

COVID-19 Vaccine Development and Rollout in Historical Perspective

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Abstract

At the start of 2022, profound inequities in the pace of access to COVID-19 vaccines and the level of coverage of COVID-19 vaccination remain, especially with regard to the world's poorest countries. Yet despite this inequity, we find that global COVID-19 vaccine development and diffusion has been the most rapid in history, and this rapid scale-up is evident not only in high-income countries but also in upper- and lower-middle-income countries, home to the majority of the world's population. This paper explores the historical record in the development and deployment of vaccines globally and puts the COVID-19 vaccine rollout in that context. Although far more can be done and should be done to speed equitable access to vaccines in the COVID-19 response, it is worth noting the revolutionary speed of both the vaccine development and the diffusion process, and the potential good news that this signals for the future of pandemic preparedness and response.

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1 Introduction

At the start of 2022, profound inequities in the pace of access to Covid-19 vaccines and the level of coverage of Covid-19 vaccination remain. As of this publishing, only 6.6 percent of the population in sub-Saharan Africa have been fully vaccinated, whereas more than 58 percent are fully immunized in the OECD countries. The emergence of new variants may demand development and delivery of a new vaccine or boosters as well as distribution of effective antivirals—all of which are likely to be slower to roll out in low income countries than high income countries.

Yet despite this inequity, we find that global Covid-19 vaccine development and diffusion has been the most rapid in history. This paper explores the historical record in the development and deployment of vaccines globally, and puts the Covid-19 vaccine rollout in that context. Although far more can be done (and should be done) to speed equitable access to vaccines in the Covid-19 response, it is worth noting the revolutionary speed and broad geographic spread of both the vaccine development and diffusion process, and the good news that this signals for not only to the next phase of the response but also to the future of pandemic preparedness and response.

The global toll taken by vaccine-preventable infectious diseases remains obscene, but it was considerably larger in the past. Smallpox killed around five million people a year in the century before its eradication.¹ In the pre-vaccine era in low- and middle-income countries, as many as one out of twenty infants would die from pertussis (at such rates, low- and middle-income countries today would lose more than 600,000 infants a year to the infection).² Rotavirus caused 528,000 deaths of children under five in 2000 and pneumococcal diseases added 826,000 more.³

Vaccinations carried out worldwide between 2000-19 against still-extant infectious threats are collectively estimated to have averted 50 million deaths.⁴ Existing rates of measles vaccination alone were estimated to prevent about 1.5 million deaths a year by 2019—although an estimated 207,000 deaths from measles still occurred that year.⁵

Covid-19 has added to the death toll; from late 2020's emergency use authorizations for vaccines, subsequent deaths have nearly all been 'vaccine preventable'—both thanks to the direct protection provided by vaccination and a vaccinated person's contribution toward herd immunity. But the challenge of converting 'vaccine preventable' into 'vaccine prevented' is particularly daunting in the current pandemic: rather than an annual program of vaccinating

newborns and children against a threat that previous cohorts have already been protected against, the Covid-19 pandemic requires an effort more akin to the response towards seasonal influenza, where the aim is to rapidly vaccinate everyone, and in particular the older population most at risk. We will see how far we fail in that aim with influenza, and this makes the (still inadequate) progress regarding Covid-19 all the more remarkable in historical perspective.

This paper reviews the obstacles to developing vaccines and delivering vaccinations including against Covid-19. It then looks at three historical cases of global vaccine rollout chosen on the grounds of their global scale and impact: the global smallpox eradication effort; the rollout of select childhood vaccinations worldwide, and the case of the annual influenza vaccine. After looking at the early experience with Covid-19 vaccine rollout, we turn to data on timelines of microbe identification, vaccine development, and vaccination delivery to put the response to Covid-19 in historical perspective. That perspective suggests the Covid-19 vaccine rollout has been unprecedented in speed, scale and reach in high- and middle-income countries, but has been far slower in the world's low-income countries.

2 Steps and Potential Obstacles to Developing and Delivering Vaccinations

Today and historically, there are many barriers to the global diffusion of vaccines in response to infectious threats. Knowledge of the infectious agent, capacity to research and develop a vaccine, capacity to produce that product, demand, ability to pay and ability to deliver to the population are high on that list.⁶ Here, we review a subset of these steps and obstacles to development and deployment of vaccines alongside historical examples to set the stage for later sections, which examine the data on vaccine development and diffusion over time.

2.1 Identifying the microbial agent

The smallpox vaccine is unique in that it was developed prior to the discovery of the infectious agent involved. In 1798, Jenner found that infecting people with a comparatively harmless case of cowpox gave them immunity to smallpox, but he had no knowledge of either the smallpox virus or its close cousin that caused cowpox. Since then, understanding the microbial agent has been a necessary prior step to developing a vaccine. Thankfully, the

technology and techniques available to make that identification have rapidly improved over time, including using more powerful microscopes and gene sequencing technologies. The first microbes related to deadly infections were identified in the 1880s, and the time between recognition of a new infectious risk and identification of the related microbe has dropped dramatically since then, to a matter of weeks in the case of Covid-19. Covid-19 was first identified as a significant health threat in China on December 31, 2019,⁷ was isolated by Chinese authorities by January 9, 2020, and was first genetically sequenced on January 11, 2020.

2.2 Research, development, and approval

Nearly all early vaccines used approaches that involved weakened or killed versions of the pathogen. Using that method to develop stable and effective vaccines that could be mass produced was a time-consuming trial-and-error effort. Such efforts have also proven (so far) ineffective for complex infectious agents like HIV.⁸ Even for successful candidate vaccines, the R&D process needs to be followed by (increasingly stringent) safety trials before licensure. The gap between the isolation of the influenza virus (1933) and the first (live attenuated) vaccine being developed in 1936 was only three years; however, the resulting vaccine was not widely adopted and its efficacy was questionable.⁹ In the period after the Second World War, the average time taken between conception of a vaccine and licensure was between 10 to 15 years; the mumps vaccine held the modern era speed record at 4 years.¹⁰

For Covid-19, the research, development and regulatory process took less than a year. This is the result of considerable advances in medical knowledge, but also the nature of the pathogen. Covid-19 was genetically similar to the MERS virus, and researchers had already begun applying mRNA and other technologies to developing vaccines to counter MERS. Moderna began its phase I trial for a Covid-19 vaccine on February 24th, less than six weeks after genetic sequencing was released. The company completed its Phase III trial in November 30th, and by December 17th, had received an Emergency Use Authorization in the US to produce its vaccines—a total time from emergence to approved vaccine of 352 days.¹¹ In addition, the Covid-19 pandemic saw the simultaneous development of vaccines using different technologies—attenuated, mRNA and vector.¹² Some of these vaccines received national regulatory approval even faster than Moderna’s vaccine. Seven different vaccines are now approved by the World Health Organization for use,¹³ and 137 vaccines are in clinical development.¹⁴

Up until very recently, there was often a considerable additional gap between the date of vaccine licensure and a government recommendation to adopt a vaccine as part of routine immunization. The pertussis vaccine was developed in 1914 but the US CDC only recommended the vaccine for routine immunization in 1948, for example. The gap was eight years for measles, which was recommended as part of the MMR shot in 1971. This gap has dropped to one year for more recent vaccines including pneumococcal conjugate and HPV.¹⁵ With Covid-19, licensure/authorization and government recommendation on use was almost simultaneous.¹⁶

2.3 Production capacity

Mass vaccination requires production at scale. For smallpox this involved widespread manufacture. Even after dry (more stable) smallpox vaccines were introduced, production of the vaccine was extremely distributed worldwide: there were thirteen production sites operating at the end of 1931 in French West and Equatorial Africa alone.¹⁷ In most other historical cases, production has been concentrated in fewer sites primarily in high income countries. Especially at product launch of a high-demand vaccine, this has led to shortages (and did so in the case of polio, for example).

With regard to the influenza vaccine (a particularly suitable comparator to Covid-19 vaccines because of the yearly effort to vaccinate a large portion of the population rather than just children), a WHO survey of influenza manufacturers in 2019 suggested global annual seasonal vaccine production capacity of 1.48 billion and the global capacity to produce 4.15 billion doses of a (two-dose) pandemic flu vaccine in 12 months.¹⁸ Seasonal capacity is enough to vaccinate 19 percent of the world's population and estimated pandemic capacity to fully vaccinate only 25 percent in the first year. Of 40 active production facilities, twenty are in the developing world, but 69 percent of total seasonal and 80 percent of pandemic capacity is in high income countries.¹⁹

With Covid-19, vaccine production remained inadequate to meet demand at the end of 2021, and there was no end-to-end production capacity for vaccines on the entire African continent.²⁰ At the same time, the ramp-up of production capacity was unprecedented. Moderna, previously a small relatively unknown biotechnology technology, now plans to ramp up production from 600 million to 1.4 billion doses by 2022.²¹; BioNTech was able to increase its annual production capacity by 250 million doses, while AstraZeneca reported it would produce three billion doses by end-2021.²² By mid 2022, a forecast 22 billion doses

of Covid-19 vaccines will have been produced globally, although new variants may demand ramp up of new capacity.²³

2.4 Delivery

Countries need the capacity to deliver shots in arms, including access to target populations (and knowledge of where and who they are), personnel, dose delivery and storage often involving a cold chain. Limitations to vaccination infrastructure have long been a considerable factor in driving a wedge between mandates and universal access goals on the one hand and actual vaccination rates on the other, and they helped determine the choice of eradication strategy for smallpox, for example. The last forty years have seen a rapid expansion of delivery networks such that at least routine childhood immunization has become nearly ubiquitous, although still profoundly inequitable within some countries.

A widespread challenge that remains, and that is particularly problematic in the case of a global pandemic like Covid-19, is the delivery capacity to vaccinate entire populations at a rapid pace, especially when the vaccines involved rapidly expire, or (in the case of mRNA vaccines) require ultra cold chain for delivery. While we will see evidence that delivery capacity has rapidly ramped up in most high- and middle-income countries, the potential scale of the delivery challenge in low-income countries is less clear.

2.5 Demand

Pockets of opposition to vaccination are a longstanding phenomenon. The UK repealed a smallpox vaccination law in 1946 because nearly half of parents in many areas were claiming conscientious exemptions.²⁴ Vaccine hesitancy remained widespread in the 21st century, worsened by social media disinformation campaigns,²⁵ and global polling suggested 13 percent of those surveyed worried that vaccines were unsafe.²⁶ On top of those who are concerned about vaccine safety there are many who are insufficiently concerned by the related infectious risk to be motivated to get vaccinated.

Both hesitancy and disinterest have been major concerns with Covid-19 as well. In March-August 2021, pharmacies and states in the US threw away more than 15.1 million doses of Covid-19 vaccines due to lower-than-expected demand for vaccination.²⁷ Surveys in Ghana and Ethiopia show 50 percent of healthcare workers intended not to get Covid-19 vaccines.²⁸

Strategies to address low demand include communications campaigns, provider education, incentives programs, in-kind gifts or vouchers, lotteries, and social media campaigns, although the record of impact (including with Covid-19 vaccinations) is mixed.²⁹ The further step of mandatory vaccination has often proven more successful.³⁰

The first laws making smallpox vaccination compulsory were passed within a few years of Jenner’s experiments—by Massachusetts in 1809, Denmark in 1810, Russia in 1812 and Sweden in 1816 (we will see evidence of the dramatic decline of smallpox in both Sweden and Denmark after compulsory vaccination in the next section). Mandates spread, especially in connection with compulsory schooling. But a 1963 survey of state laws in the US found that only 18 mandated smallpox vaccination to attend schools, 11 included diphtheria, 10 polio, 7 tetanus, and 5 pertussis. By 1970, 20 states also required measles vaccination (and by 1983 all 50 states did).³¹ A 2019 survey of 141 countries worldwide suggested 89 countries had mandatory childhood vaccination policies for all children and an additional 20 mandated vaccination for school entry, and these policies are associated with higher vaccination rates.³²

Regarding Covid-19, mandatory vaccination to date has been limited to certain groups (such as large employers, the military and government workers) or activities (such as visiting bars or restaurants) in areas where supply and cost are no longer a constraint. But there is some evidence that even partial mandates have increased vaccination rates.³³

2.6 Cost and financing

While vaccines tend to be amongst the most cost-effective health interventions, thanks both to rising prices per vaccine and a rising number of vaccinations in childhood immunization schedules, the cost of a full course of vaccinations has been climbing. A US study estimated that the cost of vaccine purchase per child increased from \$10 in 1975 to \$385 in 2001 in real terms, although most of that increase was due to the addition of new vaccines to the standard schedule.³⁴ More recent data from UNICEF suggests price increase running ahead of inflation for many basic vaccines over the past two decades.³⁵

Other related costs have trended in the opposite direction: the price of a syringe was approximately \$50 in 1900, that fell to \$10 by 1950 and by 2000 a mass-produced single-use plastic syringe cost about 1.5 cents.³⁶ In 1965, the bifurcated needle dramatically reduced the costs of administering smallpox vaccines.³⁷ Looking at the costs associated with the delivery network, while many of these are fixed, the incremental cost per dose (excluding vaccine cost)

to deliver single, newly introduced vaccines at health facilities ranged from \$0.48 to \$1.38 in surveyed low and middle income countries.³⁸

Overall expenses including vaccines, staff, and physical infrastructure, mean that it costs approximately \$40 per infant for the standard course of infant immunizations in low- and middle-income countries. Absent government subsidy or provision, this will lead to inequitable access, but governments themselves can face financial challenges: compared to this \$40 per infant cost, per capita domestic general government health expenditure in low-income countries is \$7 per year.³⁹

The costs of adding free Covid-19 vaccines and vaccination are daunting; in 25 of 54 sub-Saharan African countries, the per capita costs of Covid-19 immunization alone exceed annual per capita public spending on health, sometimes by multiple orders of magnitude.⁴⁰ In such circumstances, doubts regarding the capacity to benefit and the cost-effectiveness of a new vaccine versus other potential uses of scarce public budgets play a role.⁴¹

In part because of the costs of vaccination combined with the spillover benefits of high vaccination rates, international organizations play an increasingly important role in ensuring global availability of vaccines. The WHO smallpox eradication program began in 1959⁴² and ramped up in earnest in 1965, when the US began financial backing for the initiative. This spurred the inception of the Intensified Smallpox Eradication Program in 1967, which succeeded a decade later.

Following on from that victory, in 1974, the World Health Organization established the Expanded Program on Immunization (EPI) and, in 1977, it set the goal to make immunization against diphtheria, pertussis, tetanus, poliomyelitis, measles and tuberculosis available to every child in the world by 1990.⁴³

Gavi, the Vaccine Alliance, was established in 1999 as a public and private partnership to finance and procure vaccines for developing countries and by 2013, 73 countries received support from Gavi for a selection of new and underutilized vaccines.⁴⁴

With regard to Covid-19, the COVAX initiative, set up in the early months of the pandemic, was designed to ensure global access to at least enough vaccines to immunize 20 percent of participant country populations. This target was recently revised to support countries in reaching their vaccination ambitions in the light of the global vaccination target of 70 percent.⁴⁵ A number of donor countries are providing financing and vaccine doses, but we will see that (to date) this combined support has been very much inadequate to ensure the

same level of equitable access that the world has achieved over a period of 50 years with regard to childhood immunizations.

3 Historical Global Vaccination Efforts and Covid-19

3.1 Smallpox

The smallpox vaccine was both the first to be invented and unique in being discovered prior to the causal pathogen. Jenner's discovery is also unique in being the only vaccine (so far) to help drive a human illness to global eradication, despite never approaching ubiquitous global population coverage.

Sweden and Denmark saw the earliest truly mass vaccination campaigns in response to Jenner's invention. In Denmark's capital Copenhagen, the death rate from smallpox was reported as zero in the ten years after vaccination was mandated in 1810, suggesting widespread adherence as deaths were closer to 5 per 1,000 population in the 1790s.⁴⁶ In Sweden, vaccinations given as a percentage of infants born was 40 percent in the years 1804 to 1805, reaching 70 percent in the four years after vaccination was made compulsory in 1816. Again, reported smallpox mortality dropped dramatically.⁴⁷

But in most countries, access to and rollout of the vaccine took far longer. In the UK only 25 percent of newborns were vaccinated by 1820, the procedure was only made free in 1840 and then compulsory in 1853 (even then, penalties for non-compliance were only introduced in 1867). UK smallpox mortality did decline over the first half of the Nineteenth Century, but at a far slower rate than in Denmark and Sweden.⁴⁸

Haphazard efforts to provide smallpox vaccination and spread its use worldwide began with the Spanish royal expedition of 1803 which shipped orphan children around the world to be infected with cowpox two a turn, thus ensuring a fresh supply of vaccine material could be delivered to South and Central America, Manila, Macau and Canton. But it took until 1849 for the first vaccination material to reach Japan, for example.⁴⁹ In Mozambique, attempts to import seed vaccines from Goa and Lisbon only succeeded at the end of the nineteenth century, almost 100 years after Jenner's discovery.⁵⁰

In terms of population coverage, in late-nineteenth Century India coverage was extensive enough to lead to significantly reduced death rates from the disease.⁵¹ French West Africa

saw systematic vaccination efforts begin in 1905 and vaccination was made mandatory in the British colony of the Gold Coast in 1920. The number of smallpox vaccinations given each year in East, West and Central Africa climbed from about six million to 26 million 1929-55.⁵² Estimated annual vaccination rates against smallpox climbed as high as one vaccination for every four inhabitants of French West Africa each year by 1951. Sadly, continuing or even rising rates of smallpox suggests repeat vaccination (and substandard vaccination material and practices) must have been very high.⁵³

Efforts to reach ubiquitous rates of vaccine coverage continued in the post-independence period. By the time the WHO declared a global goal of eradication in 1966, perhaps 110 countries had eliminated smallpox and more saw very low death rates,⁵⁴ largely through a strategy of sufficiently consistent (but far from universal) vaccination. For example, the last case of variola major in South America occurred in 1962 and the last case of variola minor in 1971.⁵⁵ Two years before the last smallpox case in the region, estimates for smallpox coverage in Brazil in 1969 was 50 percent, for Bolivia 81 percent and Colombia 64 percent.⁵⁶

The WHO's initial aim was to accelerate progress toward global eradication through mass vaccination campaigns in countries where smallpox was still endemic. But vaccination networks were not sufficiently developed to allow for universal rollout. India's National Smallpox Eradication Program between 1962 and 1964 had the objective of successfully vaccinating the entire population in three years, but only raised the rate from about 60 percent prior to the campaign to an estimated 68 percent at its end.⁵⁷ Five years later the effort was abandoned, and the strategy reformulated to surveillance and ring vaccination.⁵⁸ Smallpox vaccination rates in West and Central Africa climbed from 20 to 60 percent between January 1968 and March 1969 as part of a concerted effort toward eradication, but as in India, eradication was only finally achieved through adopting a surveillance and ring vaccination approach in place of efforts to reach (close to) universal vaccination.⁵⁹

Elsewhere, smallpox vaccination rates were already declining, in part thanks to the fact that decades of reasonably high coverage had pushed the infection towards elimination. Infant smallpox vaccination rates in England and Wales fell from 42 percent in 1951 to 32 percent in 1964, for example.⁶⁰ All of this suggests global smallpox vaccination rates never approached the levels of some more recent immunization programs including that against measles.

The world was lucky with the smallpox vaccine: a naturally occurring immunization was readily available and discovered by association, not through any significant scientific understanding of the microbe, the immune process or methods including attenuation. The vaccine

was safe and (if delivered properly) highly effective. But it still took about a century before vaccination was practiced globally, and decades longer before every country was on the path towards sufficient vaccination to turn smallpox into a minor health threat. The world was lucky again, however: it did not take very high, long-sustained vaccination rates to eliminate smallpox in most countries and the microbe (which produces obvious symptoms very rapidly after infection) was well-suited to a surveillance and ring vaccination response. In addition, there was no animal reservoir for smallpox to reinfect populations. Combined, that meant smallpox could be eradicated even absent anything close to universal vaccination coverage.

The world has not had that combination of luck with other major infectious threats, and that is why advances in both microbial and vaccine research alongside ubiquitous access to vaccines and vaccination infrastructure to ensure high levels of protection even absent elimination and eradication has proven so important to global health.

3.2 Routine Childhood Vaccination

A range of vaccines were developed in the first half of the Twentieth Century against diseases including pertussis, tetanus, childhood TB, influenza, and yellow fever. But mass vaccination for those diseases was limited in that period. Even in the world's wealthiest countries, attempts to vaccinate all children as a matter of course largely had to wait until the 1950s or later.

Diphtheria vaccination was offered free to all British children starting 1940. Uptake was widespread enough that the case load fell from over 46,000 in 1940 to 962 in 1950. By 1951, 74 percent of children in England and Wales were vaccinated against diphtheria, but the 1964 infant vaccination rate for England and Wales fell to 72 percent as the perceived threat receded.⁶¹ Slow progress was replicated elsewhere: in the Netherlands, childhood vaccination against diphtheria, pertussis, and tetanus was introduced in 1953, but only exceeded 80 percent of the target population ten years later.⁶²

US immunization rates amongst preschool children had reached near 80 percent for diphtheria, tetanus, and pertussis by 1970 (and 60 percent for measles in the same year). They stalled or declined for decades after that point and only reached 90 percent in the mid-1990s.⁶³ For the year 1978, the US reported that only 72 percent of children under age two had completed their course of DPT shots and 44 percent their measles shots, suggesting many parents were waiting until children were close to school-age to get them vaccinated.⁶⁴

The gap between vaccine development and widespread rollout in rich countries was shorter for the polio vaccine, which responded to what was seen as a more urgent threat. Still, in the US, rollout after the vaccine was licensed in April 1955 was significantly hampered by the lack of a federal government plan for distribution and the ‘Cutter Incident,’ in which live polio was included in vaccines sufficient to cause eleven deaths and hundreds of cases of paralysis. By August, three months after licensure, four million doses had been administered, enough to immunize about 10 percent of U.S. children under the age of 12.⁶⁵ By 1957, a third of the population under 40 had received the recommended three doses of the Salk vaccines,⁶⁶ and by 1961 (six years after introduction), 54 percent of the population had received three doses of the vaccine.⁶⁷

In the UK, polio vaccination began in 1956, but by the end of June 1960, only 77 per cent of children had been fully vaccinated with IPV, along with half in the 16–26 age category. By 1964, England and Wales saw a childhood vaccination rate of only 65 percent.⁶⁸ Routine childhood polio vaccination in the Netherlands was introduced in 1957. It took six years to get to 80 percent coverage.⁶⁹

In poorer countries and colonies, there were sporadic attempts to introduce broader vaccination programs in the post-war period. For example, yellow fever and BCG vaccination programs began in post-war French colonial Africa.⁷⁰ In West Africa (at least), the smallpox eradication campaign also rolled out measles vaccination, but sadly the effort does not appear to have been sustained, leading to declining measles vaccine coverage rates. Out of 18 West African countries for which we have data on 1968 measles vaccination rates, the average rate for the population was 12 percent. India set the goal of extending BCG vaccination to almost all schools in the country in 1949 and in 1951 it created a plan to complete that goal within seven years.⁷¹ It is worth noting that even at the end of that decade, in 1960, only about half of primary-school age children were in school, and the low rate of BCG vaccination in India more recently (4 percent in 1981) suggests the program fell apart.⁷²

As in the US and Europe, the polio vaccine was seen as worthy of urgency and covered a large part of the infant population of developing countries at a rapid rate.⁷³ Cuba’s mass polio vaccination campaign of 1962 covered 88 percent of the population 14 and under in one year, for example.⁷⁴

Widespread and sustained progress on the range of childhood vaccinations only followed the WHO’s Expanded Program of Immunization (EPI), and it still took considerable time to build up the infrastructure and finance to deliver on that goal. India joined EPI in 1978 with

the introduction of BCG, OPV, DPT and typhoid-paratyphoid vaccines, for example, but with a vaccination infrastructure centered around major hospitals and largely restricted to the urban areas.⁷⁵ The 1980s saw a rapid rollout of global immunization infrastructure that (finally) put in place the capacity to ensure the considerable majority of the world’s children received a (lengthening) course of recommended vaccines. And the period since 2000 has seen considerable progress in ensuring high rates of vaccination even in many of the world’s poorest countries, in part thanks to international support through the Gavi partnership.

3.3 Influenza: A Yearly Vaccine, for some

To minimize mortality in high prevalence countries, combatting influenza (like Covid-19) requires vaccinating as many people as possible against a disease that largely kills the old. While research on a universal flu vaccine is ongoing, in countries with seasonal circulation of influenza, yearly vaccination is recommended for vulnerable populations against the dominant circulating strains.⁷⁶ Annual flu vaccination for lower-priority groups may not be a cost-effective intervention in many countries. But despite estimates of yearly global mortality from influenza of 250,000 to 500,000 people, there were no reported doses of flu vaccine distributed in 52 out of 199 countries in either 2008 or 2013, and in 2013, only 21 out of 196 countries saw distribution higher than 159 doses per 1000 population (estimated as the number of doses required to vaccinate the priority group of those aged 65 years or older in industrialized nations in 2008). At a global total of below 500 million, the annual influenza vaccination effort is the world’s largest regular vaccination program—and yet still only reached about seven percent of the global population, significantly concentrated in richer countries, in 2013.⁷⁷ While we have seen that more recent survey evidence suggests the capacity to produce vaccines sufficient for about 25 percent of the world’s population against a pandemic flu outbreak in the first year, this still suggests the historically unprecedented scale of the pandemic vaccination effort against Covid-19.

3.4 Covid-19

In early January 2021, the world was vaccinating around one million people with a Covid vaccine dose each day. By the end of June this climbed above 40 million. Since then the vaccination rate has plateaued to around 30 to 40 million doses a day.⁷⁸ Still, this performance means that by the end of 2021, the first year of (significant) vaccine rollout, approximately

8.47 billion Covid-19 vaccine doses had been administered worldwide. This was sufficient to fully vaccinate (prior to boosters) 47 percent of the world.

At the same time, the rollout of Covid-19 vaccines has been inequitable. As of mid-October, almost every country in the world had contracted or had been promised donations equivalent to 40 percent or more of their population.⁷⁹ Yet 66 low- and middle-income countries did not reach 40 percent coverage by the end of 2021, while 16 high- and upper middle-income countries reached above 75 percent coverage.⁸⁰ The COVAX mechanism failed in its early hopes of rapidly delivering large numbers of vaccines to poor countries. Against a goal of 2 billion doses delivered by the end of 2021, COVAX had delivered 767 million (rising to one billion on January 15th).⁸¹ In 2021, wealthy countries and countries home to Covid-19 vaccine manufacturing capacity (India, China) prioritized widespread vaccination at home over sharing doses for priority groups globally and enforced that preference through de facto or de jure export bans. This left COVAX reliant on donations of excess vaccines for much of 2021. And while donors had pledged to donate 785 million doses to COVAX as of September 24th 2021, only 18 percent had arrived by that date.⁸²

4 Data and Analysis

To assess and compare the speed of vaccine development and deployment over time and put Covid-19 vaccination in that context, we collect data on disease age, microbe recognition and vaccine development from the sources listed in the notes to Table 4.1. It is important to note that the first vaccines developed are not in many (most) cases the vaccines used today and early vaccines may have had lower efficacy and or higher risks than those that were subsequently used in mass campaigns.

4.1 Data

For vaccination coverage, we take data from the WHO/UNICEF database.⁸³ We add data from several additional sources:

- For Yellow Fever, we take Shearer et. al.’s untargeted unbiased estimates of vaccination coverage.⁸⁴ As Shearer’s data comes in a subnational format, we aggregate the data to a country level by using a weighted average by 2016 population levels (provided in

Shearer’s dataset). For global coverage estimates, we are interested only in countries where WHO suggests Yellow Fever transmission is a risk.

- For HPV, we take Global Cancer Observatory data on vaccinations.⁸⁵
- For influenza, we use the OECD data on vaccination rates.⁸⁶
- We use PAHO data for some PAHO countries covering WHO expanded program of immunization vaccines for 1978.⁸⁷
- For Covid-19 we use Our World In Data.⁸⁸

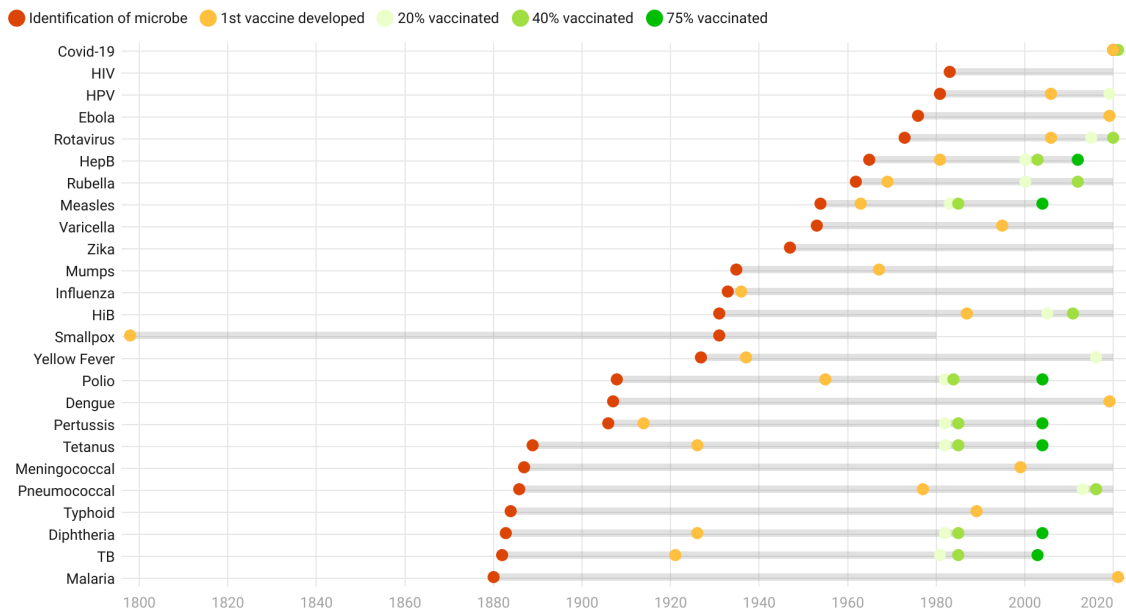
Throughout this paper, we restrict our attention to countries where the WHO has positive vaccine coverage in 2020. Where there is missing data in prior years, we follow WHO in assuming missing data is zero for the purposes of aggregation⁸⁹ but an analysis of the first years of data for vaccine coverage suggests this is an over simple assumption. Across 2,162 country-vaccine observations, there were 1,395 cases (64.5 percent) where the first year of coverage was listed as 40 percent or more. This suggests that vaccination coverage is higher than presented in our aggregate data, in particular for early periods where fewer countries report data. In turn, this suggests growth rates suggested by the data probably over-estimate the real rate of progress. See Appendix Figure A1 for more details on data availability.

Data on vaccine coverage based on government-generated administrative systems is imperfect, with errors including: reporting on doses purchased or shipped rather than people actually vaccinated; reporting doses delivered to people outside of target population groups; under-reporting of doses provided by private clinics; inaccurate target population estimates; and (potentially) incentives to report vaccinations beyond those delivered. WHO and UNICEF attempt to account for such errors cross-checking with survey evidence and local officials to create their final estimates.⁹⁰

Table 4.1: Milestones in Vaccine-Preventable Disease⁹¹

Infection	Emergence as significant human threat	ID of microbe	1st Vaccine	Target population for (recent) vaccination campaigns (infant/all/region)
Smallpox	Ancient (modern form ⁹² 16 th CE?)	1931 ⁹³	1798 ⁹⁴	All
Pertussis	Ancient ⁹⁵	1906	1914 ⁹⁶	2–23 months, 4–7 years, and 9–15 years
TB/BCG ⁹⁷	Ancient	1882	1921	Newborns
Diphtheria ⁹⁸	Ancient?	1883	1926	2–23 months, 4–7 years, and 9–15 years
Tetanus	Ancient ⁹⁹	1889	1926	12–23 months, 4–7 years, 9–15 years ¹⁰⁰
Influenza ¹⁰¹	Ancient?	1933	1936 ¹⁰²	All (elderly a priority)
Yellow Fever ¹⁰³	700 CE?	1927	1937 ¹⁰⁴	9–12 months in endemic areas ¹⁰⁵
Polio	Ancient ¹⁰⁶	1908	1955	<1.5 years
Measles	5 th C BCE? ¹⁰⁷	1954 ¹⁰⁸	1963	6 months - 12 years ¹⁰⁹
Mumps ¹¹⁰	Ancient	1935	1967	12-18 months, 2-6 years ¹¹¹
Rubella ¹¹²	19 th C CE? ¹¹³	1962	1969	9-12 months, women of childbearing age ¹¹⁴
Pneumococcal ¹¹⁵	Ancient ¹¹⁶	1886	1977	children < 5 years old ¹¹⁷
Hepatitis B	Ancient ¹¹⁸	1965	1981	newborns ¹¹⁹
HiB		1931 ¹²⁰	1987 ¹²¹	children < 5 years old ¹²²
Typhoid	Ancient ¹²³	1884	1989 ¹²⁴	children and adults > 2 years ¹²⁵
Chickenpox	Ancient ¹²⁶	1953	1995	(not widely recommended)
Meningococcal disease ¹²⁷	19 th C CE?	1887	1999 ¹²⁸	1–29 years, 3–24 months ¹²⁹
Rotavirus	Ancient? ¹³⁰	1973	2006	<3 years old ¹³¹
HPV	Ancient ¹³²	1981	2006	9–14 years ¹³³
Ebola	1970s? ¹³⁴	1976	2019	children and adults in high-risk environments ¹³⁵
Dengue	1700? ¹³⁶	1907	2019 ¹³⁷	< 1 year old ¹³⁸
Covid-19	2019	2020	2020	all >2 years (varies by vaccine type) ¹³⁹
Malaria	Ancient ¹⁴⁰	1880	2021 ¹⁴¹	5-17 months in pilots ¹⁴²
Zika ¹⁴³	2007	1947	None	None
HIV	~1900-1920 ¹⁴⁴	1983	None	None

Figure 1: The time from microbe identification to widespread vaccination has continued to shorten

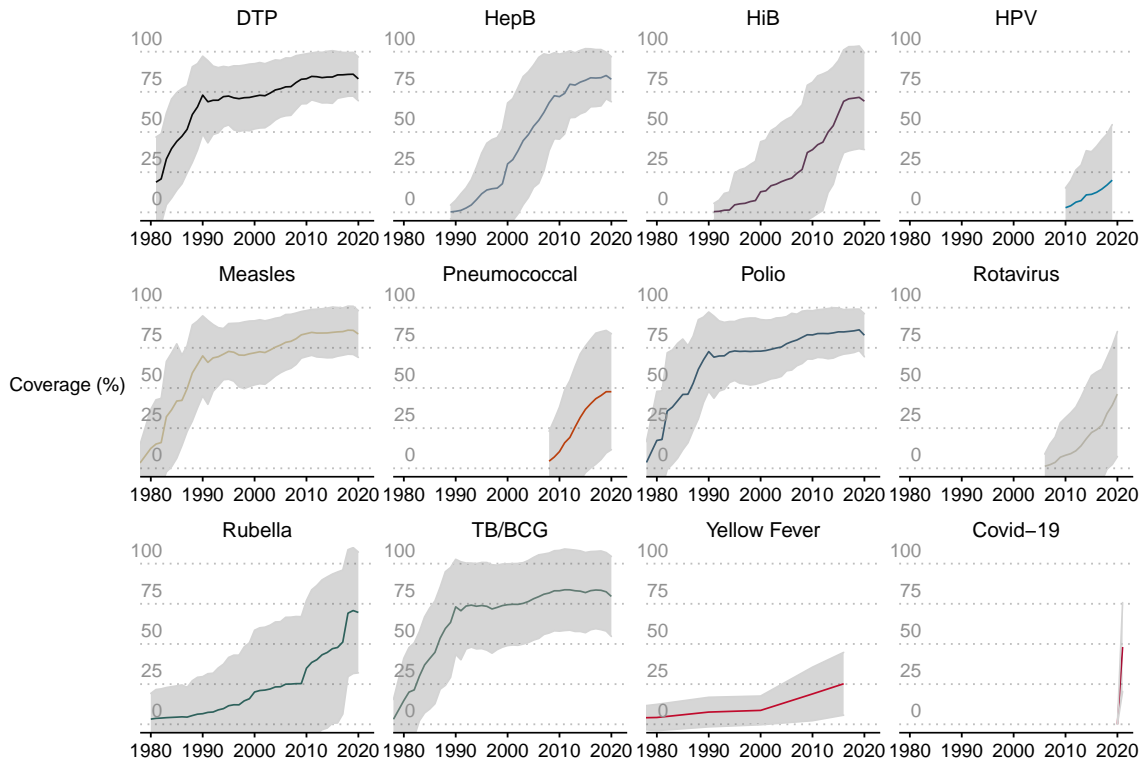


NOTE—Smallpox was the only disease for which a vaccine was developed prior to identification of the microbe (it was also eradicated in 1980, prior to good data on global vaccine coverage).

4.2 Analysis

Figure 1 illustrates (up to) four milestones for the infectious diseases listed in Table 4.1: the date of the identification of the causative microbe, the date the first vaccine was developed (licensed for later vaccines), and the date when we estimate 20 percent, 40 percent and 75 percent of the global target population was (first) vaccinated. Smallpox is unique in that the microbe was identified after the vaccine was developed, for some of the infections there is no vaccine (for example HIV) and for many more infections global coverage is yet to reach one or more of the milestones. For infections with vaccines, excluding smallpox and Covid-19, the average period between microbe isolation and vaccine development was 48 years. For vaccines that have reached a given milestone, the average time between vaccine development and 20 percent global coverage was 36 years, 40 percent coverage was 42 years and 75 percent coverage 53 years. For Covid-19 the period between microbe isolation and vaccine development was less than a year, between vaccine development and 20 percent coverage was just under 8 months, and between 20 percent coverage and 40 percent coverage was an additional 3 months. It is also worth emphasizing that the reference target group for most of the vaccines in the table is children whereas for Covid-19 it is the total population.¹⁴⁵

Figure 2: Global Vaccination Progress



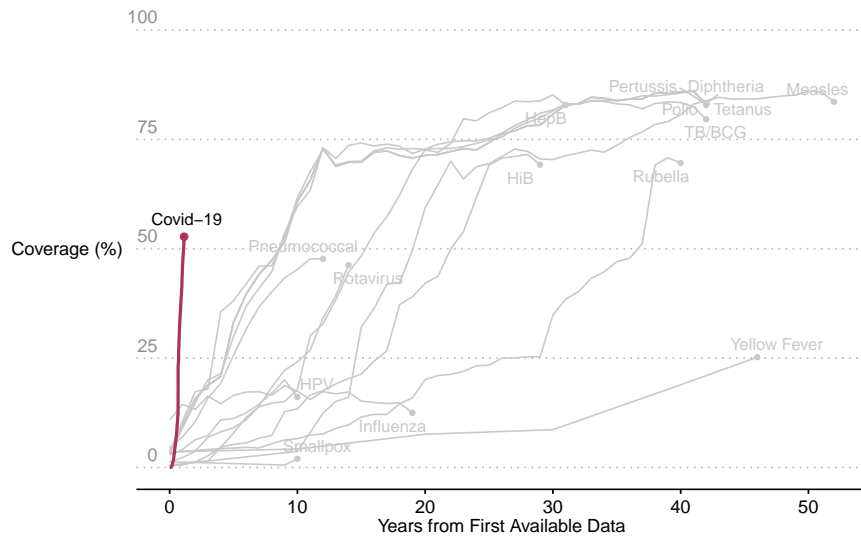
NOTE—Yellow fever is only plotted for the countries where Yellow Fever is deemed endemic in 2021. Shaded regions indicate ± 1 standard deviation across all countries. 2021 data excluded for non-Covid-19 diseases. 2020 data excluded from HPV and Influenza because of data limitations.

Figure 2 tracks the global average and variation in vaccine coverage for 14 vaccine preventable infections. It suggests the huge global progress on extending basic immunization in the 1980s, as well as the introduction of more recent vaccines and their spread to ubiquity. It is notable how there is still variation in vaccine rates even for old (and cheap) vaccines, something discussed at greater length below. It is also notable that it has usually been a two-decade or longer process to extend vaccine access past the 75 percent coverage level even in the recent past.

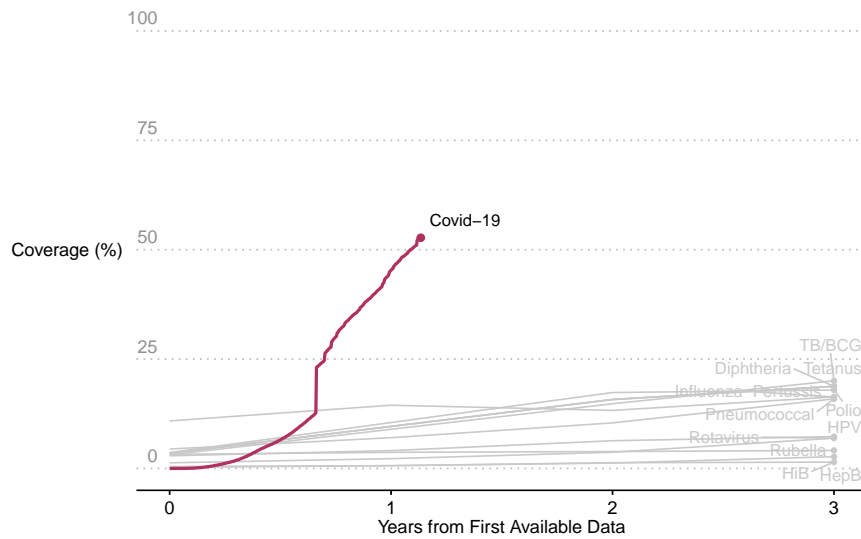
Figure 3a looks at Covid-19 rollout in the historical perspective of other vaccines. Figure 3b focuses on the first three years of available vaccine rollout data for each vaccine. Covid-19 vaccination is marked out in red and limited to one year's worth of data, but it is evident that the Covid-19 vaccination campaign, while short-lived, is the fastest campaign for which we have available data, achieving more widespread global rollout in one year than any comparator vaccination rollout did in three.

Figure 3: Covid has been the most rapid global vaccine rollout in history

(a) All Available Data

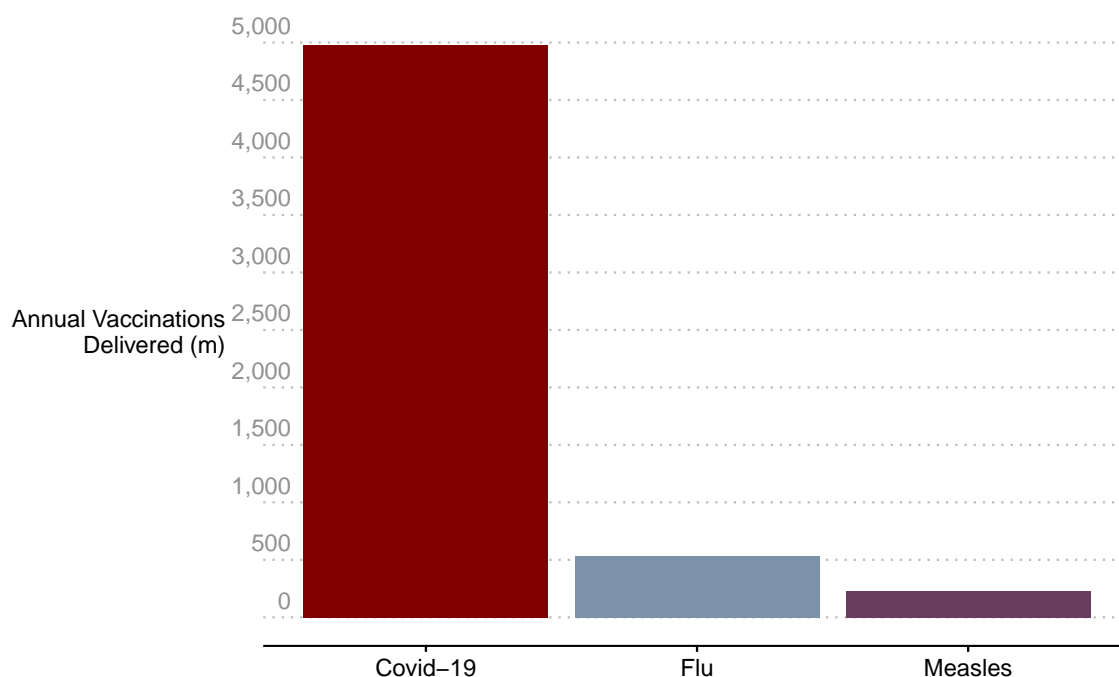


(b) The first three years



NOTE—Discontinuous jump of Covid-19 vaccinations is due to irregular reporting of Chinese vaccination figures. 2020 flu data is excluded due to low country-coverage.

Figure 4: Annual vaccinations delivered during Covid-19 pandemic is greater than that of flu and measles



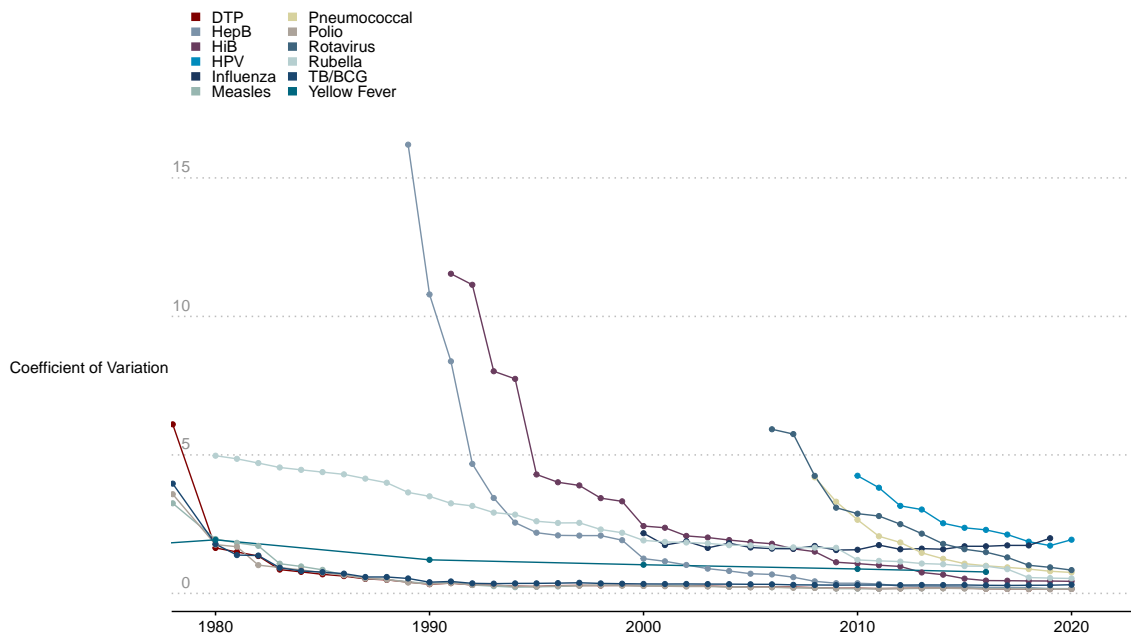
NOTE—Measles vaccinations delivered are derived by taking 2019 MCV1 coverage and multiplying by population. Covid-19 annual vaccinations delivered are derived by taking the total Covid-19 doses delivered as of this publication and dividing by two.

Figure 4 illustrates the annual average number of vaccines delivered against Covid-19 worldwide compared to the number of flu vaccines delivered in 2019 and the number of one-year-old infants who received a measles vaccination in 2019. As can be seen, the number of Covid-19 vaccinations delivered is 9.4 times that of flu and 22 times the that of the first measles vaccine.

Figure 5 plots the weighted coefficient of variation of vaccine rates across countries over time (the weighted standard deviation divided by the weighted mean). This is a measure of convergence in access to vaccines, with lower values suggesting more equitable access. Between 2000 and 2020, the weighted coefficient for HiB fell from 2.43 to 0.435. For measles, it fell from 0.28 to 0.17. For Covid-19 vaccination, the most recent coefficient of variation as of this publishing was 0.57, still significantly above many other vaccines, but rapidly declining.

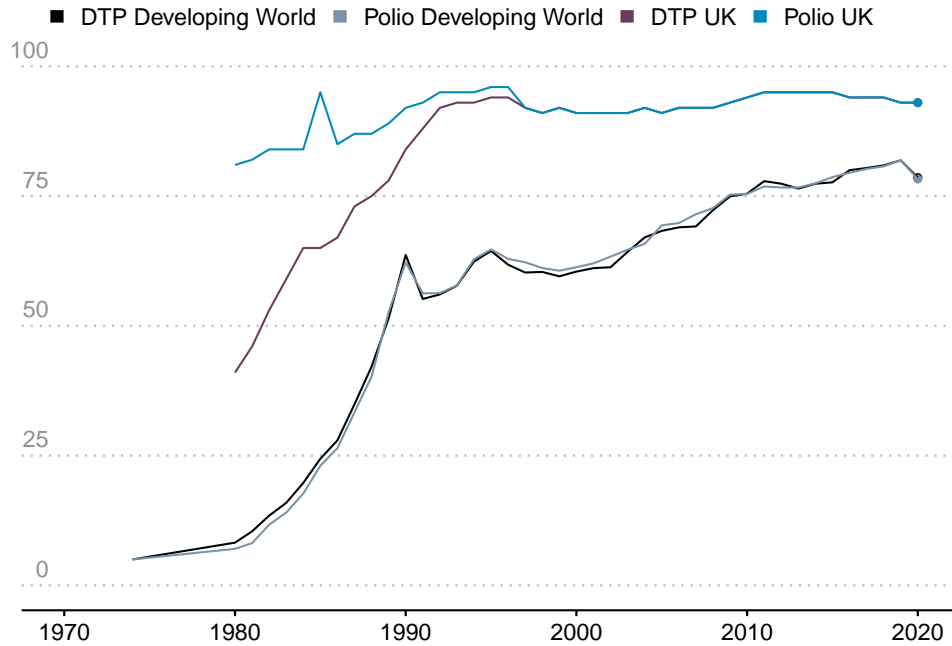
The overall picture regarding progress toward routine childhood immunization in high versus low and middle income countries is suggested by Figure 6. Despite vaccine availability since

Figure 5: Coefficient of variation shows convergence in global vaccine access



NOTE—Values are weighted by vaccine target population. HPV target population set as females ≤ 15 years old. Yellow fever target population set as all people ≤ 60 years old. For all other diseases, target population was set at those ≤ 1 year old. Data on flu is excluded for 2020, due to low data availability (see Appendix Figure A1).

Figure 6: Comparing the UK with the Developing World in DTP and Polio Vaccination

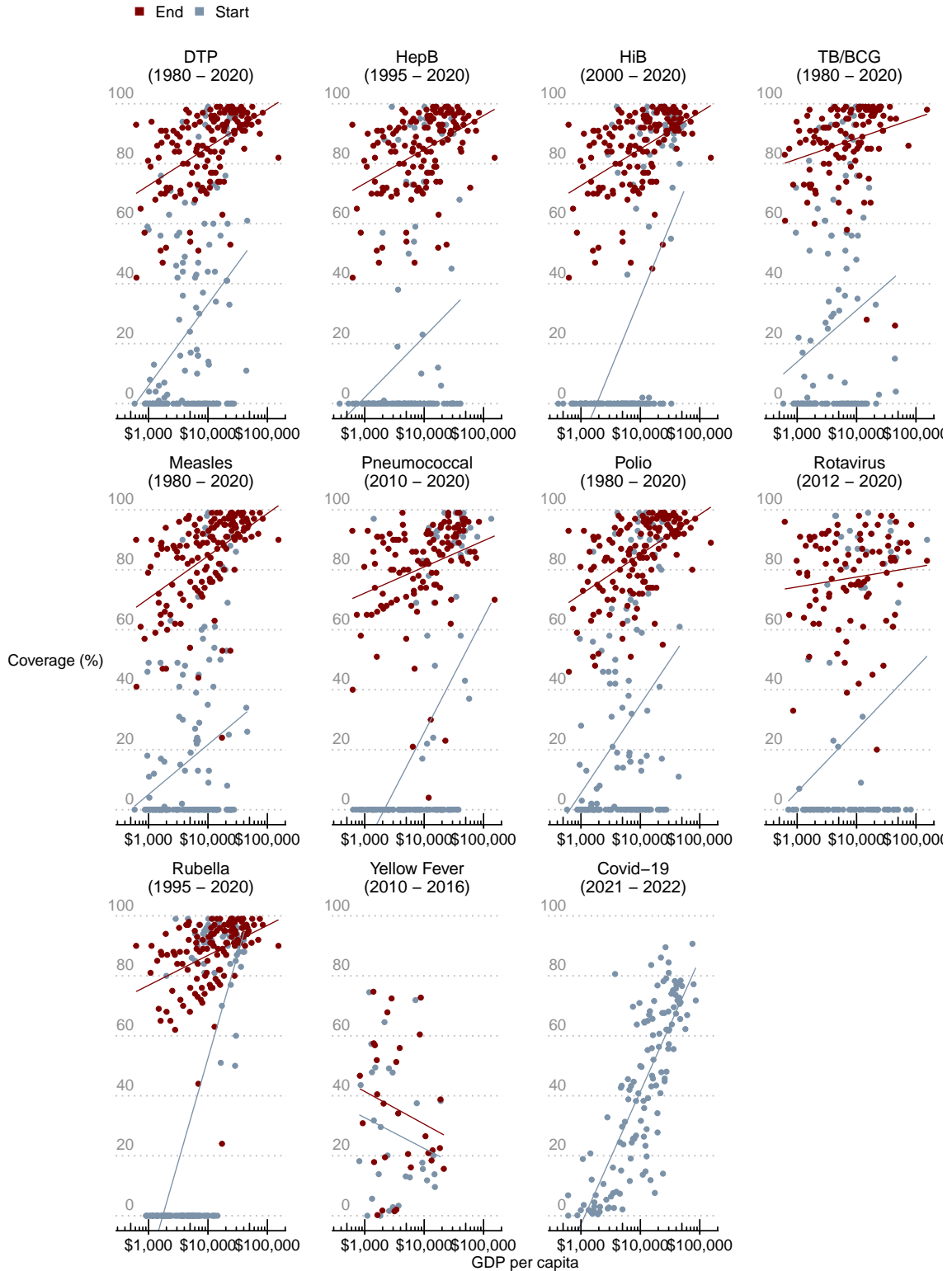


1948 for DTP¹⁴⁶ and 1955 for polio, in 1964, England and Wales saw a childhood vaccination rate of only 65 percent for polio and 72 percent for diphtheria. As late as 1980, full DTP coverage was below 50 percent. Progress was even slower in the developing world: in 1974 it is estimated that fewer than 5 percent of children in developing countries were receiving a third dose of DTP and poliomyelitis vaccines in their first year of life.¹⁴⁷ The 1980s saw the start of global progress toward ubiquitous childhood immunization coverage, however. In low and middle income countries DTP vaccination rates were 12.7 percent in 1980 and 78 percent in 2015. For polio, the rates were 10.7 percent in 1980 and 79 percent in 2015.

As suggested by the pattern of DTP, the relationship between country income and vaccination rates has flattened over time: poorer countries have dramatically caught up. This is shown in Figure 7 which plots the relationship between income and vaccination rates at two periods for each infection: the first year with data available for ten or more countries and the most recent available year of data. It suggests (except for yellow fever) poor countries still see lower immunization rates than the rich world but the gap in vaccination rates between the two has dramatically reduced over time. For example, the predicted measles vaccination rate for a country at \$1,000 GDP per capita in 1980 was 11 percent compared to 18 percent for countries at a GDP per capita of \$10,000. By 2020, the predicted vaccination rate was 80 percent at \$1,000 and 82 percent at \$10,000.

Note that, at the end of 2021, Covid-19 vaccination rates still suggested a very strong relationship with income, with a slope similar to HiB in 2000 . That said, the HiB vaccine was released in 1987, 13 years prior to that.

Figure 7: Preston curves show convergence between countries in vaccination rates



NOTE—Yellow fever is only plotted for the countries where Yellow Fever is deemed endemic in 2021 per the WHO. Start year was determined based on the year where there were more than 10 countries with non-zero data and greater than 10 percent estimated global coverage. The sample of countries for each disease is the same in the end year and the start year.

Figure 8 looks at rollout across income groups. High Income Countries (HICs) are those 47 economies worldwide with an income above \$12,695 in 2021, collectively home to 1070 million people.¹⁴⁸ The 49 upper middle-income countries (UMICs) had an income per capita of \$4,096 – \$12,695 and are home to 2920 million people. The 46 lower middle-income countries (LMICs) had an income per capita of \$1,046 – \$4,095 and are home to 2910 million people. There are 26 low-income countries (LICs) with incomes below \$1,046, collectively home to 672 million people. To take an example from the figure, HICs saw 20 percent of their target populations vaccinated against measles in 1980, for upper middle-income countries this took an additional 3 years, for lower middle-income countries 6 years and for low-income countries 5 years. For Covid-19 HICs, UMICs, and LMICs reached the 20 percent threshold separated by months, not years. Note that LICs have yet to reach the 20 percent threshold.

Figure 9 uses the same approach as Figure 3a and Figure 3b, but dividing countries by income group. For high- and middle-income countries, it is clear that Covid-19 rollout has been the fastest for the vaccines and periods for which we have cross-country data (and the analysis in previous sections suggests this almost certainly means the fastest ever). Note the story is less positive for low-income countries where first year rollout to the total population lags the speed of rollout to target age groups for the vaccination efforts for BCG and DPT.

Two significant caveats are required: first, the efficacy of vaccines varies considerably, and many of the doses delivered in middle income countries are of vaccines that provided lower protection against infection and serious illness. Second, the Omicron wave has demonstrated the importance of booster shots, and progress in delivering those shots lags. The WHO does not recommend boosters as standard, and given that third doses were only proposed recently for those who had already been vaccinated some time, it is unsurprising that the population that has received three vaccine doses is lower in every country, but the levels also reflect overall disparities in vaccine access. As of this publishing, boosted coverage is 33.6 percent in high income countries, 19.1 percent in UMICs, 1.4 percent in LMICs and 0.1 percent in LICs.

Figure 8: Change in coverage across income groups

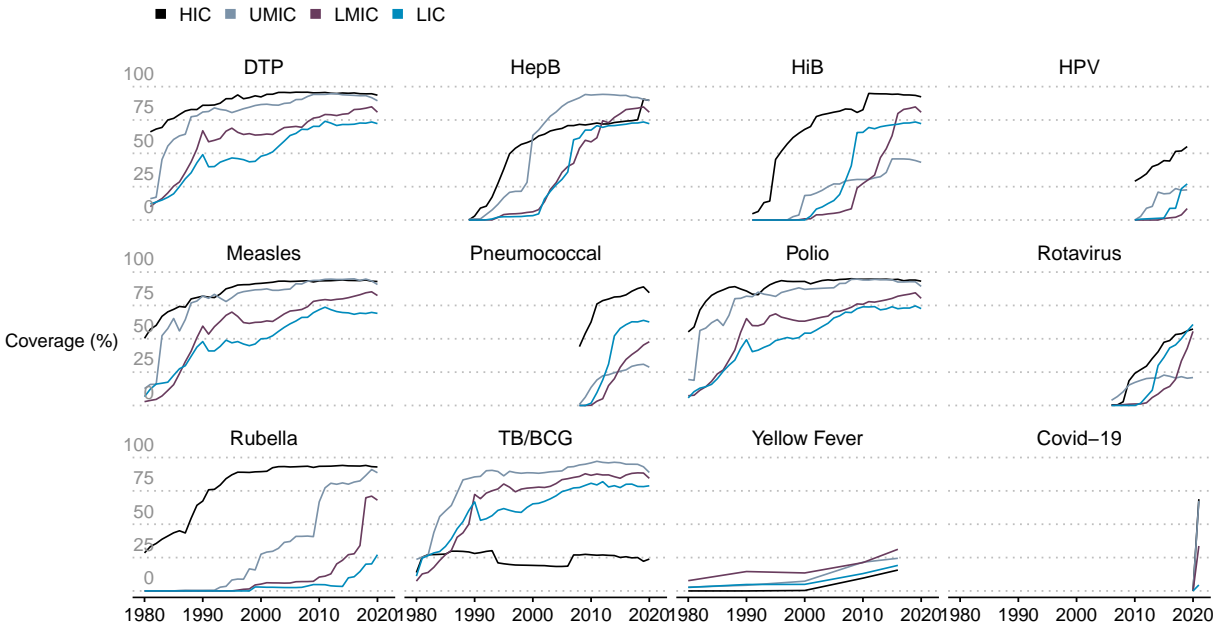
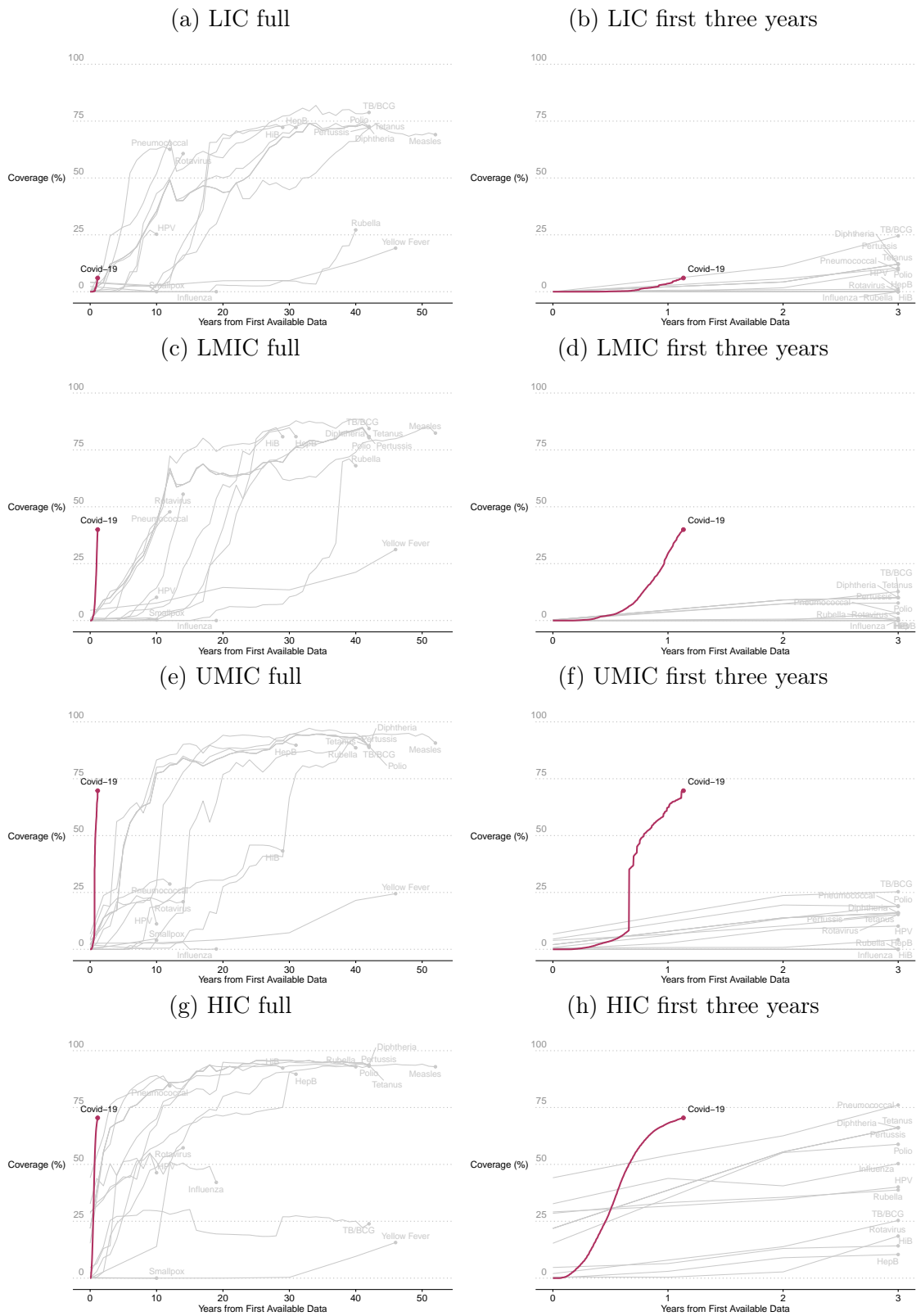


Figure 9: Fully vaccinated rollout across income groups



NOTE—Discontinuous jump of Covid-19 vaccinations is due to irregular reporting of Chinese vaccination figures. 2020 flu data is excluded due to low country-coverage.

5 Conclusion

Smallpox eradication efforts suggested the capacity to vaccinate significant proportions of populations even in some of the world's poorest countries within eighteen months. Since then, we have made significant progress in regularly vaccinating children against deadly diseases. The yearly influenza vaccination program has given some countries experience of repeatedly reaching older individuals. But the global Covid-19 vaccination effort is still (already) unprecedented in scale. Never have we seen such rapid analysis of a pandemic disease and development of a viable vaccine. This has been the fastest rollout of vaccination in high-income and middle-income countries alike. Low-income countries have received vaccines much later than countries at other levels of income, and there may be considerable heterogeneity within lower-income countries in the efficiency of their vaccine delivery.

The goal with Covid-19 vaccination was to counter an emerging global pandemic rather than lower the toll of endemic infections (the historic rationale for most vaccine programs), and that goal demanded rapid, ubiquitous rollout. Supply has not met demand during 2021 and available vaccines have not been equitably distributed between countries at different levels of income, likely at the cost of hundreds of thousands of lives. In terms of judging global performance on vaccine rollout, the morally relevant criterion is 'what did we achieve compared to what we could have achieved.' On that metric, the world—and in particular rich nations—fell tragically short with Covid-19 vaccines. Nonetheless, it is a sign of progress that what we *could have* achieved is so much greater than in the past and that what we *did* achieve is record-breaking in terms of speed and reach despite its shortcomings.

It appears that Covid-19 is likely to become endemic. New variants may also require periodic booster shots to protect against variants. If so, it will place a continuing and considerable additional global burden on vaccination infrastructure that should be upgraded to respond. For 2022, COVAX has an outstanding funding appeal of \$7 billion to respond to these contingencies and to support the delivery of donated doses. These requirements should be met immediately to accelerate the vaccination effort in low-income countries, in addition to supporting countries on delivery. And for the next pandemic, we should ensure the potential to respond is greater still—and that we use more of that potential to build the capacity to surge vaccine manufacturing around the world, thereby assuring a far more equitable and rapid global response, given that the medical reaction to a pandemic should preferably be measured in days, weeks and months rather than years.

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148. Note that we limit to HICs that are captured in the WHO sample.

Appendix

Table A1: Year world achieved a certain percent of vaccination

Disease	20	40	75
Covid-19	2021	2021	
Diphtheria	1982	1985	2004
HepB	2000	2003	2012
HiB	2005	2011	
HPV	2019		
Influenza			
Measles	1983	1985	2004
Pertussis	1982	1985	2004
Pneumococcal	2013	2016	
Polio	1982	1984	2004
Rotavirus	2015	2020	
Rubella	2000	2012	
Smallpox			
TB/BCG	1981	1985	2003
Tetanus	1982	1985	2004
Yellow Fever	2016		

Figure A1: Global vaccination data availability

