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Felix Lobo

SOUTH CENTRE

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Felix Lobo[1]

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[1] Professor Emeritus, Carlos III University of Madrid, Funcas.

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NOTE

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South Centre
International Environment House 2
Chemin de Balexert 7–9
POB 228, 1211 Geneva 19
Switzerland
Tel. (41) 022 791 80 50
south@southcentre.int
www.southcentre.int

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ABSTRACT

The purpose of this report is to analyze the impact that the COVID-19 pandemic has had on the vaccine industry from an international perspective. The objective is to learn from the experience and contribute to the design of better tools for future vaccine development and manufacturing, as we must be prepared for future emerging infectious diseases with the potential for global expansion. This industry makes fundamental contributions to global social welfare, but from a business point of view it is complex and difficult to manage, and from an economic point of view it is an industry that does not fit the paradigm of competitive market efficiency with notorious market failures.

We examine the impact of the pandemic on innovation and the scientific, technological and industrial development of vaccines and find that certain elements of the industry's structure have changed, while others have remained. We also summarize the lessons learned from the deployment of some public policies to boost supply and drive demand, paying particular attention to the inequity in the global distribution of vaccines and to the COVAX program. We conclude that some of the policies have been very effective, while others have not fully achieved their objectives. From the achievements and limitations, lessons can be drawn for the reformulation and expansion of global public policies that would stimulate R&D, manufacturing, distribution and access.

El propósito de este informe es analizar el impacto que la pandemia de la COVID-19 ha tenido en la industria de las vacunas desde una perspectiva internacional. El objetivo es aprender de la experiencia y contribuir al diseño de mejores instrumentos promotores en el futuro de su desarrollo y fabricación, pues debemos estar preparados para futuras enfermedades infecciosas emergentes con potencial de expansión global. Esta industria hace contribuciones fundamentales al bienestar social mundial, pero desde el punto de vista empresarial es un negocio complejo y difícil y desde el de la Economía es una industria que no se ajusta al paradigma de eficiencia del mercado competitivo con notorios fallos del mercado.

Examinamos los grandes efectos de la pandemia sobre la innovación y el desarrollo científico, tecnológico y fabril de vacunas y comprobamos que han cambiado ciertos elementos de la estructura de la industria, mientras que otros han persistido. También resumimos las enseñanzas deducibles del despliegue de algunas políticas públicas de impulso de la oferta y de tracción de la demanda, prestando atención especial a la inequidad en el reparto global de vacunas y al programa COVAX. Concluimos que algunas de las políticas han sido muy efectivas, mientras que otras no han alcanzado plenamente sus objetivos. De los logros y de las limitaciones pueden extraerse consecuencias para reformular y ampliar las políticas públicas mundiales de estímulo a la I+D, la fabricación, la distribución y el acceso.

L'objectif de ce rapport est d'analyser l'impact de la pandémie de COVID-19 sur l'industrie du vaccin d'un point de vue international. L'objectif est de tirer les leçons de cette expérience et de contribuer à la conception de meilleurs outils pour promouvoir le développement et la fabrication de vaccins à l'avenir, car nous devons être prêts à faire face à de nouvelles maladies infectieuses émergentes susceptibles de se propager à l'échelle mondiale. Cette industrie apporte des contributions fondamentales au bien-être social mondial, mais d'un point de vue commercial, il s'agit d'une activité complexe et difficile et d'un point de vue économique, c'est une industrie qui ne correspond pas au paradigme de l'efficacité du marché concurrentiel avec des défaillances notoires du marché.

Nous examinons les principaux effets de la pandémie sur l'innovation et le développement scientifique, technologique et industriel des vaccins et constatons que certains éléments de la structure de l'industrie ont changé, tandis que d'autres ont persisté. Nous résumons également les enseignements tirés du déploiement de certaines politiques publiques visant à stimuler l'offre et la demande, en accordant une attention particulière à l'inégalité de la distribution mondiale des vaccins et au programme COVAX. Nous concluons que certaines politiques ont été très efficaces, tandis que d'autres n'ont pas pleinement atteint leurs objectifs. Les avancées et les limites permettent de tirer des leçons pour la reformulation et l'élargissement des politiques publiques mondiales visant à stimuler la R&D, la fabrication, la distribution et l'accès aux vaccins.

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ACRONYMS

ACT	"Access COVID Tools Accelerator".
AFCFTA	African Continental Free Trade Area
AMC	Advance Market Commitments
CDC	Center for Disease Control (United States)
CDMO	Contract Development and Manufacturing Organizations
CEPI	Coalition for Epidemic Preparedness Innovations
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
GAVI	Currently the official name of this public-private organization is its own acronym. Formerly: The Global Alliance for Vaccines and Immunizations
HPV	Human Papilloma Virus
IP	intellectual property
IPR	intellectual property rights
LNP	lipid nanoparticles
MHRA	Medicines and Healthcare Products Regulatory Authority (United Kingdom)
MM.S	Member States of the European Union
mRNA	messenger ribonucleic acid
R&D	scientific research and technological development
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights of the World Trade Organization (WTO).

1. INTRODUCTION

Since Edward Jenner began to vaccinate against smallpox, in the mid-18th century, the development of vaccines and vaccination programs has been extraordinary. Today, thanks to their proven effectiveness, they prevent more than 20 life-threatening diseases (including diphtheria, tetanus, pertussis, influenza, measles, COVID-19, etc.) and save between 2 to 3 million lives a year, mainly of children (WHO 2021, May 10), not counting the anti-SARS-CoV-2 vaccines. It has been estimated that in the first year they prevented 19.8 million deaths worldwide (with excess mortality data) (Watson et al. 2022) and that, in addition to preventing mortality and severe morbidity, booster doses reduced the risk of infection by the highly transmissible Omicron variant by 51 per cent (Monge et al. 2022).

More than remarkable milestones have been reached in the last fifty years. The WHO declared smallpox eradicated from the face of the Earth (1980); since 1988, cases of poliomyelitis have been reduced by 99.5 per cent and by 2020 it has been declared eradicated from Africa (WHO Regional Office for Africa 2020); a number of innovative vaccines have been developed, based on recombinant technology (1986), polysaccharide-protein conjugates (1987), or for adolescents (Human Papilloma Virus – HPV – 2009). Progress continues to be made in the present. The first vaccine against malaria – "RTS,S" – a long-cherished dream, was recommended by WHO in October 2021.[1,2] and, for their part, vaccines against COVID-19, including mRNA technology, have been an extraordinary success story in biomedical research, but also in economics and politics (Lobo 2022). Today, vaccines are still the most effective and efficient tool to fight against disease, to reduce morbidity and mortality, especially among children, with the consequent extension of life expectancy.

The economic return on vaccines can be very high. Global vaccination against COVID-19 has been described as the public investment with the highest return in history. The benefits of vaccinating the population of all countries would outweigh the cost many times over because they would be so varied: direct health benefits to individuals; economic benefits to national economies; and global economic benefits (Agarwal and Reed 2022; Lobo 2021).

For “industry” we understand along the report the economic (Marshallian) sense of the word. It means “economic sector” or “market”, including all the relevant actors and stakeholders, not only private manufacturing firms. From what has been said so far, it is clear that the vaccine industry makes fundamental contributions to global social welfare. The interest in its study is, therefore, very high. **This report analyzes the changes that have occurred in this industrial sector as a consequence of the COVID-19 pandemic,** with the purpose of learning from the experience and contributing to the future design of better tools to promote the development and manufacture of vaccines**.** This industry has made impressive scientific, technological and industrial achievements before, during and after the pandemic. But from a business point of view, it is a complex and difficult business and from an economic point of view it is an industry that does not fit the paradigm of competitive market efficiency. In the last forty years it has presented problems such as high business and geographical concentration, product shortages and stock-outs, exit of companies from the sector, insufficient investment in manufacturing and even in research and development (R&D) (there has even been talk of an "anemic portfolio of development projects", Xue and Ouellette, 2020). All these

[1] The "RTS,S" malaria vaccine is expected to save the lives of 40,000 to 80,000 African children each year (WHO 2022, April 21). It has been approved for the first time by a national health authority, that of Ghana, in April 2023 and manufacturing capacities of "more than 200 million doses per year have already been installed by the Serum Institute of India” (Infosalus 2023).

[2] The concept of "saving lives", although legitimate and widely used, may be questionable from the perspective of epidemiology and health economics. A more rigorous concept is that of "deaths averted" (I thank J. Puig-Junoy for this observation).

circumstances are indicative of market failures that cause the industry's social performance to admit substantial margins for improvement.[3] All of this suggests that lessons should be learned from the pandemic, the industry should be thoroughly revamped, and global public policies should be rethought and expanded to stimulate R&D, manufacturing, distribution and global access to vaccines.

This study is structured in five sections. After this introduction, the second section is devoted to the profound changes that the COVID-19 pandemic has generated on the innovation and scientific, technological and manufacturing development of vaccines. The third section recalls in synoptic tables the characteristics of the structure of this industry and how the pandemic has influenced them. It then examines the growth of production and sales, developments in the business landscape, peculiarities of the demand for anti-SARS-CoV-2 vaccines, changes in the production and cost function, changes in horizontal concentration and discussion of the lack of incentives to innovate and manufacture vaccines in the light of what has happened in these years. In the fourth section attention is given to international public policies of "supply push" and "demand pull" to encourage innovation and production of these vaccines highlighting the significance of Advance Market Commitments (AMC), the special treatment of strict liability for damages and the major global health issue raised: inequity in vaccine production and distribution, the scope of the World Health Organization's COVAX program and of initiatives to encourage manufacturing in developing countries. The study concludes with a section 5 devoted to concluding remarks.

[3] This is the main conclusion of a comprehensive study analyzing the vaccine industry under the Industrial Economics approach (Lobo, 2021).

2. EFFECTS OF THE COVID-19 PANDEMIC ON VACCINE INNOVATION AND SCIENTIFIC, TECHNOLOGICAL AND MANUFACTURING DEVELOPMENT

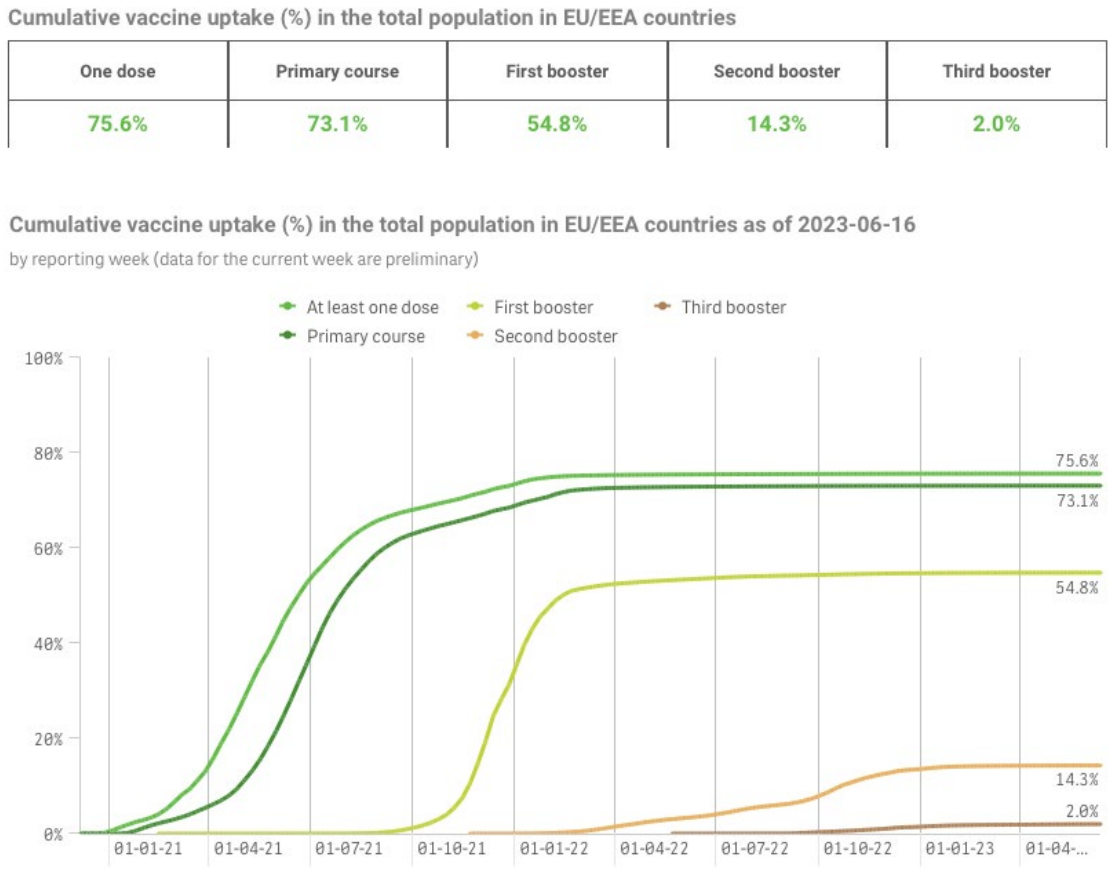
Scientific, technological and manufacturing innovation and development of vaccines have made impressive advances as a result of efforts to defeat the pandemic. Four will be mentioned:

- The development of highly effective vaccines
- Early messenger ribonucleic acid (mRNA) vaccines
- The drastic reduction of the time periods required to develop and manufacture vaccines
- The wide variety of vaccines that have been developed.

The first and decisive advance has been the development of highly effective vaccines, with certain variations. The most relevant indicators are those that refer to their **results** in terms of **health.** The reductions in morbidity and mortality have been remarkable. Watson et al. (2022) estimate that, in the first year, vaccination globally reduced deaths by 79 per cent (14.4 million deaths averted out of a total of 18.1 expected) with official data reported, and by 19.8 million out of an expected total of 31.4 million, based on proven excess mortality. In addition to preventing mortality and severe morbidity, vaccines, according to growing scientific evidence, reduce asymptomatic infection and transmission (CDC 2021), (Link-Gelles, R, Avrich Ciesla, A, lE. Roper et al. 2023).[4] The booster doses in Spain reduced the risk of infection with the highly transmissible Omicron variant by 51 per cent (Monge et al. 2022). The high effectiveness would be useless if the vaccines were not inoculated to the population. Figure 2.1 shows that 75.6 per cent of the European population (342 million) had at least one dose and 73.1 per cent (331 million) the complete primary regimen on 16 June 2023 (European Center for Disease Prevention and Control 2023).

[4] "A bivalent booster dose provided additional protection against symptomatic infection for at least the first three months after vaccination to persons who had previously received two to four doses of monovalent vaccine."

FIGURE 2.1.
Vaccinated Population in the European Union and EEA (Cumulative data as of June 6, 2023)



Note: EEA: European Economic Area, includes the European Union plus Iceland, Liechtenstein and Norway, which are also part of the European Single Market.
Source: (European Center for Disease Prevention and Control 2023)

The second most important advance has been the development of the first **messenger ribonucleic acid (mRNA**) **vaccines**, which are produced by biotechnology, as opposed to those obtained by classical biological methods. Figure 2.2 shows "classical" and "next generation" technological platforms used for the development of vaccines against COVID-19 in 2020, among the latter, messenger ribonucleic acid (mRNA) vaccines. Figure 2.3 shows a comparison between traditional vaccines and the new mRNA vaccines. The latter are characterized because they provide high levels of protection, require shorter development and manufacturing times, are very safe and can be rapidly adapted to new variants or future pandemics, which is why they have been widely used in the mass vaccination programs that have succeeded in breaking the pandemic. In addition, this technology seems to open up prospects for new vaccines and therapies in various fields. For example, BioNTech, developer and manufacturer of the Pfizer-BioNTech vaccine against COVID-19, is already developing a new antimalarial vaccine using this technology (WHO 2022 21 April). The drawback of mRNA vaccines is that they can be unstable and easily degraded, requiring them to be encapsulated in lipid-based nanoparticles, which complicates and makes them expensive to manufacture and requires storage at extremely cold temperatures, making them difficult to distribute in developing countries (Mishra 2020).

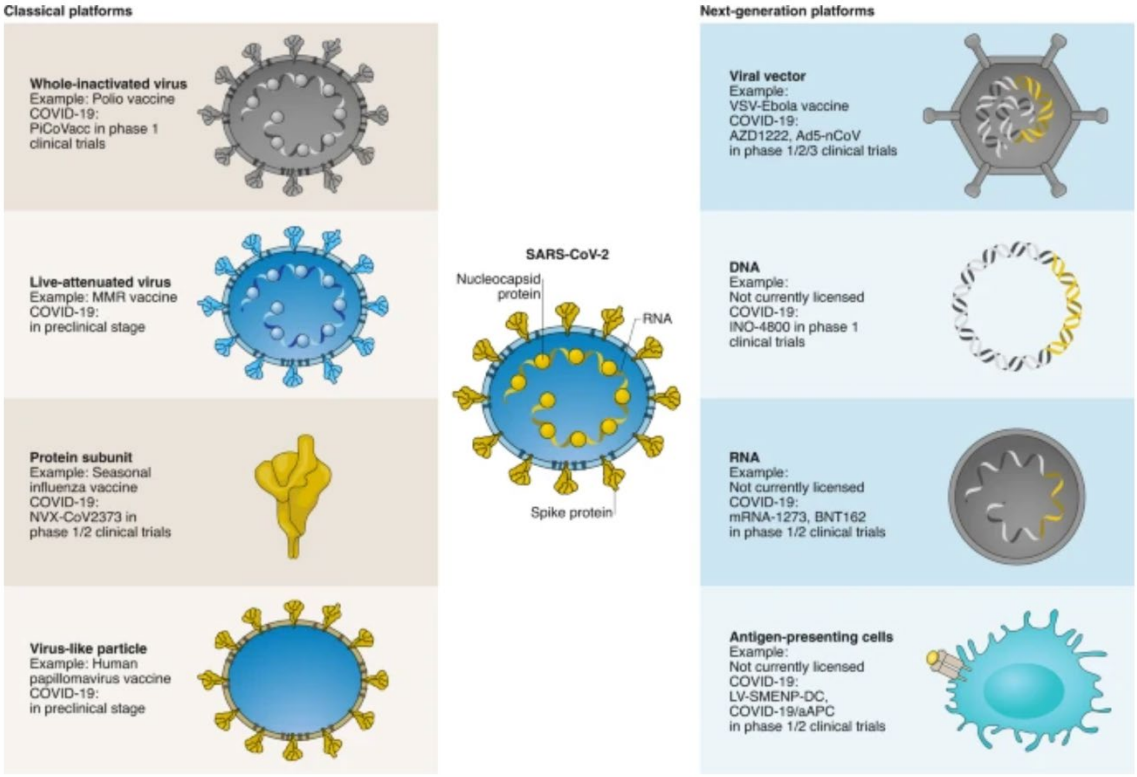
Some vaccines can produce **sterilizing immunity**, i.e., avoid infection altogether because the pathogen is eliminated by the immune system before it replicates in the host (Wahl and

Wardemann 2022). So, the vaccinated person neither gets sick, nor transmits the infection. But this is only rarely achieved. Most often, the vaccine is able to radically reduce mortality and severe morbidity or even simply symptomatic morbidity and also the transmissibility of the virus because the viral loads of the vaccinated are reduced. Through vaccination, we protect ourselves and also society. **Collective or "herd" immunity** occurs when a sufficient part of a population becomes immune - by vaccination or "naturally" if infected - to an infectious disease and the risk of person-to-person transmission is reduced. In these cases, we can speak from an economic point of view of a **positive external effect** (complete or partial), which we will discuss in the case of COVID-19 when we talk about demand in section 3.3.

The third great technological "leap" brought about by the pandemic has been a **drastic reduction in the time** required to develop vaccines, as shown in Figure 2.4. This record reduction has also occurred in the case of mRNA vaccines, although they had been under study for years. The same Figure 2.4. also summarizes the stages of development. It is a time-consuming process as it has to go through several stages (see detail in Douglas and Samant 2017): discovery of some way to induce an immune response at the molecular level; preclinical phases with animal testing, release, toxicological and immunological analyses; clinical development (itself with three phases) and industrial development; and processing of regulatory approval by national or regional regulatory agencies. The total development time for a vaccine used to be 10 to 15 years (Pronker *et al.,* 2013). The case of SARS-CoV-2 vaccines has been extraordinary. Only eleven months after the sequencing of the virus, in January 2020, the English Medicines and Healthcare Products Regulatory Authority (MHRA), the US Food and Drug Administration and the European Medicines Agency (EMA) licensed the first vaccines.[5]

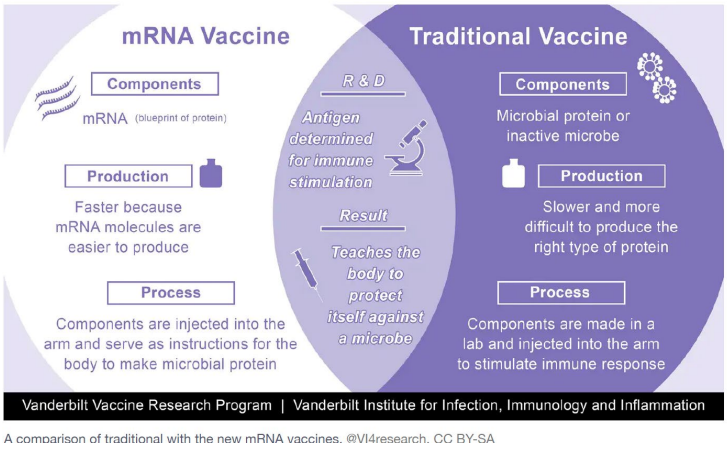
[5] The first anti-COVID-19 vaccine, obtained by the mRNA technology companies BioNTech and Pfizer, was licensed by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) on December 2, 2020 - only 349 days after China published the genetic sequence of the coronavirus and 331 days since the WHO declaration of a pandemic - followed on December 11 by the US Food and Drug Administration (FDA).On December 21, 2020, the European Commission (EC), at the proposal of the European Medicines Agency (EMA), issued the first authorization.

Figure 2.2.
Different vaccine platforms developed against COVID-19



Source: van Riel and de Wit 2020

Figure 2.3.
Comparison of traditional and mRNA vaccines

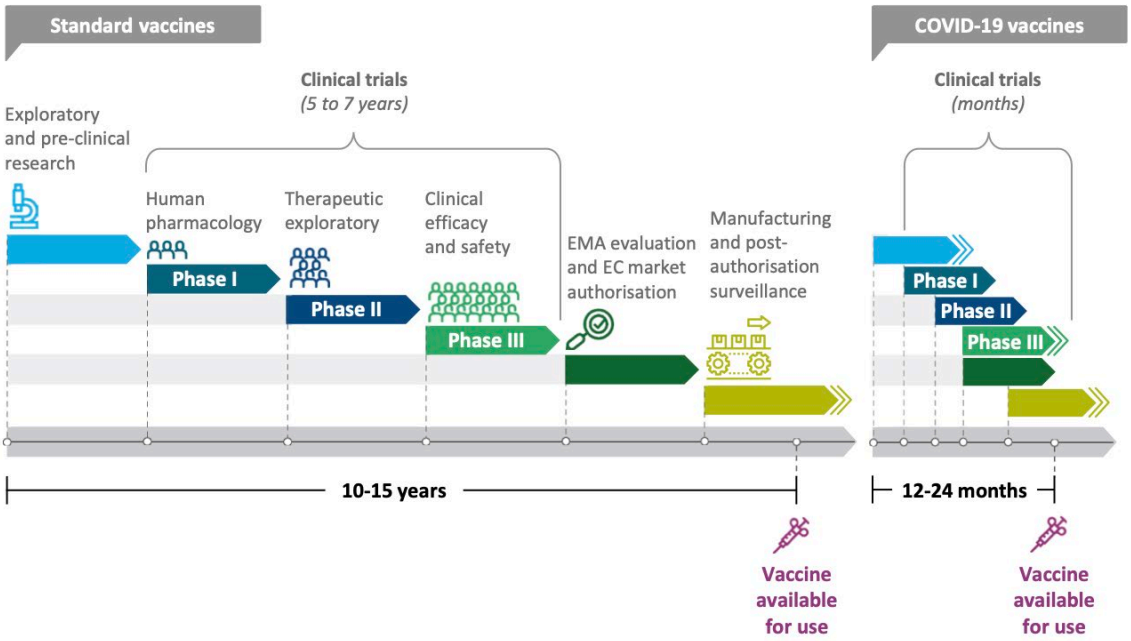


Source: Vanderbilt Institute for Infection, Immunology and Inflammation 2023.

The fourth major development is **the variety of vaccines** that have been developed against COVId-19. As of 30 March 2023, WHO counted 183 in preclinical development and 199 in clinical development from eleven different technology platforms (WHO 2023a). As of May 29, 2023, WHO had eleven vaccines with a final licensure decision (Emergency Use Listing procedure) (WHO 2023a). Table 2.1. shows the vaccines under review and licensure in the E.U. as of 26 April 2023.

The results of the development of anti-COVID-19 vaccines are therefore extraordinarily beneficial, potentially for the whole of humanity: diverse vaccines, adaptable to different variants of the virus and patients, and a certain plurality of developers and manufacturers that favors competition.[6] But it is also true that these benefits are taking too long to reach developing countries.

Figure 2.4.
Standard vaccine development process and timeline vs COVID-19 vaccine development



Source: European Court of Auditors based on EMA and EFPIA information

[6] However, the very speed of product development and vaccination deployment could lead to a "the winner takes it all" situation. (I am grateful to J. Puig-Junoy for noting this conjecture, which merits further research).

Table 2.1:
COVID-19 vaccines already licensed and in the process of review and licensure in the EU, as of April 26, 2023

Currently under rolling review. • **Sputnik V, Gam-COVID-Vac** (Gamaleya Institute) • **COVID-19 Vaccine (Vero Cell) Inactivated** (Sinovac)	Marketing authorization application submitted • **Skycovion** (SK Chemicals GmbH)
Authorized • **Comirnaty** (BioNTech and Pfizer) • **COVID-19 Vaccine Valneva** • **Nuvaxovid** (Novavax) • **Spikevax** (Moderna) • **Vaxzevria** (AstraZeneca) • **Jcovden** (Janssen) • **VidPrevtyn Beta** (Sanofi Pasteur) • **Bimervax (previously COVID-19 Vaccine HIPRA)** (HIPRA Human Health S.L.U.)	Authorized adaptations • **Comirnaty Original/Omicron BA.1** (BioNTech and Pfizer) • **Comirnaty Original/Omicron BA.4-5** (BioNTech and Pfizer) • **Spikevax bivalent Original/Omicron BA.1** (Moderna) • **Spikevax bivalent Original/Omicron BA.4-5** (Moderna)
Source: EMA. 2023, April 26	

The **manufacture** of "classical" vaccines is a slow biological process involving the production of proteins. It consists of two stages: bulk manufacturing (cell culture and purification) and formulation operations with other components, filling and finishing (Douglas and Samant, 2017). Once inspected, the product is put into vials, after which it is packaged, labeled and stored under controlled storage. All under strict aseptic or sterile conditions. The manufacturing sub-steps differ significantly depending on the respective technology platform.

The production of mRNA vaccines has a first step of biological fermentation, but then it is largely chemical. It requires formulation into lipid nanoparticles (LNPs), microscopic droplets of oily liquid that enclose and protect the fragile genetic instructions while they are manufactured, transported and finally administered (OECD, 2021b). All of this requires specialized equipment. But it is less complicated because mRNA molecules are much simpler than proteins and the human body makes viral proteins itself (Hatchett *et* al. 2021; Jackson *et al.* 2020; Mishra 2020; Sousa *et al.* 2021).

At least in the case of traditional vaccines, the **manufacturing processes are** therefore **complex**. The lead time for producing a batch of vaccines can be up to three years. In addition, producing proteins involves uncertainty and biological variability on yields, performance and production. AstraZeneca's problems in providing the EU with its initial supplies of SARS-CoV-2 vaccine in 2021 became famous. There are also contamination incidents, such as the equally famous J&J vaccine contamination at Emergent's Baltimore plant in the same year (referred to in section 3.4.). These are some of the reasons why the number of traditional vaccine manufacturers remained low before (Plotkin *et al.* 2017) and after the explosion of the COVID-19 pandemic and why manufacturing failures and supply shortages occurred.

Manufacturing also requires the organization of a complex **supply chain** of specialized substances (preservatives, stabilizers, surfactants, adjuvants, anti-contaminants, diluents,

lipid nanoparticles and all packaging materials). The difficulties in the case of SARS-CoV-2 have been: 1) the supply chain had to be organized from scratch for the new mRNA vaccines; 2) the pressure resulting from the unprecedented scale of the vaccines to be manufactured; 3) the disorganization resulting from the pandemic itself.

In deploying worldwide manufacturing networks to meet global demand, large multinationals and other companies have embarked on collaborations with contract development and manufacturing organizations (**CDMOs**) because they deal with both technical development and manufacturing. Some decentralize final preparation, filling and finishing operations. Others also cover phases or the entire active ingredient manufacturing process. The agreement between a large multinational and an emerging biotech company, Pfizer and BioNTech, which resulted in one of the first and most widely used vaccines against COVID-19 (mRNA technology and Comirnaty brand), is well known. There is also room for agreements between large multinational biopharmaceutical companies to exchange their technology and increase their aggregate production, such as that between Sanofi and GSK to develop, manufacture and market an anti-COVID_19 booster vaccine (brand name VidPrevtyn® Beta, approved in the EU in November 2022). Box 2.1. provides some examples of agreements with CDMOs in Spain to manufacture vaccines against SARS-Cov-2. Fostering these agreements, collaborations and networks is crucial to increase global capacity and production and to ensure affordable prices, as we will see in section 4.5.

The complexity of manufacturing processes and vaccine supply chains does not exclude the role of **new players** and increased competition. New opportunities are opening up with mRNA vaccines. **Technology transfers** could become decisive. The **potential of local production and of small and medium-sized companies, government research centers and universities should** not be ruled out. The examples of The Serum Institute of India - today one of the world's leading producers - and of small and medium-sized innovative companies such as BioNTech in Germany (Miller and Cookson, 2020) and Moderna in the USA (Garde and Saltzman, 2020), or the University of Oxford, whose R&D activities have been instrumental in creating one of the first vaccines developed against SARS-CoV-2 (Neville, 2020), are very clear. This would also be the case of the Catalan-Spanish company Hipra. Other development and manufacturing initiatives in middle-income countries to consider are Biovac in South Africa, the Butantan Institute in Brazil and Cuba, which has developed the Soberana and Abdala vaccines. Also, consumables can be an area of cost savings, given the lower prices in low-resource countries (Plotkin *et al.* 2017).

BOX 2 .1.
CDMOs IN SPAIN TO MANUFACTURE VACCINES AGAINST SARS-CoV-2

ROVI. had experience in biotech manufacturing (heparin) and sterile injectables This Spanish pharmaceutical company reached an agreement in 2020 with Moderna to participate in the manufacture of the mRNA vaccine. First it was a "fill and finish operation" at the San Sebastian de los Reyes plant near Madrid. Subsequently, in 2021- 2022, the company doubled its capacity with two new formulation, filling, automatic visual inspection, labeling and vial packaging lines.

The agreement was extended in April 2021 to include the production of the active ingredient (antigen). The new production line at the plant in the Metropolitan Technology Park in Escúzar, Granada, with a production capacity of 100 million doses per year, started operations in January 2022. The amount of the investment has not been disclosed, but is estimated at 60 million euros.

ZENDAL. The biotech company Zendal, through its subsidiary Biofabri, reached an agreement with Novavax to manufacture the antigen, but it seems that it did not materialize (its website in 2023 does not contain information on the matter).

REIG JOFRE concluded an agreement to refill and finish the Janssen vaccine in Sant Joan Despí (Barcelona), starting in July 2021, but it seems that it did not materialize (its website in 2023 does not contain information on the matter).

INSUD concluded an agreement to backfill and finish the AstraZeneca vaccine in Azuqueca de Henares (Guadalajara), but it seems that it did not materialize (their website in 2023 does not contain information about it).

Source: 5 Días April 12 and 29, 2021 (Cited by Lobo 2021). (Editors of Granada Hoy 2023), official websites of the companies consulted on September 19, 2023.

3. HAS THE COVID-19 PANDEMIC CHANGED THE VACCINE INDUSTRY?

We have already seen in section 2 the very important technological changes that have taken place in the industry. Let us now see how production and sales have grown, how the business landscape has been altered and how the main features of the industry structure have been affected.

3.1 Production and Sales Growth

The vaccine industry is a relatively small segment of the pharmaceutical industry as a whole. In 2019, it accounted for 3.6 per cent of sales (Lobo 2022), but in the last 20 years prior to the pandemic, the sector had seen remarkable growth thanks to innovative products, new vaccinated population groups (adolescents) and, in developed countries, more aggressive pricing strategies. As a consequence of the development, manufacture and supply of the new vaccines against COVID-19, demand, production, sales and, therefore, the size of the global vaccine market have grown dramatically. Approximately 16 billion doses of all vaccines were supplied in 2021, compared to 5.8 billion in 2019. In value the market amounted to US$ 141 billion, compared to US$ 38 billion in 2019. This represents 10 per cent of the global pharmaceutical market, compared to 4 per cent in 2019. Discounting COVID-19 vaccines the market supplied 5.3 billion doses worth US$ 42 billion, representative of 4 per cent of the global pharmaceutical market. In other words, the new anti-COVID-19 vaccines caused a six-point jump in the relative size of this subsector and accounted for more than double the volume and value of all other vaccines (data from WHO 2023, Global vaccine market report). Comirnaty, the Pfizer-BioNTech vaccine, was the top-selling drug in 2021 in the world and is still expected to be the second in 2023 (Brown, Elmhirsty Fagg 2022). In 2022, 4.7 billion vaccines were supplied against COVID-19 and the market for all other vaccines has been estimated at 5.3 billion doses (UNICEF 2023; Our World in Data, Mathieu et. al. 2023). This represents a one-time jump from the pandemic effect and it is not foreseeable that the relative size of the vaccine market will remain as high in the near future, but certainly at a higher level than previously and with valuable experience in terms of the ability to rapidly expand supply.

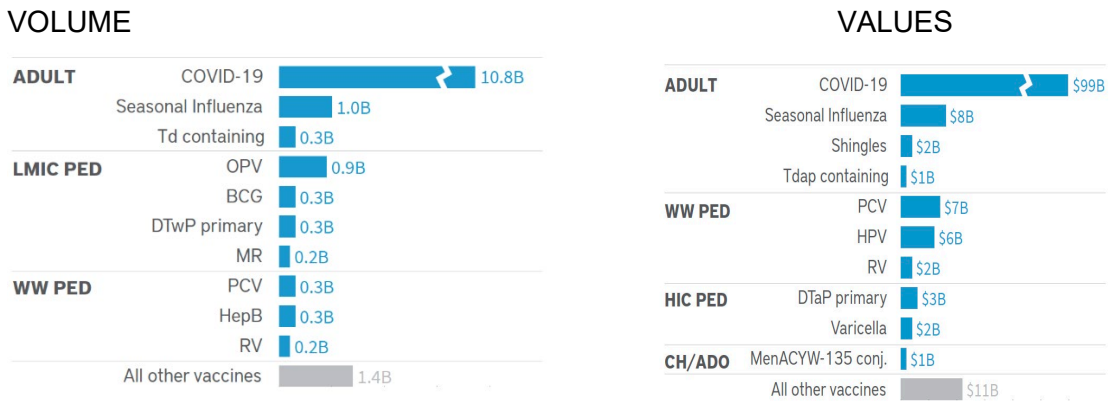
Figure 3.1. represents the distribution of the global market by type of vaccine in 2021, and clearly shows in detail this spectacular evolution. The great effect of the pandemic on the global pharmaceutical market can also be seen in Figure 3.2, which shows variations in the year-on-year growth rates with IQVIA forecasts[7] until 2027. The 2021 rates are not repeated, but COVID -19 vaccine spending continues to drive aggregate spending variations upwards, above the pre-pandemic trend. In fact, the strongest boost in drug spending over the next five years is expected to come from global COVID-19 vaccination. It should be kept in mind that the immunity it provides appears to diminish by the year and that booster doses are therefore required, as well as new variants that may require additional doses. Thus, global spending of about $40-45 billion per year on COVID -19 vaccines is projected through 2027 (IQVIA 2023). In contrast, growth in spending on the other vaccines (excluding influenza and anti-COVID-19) is expected to decline over the next five years, due to stabilization in sales of the newer vaccines (IQVIA 2023), which in the last twenty years had contributed to remarkable growth (varicella, hepatitis A, pneumococcal conjugate, herpes zoster, rotavirus, meningococcal conjugate and HPV vaccines, as well as combination vaccines (Douglas and Samant, 2017).

Another effect resulting from the pandemic has been some **reduction in vaccine utilization and vaccination rates to prevent other diseases**. This effect is in line with what has

[7] IQVIA is one of the leading companies in obtaining and processing data on medicines, the pharmaceutical industry, and other aspects of healthcare services.

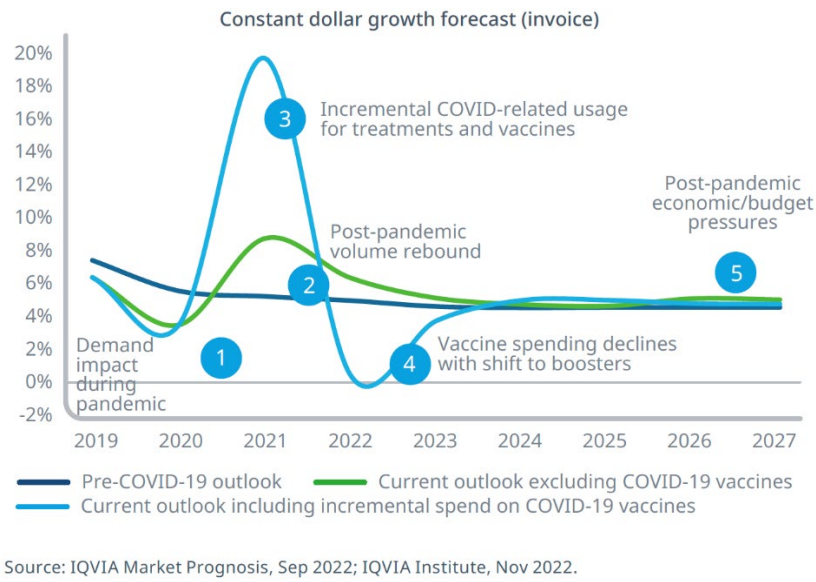
occurred in health systems where confinements and other circumstances of the pandemic have determined a decrease in utilization of services, sometimes with negative health effects. Pediatric vaccine volumes declined by 14 per cent compared to 2019, due to lower utilization of oral polio and measles/rubella vaccines, especially in lower-middle-income countries (WHO 2023, Global market report). This represents the "steepest and most sustained decline in childhood immunization in 30 years". The percentage of children who received all three doses of DTP3 vaccine,-a marker of vaccination coverage-fell five percentage points between 2019 and 2021 to 81 per cent. 25 million children missed one or more doses of DTP in routine immunization services in 2021 alone, two million more than in 2020 (WHO 2022, July 15). Although other factors played a role, COVID-19 led to supply chain disruptions, resource diversions, and containment measures that temporarily limited access and availability of vaccines for the other diseases (WHO 2022, 15 July).

Figure 3.1.
Worldwide sales of different types of vaccines. 2021 (Volume in doses. Values in US dollars.)



Notes: B: Billions
Source: (WHO 2023, Global vaccine market report 2022).

Figure 3.2.
The global pharmaceutical market before, during and after the COVID-19 pandemic. Year-on-year rates of change on spending in constant U.S. dollars.



Source: IQVIA 2023
Note*: CAGR (Compound annual growth rate)*

3.2 Business Landscape

The business landscape before the pandemic showed pronounced **geographic concentration** of production, which led to describe the industry as "the **club of vaccine producers**" (Evenett et al. 2021), as 13 developed countries (EU and USA) concentrated company headquarters, 91 per cent of their subsidiaries, production and trade (Evenett et al. 2021). In addition, global markets for component substances and reagents are also highly concentrated and highly interdependent, (OECD 2021; Evenett et al. 2021). Geographic concentration is a consequence of **concentration at the company level**.[8] According to the WHO, prior to the pandemic "about 80 per cent of global vaccine sales came from five large multinational companies (MNCs)..." (WHO, 2021, May 13). However, this picture was changing even before the pandemic: "emerging manufacturers (in India, China and Brazil), play a key role in supplying vaccines to developing countries..." which "...has resulted in lower prices due to increased competition and greater production capacity..." (WHO, 2021, May 13).

There is also vertical **specialization in R&D**. Large vaccine companies focus primarily on clinical and process development, while smaller biotech companies are engaged in early stage innovation. (On business concentration see also Douglas and Samant, 2017, and Hatchett et al. 2021).

The recent pandemic has changed the landscape in several dimensions:

- Entry into the market of small and medium-sized innovative companies with biotechnology capabilities that were developing mRNA technologies, and that have achieved highly effective anti-COVID-19 vaccines and have become leading players in the market, notably BioNTech (from Germany) and Moderna (from the USA). Other

[8] This concentration is higher than that of the biopharmaceutical sector as a whole, but the concentration in the relevant submarkets for homogeneous products is highly variable, in some cases very high.

companies such as Novavax and Hipra (Spanish) have also obtained EMA-approved products and European supply contracts. The support and collaboration of the public sector (as we see in section 4) and other private companies have been decisive in promoting them.

- Collaboration between large multinational companies with experience in the vaccine market and some of these biotechnology companies, with enormous success. The outstanding case is that of the Pfizer-BioNTech partnership that culminated the clinical development of the first mRNA vaccine (Comirnaty) and has become the world's leading manufacturer and supplier of SARS-CoV-2 vaccines (if we leave aside supplies within China).
- Collaboration, also with enormous success, between public research institutions and multinational companies with limited experience in this market, for the scientific and technological development of vaccines (beyond public financial support or through AMC). The outstanding case is that of the University of Oxford and AstraZeneca, which achieved the recombinant adenovirus vector vaccine, more traditional than mRNA (brands: European Vaxzevria, Indian Covishield) (Fortner 2022), although manufacturing and supply problems subsequently arose.
- The manufacturers of COVID-19 vaccines have increased their own manufacturing in parallel with clinical development ("scale-in"),
- Traditional manufacturers by 2021 had already concluded more than 150 agreements, on the one hand, with companies and other entities (all covered by the term "contract development and manufacturing organizations", CDMOs) and, on the other hand, with other multinational biopharmaceutical companies to transfer their technology and increase their total production ("scale-out", "external scale-up") (Hatchett et al., 2021).

Each and every one of these organizational and business developments would merit a detailed case study.

3.3 The Demand

The series of boxes 3.1. summarizes the characteristics of the structure of the vaccine industry, which we have discussed at length in another study (Lobo 2022). The COVID-19 pandemic has led to major changes and developments in this structure, which are expected to be long-lasting. We will focus on them here. Box 3.1.(I) summarizes these properties on the demand side.

Historically, the **effectiveness** of vaccines has proven to be very high, resulting in dramatic reductions in mortality and morbidity, as well as in the risk of infection, virtues that have also been demonstrated, as we have already mentioned in section 2, by the anti-COVID-19 vaccines.

The **efficiency** of vaccines is clear and this is also the case for anti-COVID-19 vaccines.[9] Although this conclusion is almost self-evident, we recall the systematic review by Utami et al. (2023) that selected 25 economic evaluation studies empirically proving that vaccination programs are cost-effective, and even cost-saving, including in lower income countries. A cost-benefit analysis on the mass vaccination campaign against SARS-CoV-2 in Catalonia estimated that its benefit-cost ratio was 3.4 from a social perspective and 1.4 from a health system perspective and the social benefits of each dose were 116.7 € and 19.9 € respectively. The conclusion was that the vaccination campaign was not only efficient but also cost-saving and therefore had high social returns (López, F. et al. 2022).

[9] A useful reference on vaccine evaluation methodology with a synthesis of the literature (in Spanish) is (Rovira Forns et al. 2021).

The **size of the market/demand** for vaccines is debated, but it is not small. For the anti-SARS-CoV-2 vaccines, the demand is the entire world population, as it is a highly transmissible virus and the constant new variants of the virus, although sometimes covered by existing vaccines, renew the demand. We have already seen in section 3.1. that some 11 billion doses were supplied in 2021, leaving unmet needs in developing countries. Bilateral and multilateral international cooperation during the pandemic has tried to meet their needs with great efforts and achievements, although ultimately insufficient. In section 4 we will focus on the COVAX international cooperation program, the most important one.

BOX 3 .1.
THE STRUCTURE OF THE VACCINE INDUSTRY (I)
DEMAND

FEATURE	EFFECTS 1	EFFECTS 2/COMMENTS
High effectiveness and efficiency	Dramatic reductions in mortality and morbidity.	Extremely high cost-effectiveness ratio of many vaccines
Market size can be large. Significant target populations	Discussed.	Lower than other Pharma subsectors
Low payment capacity of developing countries	Vicious circle poverty→ no vaccination-→ disease→ poverty. But growing demand	International cooperation that finances and manages vaccinations can break the vicious cycle
What matters is the size of the market in relation to the volume needed to realize economies of scale.	Determines the potential for multiple viable producers	
Preventive vaccines→ Consumers→ large, healthy populations	High safety requirements.	Very large clinical trials, very high cost and complexity
Infrequent and self-limited consumption	Limits demand	
Depends on epidemiological variables (incidence)	Uncertainty, forecasting difficulties,	
Heterogeneity of demand	Variable risks of becoming infected. Difficult to identify willingness to pay	Prevents price discrimination and hinders appropriation of surplus
Vulnerable subpopulations	Limiting demand	
Substitute treatments	Limiting demand	
Full or limited positive external effects	Collective or "herd" immunity: decreases the risk of person-to-person infection	Limits demand, free-rider effect, encourages vaccine hesitance. Market failure. Requires State intervention

The **frequency** with which to be inoculated against COVID-19 is not among the lowest among vaccines. Booster doses and new versions of the vaccine are necessary because immunity tends to decrease over time and new variants of the virus appear. In addition, a sterilizing vaccine, i.e. one that totally prevents infection, has not been achieved and does not appear to be forthcoming (Kyei-Barffour et al. 2021), although it does appear to limit transmission, as we have seen in section 2 above. These circumstances increase demand, although it does not seem that it can be considered a repeat purchase product and thus overcome one of the disincentives to R&D.[10] On the other hand, demand is reduced by the fact that there are **populations that,** according to their idiosyncratic benefit-risk ratio, **should not be vaccinated**, mainly children, who do not contract the disease or only contract it mildly. Nor should immunocompromised persons and persons with certain diseases be vaccinated. It helps to maintain the demand for vaccines that research into effective drug **replacement therapy** has not yielded much fruit, although it has greatly improved the management of patients.

The first and most important market failure affecting the vaccine industry is the **positive external effect** on consumption derived from the **sterilizing immunity or limited transmissibility and the collective or "herd" immunity** they sometimes generate, so that an individual who is vaccinated decreases the likelihood of others becoming infected and, in the limit, makes pathogens unable to be transmitted, although not the entire population is fully vaccinated, as we saw in section 2. Infected vaccinees can transmit the pathogen, but viral loads are much lower and therefore transmission is also lower (WHO, 2020a). As is well known, this effect can lead to "free rider" behavior, so that the vaccination rate may be lower than necessary. COVID-19 vaccines do not strictly produce sterilizing immunity. Vaccine recipients can become infected, but the vaccines prevent most infections, especially severe ones, avoiding hospitalization and mortality. Infected vaccinees can transmit the pathogen, but viral loads are much lower and therefore transmission is also lower (WHO 2022, 16 March). To overcome this and other market failures, in the case of COVID-19, governments and international agencies have developed very large incentive programs or established bans, as we will see in section 4, dedicated to public policies related to vaccines.

3.4 Supply. The Production Function – Cost Structure

Box 3.2. provides a summary of the highlights in the production function and cost structure of the vaccine industry. The high level of **R&D costs** for chemical-pharmaceutical products is probably transferable to vaccines, although information is lacking (see details on available data and evidence in Lobo 2021[11]). One of the few studies , using simulation-optimization techniques, estimates that meeting the cost of reaching completion of phase 2a of vaccine development for an epidemic infection requires substantial investments (Gouglas, Than Le, Hendeson et al. 2018).[12] **The public and non-profit contribution to R&D and development of SARS-CoV-2 vaccine production** has been extraordinary, as we will see in section 4.1.

[10] I would like to thank J. Puig-Junoy for this observation.
[11] In addition, abstracts can be found in: Lobo (2019) and Lobo and Rovira (2020) Other references are (Andre, 2002), (Scherer, 2007), Douglas and Samant (2017).
[12] Between 319-469 million. in a range 137 million - 1.1 billion US dollars starting in preclinical. After phase 2 there is a long way to go (I thank J. Puig-Junoy for this reference).

BOX 3.2. THE STRUCTURE OF THE VACCINE INDUSTRY (II) SUPPLY: THE PRODUCTION FUNCTION. THE COSTS		
FEATURE	**EFFECT 1**	**EFFECT 2/REMARKS**
High time and capital requirements to enter. Capital intensive industry.	Complex manufacturing plants Highly specialized and scarce technical staff	New methods and technologies can reduce capital and time costs
Production function: Costs	Complexity of biological production and distribution	High sunk fixed costs
High R&D costs and high risks	Long process. Very large clinical trials	Public support and funding and public laboratories reduce them.
Costs: Stochastic risk of contaminated lots	Consubstantial to biological production	Costly and risky quality analysis processes
Costs: Detailed regulation throughout the product's life cycle.	Costly and risky processes of safety, efficacy and quality assessment by health authorities	• Evaluation and authorization of the specific biological entity • Plant and process certification • Batch release • Inspections of manufacturing facilities • Annual reporting of specific manufacturing information • Export and import licenses • Risk plans • Adverse events data
Costs: Liability for damages: contaminations, defective products, adverse effects, etc.	Very high litigation costs may arise due to the large number of users.	Legislation and public measures to delimit civil liability

The **risk of contamination** during vaccine manufacturing or distribution is, for technical reasons, a major business risk. Quality assurance personnel can be half the number of production workers (Plotkin et al., 2017). COVID-19 vaccine manufacturing has been no stranger to this risk. In 2021, in a factory subcontracted by Emergent BioSolutions in Baltimore (USA), a batch of Johnson & Johnson vaccine was contaminated with components of AstraZeneca's vaccine spoiling up to 75 million doses. Production was interrupted for months and losses of at least $45 million were incurred (New York Times 2021). In Spain there was also an incident in the manufacture of the Moderna vaccine by Rovi, although minor and quickly resolved.

Since vaccines are generally administered to healthy individuals, and given the risks of adverse effects and contamination, the R&D, production and distribution of vaccines are subject to detailed **government regulations throughout** the life of the product, involving costly and risky **processes of evaluation of their safety, efficacy and quality** by the health

authority. In the case of COVID 19 vaccines, the acceleration of these processes has been extraordinarily important thanks to the rolling-reviews procedure, which means that the health authority knows the data from tests, analyses and clinical trials as they are generated, instead of waiting for the results of the studies to be available once they have all been completed.

The issue of **liability** is extremely important for the vaccine industry. The request to shift liability from the companies to governments was one of the main difficulties in the AMC negotiations between the EU Commission and the pharmaceutical companies and between India and Pfizer, unlike in the USA, where the government accepted the waiver of liability by the companies from the outset. This issue is discussed in section 4.3.

3.5 Supply: Specialization in Production, Horizontal Concentration, Exit From the Sector and Economies of Scale. Limitations to Generic Competition

Box 3.3. summarizes a third set of salient features of the structure of the vaccine industry. **Specialization,** as with other vaccines, characterizes **the production** of COVID-19 vaccines, which has led to a consequent rigidity in adapting to demand and increased risks of shortages, stock-outs and production stoppages. For these vaccines, completely new plants had to be built and equipped, without the existing ones being of much use. In any case, these plants were brought up to speed in surprisingly short periods of time.

In section 3.2 we documented the geographic and business **concentration** of supply that has led to talk of the "vaccine production club" and is explained mainly for technical reasons: the aggravated risk of biological and physical variability and contamination and economies of scale. In the vaccine industry, there are **economies of scale** in R&D, some manufacturing processes and in the evaluation, certification and inspection processes. This basically technical feature can increase horizontal concentration and at the limit lead to "natural" monopoly. "COVID-19 has shown how vulnerable medical product supply chains are when they depend on a small number of manufacturers of raw materials and final products," said Emer Cooke, director of WHO's regulatory and prequalification department (UNCTAD, 2020). This concentration, which at the limit reaches monopoly, would be the "natural state" of the vaccine industry (Lobo 2021). But the experience with anti-COVID-19 vaccines has also shown that opposing forces are at work, (as we indicated in section 3.2.): the activity of emerging manufacturers (in India, China, Russia and Brazil) and new corporate players (Pfizer BioNTech, Moderna, Hipra, the latter Spanish) that have developed new technologies (especially mRNA vaccines). It is significant that, as we have seen in section 2, as of May 29, 2023, the WHO had eleven vaccines with a final authorization decision (Emergency Use Listing procedure) and the EU had eight authorized as of April 26, 2023 (Table 2.1.). These are quasi-substitute products that could form the basis of a competitive market.

However, these technological options do not mean, at least for now, the end of concentration, even in the COVID-19 market. The EU, despite having approved eight vaccines and having entered into contracts for with eight companies, obtains 71 per cent of mRNA technology supplies and is largely dependent on a single supplier, Pfizer-BioNTech. Under the current 2021 contract this group must deliver 900 million doses in 2022 and 2023, with an option for another 900 million. It is the largest COVID-19 vaccine contract signed by the Commission and will dominate the EU vaccine portfolio until the end of 2023 (European Court of Auditors 2022, p.32). See Figure 3.3. The Commission has reported that the decision to rely on this company was motivated by its ability to reliably supply the EU (European Court of Auditors 2022, p. 34).

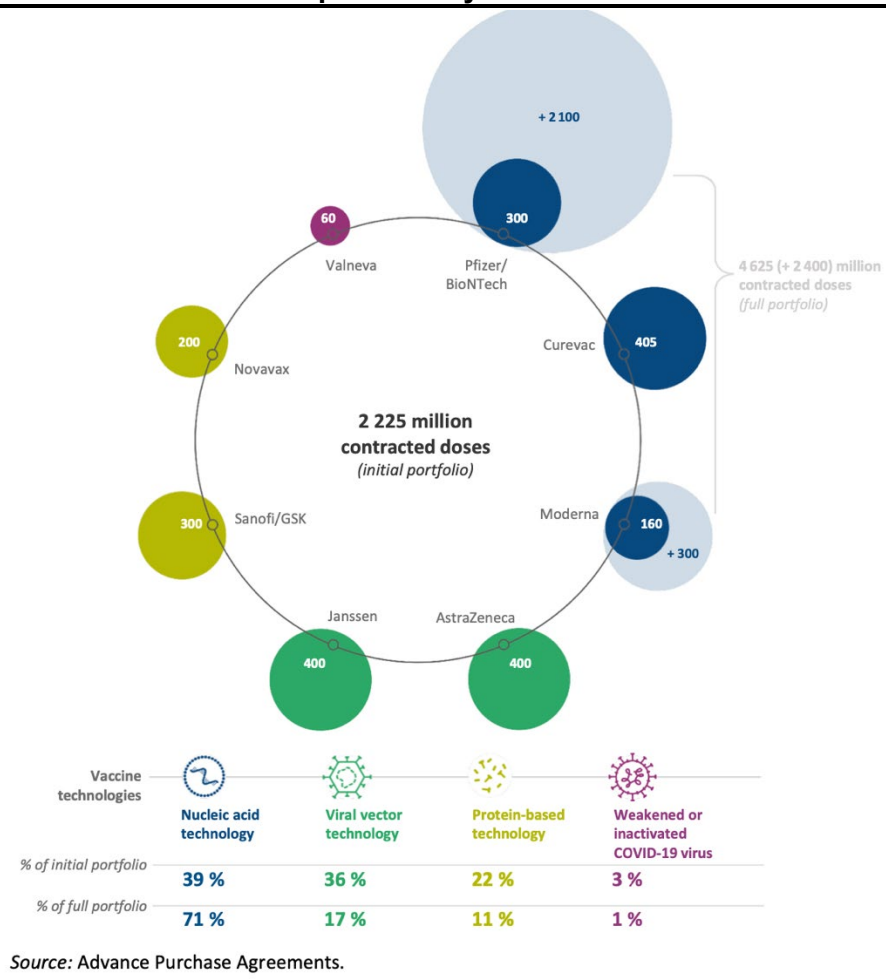
Given the inefficiencies that can result from horizontal concentration and monopoly in terms of welfare losses (fewer vaccines available than society would like) and, in particular, the risk of shortages and supply disruption, there is a need for governments and international

organizations to deploy corrective tools and to promote the new opportunities offered by technology to increase competition. In Section 4 we will examine some experiences developed for COVID-19 vaccines.

BOX 3.3.
THE STRUCTURE OF THE VACCINE INDUSTRY (III). SUPPLY: SPECIALIZATION, ECONOMIES OF SCALE AND CONCENTRATION AND LIMITS TO GENERIC COMPETITION.

FEATURE	**EFFECT 1**	**EFFECT 2/REMARKS**
Specialization in production.	Many vaccines require specialized, in-house plant, facilities and equipment.	Rigidity in adapting to demand and increased risks of stock-outs, shortages and production stoppages
Economies of scale Larger size means lower average costs. Determined by technology. In the vaccine industry, there are significant economies of scale in R&D, some manufacturing, and in the evaluation, certification and inspection processes.	Key is the relationship between market size and production level that realizes all economies of scale (minimum average cost).	They can lead to monopoly→ "natural monopoly".
High concentration	Monopoly, oligopoly and supply chain vulnerability may arise.	Countervailing Forces→ Emerging manufacturers and new technical options
Limits to generic vaccine competition.	Regulatory barriers to entry are difficult to lower because of the variability of biological processes.	In addition to expired patents, know-how must be transferred.
Insufficient incentives	Underinvestment in R&D and manufacturing, supply shortages, companies exiting the market	Two theories: concentration and monopoly vs. low profitability. Widespread market failures. Changing situation

Figure 3.3.
Initial and full EU vaccine portfolio by 2022



Source: European Court of Auditors 2022

There are **limitations to generic vaccine competition** that in principle are also present in COVID-19 vaccines, although there has been debate about the extent of evidence demonstrating safety, efficacy and quality and the possibility of lowering these regulatory barriers for potential generic follow-on vaccines. On the other hand, the impact that new technologies, such as mRNA, may have on competition between innovator and follow-on vaccines is currently unknown.

Whether **the incentives** currently offered by the market to innovate and boost vaccine production are insufficient is the subject of much discussion, which we have detailed in (Lobo 2021). Lack of incentives would lead to underinvestment in innovation and manufacturing, supply shortages and exit of companies from the market, phenomena about which we have seen evidence in the past. There has even been talk of an "anemic pipeline of development projects" (Xue and Ouellette, 2020) and a theoretical model concluded that the profitability of a vaccine pipeline is significantly negative (Vu et al. 2020). Underinvestment is also highlighted by Wouters et al. (2021) and (Grabowski and Vernon 1997).

Two theories would explain this situation. The first stresses economic concentration, oligopoly and monopoly, all of which are compatible with high profitability, shortages and the exit of smaller companies. The second theory focuses directly on the lack of profitability due to the

characteristics of the industry that we have already examined, to which would be added the low prices of public purchases and tenders.[13] The point is that both theories lead to the same conclusion: market failures are pervasive and prevent a greater flow of innovations and the industry from meeting effective demand, triggering shortages of products essential for public health and economic development. Therefore, most economists recommend a whole panoply of governmental or international actions, subsidies, design of new "push" and "pull" mechanisms and other interventions.

It is possible that prior to the COVID-19 pandemic this situation was already changing. New vaccines have been developed and brought to market by multinational companies, targeted to new populations, such as adolescents in developed countries, and marketed at relatively high prices in these countries, all of which would have raised profitability. In contrast, improvements in the development and availability of vaccines for the most prevalent diseases in developing countries have continued to require public support and support from international organizations, in some cases with good results. Significant innovations are being introduced in both markets. A vaccine against respiratory syncytial virus in adults, from GSK, is expected in 2023, after years of research. Also advanced against the same virus are vaccines from Pfizer, J&J and Moderna. Moderna has a cytomegalovirus vaccine (mRNA platform) in Phase 3 development; Pfizer/BioNTech has an influenza vaccine (Brown, Elmhirst and Fagg 2022) in Phase 3. We have already mentioned the first malaria vaccine – "RTS,S" – of extreme importance to save children's lives in developing countries.

COVID-19 vaccines are a paradigmatic case in which incentives have not been generated, far from it, by the market alone. Public intervention has been decisive in developing both supply-push and demand-pull policies. These policies to ensure the flow of innovation, manufacturing, supply and access to vaccines are discussed in the next section 4.

[13] Public procurement and bidding would determine low prices due to the monopsony power of governments and international agencies, which cover a very important part of the demand. However, Scherer (2007) attests that prices in public procurement in developed countries are significantly higher than those in international tenders organized by UNICEF (for developing countries). Danzon and Pereira (2011) empirically support the hypothesis that public procurement is not the driver of the sector's exit, but rather high sunk fixed costs and relatively concentrated demand.

4. WHAT DO THE PUBLIC POLICIES DEVELOPED TO STIMULATE R&D AND THE MANUFACTURE OF ANTI-COVID-19 VACCINES TEACH US?

In this chapter we review some of the national and international public policies deployed to stimulate R&D and production of anti-COVID-19 vaccines. We attempt to highlight the lessons that can be drawn from these experiences to restructure the industry and improve its efficiency, as well as to improve the preparedness of countries and international organizations for possible future pandemics.

4.1 Policies to "Boost" Supply

“Supply-push" policies seek to stimulate R&D and manufacturing and reduce upfront costs. We will consider the following:

- Patents,
- Measures to reduce initial costs
- Collaboration between companies
- The direct participation of the public sector in manufacturing

Patents, or more broadly intellectual property rights (IPRs), are the standard policy in all markets to stimulate R&D.[14] In the pharmaceutical market, patents are nowadays accompanied by other exclusive rights (data protection) and specific incentives for certain segments (orphan drugs, etc.). IPRs offer both light and shadow as they create a tension between incentives for innovation (long-term dynamic objective) and access to medicines, particularly for developing countries and disadvantaged social groups (short-term objective). The empirical evidence on their actual ability to foster innovation is disputed. There are many issues involved. They seem to have stimulated innovation, but only in relatively developed countries; they have not stimulated innovation in the very long run; and the conditions for them to stimulate socially valuable innovation are strict. For there to be a clear connection between profits and social value, in addition to the incentive, product and capital markets must function well. On the other hand, the effectiveness of patents depends on the characteristics of the market concerned (Budish et al. 2015; Kyle 2021; Qian 2007; Yin, 2008).

Various proposals and mechanisms to reform IPRs have been put forward over the last 20 years, but with little success. On the contrary, the period of exclusivity of IPR protection and other forms of innovator protection have been strengthened by national and international regulations, although countries have some leeway to apply flexibilities under the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). (On this complicated issue, see, for example, Correa, 2016; Lobo, 2017).

The value of vaccine patents —at least for traditional vaccines and compared to patents covering chemically synthesized drugs— is modest, for the following reasons:

- When referring to biologic products, they do not constitute an effective barrier to imitation.
- Many are only process patents that do not cover against alternatives, although sometimes they are very effective.

[14] This study does not address in detail the complex issues concerning intellectual property protection of vaccines or their components and underlying technologies. Nevertheless, it is a very important subject. The references in this section 4.1. are illustrative of the problems involved.

- Other barriers may be more effective, such as the reservation of complementary internally developed know-how, without which manufacturing cannot take place (Danzon and Pereira, 2011; Douglas and Samant, 2017; Plotkin et al., 2017).

One evidence of the limited value of patents in this field is that "prices of individual vaccines do not always decrease, even after patent expiration, in contrast to pharmaceuticals" (Plotkin et al., 2017).

On the occasion of the COVID-19 pandemic, two unsuccessful IPR initiatives were promoted: the WHO's "Covid-19 Technology Access Pool (C-TAP)" that sought to facilitate the sharing of intellectual property (IP) and know-how among vaccine manufacturers, and the proposed TRIPS exemption of intellectual property rights at the WTO. The latter was the subject of controversy and debate at all levels, including the highest national and international organizations (see, for example, Danaiya Usher, 2020; Zarocostas, 2021).

Policies to reduce upfront costs include:

- Subsidies to private R&D
- Subsidies to reduce the cost of quality control
- Basic R&D financed or executed directly by the public sector
- Public-private partnerships for R&D, quality control and manufacturing.

In the COVID-19 pandemic, all of these strategies have been implemented in an extraordinarily ambitious manner. According to a thorough investigation, vaccine developers had received, as of February 2021, approximately US$10 billion[15] (Wouters et al., 2021), (excluding payments for purchases of the vaccines themselves). The top five companies had each received between $957 million and $2.1 billion mostly from the U.S. Government and the Coalition for Epidemic Preparedness Innovations (CEPI)[16] (Wouters et al., 2021). The U.S. Federal Government's Operation Warp Speed as of March 2021 had provided more than $19 billion to seven private pharmaceutical manufacturers, including R&D for treatments and the actual purchase of vaccine doses (United States Congress, Congressional Budget Office, CBO, 2021). For its part, the EU spent more than €1 billion on vaccine research through Horizon 2020 (650 before the pandemic). Adding R&D funding, investment in the development of production capacities and payment of vaccine prices, the funds mobilized by the EU for vaccines exceeded €30 billion in 2021 (European Commission 2021, May 18).

What are the implications of the high public funding of COVID-19 vaccines? It must be taken into account that a vaccine in pandemic conditions has an extraordinary social value. These huge public investments are justified by the need to ensure their development and availability. It has been estimated that the entire cost of the first vaccination campaign in Israel (one of the countries that paid the most in exchange for priority service) was equivalent to the economic losses of only two days of confinement. Already the idea that governments should be "generous" in deciding such a profitable investment was forcefully defended by Nobel Prize-winning economist Michael Kremer and his collaborators in a famous article in The New York Times (Athey, Kremer, Snyder and Tabarrok 2020): "The fact is that, from the earliest stages

[15] Based on publicly available data on disbursements made by governments and non-profit organizations for R&D and production of advanced COVID-19 vaccine candidates. It includes funding paid upfront or through milestone payments for late-stage development of an experimental vaccine or production scale-up at risk prior to the completion of clinical trials awarded in AMC between governments and companies. These figures, the authors caution, are likely an underestimate because of missing data on some projects (Wouters et al., 2021).

[16] The Coalition for Epidemic Preparedness Innovations (CEPI) is a collaboration of public, private and philanthropic institutions, and civil society organizations with the goal of accelerating the development of vaccines against emerging infections. It was founded by the governments of Norway and India and the Bill and Melinda Gates Foundation, the Welcome Foundation, and the World Economic Forum. Today it receives funding from numerous governments and other private and public entities.

of development, most vaccines fail. We can't afford to fail, so we have to plan for success. To do that, we need to think and invest as ambitiously as possible" (Athey et al., 2020). And The Economist blamed the initial delays in Europe in vaccine availability, compared to the US: and the UK, on overly strained negotiations by the Commission (The Economist Editors 2021). In any case, it seems reasonable that these negotiations should not end in unjustifiable burdens on the public purse (Lobo 2022).

Collaboration and alliances between companies to increase capacity and production can be very important. These are usually the result of private agreements, but can also be fostered by public support and encouragement. Such collaborations have been extremely important during the COVID-19 pandemic because of the need to rapidly increase production. The agreements involved extensive technology transfer, so that innovative companies have voluntarily and actively shared knowledge, technology and data with domestic manufacturers (Wouters *et al.*, 2021). Industry preferred this policy to regulatory solutions (such as patent suspension) or intervention by public agencies, and numerous such agreements were signed and implemented (Hatchett et al., 2021). The question is whether these voluntary agreements were insufficient to expand supply, especially in relation to developing countries. Encouraging production and meeting global vaccination needs worldwide would require elucidating which instruments would be most effective and what would be the appropriate mix of voluntary private market agreements and national and international public policies.

In market economies**, direct public sector involvement in manufacturing** is very rare, but it is a possibility that has been advocated[17] in the case of vaccines, given their effectiveness and external effects. This option has been supported for small countries, "which cannot sustain private vaccine production because they risk being deprived of essential vaccine supply in times of shortages, especially in the case of pandemics." (Sloan, 2012, p. 542). However, it seems that there are more realistic and effective alternatives that pass through regional or international cooperation, as demonstrated in the case of anti-SARS - CoV-2 vaccines.

4.2 Demand "Pull" Policies During the COVID-19 Pandemic – Advance Market Commitments

Incentivizing R&D and manufacturing can be achieved by expanding solvent demand, thus overcoming some of the present market failures and, of course, increasing the vaccination of the population. Some possibilities are as follows:

- Information and education programs
- Subsidies or free of charge
- Free direct provision by the public sector, vaccination campaigns, etc.
- Legal obligation to vaccinate
  - ✓ General in scope
  - ✓ For specific groups
  - ✓ For certain activities: kindergartens, schools, universities, health services personnel, companies, travel...
- Philanthropic initiatives, volunteering...

In this context, it is necessary to refer to Advance Market Commitments **(AMC)**,[18] especially those concluded by the EU for anti-COVID-19 vaccines, analyzed in detail in (Lobo 2022). New data on these have been published in a recent report by the European Court of Auditors. This is the demand-stimulus program devised in 2000 by Nobel laureate Michael Kramer and

[17] Even in the U.S., a bill, the "National Vaccine Authority Act," was introduced in the House of Representatives that provided for the development and production of vaccines by the public sector (Sloan 2012; Lichtemberg 2007).
[18] The European Commission has called AMC as Advance Purchase Commitments.

his collaborators (Kremer 2000a; Kremer 2000b) consisting of a contract in which funders are bound to purchase a specific number of doses at a given price if the condition that a vaccine is developed under certain specifications by the developer/manufacturer. AMC are intended to address static (irrecoverable loss or "deadweight" of monopoly) and dynamic (poor R&D incentives) distortions in the vaccine market by encouraging innovation and production of the vaccine once developed, as they reduce uncertainties for both parties and ensure solvent and reliable demand for the developer (Kremer, 2002; Kremer and Glennerster, 2004; Glennerster et al, 2006; Berndt, Glennerster, Kremer, et al. 2007; Kremer M, Levin JD. and CM. Snyder 2020 December, etc.). In particular, they solve the "hold up" problem - i.e. the fear of companies that if they develop and invest in a product of such high social value as a vaccine, they will be forced to supply it at low prices and their investment will not be remunerated.

AMC have been very successful. In the last ten years, within the framework of contracts of this type, the vaccine against pneumococcus and the vaccine against Ebola have been developed with impressive results. Of the former in 2016, 160 million doses were already distributed annually in 60 countries, enough to immunize 50 million children per year, and it has been estimated that 700,000 lives had been saved by 2021 (Kremer, Levin and Snyder 2020 February; Lobo 2022). The clinical development, manufacture, and delivery of a vaccine against Ebola infection, with very high lethality, has been another AMC success story (Gavi 2016). Between 2018 and 2020, the vaccine was already used in response to three epidemics in the Democratic Republic of Congo. It achieved full authorization in 2019 from the EMA and FDA and WHO prequalification. (Doctors Without Borders 2021), (Lobo 2022).

When the COVID-19 pandemic started, AMC had the advantage that they were based on sound economic theory and had already been successfully tested. The WHO - with the "COVAX" mechanism – the EU[19] and the US agreed such contracts with potential developers/manufacturers that were crowned by the unprecedented success of getting several SARS-CoV-2 vaccines in less than a year. This success must be attributed not only to science, policy and business determination, but also to Economics, for the correct design of the AMC contracts (Lobo 2022). On December 21, 2020, the European Commission (EC), at the proposal of the European Medicines Agency (EMA), already issued the first authorization, only eleven months after the sequencing of the virus in China. In April 2023 we have eight vaccines approved by the EMA, one of them from the Spanish company HIPRA Human Health (European Commission 2022 August; EMA 2023), the details of which we have already seen in Table 2.1. By June 2022, under the AMC, the EC had bound 4.2 billion doses, of which manufacturers had delivered 1.7 billion to the European MM:S, with which 86 per cent of the European population had been fully vaccinated (European Commission 2022 August). By November 2021, the Commission had signed 11 contracts with eight manufacturers worth €71 billion on behalf of the Member States (European Court of Auditors 2022).[20] The weighted average cost per dose is approximately €15 (European Court of Auditors 2022).

Another question, which has been much discussed, especially in Europe, is the "price" paid for AMC and the "generosity of public aid" to developers and manufacturers, with opinions in both directions. As this has been as much about support for cost reduction as about stimulating demand, we refer to what has already been said in general about public support for R&D, manufacturing and access to vaccines in conditions of an extraordinarily lethal pandemic in

[19] On the European experience see (Lobo 2022). "...the PPPs concluded between E.C. and Member States (MM.S.) and pharmaceutical companies between summer 2020 and summer 2022...have fully achieved their objective, so that vaccines have been made available to European citizens unusually promptly having largely prevented severe disease episodes and mortality from COVID 19." By June 2022, under the AMC, the EC had bound 4.2 billion doses, of which manufacturers had delivered 1.7 billion to the US, with 86 per cent of the European population fully vaccinated (European Commission 2022 Aug).

[20] The European Court of Auditors reports that the volume of these committed acquisitions could amount to 4.6 billion doses in November 2021.

section 4.1. Here we add the need to overcome the depression in demand that inevitably generates the positive external effect of vaccines and which is an additional justification for the impressive European effort of joint acquisition of the doses necessary to vaccinate the entire population of the E.U. We also recall the clearly positive balance that has resulted from the efficiency studies (cost-effectiveness and cost-benefit) of these vaccination programs that we mentioned in section 3.1. on demand.

The European AMC must be placed in the context of a European policy in the face of a pandemic that has had very important economic and health dimensions. Despite the fact that the EU has limited competences in health and public health (cross-border threats, legislation and authorization of medicines), after some unilateral manifestations of "health and vaccine nationalism" by some Member States, the EC took the reins of a pan-European solidary response policy, in an unprecedented operation, as the European Court of Auditors states (2022). In 2020 it was not known if or when a vaccine against COVID-19 would reach the market. The Commission chose to endorse a number of candidates to create an initial pipeline with different vaccine technologies and manufacturers to promote a rapid market response and spread the risk of failure and delay (European Court of Auditors 2022).

In June 2020 the Commission already defined an EU Strategy "to accelerate the development, production and deployment of vaccines against COVID-19" (European Commission 2020 a 7 June; European Commission 2020 b 17 June). The strategy is based on two pillars:

1) EU production and sufficient supplies for its member states, including a **central procurement process.**
2) Adaptation of the EU regulatory framework to the urgency and use of available regulatory flexibility.

As the European Court of Auditors (2022) says, this strategy - apart from its own report - has not been sufficiently evaluated. The Commission has not done so. However, it seems clear that the balance is very positive. The European AMC negotiated centrally by the EC, with the collaboration of the US, despite some initial difficulties, have succeeded in stimulating and shortening R&D and manufacturing and in ensuring that SARS-CoV-2 vaccines have reached all US citizens on equal terms and at the same time. It can be considered an extraordinary success whose consequences go beyond the health field and are even projected into new and expanded perspectives for European integration (Lobo 2022).

On a global scale, as is well known, COVAX used the AMC mechanism and other cooperative actions. We will study in section 4.4. how and why this well designed program could not manage to solve, or only partially and belatedly, the problem of equitable distribution of vaccines to at-risk populations worldwide.

4.3 Special Treatment During the COVID-19 Pandemic of Civil Liability for Damages

The issue of civil liability for damages (in this case adverse reactions) has been decisive in AMC of anti_COVID-19 vaccines in all developed countries and, moreover, it was resolved differently in the United States and in the European Union. It is an extremely important problem for all consumer goods industries and, in particular, for the vaccine industry as we have already mentioned in section 3.4. Litigation over claims by patients for eventual adverse reactions and other injuries can be extremely costly for suppliers (because the number of vaccinated healthy people tends to be large), to the point of deterring investment in innovation and manufacturing. They can also be unaffordable or cost-prohibitive for consumers (because of procedural difficulties). Special rules that seek to eliminate or alleviate these difficulties simultaneously affect both supply and demand.

In various jurisdictions, **objective** tort liability legislation **for damage caused by consumer products** in general ("no tort liability" and "strict liability" in Anglo-Saxon systems) has been adopted to avoid or limit these problems. But a balance must be maintained between the interests of companies without discouraging investment in, for example, novel vaccines, and those of consumers who must be compensated for the damages they suffer. The central idea is that the supplier of a product is liable for damages that may arise simply by placing it on the market. Proof of a wrongful act, negligence or fault on his part is not required from the part of the plaintiff. On the other hand, the plaintiff must prove the damage, the defect of the product and the causal link. The European Union introduced this system in 1985 by Directive 85/374/EEC for all consumer products, including pharmaceuticals and vaccines. However, there is currently a tendency to relax the requirements of the claim, so that it would not be necessary to prove the causal link, or else the burden of proof is reversed (it is the supplier who has to prove that the damage was not caused by the product). This trend has been driven by the legislation of certain U.S. states and their case law, as well as by the case law of the European Court of Justice. Precisely, it was a vaccine litigation that triggered these changes in Europe, the Sanofi-Pasteur case (Court of Justice of the European Union 2017).[21]

A revision of the 1985 Directive is currently being processed (European Commission 2022 September). The draft Directive, in addition to other important novelties, exceptionally admits reversing the burden of proof, which would be the "most radical provision because it implies reinforcing the objective nature of liability by presuming the defect and the causal relationship as long as the economic operators do not provide evidence of its non-existence" (Atienza Navarro 2023). The proposal maintains the general obligation for the plaintiff to prove the defect, the damage and the causal relationship, but admits exceptions. Damage is presumed when the defendant has failed to comply with the obligation to show evidence; when the product does not comply with the mandatory safety requirements established by law and when the plaintiff proves that the damage was caused by an evident malfunction of the product during normal use or under normal circumstances. Causation is presumed when the product has been proven to be defective and provided that the damage caused is "normally compatible" with the defect in question. The defect or causal link are also presumed when the plaintiff faces undue hardship due to the technical or scientific complexity of the product.

In addition to this general regulation, special measures have been adopted in the case of vaccines in an attempt to strike a balance between the rights of users and the limitation of risk in order to maintain investment in innovation. These include indemnity guarantees or public insurance, exemptions from liability and limitations on compensation. In the USA, in 1986, the National Childhood Vaccine Injury Act created no-fault compensation for childhood vaccines and the Vaccine Injury Compensation Trust Fund, financed by a special tax on the vaccines themselves paid by consumers (Grabowski and Vernon, 1997; Finkelstein, 2004; Sloan, 2012). In 1993, Medicare began providing insurance coverage for flu vaccines (Sloan, 2012).

Also in the USA, following several petitions from the pharmaceutical industry, a legal provision, the "Public Readiness and Emergency Preparedness Act" of 2005 (initially motivated to encourage influenza vaccines) exempts vaccine manufacturers, managers and distributors, as well as health care personnel, from legal liability for damages that may result from the administration or use of "health countermeasures" (including vaccines). The exemption requires a previous formal declaration of threat or risk to public health from the Department of Health and Human Services (HHS) including certain details (type of disease, duration, geographic scope, etc.). This legislation also established a compensation fund ("Covered

[21] The judgment considers that the Directive prevents a general regime of presumptions and the reversal of the burden of proof of the causal link, but allows it to be considered proven when certain circumstances are present. It would go in the direction of admitting that despite the fact that the medical research had neither proved nor disproved the existence of a relationship between vaccine and the appearance of the disease suffered by the injured party, some solid, concrete and concordant evidence could allow concluding that the vaccine suffers from a defect and that there is a causal link between said defect and the disease (Torrubia Chalmeta 2017).

Countermeasures Process Fund") for persons suffering significant health damage from these measures. (Administration for Strategic Preparedness and response ASPR 2023; European Court of Auditors 2022). There is evidence that these regulations in the U.S. were positively associated with R&D, investment and manufacturing (Finkelstein, 2004). Some other jurisdictions also limit the amount of compensation.

With the advent of the COVID-19 pandemic in 2020 the extreme urgency to develop and manufacture effective vaccines prompted the earlier mechanism in the U.S. to be put in place very early, on March 10, 2020, and companies were assured of immunity from potential claims from the outset (U.S. Department of Health and Human Services, Office of the Secretary 2020).

On the other hand, the European Union, when negotiating AMC with pharmaceutical companies, maintained the validity of the 1985 directive, i.e. the civil liability of the companies. This seems to have been the determining reason for the delay in the conclusion of these contracts, in comparison with the United States and the United Kingdom. Finally, very detailed provisions were agreed in the AMC, according to which a citizen who has suffered adverse effects from one of the COVID-19 vaccines purchased under the contracts can bring an action for damages against the manufacturer. But if the action is successful, the Member State that administered the vaccine will be liable to compensate the injured party and to pay the vaccine manufacturer's legal costs (except if the damage or loss is due to wilful misconduct or non-compliance with EU good manufacturing practice) (European Court of Auditors 2022). The uncertainty for companies is thus greatly reduced, although not as much as in the USA, as they are exposed to litigation which, although its costs are compensated by the State, may have, for example, additional reputational costs. The Commission justifies this unusual exemption by the very special circumstances of the pandemic and the interest in the urgent development of vaccines (European Commission 2022). This decision has been widely criticized. But it must be said that the risk of facing very large damage awards - given that the vaccine is administered to a large healthy population - is one of the most complicated market failures in this industry. (See Lobo 2022; Borghetti, Fairgrieve, Goldberg et al. 2021; Hoen and Boulet. 2021).

4.4 Global Inequity and the COVAX Program

The proportion of the population vaccinated against COVID-19 with at least one dose, as of December 8, 2021 (one year after the first vaccines became available), was 8.3 per cent in lower-income countries. In Spain - one of the countries with the highest vaccination rate - it was 82 per cent (Our World in Data 2021*).* The imbalance in vaccination coverage between countries according to income levels has persisted, as can be seen in Figure 4.1, and lower-income countries remain far behind over time.[22]

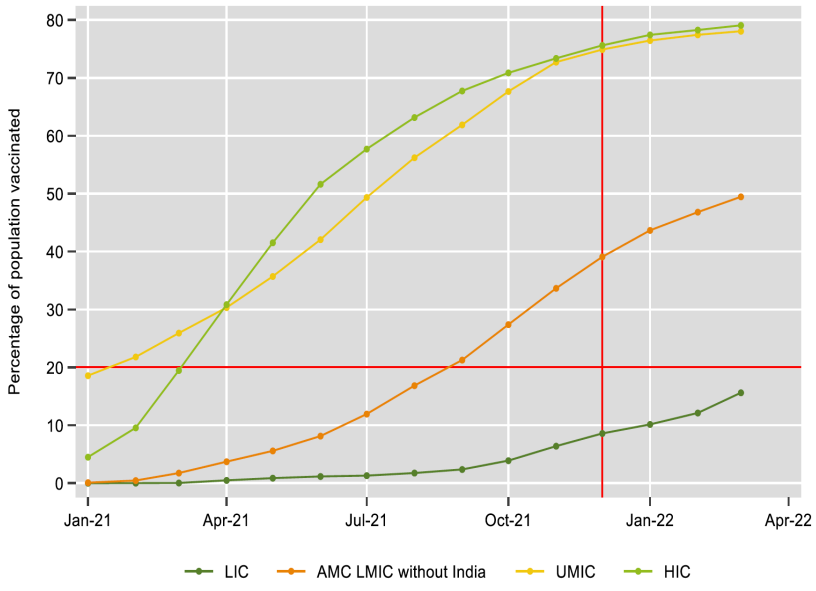
Figure 4.2. graphically represents the different vaccination rates in the world in December 2022, two years after the first vaccines became available. At that time there were still significant differences in vaccination rates between countries by income level. Eighty percent of the population in high-income countries had received at least one dose, in contrast to 24 percent in low-income countries. Given the proportion of young people in the latter, in general, 22 per cent covers all high-risk groups (mainly persons over 60 years of age). In any case, 76 per cent of the population in low-income countries and, on a global scale, one third of the world's population, 2.5 billion people, remained unprotected. However, by 2022, major progress had been made in vaccinating some low-income countries. 63 countries reached the

[22] Vaccination coverage is actually lower than that shown in the figure, since it divides doses by population and some groups have been vaccinated with multi-dose schedules. Coverage would drop to 9 per cent taking this circumstance into account (Cooper, Jain, Janssen et al. 2023).

WHO target of 70 per cent of the population vaccinated, of which 41 are high-income, 15 are upper-middle-income and only seven are lower-middle-income. 138 countries had not reached the 70 per cent target and 30 were below 20 per cent, of which 16 are low-income countries (UNICEF 2023; Our World in Data, Mathieu et al. 2023). The WHO stated in May 2022 the inequality gap with the following words: “In some low-income countries, many of the most at-risk people (health workers, older people and people with underlying health problems) are still unprotected, while in wealthier countries young, healthy adults receive booster doses”, (WHO 2022 May).

These inequalities are not only related to ability to pay, but are also influenced by other factors such as deficiencies in the health and logistical distribution systems (countries' capacity to distribute and "reach into arms" of their inhabitants), the acceptance of vaccines and hesitance by populations, and, sometimes, the lack of political priority by governments. Many developing countries are therefore dependent on international cooperation for the immunization of their populations. This cooperation is a way of stimulating global demand for vaccines that deserves special consideration. Since its inception, WHO has developed a whole series of initiatives (prequalification of products and manufacturers, technical assistance...); UNICEF has a large and successful program of cooperative procurement through competitive bidding. Also very important are the philanthropic and public-private initiatives contributing to the development and distribution of vaccines and treatments for tuberculosis, human immunodeficiency virus (HIV), malaria and now COVID-19. The main players are GAVI, CEPI, Unitaid, The Global Fund and the Gates Foundation (BMGF).

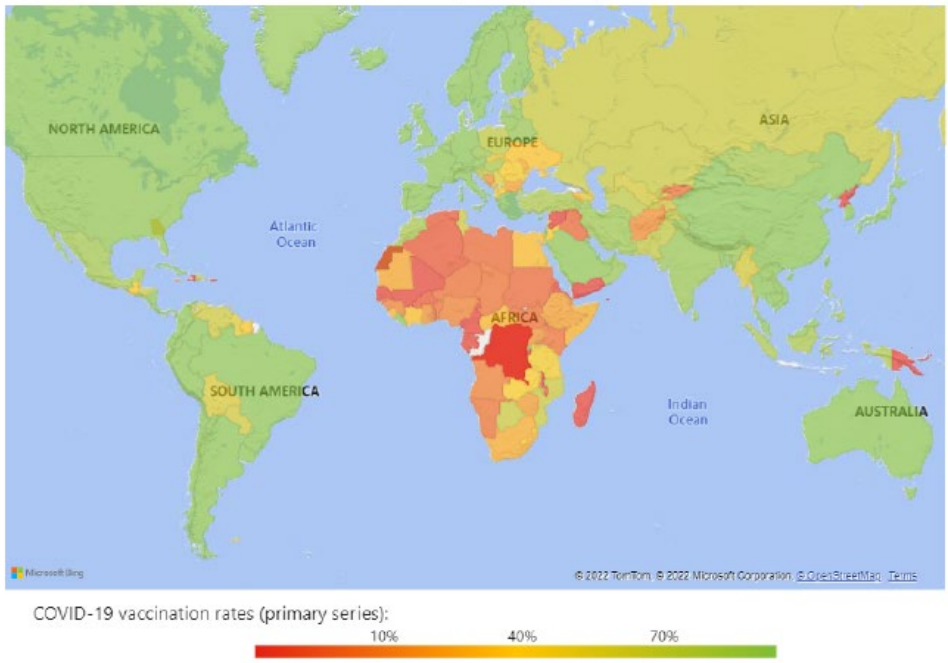
Figure 4.1.
Vaccination coverage of countries by income level (World Bank classification)



Source: COVID-19 Data Dashboard, https://infohub.crd.co/ accessed August 2022

Source: (Cooper, Jain, Janssen et al. 2023).

Figure 4.2.
Vaccination rates per country in the world. December 2022



Note: Vaccination rates for the first schedule
Source: UNICEF 2023; Our World in Data, Mathieu et al. 2023.

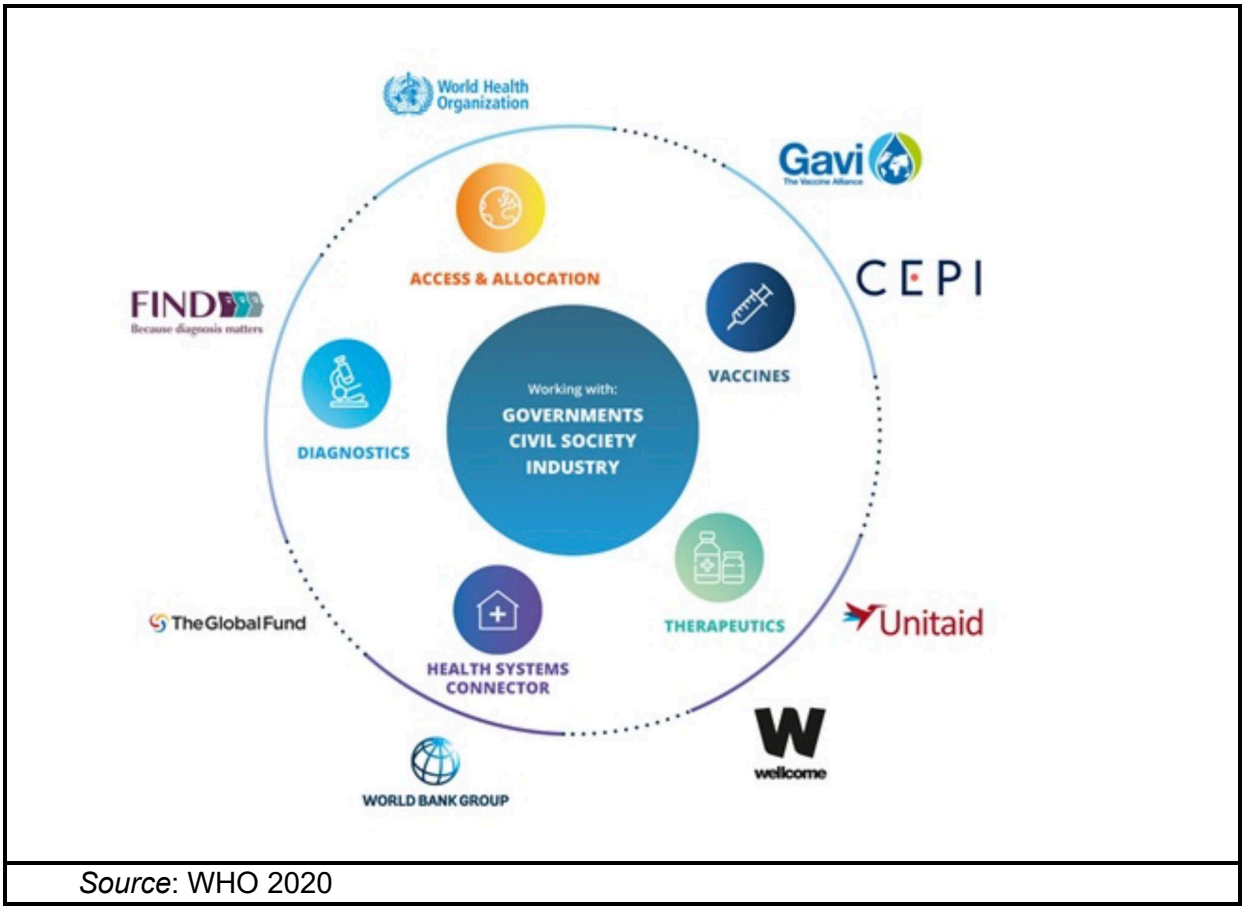
The main international cooperation program for COVID-19 vaccines was **COVAX** (COVAX-19 Vaccine Global Access Facility), particularly for developing countries (low and lower-middle income), although they were not the only ones covered. On March 26, 2020, the G20 proposed a united front against the pandemic by pledging to provide the necessary resources to international public and private health organizations engaged in the fight against the pandemic (G20 Leaders' Summit 2020). WHO on April 24, 2020, proposed a global collaborative program to accelerate the development, production and equitable global access to COVID-19 tools (Access COVID Tools Accelerator, or **ACT Accelerator**). These tools were diagnostic tests, treatments and vaccines, as well as a sub-program to facilitate their incorporation into *health* systems. The ACT Accelerator brought together governments, scientists, companies, civil society organizations, philanthropists and global intergovernmental and non-governmental health organizations (the Bill & Melinda Gates Foundation, CEPI, FIND-Diagnosis for all, the GAVI Alliance, the Global Fund (initially for AIDS, tuberculosis and malaria), Unitaid, Wellcome, WHO and the World Bank) (WHO 2020). For its part, the European Commission adopted, in addition to its own extensive pandemic response programs, the Global Coronavirus Response Initiative with matching objectives and initial funding of 15.9 billion euros up to August 2020 for vaccines, treatments and diagnostics (European Commission 2020).

COVAX was launched by WHO in 2020, as one of the pillars of the ACT Accelerator, and closed at the end of 2023. It has been an absolutely pioneering and unprecedented global initiative, developed under extreme circumstances. Its **mission** was very ambitious (Cooper, Jain, Janssen et al. 2023):[23] support the development, manufacture and negotiate the prices of anti-COVID-19 vaccines and ensure that they were distributed worldwide in an equitable

[23] This work by Itad, a consulting firm specializing in international cooperation projects, is an evaluation of COVAX as a whole, commissioned by Gavi, going up to early 2022. It is very comprehensive and has been published in March 2023. We rely extensively on their data and adjusted assessments.

manner (Berkley 2020; Gavi 2022), unlike in previous pandemics and epidemics, where bargaining power and ability to pay had prevailed. To this end, it mobilized financial resources, mainly abundant donations, aggregated demand and negotiated AMC. Never before had **global mechanisms** for financing, public procurement, allocation and distribution of complex industrial products been put in place. It can be said, without exaggeration, that it has been an experience of global governance - with inevitable limitations - in a specific area. With public-private participation, it was **led** by the Coalition for Epidemic Preparedness Innovations (CEPI), the World Health Organization, Gavi, the Vaccine Alliance, and from 2021 UNICEF.

Figure 4.3.
Accelerator of access to WHO anti-COVID-19 (ACT) tools: organizations involved and fields of work



Source: WHO 2020

COVAX was **justified** on grounds of justice and solidarity, but also out of selfishness in this interconnected global world where infections are transmitted over long distances with enormous ease and can have devastating economic consequences, as has happened with COVID-19. As the WHO director said, we were "on the brink of catastrophic moral failure" if we did not show solidarity: "vaccines are weapons of mass salvation". Moreover, vaccinating all countries - rich and poor - protects the populations of rich countries and is a necessary condition for overcoming the pandemic. "As long as we are not all safe, no one will be safe." (Ghebreyesus 2021). Some approaches to the cost-benefit analysis of equitable global vaccination made it clear that "vaccine nationalism" is self-defeating. "No economy is an island and none will fully recover until all economies recover," given the intense interrelationships of the global economy. It was estimated that High Income Countries[24] could have lost up to 4

[24] We use the World Bank's well-known classification by income level: High Income, Middle Income (both High and Low Income) and Low-Income countries.

per cent of GDP if vaccination was not global (Çakmakli, Demiralp, Kalemli-Özcan et al. 2021). The donations needed to vaccinate everyone added up to much less than the losses to High Income Countries from the slower economic growth of unvaccinated Middle and Low Income Countries. The return on investment required for all WHO COVID-19 projects were 166 times (Access to COVID-19 Tools, ACT). WHO-led international cooperation initiatives helped high- and middle-income countries to achieve full recovery by supporting all economic sectors, protecting global value chains and ensuring long-term global growth (WHO 2020, 25 September).

The participation of **countries** in COVAX was envisaged to be of **two types,** free of charge and onerous. The purchase of vaccine doses was free, in whole or in part, for the 92 middle- and low-income countries that were to receive donations to protect up to 20 per cent of their population in the long term. The initial intention was that they would receive them under the same conditions and schedule as the higher-income self-financing countries. Self-financing countries with higher income levels were guaranteed to receive doses based on the volume they choose to purchase and pay for with their resources, under the favorable conditions of the COVAX framework, thus covering themselves with a kind of "procurement insurance" (Berkley 2020; Gavi 2022).

On the other hand, COVAX had two major operational components: the support and financing mechanism **("COVAX Facility")** and the AMC-type contracts. The COVAX Facility identified the vaccines to be purchased, collaborated with manufacturers to encourage them to promote and expand manufacturing, used the collective purchasing power to negotiate prices, and managed the mobilization and use of financial resources. The second operational component was the **AMC** managed by COVAX for the donor countries, the characteristics of which are those already described in section 4.2. As for distribution, the general rule was that the available doses were to be distributed among countries in proportion to their population size, with a maximum coverage of 20 per cent. Higher amounts were only to be provided if all the other countries had already covered this percentage.

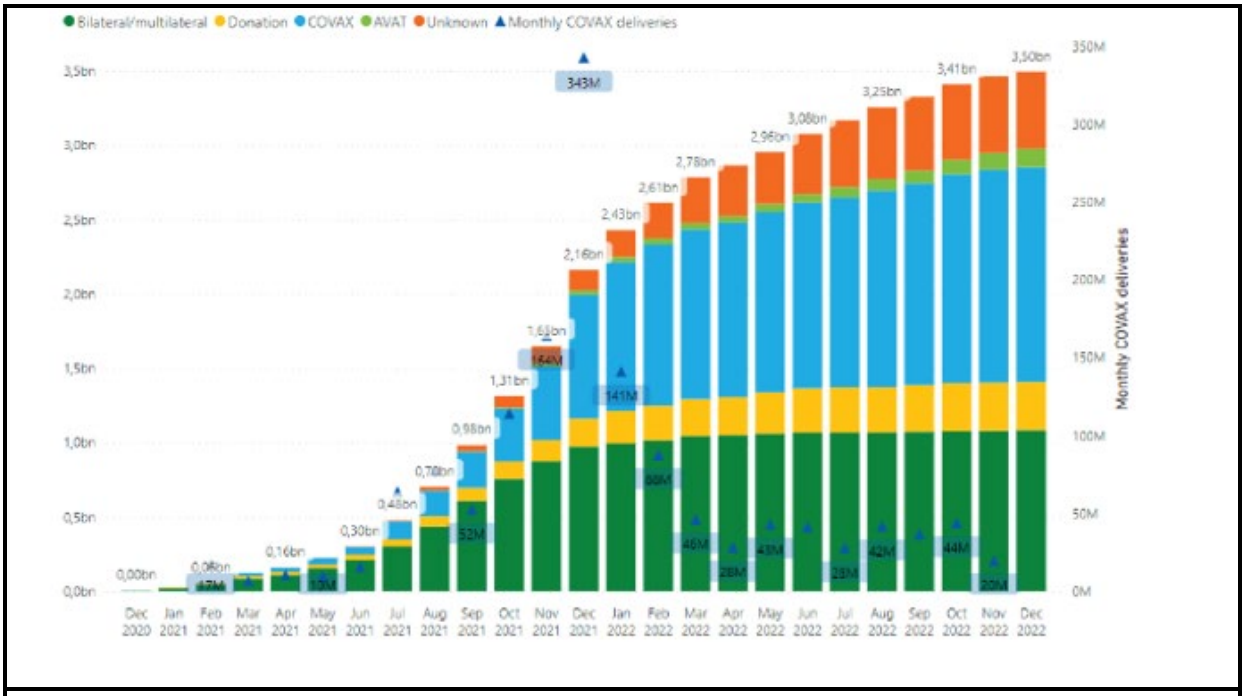
Self-financed countries had two options:

1) Committed Purchase Arrangements, which required an upfront payment of $1.60 per dose, or 15 per cent of the total cost per dose. In return they received a certain number of doses, subject to COVAX's equitable allocation rules.
2) Optional Purchase Arrangements (OPAs), designed for countries that wanted to supplement the supplies they had already agreed to in other ways. In this case the cost was higher ($3.10 per dose, plus a risk-sharing guarantee of $0.40 per dose).
3) In addition, COVAX had other complementary components:
    - Provisions to exempt developers, manufacturers and suppliers from civil liability for damages ("Indemnity and Liability" and "No Fault Compensation Scheme").
    - The "humanitarian buffer" (Humanitarian buffer) of last resort, designed to vaccinate groups in high-risk situations (refugees, displaced persons, marginalized people...), outside organized national vaccination programs.

COVAX's **initial objective** was to obtain 6 billion doses to cover at least the population of the most at-risk LMICs - including healthcare professionals - estimated at 20 per cent of the total by 2021. To achieve this, it envisaged initially procuring and distributing 2 billion doses for 190 countries, of which 1.3 billion for the 92 low- and middle-income countries covered by the AMCs (GAVI 2020 Dec. 18; Berkley 2020; Ghebreyesus 2021). The **result**, by the end of 2021, was that COVAX and its AMC had made a substantial contribution to vaccine **supply** and coverage in low-income countries and a moderate contribution in middle-income countries. By the end of 2021 it had distributed 957 million doses to 145 countries including 28 low-income and 46 middle-income countries. Lower income countries obtained 79 per cent of all vaccines received by them through COVAX (Cooper, Jain, Janssen et al. 2023). This is

a remarkable result, but below the targets set. In 2022 it supplied 1.961 billion doses, of which 918.980 million were donated, to 146 countries, doubling the 2021 supplies (UNICEF 2023). Figure 4.4. shows the development of COVAX supplies and the great weight they have had on the total received by low and middle/low income countries.

Figure 4.4.
COVAX. Vaccine supply to low-income and lower-middle-income countries by channel. Cumulative doses



Notes: India is excluded. AVAT: African Vaccine Acquisition Trust.
Source: UNICEF 2023

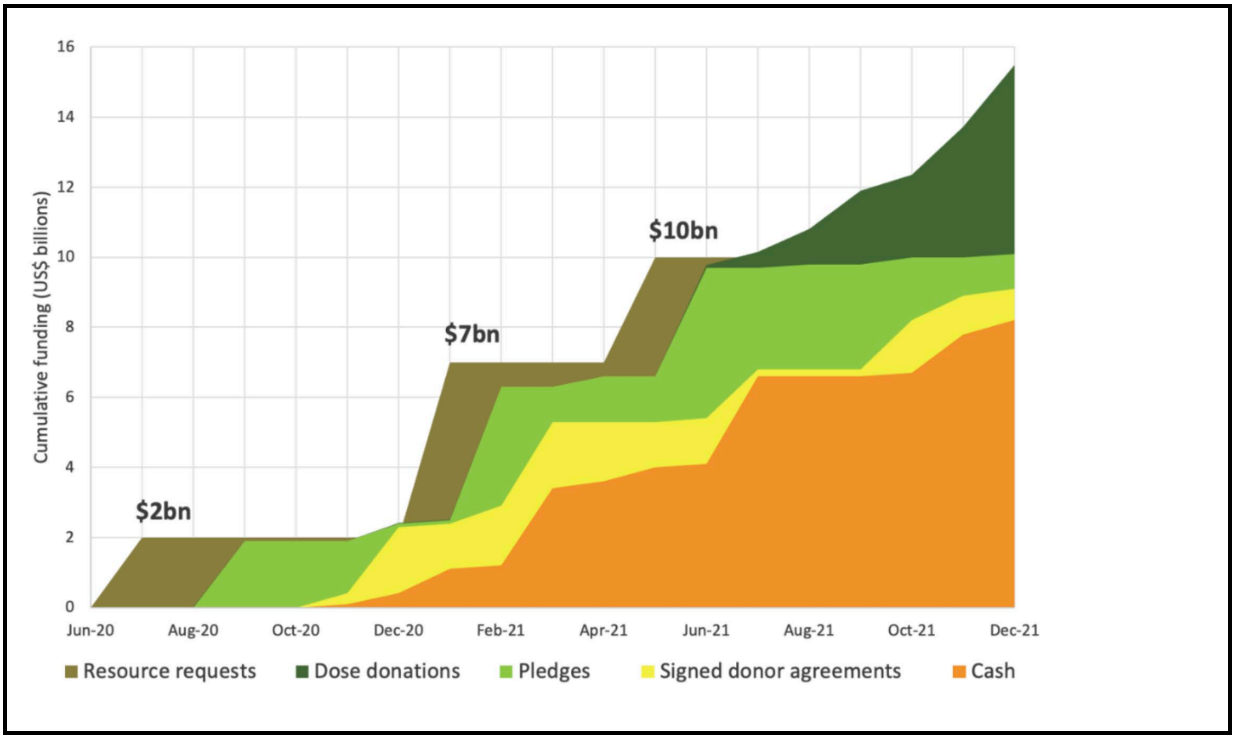
The most relevant performance indicators are those that refer to the health outcomes achieved with vaccination. Reductions in morbidity and mortality were very important, as we have seen in section 2. For COVAX/AMC countries, vaccination prevented 7.4 million out of an expected total of 17.9 million deaths, all by 2021 Watson et al. (2022).

On the **funding side**, COVAX achieved "resource mobilization of unprecedented scale and speed in the field of global health-related initiatives" (Cooper, Jain, Janssen et al. 2023). Although in 2020 the funds received were limited ($400 million), in 2021 a remarkable mass of resources was made available. Looking at the different stages of the process, it achieved pledges of US$10.1 billion; US$9.1 billion in signed donor agreements and US$8.2 billion immediately available cash. This is well above the target of US$9.3 billion by 2021, as can be seen in Figure 4.4. About 80 per cent of these funds came from donations for dose purchases, 7 per cent from direct contributions to support vaccine supply; 11 per cent from the International Finance Facility for Immunisation (IFFIm) and the remainder transfers from funds previously available for the pneumococcal vaccine AMC. Adding the value of direct dose donations (about $5 billion) brings the total amount of funds mobilized by COVAX at the end of 2021 to $15.5 billion (Cooper, Jain, Janssen et al. 2023). Another assessment has estimated $16.073 billion in funding for COVAX through September 2022 (excluding dosed grants), 68.5 per cent of the total mobilized for the ACT Accelerator (Figure 4.5.) (Open Consultants 2022). As of June 1, 2023, according to WHO, total pledges amount to $16.353

billion, to which dose donations, valued at an additional $7.5 billion, should be added (WHO 2023b. ACT-Accelerator Financial Commitment Tracker Overview).

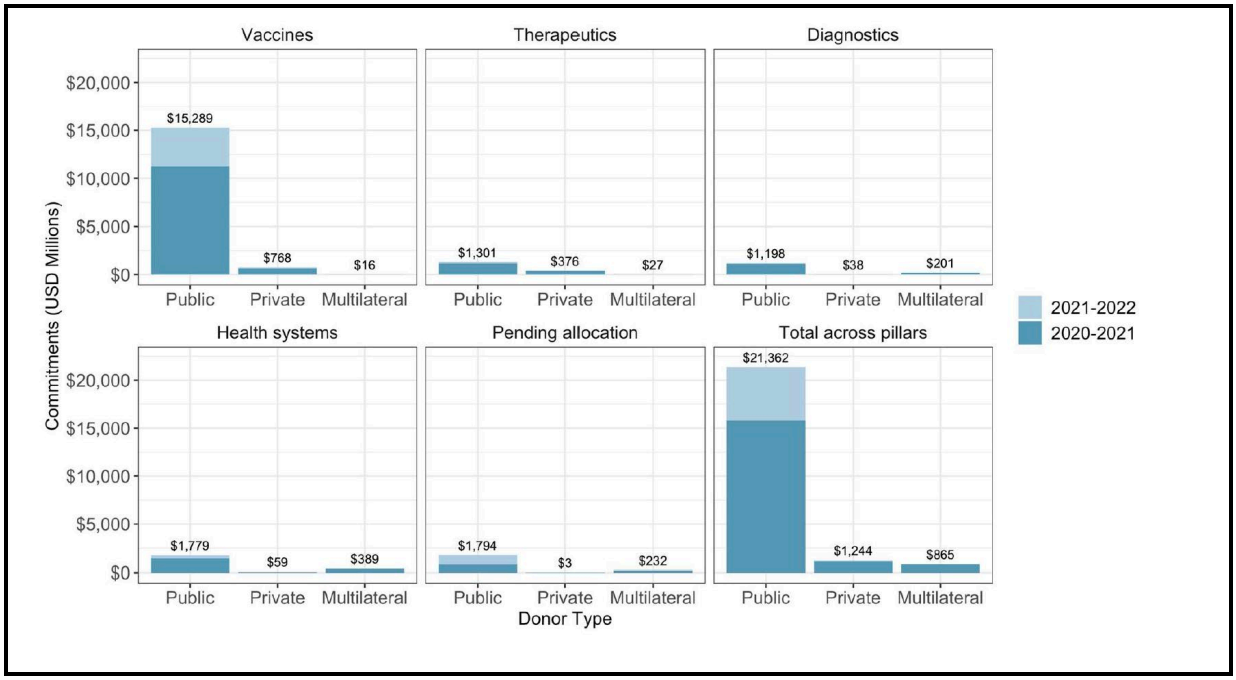
It has been suggested that, with the same donor effort, better results would have been achieved in lower-income countries if the funding would have arrived more quickly, so that they would have been able to sign AMC earlier and move further down the supply order list, headed by the more developed ones. Mechanisms have been designed to prevent such delays in future pandemics (Agarwal and Reed 2023).

Figure 4.5.A.
COVAX and its AMC. Funding requested, pledged and received and estimated value of dose donations



Source: (Cooper, Jain, Janssen et al. 2023).

Figure 4.5.B.
ACT Accelerator funding, by pillar type and funder. As of September 5, 2022. Millions of US dollars



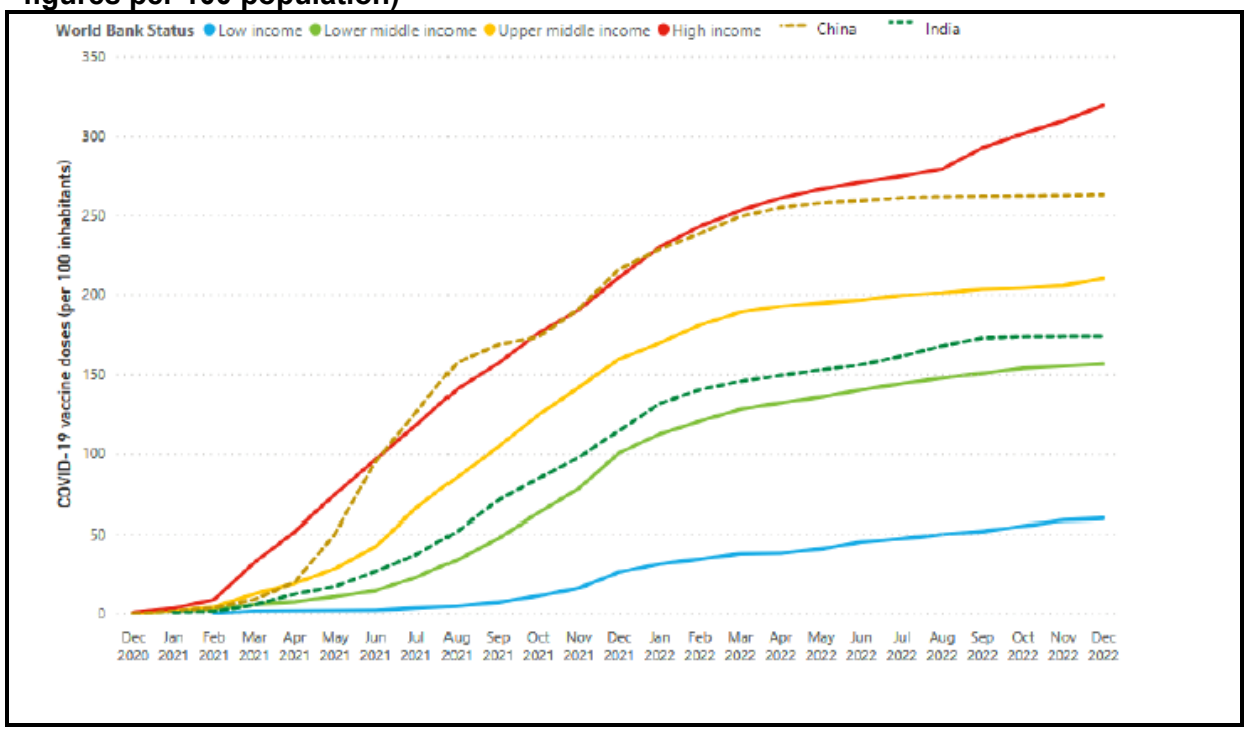
Source: Open Consultants 2022 and WHO ACT-A Commitment-Tracker

The **range of vaccines** susceptible to be subject to any COVAX AMC and supplied were the same the WHO admits in its qualification system (according to the Emergency Use Listing procedure). In December 2022 there were eleven, belonging to different technological platforms (Gavi 2022 December; UNICEF 2023; WHO 2023 b).

The main shortcoming of COVAX has been that, despite its achievements, it **did not achieved equity in global distribution,** as we have already seen at the beginning of this section in terms of vaccination coverage. This shortcoming is also confirmed by data on supplies. In the year 2021, 4.5 billion **doses of** anti-COVID-19 vaccines were supplied, and in the year 2022 just over 15.7 billion, with a very unequal distribution by income level, as shown in Figure 4.6. High-income countries received more than 300 doses per 100 inhabitants, while low-income countries received only 60. Despite the increase in production and manufacturing capacity over 2021 and 2022, there was no convergence between countries. (All these data in UNICEF 2023).

If the targets had been met (20 per cent vaccination coverage by 2021 in low-income countries), 45 per cent of deaths would have been averted (Watson et al. 2022). Another estimate calculated that an equitable global distribution of the first 2 billion doses would have prevented up to 61 per cent of deaths, whereas their exclusive attribution to EPIs would have prevented only 33 per cent (Chinazzi et al 2020).

Figure 4.6.
COVAX. Anti-COVID-19 vaccine supplies December 2020 - December 2022 (cumulative figures per 100 population)



Note: Includes all supplies: bilateral, multilateral, COVAX, AVAT and others from unknown channels.

Source: (UNICEF 2023)

There were several distributional problems. When production was still insufficient, the dilemma —both moral and health-related— was whether to vaccinate first the non-vulnerable groups in rich countries or the priority groups —health personnel— and vulnerable groups in poor countries. An ethical and certainly also a global health strategy required vaccinating the latter first, since they were the ones who stood to gain the most from vaccination. This was the request of the WHO director. The inequity was clear since, according to the known AMC, the High Income Countries reserved doses far in excess of their needs, which were expected to be surplus. In March 2021, the doses reserved by high-income countries were put at 4.6 **billion**, compared to 670 **million** for lower-income countries. Many of those had reserved doses to vaccinate their populations multiple times, Canada in particular five times. (Duke Global Health Innovation Center. Launch and Scale Speedometer 2021; The Economist Intelligence Unit 2021 January 27).

Itad's assessment indicates that "the design – of COVAX – underestimated the extent to which rich countries would serve their own populations first and companies would pursue their commercial interests, despite expressions of global solidarity..." (Cooper, Jain, Janssen, et al. 2023, p. vi).

The **cooperation of developed countries with COVAX** has been, in spite of everything, of great magnitude, as can be seen in Table 4.1, which shows the breakdown of donations of funds by donor country and makes it possible to gauge their contribution (those included in the table account for 95 per cent of the total). The US has contributed $4,352 million and the EU $5,714 million, to which must be added the donations of doses. After Trump's departure from the presidency, the US rejoined the WHO and continued an active cooperation policy. The EU was also very active. It spearheaded, with WHO, the launch of the ACT Accelerator

in April 2020; on May 4 it convened an international donor conference ("Global Goal: Unite for our Future") in the framework of the "Coronavirus Global Response" and in September 2020 it joined COVAX. EU Aid-for-Trade contracts provide that recipient states can donate surpluses and the European Commission organizes supplies (first for the Western Balkans, Eastern and Southern neighbors and Africa). European Commission 2021, January 19). For its part, **Spain** contributed 128 million dollars to COVAX and elaborated a Plan for Universal Access to Vaccines for Spanish Cooperation (Ministry of Foreign Affairs, European Union and Cooperation 2021). In execution of this plan, it delivered doses (from the supply of vaccines acquired by Spain in the framework of the joint EU purchase) to refugees, displaced persons and asylum seekers, least developed countries and partner countries of Spanish Cooperation where access to the 20 per cent priority was not guaranteed.

Table 4.1.
Monetary contribution commitments for COVAX
As of June 1, 2023. Millions of US dollars

Of public origin	15.569
From the U.S:	4.352
From the European Union ("Team Europe")	5.714
From Spain	128
From Japan	1.800
From Canada	1.783
From the United Kingdom	1.215
From Norway	727
TOTAL	16.353
Note: Team Europe is composed of the European Union, its Member States, including public development banks and implementing agencies, the European Investment Bank (EIB) and the European Bank for Reconstruction and Development (EBRD). Team Europe was initially created to ensure a coordinated and comprehensive response between the EU and its Member States to the COVID-19 pandemic and its consequences. Today it is the backbone of "Global Europe", the EU's main financial instrument for international cooperation.	

Source: WHO 2023b (ACT-Accelerator Financial Commitment Tracker Overview).

It seems that the main shortcoming of the cooperation of developed countries was not so much the shortage of donated funds, but rather their timing and, above all, the preference given to their populations and the supply reserves of doses implicit in their AMC sometimes in excess of needs. The priority achieved in supplies by developed countries, coupled with the suspension of exports in April 2021 from India, where a key vaccine manufacturing company (the Serum Institute of India) is located, delayed the vaccination of developing countries at critical times, in early 2021, when supply could not meet global demand.

In conclusion, a detailed evaluation (Cooper, Jain, Janssen et al. 2023) has highlighted that the design of COVAX and its AMC has been coherent, ambitious, and responsive to a rapidly changing complex context. It failed to reach its target of supplying 2 billion doses by 2021, but its support was very important for the Low Income Countries, for which it was the main source of vaccine supply. However, it is noted that COVAX was not able to transcend the traditional rules of the vaccine market game. "It was a failure of international solidarity to condition the self-interested behavior of the most powerful players. .... It did not have sufficient market power to compete successfully for vaccines against the far superior resources of High Income Countries, nor to influence most manufacturers' decisions on manufacturing capacities" (Cooper, Jain, Janssen et al. 2023, p. 50). As just noted, the precedence given by developed

countries to their not particularly vulnerable populations over the priority and vulnerable ones in developing countries and the stockpiling of supplies in excess of the needs implicit in their AMC were critically detrimental decisions for the latter.

Looking ahead, COVAX's expertise should be developed and expanded in several dimensions:

- Guarantee of the necessary financing
- Ensuring a balance in the stockpile of doses in the AMC and in the availability of surplus doses from other countries where they are most needed.
- Continue to encourage inter-company agreements to increase global manufacturing
- The WHO technology access consortium (C-TAP) should be revitalized.
- Promoting manufacturing in developing countries

On this last issue, which is of utmost importance, we make some notes in the following section.

4.5 Manufacturing Promotion

Increasing vaccine manufacturing capacity worldwide seems a desirable goal. As we have seen with the anti-COVID-19 vaccines, manufacturing capacity has been a major bottleneck and developing countries have been particularly affected. The point is that, as we have seen at the end of section 2 and in section 3.5, manufacturing processes are complex, require mastering demanding and advanced technologies and deploying long and intricate supply chains of specialized substances. Furthermore, production plants are very specific and specialized and it may be unavoidable to undertake major investments and build and equip them "ex novo" to produce the new vaccines that would be needed against new pathogens, as has been the case with COVID-19. Against this backdrop, developing countries face all kinds of problems of their own that limit their possibilities for developing new plants.

However, with new technologies and an adequate investment and organizational effort, significant increases in capacity can be achieved and the necessary lead times can be reduced. In the case of anti-COVID-19 vaccines, although there were some months of inevitable mismatch between supply and demand, the expansion of supply was rapid and very significant. The potential of local production and of small and medium-sized companies, government research centers and universities, including in developing countries, must also be taken into account, as mentioned in section 2, with the example of the Serum Institute of India, today one of the world's leading vaccine producers.

To achieve these objectives in the short term, the market offers possibilities including **agreements with other companies and entities** characterized as "Contract Development and Manufacturing Organizations" (CDMOs), the concept and typology of which are discussed at the end of section 2. The question is whether these mainly private market arrangements are sufficient to meet the needs of the entire world population and reverse the current highly unequal distribution of vaccines. Independent information and detailed studies are needed to clarify the extent of these arrangements and technology transfers. The COVID-19 pandemic has demonstrated how important it is for developing countries to move beyond outsourced manufacturing for fill-and-finish operations and surpass the limited objectives of reducing costs and increasing manufacturing capacity. In the long term, technical R&D and manufacturing capabilities need to be significantly increased and distributed to meet global needs and to prevent and respond rapidly to emerging infections and future pandemics in all regions of the world.

To this end, the role of **states, international organizations and international cooperation** can be decisive, as has already been demonstrated with anti-COVID-19 vaccines. In this direction, the proposals of the Rome Declaration of the World Health Summit of the Group of Twenty (G20) of May 21, 2020, stand out. The G20 established the ACT-Accelerator Facilitation Council Vaccine Manufacturing Working Group (VMWG) to create broader vaccine manufacturing bases, technology transfer centers in various regions, such as those recently established for mRNA in South Africa, Brazil and Argentina and to support the COVAX Manufacturing Task Force led by WHO, Gavi and CEPI, which has developed measures to respond to the challenges presented by vaccine manufacturing (G20 Italy, 2021), (ACT-Accelerator Facilitation Council Vaccine Manufacturing Working Group, VMWG, 2021).

New manufacturing plant projects in developed and developing countries, including public-private partnerships, are under serious consideration. The European Commission Task Force on Industrial Expansion of COVID-19 Vaccines (EITF) was established in February 2021 and the European Union is involved in vaccine manufacturing investment projects in Africa and South America (European Commission 2021, May 21). Indeed, in international cooperation, the EU initiative to implement capacity in Africa through the Sustainable Health Industry for Resilience in Africa (SHIRA) initiative stands out (European Commission, 2021, May 21). The U.S. President also announced a plan to expand vaccine production for local and developing country needs by an additional one billion doses in the second half of 2022 (Stolberg 2021). The African Union, for its part, has launched an initiative to meet 60 per cent of African vaccine demand with production on the continent itself by 2040. This initiative has been found to be well founded from an economic point of view. Although establishing a viable vaccine industry on the continent presents very serious challenges, the African Continental Free Trade Area (AfCFTA) can provide the right framework to achieve the economies of scale needed to stimulate production (Correa 2023).

5. CONCLUDING REMARKS

Previous analyses have shown that the vaccine industry makes fundamental contributions to global social welfare, that from a business point of view it is a complex and difficult business and that from an economics perspective it does not fit the paradigm of competitive market efficiency, with notorious market failures. The latter include high levels of economic concentration. Consequently, the industry's performance is below the required level in terms of innovation and demand satisfaction, despite its achievements, before and after the COVID-19 pandemic, in the development of new vaccines and in manufacturing.

In this report we have examined the initiatives and policies to address the pandemic and their major driving effects on innovation and scientific and technological development (development of highly effective vaccines, including the first mRNA technology vaccines, drastic reduction of the time required for their development, large variety of vaccines with extraordinary health benefits and competition advantages). The complexity of manufacturing and supply chains has been overcome, but not without problems and incidents. We also found that certain elements of the industry structure have changed, while others have persisted. Concentration has remained high, but new technologies and the emergence and empowerment of new business players have made the traditional "club" of suppliers less exclusive.

The deployment of public supply-side and demand-pull policies discussed above has provided fundamental lessons for the future. Governments and international organizations have developed very broad policies to boost supply, with very substantial financial aid that reduced development and manufacturing costs. AMC, which have ensured solvent demand and eliminated corporate commercial uncertainties, have also been instrumental, and this is a lasting lesson. The COVAX program, which also initiated AMC, has made a critical contribution to achieving solvent global demand and access to vaccines for populations in developed and developing countries. But it did not achieve global reach and developed countries gained priority in access, determined by their ability to pay and the securing of doses implicit in the AMC that they signed before COVAX could obtain the financial resources needed. This resulted in global inequity to the detriment of priority and vulnerable populations in developing countries.

The COVID-19 pandemic has thus demonstrated that some policies to stimulate vaccine R&D and manufacturing can be very successful, while others have not fully achieved their objectives. The performance of vaccine innovation, research and development, and manufacturing has been outstanding, having been decisively supported by the public sector, appropriate funding and certainty mechanisms (such as AMC), and collaboration between scientists and companies, and these lines should be persevered with. One clear lesson is that these successes require that the role of the public sector be expanded to unprecedented dimensions of leadership, organization, financing and technological support, with the collaboration of the private sector. Another lesson is that when it comes to global goods and ills with significant external effects, in a highly interconnected and integrated world, international cooperation is decisive. In this sense, the International Pandemic Treaty currently under discussion can be an essential instrument.

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SOUTH CENTRE

International Environment House 2
Chemin de Balexert 7-9
POB 228, 1211 Geneva 19
Switzerland

Telephone: (41) 022 791 8050
E-mail: south@southcentre.int

Website:
http://www.southcentre.int

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