006 to 2015, the first of their 10-year plans. The goal was to protect more people against more diseases by expanding the reach of immunisation to every eligible person. This, and its guiding principles of equity and equality meant it was the first plan to extend its mandate beyond infancy. It was also the first to overtly place immunisation firmly within the context of the broader health system, and underline the importance of immunisation programmes for global preparedness for epidemics.

However, the urgency to accelerate the introduction of already available life-saving vaccines in LMICs led to the dissolution of CVI in 1999 and the establishment of Gavi in 2000 [44].

Gavi encouraged manufacturers to make vaccines and to reduce their unit cost by creating a guaranteed market for the manufacturers’ products. Gavi’s approach was to pool demand from multiple countries while raising sufficient funds to finance such large-scale demand.

To raise funds, Gavi worked with the World Bank to create the International Finance Facility for Immunisation (IFFIm) [46]. With the World Bank acting as treasury manager, and partner donor nations making legally binding, long-term pledges, the IFFIm was able to convert the pledges into vaccine bonds it could sell in the international bond markets to raise funds for Gavi projects [47]. In 2021 IFFIm raised US$1 billion on international capital markets through vaccine bonds [48].

Gavi also adopted the advance market commitment (AMC) strategy to create a centralised and guaranteed market. This created an incentive for the pharmaceutical industry to invest in R&D for new vaccines and also to set up a tiered pricing policy that allows LMICs to pay less for their vaccines than HICs. For example, between 2006 and 2009, Gavi paid just 12% of the US public market price for the one-in-five combination pentavalent vaccine [49].

To focus its support on the world’s poorest countries, Gavi uses national income as a guideline, with the poorest countries receiving the most pricing support and prices gradually rising after countries attain a certain level of income.

During Gavi’s third Global Vaccine Summit held in June 2020, governments, companies and institutions committed to contributing US$8.8 billion for the immunisation of over 300 million children in the world’s poorest countries by 2025 [46].
The Global Vaccine Action Plan

In 2010, building upon the Global Immunization and Vaccine Strategy (GIVS), the WHO and UNICEF announced the Global Vaccine Action Plan (GVAP). It expanded the partnership, laid out a framework with monitoring and accountability with an independent assessment of progress, and established measurable goals and targets for the coming decade, which included:

- Stopping wild polio transmission
- Eliminating neonatal tetanus, measles, rubella, and congenital rubella syndrome
- 80% to 90% three-dose diphtheria, tetanus toxoid and pertussis vaccine (DTP3) coverage
- Introducing new vaccines and technologies
- Reducing child mortality

In September 2020, Gavi joined a coalition to create COVAX, the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator, to support the research, development and manufacturing of COVID-19 vaccine candidates, and negotiate their fair and equitable pricing. COVAX is co-led by CEPI, Gavi and WHO with UNICEF as a key delivery partner, and Pan American Health Organization (PAHO) acting as procurement agent. The core foci of COVAX are vaccine equity, supply, country readiness and delivery, as well as generating acceptance and demand for COVID vaccines [50].

Philanthropic foundations and PPPs

Gavi is a prime example of the kind of public-private partnerships (PPPs) which have played an increasingly important role in global health in the 21st century. Philanthropic foundations have a long history of involvement in public health projects, including vaccine development and vaccination drives. As early as the 1920s, the Rockefeller Foundation, working with NPOs and government agencies played a leading role in yellow fever research and the development and delivery of a vaccine [51].

However, in the 1990s philanthropic foundations began assuming greater importance in the global public health ecosystem and by the late 1990s they were driving the creation of a new kind of entity, public-private partnerships (PPPs). They are not a new concept; private investment, industry and national governments have often formed PPPs in the past for capital-intensive infrastructure projects, but they were new to the global health ecosystem. The idea or belief driving the formation of PPPs was that by applying the management practices and development strategies commonly used in the private sector, PPPs would be able to solve many of the complex problems experienced by LMICs resulting from state and market failures [52].

The exact structure of PPPs varies but they usually have a philanthropic foundation as a significant, if not lead donor. They bring together a range of other stakeholders such as nation states, international organisations, NGOs, industry, etc., to form a partnership to collaborate on specific issues or objectives. Some PPPs set up their own administrative structures and headquarters while others rely on the workforce and resources of one or more of the partners [53,54].

Possibly the biggest impact PPPs have had on the vaccine ecosystem is the introduction of new funding mechanisms such as AMCs and bonds. Today PPPs are particularly active in the areas of pharmaceutical and technological development and integral to many global health policy interventions [53-57].

Although participating in PPPs is ostensibly voluntary, with equality among partners who share a common goal and have clearly defined roles [54,58], PPPs are not without their critics, particularly around the efficacy of service provision and the reality of partner relationships — similar to the accusations made against some supernational bodies and NPOs in the 20th century; i.e., top-down policy decisions being imposed by dominant members [59].

Some say PPPs have also created complex global health governance architecture in which industry and market mechanisms are often given precedence over traditional public sector approaches [60].

However, no one can deny that PPPs have transformed the global health and vaccine ecosystems with their ability to engage a wider range of interest and participation than ever before and by creating new financing mechanisms that have increased the financial resources available for global health significantly.

References:
Coalition for Epidemic Preparedness Innovations

Coalition for Epidemic Preparedness Innovations (CEPI) was founded in 2017 by Norway, India, the Bill & Melinda Gates Foundation, Wellcome, and the World Economic Forum. They are also supported by the United States Agency for International Development (USAID), the European Commission and 29 countries; plus, private sector support through the UN Foundation COVID-19 Solidarity Response Fund.

The coalition's objectives are to develop vaccines and other biologic countermeasures against epidemic and pandemic threats and build pandemic resilience and capacity. By focusing on the 25 viral families most implicated in human disease, they aim to build a library of prototypes that would provide the groundwork for emergency vaccine development when another novel virus appears; just as previous work on vaccines against MERS provided a jump-start for COVID-19 vaccine development.

CEPI works with multiple partners to develop novel vaccines; with academic institutes, the National Institutes of Health (NIH) and biotech companies at the discovery stage; industry, WHO and regulators during the development and licensure stage; WHO, governments and regulators during the manufacturing stage; Gavi, UNICEF and PAHO during the delivery and stockpiling stage, and ultimately with individual countries for vaccination programmes.

CEPI provides investment decision recommendations for COVID-19 vaccine projects in the COVAX R&D and manufacturing portfolio, helps to make vaccines equitably accessible to 190 participating economies through COVAX, and is also investing in the ‘next-generation’ COVID vaccine candidates.

CEPI has a US$3.5 billion pandemic preparedness plan to reduce the impact of future pandemics which comprises of the following:

- Compress the pandemic vaccine development cycle to 100 days
- Develop a universal vaccine against coronaviruses
- Develop a library of vaccine candidates against other likely threats

Examples of collaborative and equitable vaccine success stories

Ebola

In 2014 the largest ever outbreak of Ebola Virus Disease (EVD) began to sweep across West Africa. By the time it was brought under control in March 2016, more than 28,000 people had been infected and over 11,000 had died [61].

The Special Pathogens Unit at the National Microbiology Laboratory in Winnipeg, Canada followed the news closely; they had been working on Ebola, funded by a grant from a Canadian defence programme. After the 9/11 World Trade Centre attack, the US and Canadian governments began funding biodefence research, fearing bioterrorism [62]. An arm of the Public Health Agency of Canada, the Winnipeg laboratory had developed a promising Ebola therapy and a viral vector vaccine called rVSV-ZEBOV, which they had tested successfully in animals [63,64].

They contacted the WHO to offer the vaccine but it was initially declined as Guinea lacked the infrastructure to approve the use of an experimental vaccine — a typical problem faced by academic bodies and pharmaceutical companies conducting Ebola research. In the 30 years before 2014 there were around 1,300 cases and just over 800 deaths (61.5% fatality rate) [65]; all in African LMICs with limited finances and healthcare infrastructure. Such small and sporadic outbreaks provided little opportunity to conduct rigorous vaccine tests, and even less potential to recoup development costs if they were successful.
With a patent but no development partner, Winnipeg, and the Canadian government who owned the patent, licenced the vaccine to a small biotech company, NewLink Genetics [66]. The vaccine may have remained undeveloped at NewLink had the WHO not declared the Ebola outbreak a global health emergency in August 2014, prompting the Canadian government to donate the rVSV-ZEBOV vaccine to them.

The WHO, supported by international stakeholders, fast-tracked Phase I and II trials in several countries [67] and began searching for a larger pharmaceutical company to take over NewLink’s licence and develop the vaccine. Fortunately, Merck stepped up and took on the challenge. By March 2015, Phase III trials for Merck’s rVSV-ZEBOV vaccine called Ervebo [68,69] began in Guinea, utilising a ‘ring vaccination’ strategy [70]. Almost 12,000 people who had contact with a symptomatic individual were vaccinated either immediately or after 21 days, creating a ‘ring’ of immunity around every Ebola case.

By the end of 2015, two other vaccine candidates emerged: GlaxoSmithKline’s chimpanzee adenovirus vaccine containing a surface Ebola protein (ChAd3-EBO-Z) [71], and a two-vaccine regimen to protect against all filovirus strains (Ebola and Marburg) developed by Johnson & Johnson in collaboration with Bavarian Nordic [72].

In 2015, Gavi offered vaccine manufacturers an Advance Purchase Commitment (APC) to pre-purchase doses of licenced vaccines once they became available [73]. Merck signed the APC with Gavi in January 2016, making its vaccine, Ervebo, available for all future Ebola outbreaks. Merck committed to make 300,000 doses of the vaccine available for emergency use in the interim, and to submit the vaccine for licensure by the end of 2017. The vaccine was also submitted to WHO’s Emergency Use and Assessment Listing procedure, so as to make the vaccine available for use prior to formal licensure [74].

Since the 2014 to 2016 outbreak, Ervebo was found to yield 97.5% efficacy in stopping Ebola transmission [75], compared to no vaccination, during the large-scale ring-vaccination scheme in a 2018 outbreak in the Democratic Republic of the Congo (DRC). Ervebo was used successfully to vaccinate more than 90,000 people in the 2018-20 Kivu Ebola outbreak.

The rapid development of rVSV-EBOV contributed to the development of WHO’s R&D Blueprint, a global strategy to fast-track the development of effective tests, vaccines and medicines during epidemics [74].

MenAfriVac

In the 1990s, a meningitis-A epidemic was sweeping Sub-Saharan Africa. The affected countries were desperate for a new vaccine as the existing one was costly and ineffective against the N. meningitidis serogroup A meningitis, affecting their countries. In response, the WHO formed a partnership with PATH which had experience in collaborative vaccine development, and with funding in the form of a generous research grant from the Bill & Melinda Gates Foundation, the Meningitis Vaccine Project (MVP) was born.

Importantly, MVP met with and listened to health ministers and officials from the affected African countries to learn not just what kind of vaccine was needed but what would be needed for them to adopt and use the new vaccine; such as an affordable unit price, and the ability to survive for a few days beyond the cold chain.

Collaboration and tech transfers enabled the MVP programmes to be successful. Scientists at the Center for Biological Research (CBER) at the US Food and Drug Administration (USFDA) came up with a novel technology for conjugate vaccine production and gave it to PATH and MPV [76,77].

PATH partnered with SynCoBioPartners and the Serum Institute of India (SII) to provide raw materials and support as SII developed the vaccine through Phase III trials. Cooperative regulatory authorities made rigorous Phase III trials in Africa and India possible and demonstrated the vaccine was safe, highly immunogenic, able to enhance immunologic memory and antibody persistence in one- to 29-year-olds [78].

WHO prequalification was granted in June 2010 and SII agreed to scale up production and supply it at an affordable, equitable price to the countries that needed it. The vaccine was supplied to those countries for tens of cents rather than price of the previous vaccine at tens of dollars. The Drugs Controller General of India granted an export licence so the vaccine could be used in Africa. Finally, WHO and UNICEF, funded by Gavi, led national immunisation campaigns, working with a variety of NPOs and national programme officials.

MenAfriVac was the first new vaccine to be developed, globally qualified and produced by a member of the Developing Country Vaccine Manufacturers Network (DCVMN) rather than one of the big multinational pharmaceutical companies [79].
Since the introduction of MenAfriVac, the overall incidence of meningitis in the countries in the African meningitis belt has decreased steadily along with the risk of meningitis epidemics. NmA cases have disappeared completely in most countries, with sporadic cases reported in unvaccinated individuals in Burkina Faso, Cameroon, Chad, Guinea, Niger, Nigeria and Senegal [80].

The whole process took a decade, but it still stands out as a positive example of how to collaboratively develop and provide an equitably priced vaccine.

Where we are today

There is no question that over the last three decades, there have been significant advances and success stories; in vaccine development, in international cooperation, and in harmonising objectives and regulations.

The first two decades of the 21st Century saw significant advances in vaccine development and deployment as well as in the total numbers of children receiving vaccines. By WHO calculations, the measles vaccine alone saved the lives of around 25 million children between 2010 and 2020 [81,82]. In the years leading up to the COVID-19 pandemic, more than 80% of infants globally were being vaccinated against at least the original EPI schedule: measles, pertussis, diphtheria, tetanus, tuberculosis and poliomyelitis, with many also receiving whooping cough, Hib (Haemophilus influenzae), and hepatitis B vaccines [83,84].

Of course, the schedules of NIPs vary from country to country for reasons ranging from local disease burden and financing, to programme and facility capability, and cultural considerations like the population’s acceptance [85]. Many countries have added to their original schedules of vaccines in the past decade. GVAP reported that since 2010, 116 countries have added one or more new vaccines to their infant immunisation programmes [86].

Recent years have seen some notable successes in vaccine R&D which have added to the global arsenal of vaccines to protect against malaria, dengue and Ebola [86]. Many of the organisations previously mentioned in this section, both industry and NPOs, also have promising new vaccines in their pipelines, while novel technologies such as mRNA and broadly neutralising antibodies (bNAbs) have opened up new avenues of research.

Initially developed to neutralise multiple HIV-1 viral strains, bNAbs could have vaccine applications for other rapidly mutating viruses such as influenza as they target the conserved epitopes of the virus, and might be a way to target viral strains that can evade vaccine-induced immune response [87].

Technological advancements in many fields — both those developed specifically with vaccines in mind and those adapted for vaccination programmes — show promise for the future.

More stable vaccine formulations and more robust vaccine storage and supply chains could bring more vaccines to those most in need. Polymer microneedle patches containing vaccine, which can be quickly and painlessly applied by non-medical personnel, could significantly simplify and speed up last-mile and final-inch vaccine delivery. Mobile digital technology to better record and analyse data from vaccination programmes could help monitor and improve programme performance in remote locations.

But there is still much to be done to improve the equitable delivery of vaccines — existing and in the pipeline — to those that need them for a healthy and productive future. And before we can begin to move forward, we will have to regain some of the ground lost during the COVID-19 pandemic which ironically negatively impacted immunisation programmes in many regions [88].
The current vaccine technology platforms

**Live attenuated vaccines** contain a weakened version of the living virus that does not cause serious disease in healthy people [CDC]. Examples: Measles, mumps, and rubella (MMR vaccine), varicella (chickenpox) and oral polio.

**Inactivated vaccines** use cultured virus particles, bacteria, or other pathogens which are inactivated or killed, leaving them just strong enough to create an immune response yet incapable of causing disease [HHS]. Examples: Flu shots, Hepatitis A and the injected polio vaccine.

**Toxoid vaccines** use the inactivated form of toxins created by the bacteria to train the immune system to neutralise the toxins, rather than targeting the bacteria itself [HHS]. Examples: Tetanus and diphtheria.

**Subunit vaccines** use pieces of the virus or bacteria such as the capsid, a protein, a polysaccharide, or a conjugate of a protein and polysaccharide. They are safe as they do not contain any live pathogens but often require booster shots [Gavi]. Examples: Hepatitis B and MenACWY.

**Viral vector vaccines** cannot cause disease as they do not contain any actual antigen. Instead, they use a harmless virus modified to carry parts of the antigen’s genetic code into the recipient’s cells, infecting the cells and instructing them to make large amounts of the antigen to trigger an immune response [Gavi2]. Examples: Some COVID-19 vaccines and some recent Ebola vaccines.

**Messenger RNA (mRNA) vaccines** like viral vectors, mRNA vaccines contain no antigens. Instead, they instruct our cells to produce a specific protein unique to the virus. The protein triggers an immune response, including antibodies that will recognise the protein on the virus if they encounter it in the future [CDC2]. Examples: The first two COVID-19 vaccines.
Observations on the response to the COVID-19 pandemic

History has repeated itself with another pandemic sweeping the world. But unlike previous pandemics, modern technology has allowed both the progression of the pandemic, and our global response to it, to be meticulously recorded in billions of data points. While there will be plenty of lessons to be learnt from studying that mass of data in the future, today we need to focus on some of the key learnings we have already captured.

One of the earliest identified shortcomings was the varied levels of preparedness demonstrated by different regions when COVID-19 arrived. The previous experience some Asian countries had gained with disease outbreaks such as Nipah, Severe Acute Respiratory Syndrome (SARS) and MERS had taught them valuable lessons on how to contain the early spread of disease outbreaks, and meant they were much more prepared to cope with a new threat.

Some other countries which lacked either the previous experience or the extensive public health infrastructure of places like Singapore, South Korea, and Taiwan, were slower to react and impose restrictions. Some countries may have underestimated the virus’s ability to spread rapidly, and allowed their populations to carry on as normal for too long. This unpreparedness, and delay in response, although later corrected, contributed to the huge variance in the numbers of cases and deaths between different countries in the first few months of the pandemic [1].

Invaluable experience in emergency vaccine production had also been gained by multiple international stakeholders during the response to the meningitis A epidemic that swept Sub-Saharan Africa in the late 1990s and more recently in 2014 during the Ebola outbreak in West Africa. Invaluable experience in emergency vaccine production had also been gained by multiple international stakeholders during the response to the meningitis A epidemic that swept Sub-Saharan Africa in the late 1990s and more recently in 2014 during the Ebola outbreak in West Africa.

The responses to these outbreaks provided the world with positive examples of how to collaboratively develop and provide effective vaccines. In both instances, multistakeholder collaborations that brought together national governments, supranational organisations, academia, and industry were able to produce and distribute life-saving vaccines in what were then record-breaking times (See the Ebola and MenAfriVac sections on pages 31 and 33 respectively).

However, once the world realised the real threat COVID-19 presented, vaccine development moved at an unprecedented speed. In less than a year after the WHO declared COVID-19 a pandemic, vaccines were being rolled out of factories. But that shining success was soon marred by the darker mishandling of any equitable global distribution of those vaccines.

Undeniably, the richer Western nations were able to secure the vast majority of the vaccines produced in 2021, while LMICs were left struggling to secure enough doses to vaccinate even the most vulnerable segments of their populations [2].

Although some countries with domestic production were able to secure a limited supply, the great majority of the world’s supply of COVID-19 vaccines, which were manufactured in LMICs, were shipped to HICs [3-5]. In the first month after the first vaccines were approved and production was ramped up, demand far exceeded supply; this was true even for wealthy, western nations. But it soon became apparent that vaccine distribution was strongly skewed in favour of HICs [3-6].

A formulation in a vial does not become a vaccine until it’s injected into the arm of a recipient. It has become pretty apparent now with COVID-19 vaccines that it’s a whole lot easier to make billions of doses of vials filled with a formulation, and much, much harder to get those doses into the arms of people who might benefit from them.”

- Dr David C Kaslow,
  Chief Scientific Officer,
  Program for Appropriate Technology in Health (PATH) [2012-2022],
  From an interview with the authors, Apr 11, 2022.
This disparity was also exacerbated because the developing nations frequently lacked the necessary infrastructure required to store, distribute and use the vaccines. In March 2021, the OECD issued a report on vaccine access which stated that “the currently skewed distribution of vaccines is both inequitable and inefficient” and requested that governments should act collectively to accelerate vaccination in all countries [6]. By early 2022 the distribution situation had improved significantly and COVAX was able to announce reaching the milestone of 1 billion distributed doses [3].

Much of the world is now fully or partially vaccinated and there is a concerted effort to reach those who have yet to be vaccinated. However, immense challenges remain not only in vaccine production, supply, and distribution, but also in creating the infrastructure and managing the logistics needed to get vaccines into arms.

The response to the pandemic also revealed shortcomings in supply chains and vaccination programme infrastructure in many LMICs, where even standard cold chain storage, logistics, and management services were often rudimentary, and the ultra cold-chain logistics capabilities required by some mRNA-based COVID-19 vaccines were almost non-existent. This was particularly vital for distribution from regional distribution hubs to vaccination teams in the field.

“What we should really be doing is figuring out where to optimize benefit and risk aversion.”

- Dr David C Kaslow,
Chief Scientific Officer, (PATH) [2012-2022]

While many LMICs have significantly improved their child vaccination infrastructure over the past two decades, few have much experience with large-scale, emergency, adult vaccination programmes. It is evident that considerable investment is needed if these unmet needs in manpower, skillsets and vaccine infrastructure are to be met.

Remarkably, in less than 18 months from the day the first shot of a COVID-19 vaccine was administered, more than two-thirds of the world’s population had received at least one dose of a COVID-19 vaccine. However, on closer inspection that achievement is not as positive as it might seem. There were extreme variations in vaccination rates from country to country.

The wealthy United Arab Emirates claimed to have given 99% of its population two doses of the vaccine, while the resource-poor Republic of Burundi had only managed to give 0.1% of its population a first dose. All but four — Haiti, Yemen, Papua New Guinea, and Afghanistan — of the 20 least vaccinated countries in the world are in Africa. By the end of April 2021, only one of the 54 countries in Africa had reached or exceeded the then global vaccination rate of 66.8%; less than 48% of the populations in 50 African countries had received a first vaccine shot [7].

For some LMICs, vaccine availability proved to be only one of a host of contributing factors that complicated and delayed getting shots into arms. Other factors included already overstretched healthcare systems, limited experience with mass adult vaccination, even more limited cold chain logistics infrastructure, finding financing to address those problems, political priorities, civil unrest, and that perennial problem for new vaccines winning multi-level community buy-in.

This last problem, although as old as vaccination itself, has been complicated in recent years by the exponential growth in anti-vaccine misinformation. Vaccination programmes have always faced some suspicion and doubt, or what we today call ‘vaccine hesitancy’.

In the past, it was sometimes regarded as a cultural issue but more often a lack of knowledge that could be addressed with localised educational outreach. In recent years, it has been exacerbated in HICs and LMICs alike by misleading or plain false information spread largely via social media and the internet.
In some countries, both HICs and LMICs, it is arguable politics may have influenced pandemic planning and response decisions that should have been left to public health professionals. This may in turn have led to the less than ideal implementation of non-clinical interventions as well as limiting access to vaccines.

There were many factors that contributed to the unprecedented rapid development of the first COVID-19 vaccines. Breakthrough technologies, particularly in the field of mRNA, have received a lot of public attention and credit, as have unusually high degrees of cooperation and even information sharing among government bodies, big pharma, NPOs and academia. Individual academics and academic institutions partnered with pharma companies and shared pre-pandemic research, and in some cases were involved in the subsequent preclinical research and clinical trials of the resulting vaccines.

Thought leaders within the vaccine ecosystem and industry point to the more flexible attitudes of regulatory bodies to clinical trials and the adaptations made — without compromising ethics and safety — to regulatory standards; which greatly expedited the trial process.

The initial emergency use authorisation (EUA) which the US Food and Drug Administration (USFDA) and other authorities issued for the early vaccines also greatly speed up their availability. The USFDA issued the first of the EUAs to Pfizer-BioNTech COVID-19 vaccine for distribution in the US on 11th December 2020, for the prevention of COVID-19 disease in people 16 years of age and older [8], a little more than nine months before the vaccine received full FDA approval for individuals of 16 years and older on 23 August 2021 [9].

The COVID-19 pandemic significantly shifted the regulatory risk tolerance curve to the left, as the huge potential benefits of vaccines were seen to outweigh the apparently low risks.

This is an important lesson we can learn from the response to the pandemic. The cost of early discovery and development stages and the time and funding required for trials, particularly Phase III trials, have for decades been one of the biggest hurdles in vaccine development.

In the past, the standard sequential vaccine development approach which required developers to proceed step by step, and trial phase by trial phase, could cost billions of US dollars and take 10 or even 15 years to complete. Only after a successful Phase III trial and regulatory approval could companies consider scaling up manufacturing capacity.

Because of the inherent risk of failure and the huge costs involved, big pharma had always been very cautious in their approach to vaccine development. The riskiest early stages of discovery through Phase I and Phase II were nearly always funded by a mixture of government grants and support from philanthropic donor organisations; unless there was an obvious market for a vaccine in developed western countries [10].

Approval by the USFDA, CE or similar body is often not the end of the process, particularly for unincentivised vaccines* addressing unmet needs in LMIC countries, which have no ready market in developed countries. The next step for them is a pre-qualification application with WHO. After authorisation by WHO, the vaccine enters a Phase IV clinical trial. Organisations like the International Vaccine Institute (IVI) then bring that data to other organisations such as WHO-SAGE which could recommend the vaccine. Gavi then has to agree to put the vaccine on the list of no-cost vaccines for LMICs. Even then, although free to governments in LMICs, the vaccine may not be widely adopted unless championed by organisations like IVI working with governments to demonstrate the impact and cost-effectiveness of administering it.

* Unincentivised vaccines are vaccines that target diseases that the public, policymakers and scientists have limited awareness of. These vaccines have little perceived incentive for major vaccine manufacturers to engage in development [11].

Sources:
3. AstraZeneca’s COVID-19 vaccine authorised for emergency supply in the UK. Accessed 15 June, 2022
The response to the pandemic changed much of that, particularly the US’s Operation Warp Speed and similar undertakings in Europe and China. The once sacrosanct sequential vaccine development approach was condensed and the various stages allowed to run in parallel. Because it was a pandemic, there was also an abundance of cases to rapidly assess vaccine efficacy. Even manufacturing capacity could be safely scaled up while the clinical trials were still ongoing because the promise of speedy approval and guaranteed markets removed much of the risk for the industry [10,12,13].

Many factors played a part, but by far the most important were the massive amounts of government funding and the race to pre-order millions of doses, even before trials were completed. This removed much of the financial risk and allowed the pharmaceutical industry, from biotech start-ups, to giants like Pfizer and Johnson & Johnson to commit themselves to the hunt for a vaccine. With their research funded and distribution markets guaranteed for any effective vaccine developed, the pharma giants were able to devote huge amounts of resources to the search.

Another enabler of the rapid production of COVID vaccines was technology transfers. According to the Developing Countries Vaccine Manufacturers Network (DCVMN), technology transfers enabled their members to produce almost 6 billion of the 11 billion doses of COVID-19 vaccines manufactured globally in 2021. They also managed to increase the production of many of the other vaccines they produce, more than tripling the total global vaccine production from 3.5 billion in 2019 to 11.3 billion in 2021 including COVID-19 vaccines [14].

“Collaborations and technology transfers have always played an important role in vaccine manufacturing, even pre-pandemic but the pandemic certainly provided a great stimulus to expedite technology transfers to help make vital vaccines available for billions of people worldwide.”

- Rajinder Suri, Chief Executive Officer, Developing Countries Vaccine Manufacturers Network (DCVMN), Interviewed by the authors, Feb 24, 2022.

As of July 2022

A technology transfer is the knowledge transfer of any process, together with its documentation and professional expertise, between development and manufacturing, or between manufacturing sites [15]. The technology transfers, which propelled vaccines and other pharmaceutical products into overdrive production, would not have been possible without the organisational collaborations and huge amounts of funding the pandemic necessitated.

Collaborative efforts also help with the supply of vaccines to developing countries as well as the analysis of data from disease burden, infection spread and vaccination programmes. For example, in the past decade, billions of dollars came from the US National Institutes of Health (NIH), the European Union, the Wellcome Trust and the Bill & Melinda Gates Foundation to help the first-phase development of vaccines for diseases affecting developing countries [16].
Observations on the response to the COVID-19 pandemic

Within the span of one year, the World Bank Group had committed over US$200 billion to public and private sector clients around the world to curb the impact of the pandemic [17]. These multi-sourced investments helped numerous vaccine candidates see the light of the day. Other collaborative schemes hope to make existing vaccines and other treatments available for populations in developing countries.

The world’s most comprehensive response to COVID-19, the Access to COVID-19 Tools (ACT) Accelerator, could offer the biggest lesson for the future. It has brought together governments, health organisations, scientists, businesses, civil society, and philanthropists to accelerate not just the distribution of vaccines but importantly also scaling up development, manufacturing, and shipping capabilities in all the participating countries, of vaccines, tests kits and treatments, in effort to provide equitable access for LMICs [18].

COVAX, the vaccine pillar of the Access to COVID-19 Tools (ACT) Accelerator, although slow to start, and still far short of its original goal of delivering two billion vaccine doses by the end of 2021, had delivered 1.61 billion doses to 146 countries according to Gavi data as of August 2022 [19].

It remains to be seen whether this unique collaborative effort can deliver vaccines to all its participating countries. But regardless, this ambitious effort to provide novel vaccine technology to develop, manufacture, and distribute vaccines could provide a template for addressing the un incentivised vaccine needs of LMICs in the future.

But we can’t let successes blind us to the failings and shortcomings that still lead to vaccine inequity today; both those relating to global COVID-19 responses and those that have long pre-dated the pandemic.

The speed with which COVID-19 vaccines were developed and the astonishing number of doses administered since they were approved are commendable. But we must not forget the way those doses were distributed around the world was far less admirable. Nor can we ignore the detrimental impact pandemic measures had on pre-existing immunisation programmes.

In 2020, fewer infants under one year of age received a basic vaccine panel than any year since 2009; an estimated 23 million went unvaccinated, which is 3.7 million more than in 2019. Globally, vaccine coverage dropped from 86% in 2019 to 83% in 2020. Older children also missed out with 1.6 million fewer girls receiving a HPV shot compared to in 2019.

The pandemic strained the healthcare systems of even the wealthiest nations and impacted immunisation programmes globally. Lockdowns, staff shortage, supply problems and parents’ concerns about taking their children to healthcare facilities may have put as many as 80 million children at risk of disease such as diphtheria, measles and polio, which they would normally have been vaccinated against [20].

The focus on the pandemic is probably also responsible for the drop in the number of countries adding new vaccines to NIP schedules. In 2021, the WHO recorded only 25 vaccine introductions not including COVID-19 vaccines; well below the number introduced in any year in the past two decades [21]. This slowdown is likely to continue as countries focus on ongoing efforts to control the COVID-19 pandemic, and on the introduction of COVID-19 vaccines.

The Uneven COVID-19 Vaccine Rollout

Share of world population fully-vaccinated against COVID-19, by region

Legend:
- As of December 2021 (%)
- As of September 2022 (%)

**Sources:**

The focus on the pandemic is probably also responsible for the drop in the number of countries adding new vaccines to NIP schedules. In 2021, the WHO recorded only 25 vaccine introductions not including COVID-19 vaccines; well below the number introduced in any year in the past two decades [21]. This slowdown is likely to continue as countries focus on ongoing efforts to control the COVID-19 pandemic, and on the introduction of COVID-19 vaccines.
We must not forget the immense toll that infectious diseases take on the world today, and have taken for many years. Every year almost 9 million people die from infectious diseases, but not in the rich, developed world; 94% of these deaths occur in LMICs. Of those deaths 46% are from diseases for which there isn’t a registered vaccine. That means 54% have died from a disease they could have been vaccinated against, but weren’t.

In response to the pandemic, individual and institutional philanthropy gave more money, more quickly and with fewer strings attached than ever before [22]. But can we expect philanthropy alone to finance the world’s future vaccine needs? In the 21st century when the annual global expenditure on arms is more than 2 trillion US$ [23], we can and must do better. There are practical and achievable steps that can be taken to reach more equitable vaccine access; we just have to collectively take them.

“In 2020, 5.0 million children under five died, translating to 13,800 children daily. Globally, infectious diseases, including pneumonia, diarrhoea and malaria, remain a leading cause of under-five deaths...”

- UNICEF
Capacity building, and data and technology sharing

The COVID-19 pandemic has highlighted the shortfall in vaccine supply to some regions, caused mainly by a lack of manufacturing and logistics capabilities; in particular mRNA production facilities and the ultra cold-chain logistics facilities required by some mRNA vaccines.

The need to provide LMICs with novel vaccine technology to develop, manufacture, and distribute vaccines was recognised by many within the vaccine ecosystem, and led to the establishment of Access to COVID-19 Tools (ACT) Accelerator, in an effort to improve vaccine supply and vaccination rates in countries in need. If this programme could be continued into the future and its remit extended to the many other unmet vaccine needs of the developing world, it could become one of the few positive legacies of the pandemic.

The WHO has recognised the importance of regional technological hubs and the sharing of mRNA vaccine technology. In June 2021, they announced the establishment of technology hubs to build capacity in LMIC geographies to produce mRNA-based vaccines [1]. In February 2022, the Director-General of WHO announced that Egypt, Kenya, Nigeria, Senegal, South Africa, and Tunisia were selected to receive mRNA technology to start producing vaccines [2], eventually to be followed by Bangladesh, Indonesia, Pakistan, Serbia, and Vietnam [3].

“One of the biggest advantages of vaccine technology advancement is its power to increase productivity that ultimately improves availability, affordability and accessibility.”

- Rajinder Suri,
Chief Executive Officer, DCVMN

Speaking to the Financial Times in April 2020, Bill Gates also spoke to the need to increase preparedness and vaccine capabilities around the world, covering everything from surveillance and diagnostics, to deep antiviral libraries, antibodies, vaccine platforms, and manufacturing capabilities around the world. He even went as far as to suggest that industry and philanthropic organisations could not be expected to carry the cost of maintaining ‘spare’ capacity alone, and that there will be a need for governments to offer financial support. Gates pointed out that a few billion wisely invested in the years before the pandemic could have saved the global economy from its trillion-dollar impact.

Gates suggested such facilities could be used for research, development and testing of vaccines for non-pandemic diseases in peace time but be available to ramp up response to the next pandemic disease when it emerges [4].

To improve their sustainability and preparedness, such manufacturing facilities should ideally also produce other biologics, consumables and reagents that support the vaccine technology.

This is an operational model which is similar to the agreement Hilleman Laboratories entered into with the Singapore government in 2022 [5]. If successful, Singapore’s example could provide a model more countries and organisations could follow.

“The ‘spare capacity’ model could function well for as long as the facilities are sustainable, innovative and provide quality products.”

- Dr David C Kaslow,
Chief Scientific Officer, PATH [2012 - 2022]

There is also a need to develop and upskill scientists and technicians from LMICs to equip them with the skills required to run vaccine laboratories and manufacturing facilities — something else the Hilleman facility in Singapore will be doing. In addition to hiring 50 staff locally for the facility, Hilleman also intends to run training courses at their facilities for scientists, engineers and technicians from other countries in the region.
Surveillance and screening

For decades, before and after SARS-1 and MERS, the scientific community has warned it is not a matter of if but when the next pandemic will happen. The current COVID-19 pandemic does not change that. It might be next year; it might be in a decade but at some point in the future, there will be another pandemic.

The two most likely candidates are an influenza virus or another zoonotic, bat-borne coronavirus [6]. In recent decades the world has seen more instances of zoonosis, i.e., animal to human transmission of viral disease. Growing populations, climate change and the rising demand for agricultural land continue to drive encroachment into the habitats of wild animals. Wildlife trade, a major concern for zoonosis, is already illegal in many countries including in Africa and Asia, but is still flourishing. This makes surveillance, screening and rapid containment of outbreaks essential.

“Our best defence needs to be improved surveillance, the regular screening of at-risk populations and international sharing of data. And once an outbreak is detected, a rapid response to isolate and contain it is crucial; every day counts.”

- Professor Wang Linfa,
Professor Wang Linfa, Emerging Infectious Diseases Programme, Duke-NUS Medical School, Interviewed by the authors, Mar 31, 2022.

Bacterial infections are another potential pandemic risk. Diseases such as tuberculosis, non-typhoidal salmonella and cholera are endemic in many LMICs, while novel species of bacteria as well as new variants of familiar species are regularly discovered [7]. Once again encroachment into wilderness habitats plays a role. Recently discovered bacterial infections include Lyme disease and Legionnaire’s disease, both discovered in the 1970s.

Although an unlikely candidate for becoming pandemic, Legionnaire’s disease (caused by the bacteria Legionella pneumophila) is an example of antimicrobial resistance (AMR). Legionella pneumophila, the bacteria that causes it is highly resistant to at least 10 commonly used antibiotics [8]. Experts fear AMR could leave us with limited treatment options if we ever did face a bacterial pandemic.

Whether the next pandemic is viral or bacterial, the world will need to pay more attention to surveillance, screening and rapid containment of outbreaks to manage it.

Antimicrobials

While the current increased global awareness of the importance of vaccines against virus-borne diseases is welcome, we must not forget other disease threats such as antimicrobial resistance (AMR). Infectious disease experts and doctors who see first-hand the depleting arsenal of effective antimicrobials have repeatedly warned of the increased burden caused by AMR.

Just as we need to develop novel vaccines and drive vaccination programmes to meet the unmet needs of LMICs and be prepared for future pandemics, we must also tackle AMR. The effective deployment of existing vaccines, and the development of novel vaccines, can help to mitigate the spread of the growing number of antibiotic resistant pathogens [9]. But we also need to develop new antibiotics by investing more in R&D.

Pathogens with resistance or growing resistance are circulating in communities, posing a threat to lowering morbidity and mortality numbers, thus further creating the need for vaccines. The emergence and spread of AMR can be mitigated with vaccination [9]. The protection would particularly favour high-risk and vulnerable populations such as the aged, under-aged, pregnant or those who have higher exposure due to living conditions or line of work.
As new pathogens or variants emerge, experts in pathogenicity would need the support to continue fundamental research on how pathogens of interest are wired, adapt and spread. The entire ecosystem needs to work together towards the common goal of reducing morbidity and mortality caused by infectious agents around the world through vaccines and therapeutics.

“We must be careful that our pandemic focus does not make us blind to the dangers of antimicrobial resistance. For example, salmonella doesn’t have the same kind of advocacy as tuberculosis or malaria, but non-typhoidal salmonellosis is a leading cause of sepsis in children in Africa, with an extremely high fatality rate. And it is now becoming resistant to first- and second-line antibiotics. We don’t talk enough about these emerging threats.”

- Dr Francesco Berlanda Scorza, GSK Vaccines Institute for Global Health (GVGH), Interviewed by the authors, Apr 6, 2022.

Antibiotics: The looming antimicrobial resistance crisis

The WHO says new antibacterials are urgently needed because those we currently have are becoming increasingly ineffective as drug resistance spreads globally, leading to more difficulty in treating infections [10].

Hundreds of thousands of people, and possibly even millions, die from AMR-related causes every year, and the numbers are growing as AMR increases. According to a recent study, the six leading pathogens for deaths associated with resistance are *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. The study estimated around a million deaths directly attributable to AMR in 2019, with around another 3.5 million deaths associated with AMR, the great majority occurring in LMICs [11].

The economic impact of AMR goes far beyond the growing number of deaths as the impact on national economies and their health systems are significant, considering lost productivity of patients and those caring for them, prolonged hospital stays, and more expensive and intensive hospital care [10].

The last entirely new class of antibiotics discovered was daptomycin, which was discovered in 1984 but did not receive USFDA approval nor reach the market until 2003 [12]. New candidates for antibiotics are hard to find and the process of developing them and bringing them to market is lengthy and costly; at around US$1.5 billion according to a 2017 estimate.

However, both per-dose prices and sales volumes are low compared to other kinds of drugs. Prices are low because in many countries, government agencies have a role in assessing and setting prices, and pharmaceutical companies are bound up in complex pricing deals [12,13]. Unit sales are low because antibiotics are usually only prescribed for a few weeks at a time; unlike drugs for chronic conditions like high blood pressure or diabetes which patients take for months or even years [14]. This has possibly led to many companies having left the antibiotics field in favour of more profitable sectors such as oncology and cardiology drugs.
Funding R&D

As with vaccine development, the preclinical stages of antibiotic R&D carry the biggest financial risk. Tens, even hundreds of millions can be spent on identifying a target compound and working it up through initial development stages only to have it fail at Phase I or even earlier.

Also, like vaccines, antibiotic development seems to be increasingly reliant on philanthropy, donor organisations and novel investment funds to finance early-stage R&D, such as Novo Holdings’ fund, Replenishing and Enabling the Pipeline for Anti-Infective Resistance (REPAIR), a US$165 million initiative to support companies in the early stages of antibiotic R&D. Rather than making a profit, REPAIR was intended to fund antibiotic companies through Phase I trials in the hope it would help them find further investment from big pharmaceutical companies to bring their drug to market. But investors have been hard to find as many of the larger companies such as AstraZeneca, Novartis and Sanofi are no longer interested in developing antibiotics and many smaller independent companies have gone bankrupt or closed down [15].

The larger CARB-X programme is experiencing similar problems. Despite initial funding of $500 million from the US, Germany and the UK governments, as well as from foundations and charities like the Wellcome Trust and the Bill & Melinda Gates Foundation, finding the additional industry investment to bring projects to fruition has proven to be difficult [15].

The industry is beginning to take some notice of the looming AMR crisis. In July 2020, the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) announced the creation of the AMR Action Fund to support the clinical development of innovative new antibiotics to address multi-drug resistant bacteria and other life-threatening infections.

“The biggest challenge in antibiotic research is not identification and early research but large, late-stage clinical trials. We need a mechanism to bridge some of the evolutionary R&D steps and improve the design of clinical studies for efficacy. International NGOs and NPOs like PATH, Bill & Melinda Gates Foundation and Wellcome are crucial in paving the way to potential licensure for antibiotics.”

- Dr Raman Rao,
CEO, Hilleman Laboratories

Valleys of Death from Vaccine Development to Administration

Massive Investments + Ethical Simplification of Processes + Collaboration

Potential Vaccine Candidate Vaccine Candidate Proof of Concept Vaccine Candidate Efficacious, Safe, Approved and Licenced Vaccine Recommended for Use Vaccination of the Public

Death Valley 1: Early Clinical Development Death Valley 2: All Phases of Clinical Trials Death Valley 3: Vaccine Recommended for Use

Source:
2. Kaslow DC. Chief Scientific Officer, PATH. Interviewed by authors, 11 Apr 2022

The process of developing, testing and recommending a vaccine candidate which has demonstrated potential effects is inevitably challenged by the ‘valleys of death’. Overcoming these death valley’s require multipronged approaches.

The initiative involves 24 companies and has so far committed nearly US$1 billion with the aim of developing and bringing to market two to four new antibiotics by 2030 [16].

More needs to be done; this is not an LMIC problem, it is a global issue. Currently, LMICs are the most negatively impacted, particularly when it comes to diarrhoea and sepsis, but AMR is also on the rise in the West. Many common bacterial infections the HICs thought they had conquered, such as urinary tract infections (UTIs) and some sexually transmitted diseases (STDs), are rapidly developing resistance.

According to the Global Antimicrobial Resistance and Use Surveillance System (GLASS), resistance to carbapenem antibiotics, the last resort treatment for *Klebsiella pneumoniae*, has reached all global regions. *Klebsiella pneumoniae* is not only a LMIC problem, it is a major cause of hospital-acquired infections such as pneumonia, bloodstream infections, and infections in newborns and intensive-care unit patients in HICs. But due to resistance, carbapenem antibiotics do not work in more than half of the patients treated for *K. pneumoniae* infections [17].

Once again, the answer lies in multi-stakeholder collaboration and the sharing of the financial risks of early development. We must also consider a fairer pricing mechanism for newly developed antibiotics, one which recognises the value they represent to the broader economy, and allows manufacturers to recoup their investment and make a reasonable profit.
Where we go from here

The changing regulatory landscape

When SARS-CoV-2 emerged, the rapid investment of huge quantities of public money from the US and other HICs, cross-country and cross-organisational collaboration by researchers and policy-makers to promote rapid information sharing, and the heroic efforts of many parties including academia, industry, and regulatory agencies allowed for the rapid development and scaled-up production of vaccines.

The US Food and Drug Administration (USFDA) granted emergency use authorisation (EUA) for the first vaccine against SARS-CoV-2 just 10 months after the virus was first discovered and its genome sequenced. But that was only possible because the extraordinary collaborative efforts of regulatory agencies allowed manufacturers to develop vaccines and scale up manufacturing in parallel, along with the most intensive vaccine safety monitoring effort in US history to ensure safety [18].

While the USFDA and a few other regulatory agencies in other HICs were able to perform such monitoring, many countries, particularly LMICs, lacked the capabilities to expand and expedite regulatory capacity [19]. Even in the wealthiest countries, there was insufficient capacity, and speed and monitoring were only maintained by focusing regulatory review resources on COVID-19 vaccines, asking for herculean efforts from the regulatory staff; neither of which tactics could have been sustained for an extended period. In fact, even in the short term it considerably slowed the approval of other vital products.

Luckily, the innovative regulatory response to COVID-19 was successful this time but the pandemic clearly highlights that moving forward, greater flexibility, innovation, and capability need to be developed in regulatory agencies around the world; both to speed up the development and production of vaccines for known threats and to prepare for future pandemics.

If we go back to the conservative nature of the pre-COVID regulatory process, when vaccines went through field efficacy studies before subsequently going into the approval process, including further post-marketing commitments, those effectiveness studies could take up to five years or more before the results could be reported. During the pandemic, the regulatory environment became less risk-averse when weighing the benefits of a vaccine against potential risks and that process was shortened.

We can and should also shorten that process for other vaccines. Of course, safety and ethical considerations must always remain paramount, but we should strive to develop a more dynamic model, perhaps one where vaccines could be approved based on a safety database.

For example, when WHO requests a safety database of 3,000 subjects, we could be more innovative in how we use it, perhaps working with potential surrogate markers for efficacy. We could also adopt the parallel rather than the sequential model for the approval process. While field efficacy studies are continuing, we could work on other requirements and check off the significant milestones to approval as they are reached, rather than waiting to complete one stage before embarking on the next stage. Then, as with the COVID-19 vaccines, efficacy studies could be carried forward into the real world and be added to the entire regulatory file.

Getting the most shots into as many arms as quickly as possible is what is needed to slow infection rates and prevent disease [20]. One of the best options we have for speeding up the process of delivering vaccines and getting shots in arms is adopting innovative ways to streamline the regulatory process.

Eliminating infectious diseases in low- and middle-income countries (LMICs) as well as pandemics, will require solutions offered by medical science, technology and human commerce working together under a colossal umbrella.

Non-vaccine approach

- Disease surveillance
- Test and treat strategy
- Addressing antimicrobial resistance

Vaccine R&D

- Funding
- Collaboration
- Technology transfers
- Manufacturing hubs
- Trained expertise

Managing infectious diseases

- Effective vaccine supply chains
- Adult & child vaccination Programs
- Better vaccine reception

Vaccination

- Adult & child vaccination Programs
- Better vaccine reception
Where we go from here

In conclusion

The vaccine ecosystem has progressed tremendously in the past 30 years; at first glance nearly all the numbers and statistics are positive. We have more vaccines, more vaccine platforms, more ways to administer vaccines, more countries giving more kinds of vaccines to children and adults, more funding for immunisation programmes, and more ways of raising funds to help with vaccine research and delivery. But some of the worst numbers and statistics have barely shifted.

In 1990, 20% of the world’s children were not receiving even the basic six vaccines recommended by the EPI. And 95% of deaths and cases of disability that occurred as a result of diseases that could have been prevented by vaccination were in LMICs [1].

In 2020, the statistics were eerily similar, still around 17% of children did not receive the basic six vaccines, and 94% of all infectious disease deaths occurred in LMICs, with 46% of those easily prevented with existing vaccines [2].

Of course, the statistics are not directly comparable. In total, more children are being vaccinated simply because the global population has grown by almost 50% from around 5.25 billion in 1990 to 7.85 billion today but that also means the total number of children not receiving vaccines has also grown [3]. Today we have vaccines for more diseases and more children are getting more of those additional of vaccines but those most in need are still not receiving any.

According to UNICEF, in 2020 around 23 million children were unvaccinated or under-vaccinated (not receiving the first dose of DTP or not receiving the third dose of DTP, respectively) and 17 million of them were the so-called zero-dose children who did not receive any kind of vaccines [4].

We can point to many reasons why some of the poorest and most in need of vaccines are not receiving them; conflict, culture, hesitancy, remote locations and logistical issues among many others.

But if the world agrees that 17 million zero-dose children is not acceptable we have to take action today to make sure the statistics are very different by 2030.
Contributors

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