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Restructuring the Global Vaccine Industry

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RESTRUCTURING THE GLOBAL VACCINE INDUSTRY

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SOUTH CENTRE

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ABSTRACT

The purpose of this report is to analyse the vaccines industry under the focus of Industrial Economics as an input for the design of the pertinent instruments to promote development, manufacturing and distribution of vaccines against SARS-CoV-2 in sufficient amounts to immunize all countries as soon as possible. We also need to be prepared for future emerging infectious diseases with the potential of global expansion.

The report shows that the vaccines industry is – and has been for a long time - far away from the competitive market paradigm with notorious market failures. As a result, the industry is underperforming with shortages and stockouts, exit of firms from the industry, underinvestment in research and development (R&D) and manufacturing, even an "anaemic development pipeline", all signs of market failure.

After a brief review of policies implemented to tackle these problems we conclude that after the COVID-19 pandemic there is a need to implement a profound overhauling of the industry and to fundamentally reformulate and extend global public policies to stimulate R&D, manufacturing, distribution and access.

L'objectif de ce rapport est d'analyser le secteur des vaccins sous l'angle de l'économie industrielle afin d'une part, de contribuer à la conception d'instruments utiles pour promouvoir le développement, la fabrication et la distribution de vaccins contre le SRAS-CoV-2 en quantité suffisante pour immuniser tous les pays dès que possible et d'autre part, de mieux nous préparer à faire face aux maladies infectieuses émergentes susceptibles de se propager à l'échelle mondiale.

Le rapport montre que le marché des vaccins est, et a été pendant longtemps, très éloigné du paradigme de la concurrence et marqué par de nombreux dysfonctionnements. En conséquence, le secteur, qui est souvent confronté à des pénuries et ruptures de stock, affichent des résultats décevants, qui ont amené certains entreprises à s'en retirer. Il accuse par ailleurs un déficit d'investissement dans la recherche et le développement (R&D) et la fabrication, et son pipeline de développement est inexistant ou presque. Ce sont autant de signes qui montrent que le marché dans ce secteur est défaillant.

Après un bref examen des politiques mises en œuvre pour résoudre ces difficultés, le rapport conclut, après la pandémie de COVID-19, à la nécessité de procéder à une refonte totale du secteur et de reformuler en profondeur les politiques publiques à l'échelle mondiale et de les étendre afin de stimuler la R&D, la fabrication et la distribution de vaccins et d'améliorer leur accès.

El propósito de este informe es analizar la industria de las vacunas bajo el enfoque de la economía industrial como aportación para el diseño de los instrumentos pertinentes que permitan promover el desarrollo, la fabricación y la distribución de vacunas contra el SARS-CoV-2 en cantidades suficientes para inmunizar lo antes posible a la población de todos los países. Además, hemos de prepararnos para enfermedades infecciosas que puedan aparecer en el futuro y que tengan el potencial de expandirse a escala mundial.

En el informe se indica que la industria de las vacunas se ha alejado —y lleva así mucho tiempo— del paradigma de mercado competitivo con infames fallos del mercado. Como resultado, la industria está teniendo un pobre desempeño con escasez de productos y falta de existencias, la salida de empresas del sector, la falta de inversión en investigación y

desarrollo (I+D) y en fabricación, e incluso una "cartera anémica de proyectos de desarrollo", todos ellos síntomas de fallos del mercado.

Tras un breve examen de las políticas aplicadas para hacer frente a estos problemas, concluimos que, después de la pandemia de COVID-19, existirá la necesidad de efectuar una renovación a fondo de la industria y replantear por completo y ampliar las políticas públicas mundiales con el objeto de estimular la I+D, la fabricación, la distribución y el acceso.

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EXECUTIVE SUMMARY[1]

Vaccines are our arms of mass salvation to overcome the Coronavirus Disease 2019 (COVID-19) pandemic. There is also a large consensus that globally we will not be safe until we are all safe. Vaccines, now that they are available, have to be manufactured in sufficient amounts and distributed to all countries as soon as possible. We also need to be prepared for future emerging infectious diseases with the potential of global expansion. The purpose of this report is precisely to analyse the vaccines industry under the focus of Industrial Economics as an input for the design of the pertinent instruments to reach these goals. Economics certainly can help in this endeavour.

The vaccines industry is – and has been for a long time - far away from the competitive market paradigm with notorious market failures. As a result, the industry is underperforming. After a brief review of policies implemented to tackle these problems, we conclude that after the COVID-19 pandemic there is a need to implement a profound overhauling of the industry and to fundamentally reformulate and extend global public policies to stimulate research and development (R&D), manufacturing, distribution and access.

1. THE TECHNOLOGY OF VACCINES

We now have vaccines to prevent more than 20 life-threatening diseases, saving 2-3 million deaths every year. Vaccines are biological products made of large, complex molecules more difficult to characterize, with greater variability in production and problems of reproducibility and quality control because of contaminations in comparison with small molecule drugs (chemical pharmaceuticals). As most vaccines are designed for primary prevention and applied to large populations of healthy people, safety requirements must be reinforced. To note, they have a long life-cycle.

Vaccines may be produced by classic biologic methods or, nowadays, also through biotechnology. We can divide vaccines into two broad **types**: “classic or traditional” (Live-attenuated vaccines, Inactivated vaccines and Toxoid vaccines) and “innovative” (Subunit, recombinant protein, polysaccharide, and conjugate vaccines; Virus-like particles and Nucleic acid vaccines). Among the latter, Messenger Ribonucleic Acid (mRNA) vaccines are at present the most important, offering high levels of protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and providing in the first half of 2021 a substantial part of supplies. They require shorter developing and manufacturing times and are very safe. But they may be unstable and easy to degrade requiring to be encapsulated into lipid-based nanoparticles and extreme cold temperatures to store.

As of 1st of June 2021, six vaccines against SARS-CoV-2 are already approved by the World Health Organization (WHO), the Food and Drug Administration (FDA) or the European Medicines Agency (EMA). The technology platforms are as follows: two mRNA; two Non-replicating viral vector (adenovirus); two Inactivated virus. As of 7th of May 2021, there were 183 vaccines in pre-clinical and 97 in clinical development, according to WHO.

R&D of vaccines undergoes several **steps**. After the initial discovery research and pre-clinical stages, there are two interrelated streams of innovation: Clinical Development (with the well-known three phases) and Bioprocess Development (more of an industrial nature and with three steps in turn). Finally, regulatory approval by national or regional agencies involves the extensive review of all data to asses safety, efficacy and quality. The total time for development of a vaccine usually amounted to 10 to 15 years. The case of vaccines

[1] References can be found in the main report.

against SARS-CoV-2 has been extraordinary. In approximately ten months since sequencing the virus in January 2020, the first vaccine was licensed by FDA and EMA.

In the last fifty years R&D and deployment of vaccines offer impressive **milestones**: the global eradication of smallpox (1980); the reduction of polio cases by 99.5 % since 1988; the first vaccine based on recombinant technology (1986); the first polysaccharide-protein conjugate vaccine (1987); the extension to adolescent vaccines (Human Papillomavirus (HPV) 2009); and, of course, the approval of the first two mRNA vaccines at the end of 2021. mRNA vaccines eliminate some of the difficulties in development, shorten the time needed and can be quickly tailored for new variants or future pandemics.

R&D of vaccines is not only lengthy, it is **risky**. It is estimated that less than 1 in 15 vaccine candidates entering Phase II Clinical development achieves licensure. The average vaccine, taken from the pre-clinical phase, requires a development timeline of 10.71 years and has a market entry probability of 6 %. Nevertheless, vaccine timelines remain significantly shorter when compared to New Chemical Entities development. In sum, R&D of vaccines is a complex, lengthy and risky process.

Vaccine **manufacturing** requires high technological and organizational levels on the part of the manufacturer, substantial investments in plant and equipment and highly trained technical staff. It involves selecting suppliers of key ingredients, setting up manufacturing processes and quality checks, and sourcing primary and secondary packaging. Manufacturing “classic” vaccines is a slow biologic process involving the production of proteins. After inspection, the product is filled into vials, followed by packaging, labeling, and controlled storage. The production of mRNA vaccines - largely chemical and requiring specialized equipment – is less complicated because mRNA molecules are far simpler than proteins and the human body manufactures viral proteins itself.

At least for traditional vaccines, manufacturing processes are therefore **complex**. The lead time to produce a vaccine lot may be as long as three years. Furthermore, to produce proteins involves uncertainty and variability about yields, performance and throughput due to biological variability. There are also contamination incidents. These are some of the reasons why the number of vaccine manufacturers remained low before and upon the explosion of the COVID-19 pandemic and for manufacturing failures and supply shortages.

Manufacturing requires also the organization of a complex **supply chain** of specialized substances. 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 on global supply chains given the unprecedented scale of vaccines to manufacture.

To cover world demand, **global manufacturing networks** were under deployment in the first half of 2021. Large multinationals and other companies have embarked in agreements with contract development and manufacturing organizations (**CDMOs**). Promoting these arrangements is crucial to increase global capacity and production. The question remains **whether these mainly private market arrangements are enough** to match the entire world population needs and reverse the present highly inequitable distribution of vaccines.

The complexities of manufacturing processes and supply chains for vaccines do not exclude the role of **new actors and increased competition.** Appropriately organized **transfers of technology,** as the hubs initiated by WHO, would be instrumental. **The potential of local production and smaller firms, government research centers and universities** is not to be discarded. The examples of The Serum Institute of India and small/medium innovative firms like BioNTech and Moderna, or the University of Oxford are very clear. Also, consumables can be an area of cost saving given lower prices in low resource countries. **Purely public and private/public collaborative internationally driven new projects** of

manufacturing plants in developed and developing countries are also under serious consideration.

2. A DESCRIPTION OF THE VACCINE INDUSTRY

The **second chapter** describes the vaccine industry. It is a relatively small segment compared to the pharmaceutical industry as a whole. In 2019, it held 3.6 % of the total world market for pharmaceutical products (prescription and over the counter (OTC)) with **sales estimated at 32,500 Million USD worldwide**, being the fifth largest among 14 therapeutic areas.

The sector in the past 20 years has shown **remarkable growth** thanks to innovative vaccines, new target population groups (adolescents) and more aggressive pricing strategies. The COVID-19 pandemic has brought an enormous increase in production and sales to attend the global demand. Therefore, growth is expected to be very high in the next and forthcoming years with estimates between 8.1 and 15 % from 2020 to 2026.

Geographical concentration of production is high. The "vaccine production club", a small number of nations, concentrates the production and trade of both COVID-19 vaccines and ingredients. This is a consequence of concentration at the firm level, with a small number of multinational companies and plants mostly located in developed countries. Developing economies depend on high-income countries for vaccines. This state of affairs has important policy implications at a time of significant shortages of COVID-19 vaccines. However, East Asia and South Asia are increasingly becoming a source of vaccines for other developing regions. China and Russia have emerged as developers and producers of COVID-19 vaccines.

According to WHO, before the pandemic "about 80% of global vaccine sales come from five large multi-national corporations (MNC)… While maintaining a strong focus on vaccines for industrialized country markets, MNCs also sell their products in developing countries…". Now, "emerging manufacturers (in India, China, and Brazil), play a critical role in the supply of vaccines of developing countries, particularly basic and some combination vaccines". It "…has resulted in lower vaccine prices due to increased competition and higher production capacities…".

There is also vertical **specialisation in R&D** as in other segments of the pharmaceutical business. Large vaccine companies mainly focus in clinical and process development, while smaller biotechnology companies are cantered in the earlier innovative stages.

There are strong **trade interdependencies** in the goods needed to produce, distribute and administer vaccines (access is required to goods produced across a range of countries), in accordance with the concentration of production. Exports of vaccines are significantly concentrated in the European Union (EU) and United States of America (USA). Imports are, in relative terms, less concentrated.

Probably the COVID-19 pandemic is changing the landscape. The rise of capacity in existing firms ("scale-in") and the unprecedented deployment of agreements and transfers of technology to CDMOs ("scale-out") and particularly the leading role of innovative new small/medium companies introducing mRNA vaccines are depicting a new reality. More studies are needed to know whether the network of scaling-out agreements will go beyond fill and finish for cost reduction and increasing manufacturing. In the long run the technical capabilities of R&D and manufacturing have to be significantly increased and distributed to meet the global needs and to prevent and respond rapidly to emerging infections and future pandemics in all regions of the world.

3. THE STRUCTURE OF THE VACCINE INDUSTRY

The structure of the vaccine industry is the purpose of chapter three. The first fact is that the **benefit/cost ratio of many vaccines is extremely high**. For every dollar invested the return may rise up to 27. Their performance is outstanding: highly positive health outcomes and reduction of the financial burden on health systems.

The first factor relevant to **demand** is that consumers usually are large, healthy populations. It implies stringent safety standards requiring clinical trials enrolling large groups of subjects. Other factors are that consumption of vaccines is an infrequent event; individual and aggregate demand depends on epidemiological variables, mainly incidence of illness; frequently there are vulnerable subpopulations; and effective treatments may function as a substitute good.

The **market size** for vaccines is not small. For anti-SARS-CoV-2 vaccines of course demand is the whole global population. If we examine vaccines designed for children alone, the number of births per year worldwide (140.1 million in 2019, of which 7.7 million was in Europe and 4.3 million was in North America), though declining in most developed parts of the world, provides a significant target population. Developing countries have a low ability to pay and provide limited sales potential but in the future, their demand will grow because of economic growth and high birth rates. International cooperation has been and will certainly increasingly be a key source of financial support and technical assistance. COVID-19 demand for effective vaccines already available has skyrocketed to 9,000-11,000 million doses for 2021 but it is unlikely it will be fulfilled. The unbalance in supplies and vaccination rates between developed and developing countries is currently the most important global challenge to tackle with the pandemic and recover the international economy. It is also anticipated that COVID-19 will prompt increased demand for new vaccines and therapeutics and shifts in demand for existing therapies.

In the case of vaccines, **"herd immunity"** – a positive externality - occurs when a sufficient portion of a population becomes immune to an infectious disease and the risk of spread from person to person decreases. Those who are not immune are indirectly protected. "Free-riders" may then refuse vaccination expecting others to do so and getting the benefit of herd immunity at no cost. Therefore, the rate of vaccination could fall short of what is needed. This is the first and very important market failure afflicting the vaccine industry. Subsidies, direct provision free of charge, legal requirements to enter schools, work premises, to travel… have to be implemented by the State to overcome free riding.

From the **supply** side there are five points to be highlighted: capital requirements; the production function; product specialization in manufacturing; horizontal concentration and the absence of generic competition.

Information about costs and profits in the pharmaceutical industry at large and in the vaccine segment is scarce, but it seems that the production function involves substantial complexities and high costs in R&D, production, testing, evaluation and distribution.

The vaccine industry is, for technical reasons, a **capital-intensive** business requiring considerable investments in time, manufacturing assets, facilities, and technical staff as was mentioned in chapter 1. This is a barrier to competition from new firms undertaking production. The financial investment in manufacturing plants circa 2017 was in the range of 50 to 700 M USD according to different estimates, countries and types of products. But new methods and technologies are lowering capital costs and time giving room to deploy and switch on small facilities more broadly and quicker.

The **production function** includes different cost items. The high level of **R&D costs** for chemical pharmaceuticals probably is transferable to vaccines. Success rates are better, but size of clinical trials is larger and a number of unavoidable stages must be passed for vaccine development (mentioned in chapter 1). These high sunk fixed costs are a barrier to new competitors and encourage market concentration (section 3.3.4.). The support of governments, **public funding** and state laboratories to vaccines R&D is very important. Circa 2000, in the USA one third of all funding were provided by the National Institutes of Health (NIH). Operation Warp Speed of the US Federal Government has provided more than 19,000 M USD to seven private pharmaceutical manufacturers including R&D for treatments and the actual purchase of the vaccine doses. Adding up actual purchasing of doses by Member States the total amount of funds mobilized by the EU for vaccines is over €30,000 M.

Risk of batch contamination in manufacturing or distribution is, for technical reasons (section 1.3), a significant entrepreneurial risk, giving rise to significant costs. Current Good Manufacturing Processes (cGMP) have to be followed and enforced.

Given that vaccines are generally administered to healthy individuals, and the risks of adverse effects and contaminations, R&D, production and distribution of vaccines are subject to detailed **regulations** all the life of the product. Regulations include evaluation, licensure and control of the product, the manufacturing plant, the process, the batch, trade operations, adverse events and risk management plans.

Eventual adverse events and contaminations (with or without fault) may give rise to difficulty in insuring **product liability** with very large financial consequences. These risks increase suppliers' costs and diminish incentives to enter the industry and to manufacture and have led firms to discontinue operations and exit the market, as well as to shortages, rising prices and falling number of suppliers. It was one of the main complications in negotiating purchase of anti-COVID-19 vaccines by the EU Commission or India and pharmaceutical companies. Different remedial policies are reviewed in part 5.

In view of these peculiar sources of costs we can conclude that **the production function** is more complicated in the vaccine industry than expected in many industries and goes far beyond the usual components of costs. It is worth noting, nevertheless that manufacturing costs fall once the fixed costs are covered and with higher volumes of production to satisfy larger market demand.

In the vaccine industry plants and equipment are specific for each product. **Product specialization in manufacturing** implies lack of flexibility to adapt to shocks in demand and increased risk of shortages and production dead stops.

High **horizontal market concentration** leads to market power, monopoly or oligopoly and vulnerability of supply chains. The vaccine industry has been depicted as the "vaccine production club". Concentration has evolved along time as some firms exited the market or as a result of mergers and acquisitions. Top four Western suppliers accounted in 2014 for 85 % of global sales for all vaccines. According to the WHO, nearly one third of vaccines have fewer than four suppliers, while nearly two thirds have two or fewer prequalified products. The negative consequences of concentration are that when key suppliers experience manufacturing problems, supply interruptions and vaccine shortages interrupt immunization schedules, posing risks to vulnerable populations. Nevertheless, emerging manufacturers (in India, China, and Brazil) play a critical role in the supply of classical vaccines for developing countries.

High concentration is rooted in technical reasons, chiefly **economies of scale** (average costs decreasing with increasing levels of production) that may lead to "natural monopoly",

the “natural state” for the industry. Governments and international organizations have to deploy policies to overcome the inefficiencies of monopoly in terms of welfare loss, particularly the risk of shortages and supply breakdowns.

In the case of vaccines, the barriers to entry to the industry cannot be moved away to implement a market for “**generic” vaccines** in the same way as for chemical pharmaceuticals. For follow-on vaccine manufacturing, not only the impediment raised by patents has to be removed, but also the know-how to perform the manufacturing processes has to be transferred. Moreover, follow-on versions of existing vaccines are treated as originators by regulation and detailed tests and clinical trials are generally required. In this respect debates are going on in the context of the COVID-19 emergency. It is not known as of today the impact that new technologies such as mRNA may have on this matter.

In sum, in the **structure of the vaccine industry,** demand by large, healthy populations imposes very stringent safety standards and large clinical trials raising upfront costs, and externalities like “herd immunity” compel public intervention to foster vaccination. In turn, the map of supply is demarcated by high capital-intensity, the production and cost function made of high R&D costs, risks of batch contamination, detailed regulations, product liability and product specialization in manufacturing, all barriers to competition. High horizontal market concentration (rooted in technical reasons, chiefly economies of scale leading to “natural monopoly”) ends in market power, monopoly or oligopoly (the “vaccine production club”) and vulnerability of supply chains. Finally, know-how and regulations prevent competition from generics. To overcome all these market failures governments and international organizations must implement a full array of policies to guarantee supply and access to vaccines.

4. INCENTIVES TO INNOVATE AND BOOST PRODUCTION. ECONOMIC CONCENTRATION, EXIT, UNDERINVESTMENT, SHORTAGES AND PROFITABILITY

In previous sections we have extensively documented high levels of market **economic concentration** and provided some data on **industry exit**. Historically **shortages** have been relatively frequent in vaccine supply. We provide clear evidence from the USA and Spain and warnings from experts on repeated mismatch between supply and demand. **Underinvestment in R&D and manufacturing** is a related problem often signalled by experts. The poor performance may be explained by reasons linked to the structure of the industry already considered in this report: demand (externalities) and supply factors (capital requirements; R&D costs; risk of batch contamination; regulation; liability risks; product specialization in manufacturing and concentration). Three more factors have been considered in different studies on profitability of vaccines: heterogeneity of demand, that immunization acts like durable goods (less profitable than non-durable) and public purchasing and tenders driving prices to low levels.

Reduced **profitability** sometimes is signalled as the main cause for exit from the industry, underinvestment, shortages and general underperformance**.** But this is an empirical question where different analyses, opinions and estimations are flawed because of lack of conclusive data, though some partial evidence and opinions of experts point to high profits. 2002 partial figures provided by Scherer on “price-cost margin” from the US Census of Manufactures showed a margin of 56.4 % for the sector of Vaccines, toxoids and antigens and 62.3 % for Pharmaceuticals vs. 28 % for Manufacturing Industries as a whole.

In conclusion, **two theories would explain** underinvestment, shortages and exit of firms from the market, both highlighting demand and supply factors in the structure of the industry. The first underlines economic concentration, oligopoly and monopoly, all compatible with high profitability, shortages and exit of smaller firms. The second theory directly focuses on

lack of profitability, although there are some partial data challenging this assumption. The point is that both theories lead to the same conclusion: market failures are pervasive and prevent the industry from satisfying effective demand, triggering shortages of products that are essential for public health and economic development.

To overcome all these market failures governments and international organizations must implement a full array of policies to guarantee supply and access to vaccines, breaking concentration and favouring competition and a more dense and even distribution of manufacturing facilities.

5. A BRIEF INVENTORY OF POLICIES TO STIMULATE R&D AND MANUFACTURING

Though the objective of this report is not an in-depth examination of policy options, chapter 5 very briefly summarizes public policies enforced or proposed to solve market failures in the vaccine industry, stimulating R&D and manufacturing.

"Supply push" policies try to stimulate R&D and manufacturing and reduce upfront costs. Patents or more broadly **Intellectual Property exclusivity rights (IP)** are controversial insofar as they create a tension between incentives to innovate and access to medicines, and because the empirical evidence on their actual ability to foster innovation historically is not clear. Proposals to reform IP have been advanced in the last 20 years, but with little success. The fact is that exclusivity rights have been reinforced, with the exception of the so-called flexibilities of the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights ("TRIPs flexibilities").

Other policies to reduce upfront costs are:

- Subsidies to private R&D
- Subsidies to reduce quality control costs
- Government financed or directly implemented basic research and development
- Public-Private partnerships in R&D, quality control and manufacturing

Collaboration among firms to increase capacity and production can be also fostered with government support and stimuli. The issue is extremely important in 2021 for the need to increase production of anti-SARS-CoV-2 vaccines rapidly. **Direct involvement of government in manufacturing** is also a possibility, envisaged for instance in US legislation.

"Demand-pull" policies to expand demand may also contribute to overcome market failures and increasing vaccination of populations:

- Information and education
- Subsidies at the level of the immunization point
- Direct provision by the public sector, vaccination campaigns
- Legal obligation to be vaccinated
- Philanthropic initiatives, voluntary work…

Advance Market Commitments (AMC) are commitments to purchase a specified number of doses at a specified price if a vaccine meeting certain specifications were developed, reducing uncertainties for both parties and ensuring a solvent and reliable demand for the developer. AMC have been extremely successful in stimulating R&D of vaccines against SARS-CoV-2, but once the vaccines are developed and available they have to be redistributed to guarantee access in favor of all populations at risk in the world through international cooperation.

There are also policies influencing **supply and demand** simultaneously. There is evidence of the positive effects of special civil liability regulations for vaccines, like “no tort liability” and limits to compensations. These rules are intended both to guarantee consumers rights and reduce the very important risk for manufacturers of claims for injuries.

International cooperation with developing countries has included up until the pandemic a variety of initiatives by national governments, international organizations and philanthropic institutions, sometimes through private-public collaborations, with important accomplishments. Nowadays the main global international program for vaccines is the COVID-19 Vaccines Global Access (COVAX) facility. But the program needs to be greatly expedited now with determination and political will from partners and in the future in the face of new pandemics and emerging infections much more resolute and overarching strategies have to be deployed.

After the COVID-19 pandemic all these policies – and particularly international actions - will certainly have to be reformulated and extended on the basis of universal cooperation including a profound overhauling of the industry to overcome the market failures afflicting the sector.

CONCLUDING REMARKS

Market failures are pervasive in the vaccine industry, an essential industrial sector that is far away from the competitive market paradigm, both in national and international terms. High levels of market economic concentration limit “the vaccine production club” to a handful of firms and countries. Consequently, performance of the industry is below the needed level, notwithstanding important successes in development of new vaccines and manufacturing before and after the pandemic of COVID-19. But shortages and stockouts in developed and developing countries, exit of firms from the industry, underinvestment in R&D and manufacturing, even an “anaemic development pipeline”, all signs of market failure - and most probably compatible with high profitability (see chapter 4) – are the dimensions of underperformance in the vaccine industry. Furthermore, the non-competitive and concentrated structure of the industry is one of the reasons explaining continuing insufficient access to vaccines in less developed countries, in spite of recent progress powered by national economic development, public health advancements and a number of meritorious actions carried under the auspices of international cooperation. The sharp unbalance in vaccination rates to prevent COVID-19 between developed and developing countries at the middle of 2021 is a clear demonstration. Vaccine deprivation is not only due to deficient health systems, lack of economic development and finance but also to the configuration of the industry.

The COVID-19 pandemic has demonstrated the need to drastically reformulate and extend policies to stimulate R&D, manufacturing, distribution and access to vaccines. The private sector is not enough, though public/private cooperation particularly in industrial endeavours will be the most efficient orientation. There is a need to implement a profound overhauling of the industry with the goal of universal access of all populations to all vaccines. Box 5.1 provides some suggestions for this profound reform. The present and future pandemics and emerging infectious diseases have to be prevented and treated on the basis of universal cooperation and multilateralism for R&D, manufacturing, immunization and distribution, including increased capacity to develop and manufacture new vaccines in all regions, paying particular attention to less developed countries. This is not only mandated by solidarity among human societies but also by the fact that in front of very contagious pathogens in a world of global and fast interrelations no one is safe until everyone in the Earth is safe.

A last remark is the need for reliable, comprehensive and detailed data and statistics as well a whole battery of studies on the Industrial Economics of the vaccine industry. Increasing our

knowledge of the vaccine segment of the pharmaceutical industry is essential for planning and achieving the deep reforms to be implemented in the future.

INTRODUCTION

As of June 17, 2021, the Coronavirus Disease 2019 (COVID-19) pandemic has caused 3,835,504 deaths and 177,176,595 cases, as estimated by Johns Hopkins University. It has resulted in painful contagion, long-lasting ailments, collateral health damages, and economic catastrophe. The World Health Organization (WHO) Director-General Tedros Adhanom Ghebreyesus (2021) emphasized what Jeffrey Sachs said in 2002—that successfully developed vaccines are our arms of mass salvation to stop devastation. Nowadays, the hopes of humanity are focused on the vaccines to overcome the worst pandemic in this century. Many say that we will not be safe until we are all safe. The COVID-19 vaccines must be manufactured in sufficient amounts and distributed by all available means to all countries as soon as possible. We also need to be prepared in the event of the emergence of other infectious diseases with the potential of global contagion and expansion.

To attain the above-mentioned goals and properly understand the complex aspects of the development, production, and distribution of vaccines, studying the economics of vaccines will be helpful. This motivation is far more reaching than academic interest. **The purpose of this research paper is to provide an understanding of the vaccine industry and market from the industrial economics perspective. This approach will inform the design of more efficient policies and mechanisms, substantially increasing the manufacturing of vaccines and the global equitable access to them.** Industrial economics is a branch of microeconomics dedicated to the study of the dynamics of industries (markets), providing guidance to policies to enhance competition and efficiency and, thus, improve social welfare

This report shows that market failures are all-pervasive in the vaccine industry and that the essential industrial sector is far away from the competitive market paradigm. As a result, the performance of the industry is below the needed level in developed and developing countries. Shortages, the exit of several firms from the industry, underinvestment in Research and Development (R&D) and manufacturing, and insufficient access to products that are essential to public health and economic development are all very real problems despite the recent progress powered by national economic development, public health advancements, and several meritorious actions supported by international cooperation. We conclude that after the COVID-19 pandemic, there is a need to profoundly overhaul the vaccine industry and fundamentally reformulate and extend public policies to improve R&D, manufacturing, distribution, and access to vaccines.

This report relies on a selective review of the available literature, mainly in the field of economics, particularly industrial economics. Data and analysis at the desegregated level of the vaccine industry are by no means abundant. However, even with uncertainties in important areas, we have been able to reach some conclusions based on sufficiently solid data.

The layout of the report is as follows. Section 1 reviews the technology of vaccines, analysing different types, research and development, and manufacturing processes. A description of the vaccine industry follows in section 2, highlighting size and sales forecasts, geographical concentration, and the profile of the companies involved. The core of the report is section 3, which discusses the structure of the vaccine industry. The main points are demand, externalities, and in the supply side, capital intensity, R&D costs, risks of batch contaminations, regulations, product liability, product specialization in manufacturing, and absence of generic competition as it exists for products obtained by chemical synthesis. Section 4 discusses the implications of economic concentration, incentives, and profitability. A brief summary of the public policies advanced or proposed to solve market failures is provided in section 5 as an invitation for future research and discussion. The last

section presents concluding remarks. An executive summary at the beginning of the report covers the main points.

1. THE TECHNOLOGY OF VACCINES[1]

Vaccines are generally designed for primary prevention—that is, to prevent illnesses before diseases develop—and are administered to large populations of healthy people. On the other hand, pharmaceutical products are mainly aimed to treat illnesses.[2] Vaccines designed for prevention and for healthy people must meet stricter safety requirements. The requirements for obtaining regulatory authorities' approval can be more demanding than those for the approval of medicines, accounting for the balance between benefits and risks. The risk of adverse events has to be very low to meet regulatory requirements. This requires numerous, longer (several years), and more expensive clinical trials.

1.1. Types of Vaccines

A vaccine is a biological preparation that stimulates active acquired immunity to prevent a particular infectious disease. It is designed to teach the body's immune system to safely recognize and block the pathogen (bacteria, viruses, etc.) that causes an infectious illness. Vaccines build immunity to a disease without the body getting sick first. When people are inoculated, their immune system responds by producing antibodies that lead to cellular immunity, which prevents symptoms and damage from the contagion or, at the very least, limits the severity of the infection to mild symptoms. According to the WHO, "we now have vaccines to prevent more than 20 life-threatening diseases, helping people of all ages live longer, healthier lives. Immunization currently prevents 2-3 million deaths every year from diseases like diphtheria, tetanus, pertussis, influenza and measles" (2021, May 10).

Vaccines are biological products, a diverse category of medicines, including therapeutic proteins (such as filgrastim) and monoclonal antibodies (such as adalimumab). Biological products are used to diagnose, prevent, treat, and cure diseases and medical conditions. They are very different from pharmaceuticals obtained by chemical synthesis. They are generally large, complex molecules often more difficult to characterize than small-molecule drugs. Biological products exhibit greater variability in results, more reproducibility problems, and often more challenging quality control.

These products may be produced by classic biological methods or, nowadays, through biotechnology in a living system, such as a microorganism, plant cell, or animal cell. "Indeed, biotech approaches have been at the forefront of the efforts to develop a new generation of vaccines using genetic engineering techniques" (Grabowski and Vernon, 1997). The biotechnological revolution has changed the landscape of vaccines as much as it has changed the pharmaceutical industry as a whole. For example, vaccines to prevent COVID-19 have been developed with new biotechnology methods (such as recombinant subunit vaccines and Deoxyribonucleic acid (DNA)- and Ribonucleic acid (RNA)-based vaccines).

To understand vaccine development, it is useful to classify vaccines into two broad groups: classic or traditional and innovative.

Classic vaccines

- Live attenuated vaccines: The germ is alive but weakened. These vaccines are potent and create a strong and long-lasting immune response but need extensive safety studies.

[1] For this section we have checked the following sources: Alcamí Pertejo (2020), Callaway (2020), Céspedes (2021), Hatchett *et al.* (2021), Le *et al.* (2020), Mishra (2020), Pollard and Bijker (2021), U.S. Department of Health and Human Services (2021), WHO (2020), WHO (2021, 7 May), and WHO (2021, May 10).
[2] Nevertheless, interest in developing vaccines for the therapeutic treatment of ill people is growing.

- Inactivated vaccines: The killed version of the germ that causes a disease is used. The vaccine is less potent, and booster shots may be needed. However, they are very safe and relatively easy to manufacture.

- Toxoid vaccines: A toxin (harmful product) from the germ that causes a disease is used. The immune response targets the toxin instead of the whole germ. Booster shots are needed.

Innovative vaccines

- Subunit, recombinant protein, polysaccharide, and conjugate vaccines: Specific pieces of the germ—like its protein, sugar, or capsid (a casing around the germ)—that mimic its pathogen are used to safely generate an immune response. They produce very strong immunity and are suitable for people with weakened immune systems and health problems. These vaccines are safe, but booster shots may be needed.

- Virus-like particles: Empty virus shells mimic the coronavirus structure but aren't infectious because they lack the genetic material. They can trigger a strong immune response but can be difficult to manufacture.

- Nucleic acid vaccines:

    - Viral vector vaccines: They are quite recent and have been developed for Ebola outbreaks and to make COVID-19 vaccines as well. They use a modified version of a different safe virus as a vector or platform to produce proteins to generate an immune response.

    - DNA vaccines: A cutting-edge approach uses genetically engineered DNA to generate a protein that safely prompts an immune response. Easy and inexpensive to make, DNA vaccines offer strong, long-term immunity.

    - Messenger RNA vaccines deserve special consideration.

Messenger RNA (mRNA) vaccines are currently the most important innovative vaccines. Although they have been studied for years, the first vaccines of this kind have been developed against COVID-19. They involve an effective technology that offers high levels of protection. In the first half of 2021, mRNA vaccines have been used for a substantial part of large-scale vaccination programmes decisively helping to control the pandemic. These vaccines promise future scientific developments besides the control of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus itself. mRNA vaccines work by introducing an mRNA sequence (the molecule that tells the cell what to build) coded for a specific antigen. Rather than having the viral protein injected, a person receives genetic material (mRNA) that encodes the viral protein, and the human body uses the instructions to manufacture viral proteins. In other words, when these genetic instructions are injected, the muscle cells translate them to make the viral protein directly in the body. Once this antigen is reproduced within the body, it is recognized and triggers an immune response. As shown in section 1.2, mRNA vaccines require shorter developing and manufacturing times. Also, because they do not contain a live virus, there is no risk of causing a disease in the person getting vaccinated.

The main setback is that these vaccines are unstable and easily degraded and destroyed by immune defences, requiring to be encapsulated into lipid-based nanoparticles that shield them from destructive enzymes and shuttle them into cells. This is why some of them require

extremely cold temperatures for preservation and distribution encumbering logistics, particularly in developing countries.

Figure 1.1 shows the different types of vaccines, and Figure 1.2 shows a comparison of the traditional and the new mRNA vaccines. Table 1.1 shows the global number of vaccines for COVID-19 in pre-clinical and clinical developments as of May 7, 2021, and by platform or technology. The breakdown by technology of vaccines against COVID-19 presently approved as of 1st of June 2021 in different jurisdictions appears in Table 1.2.

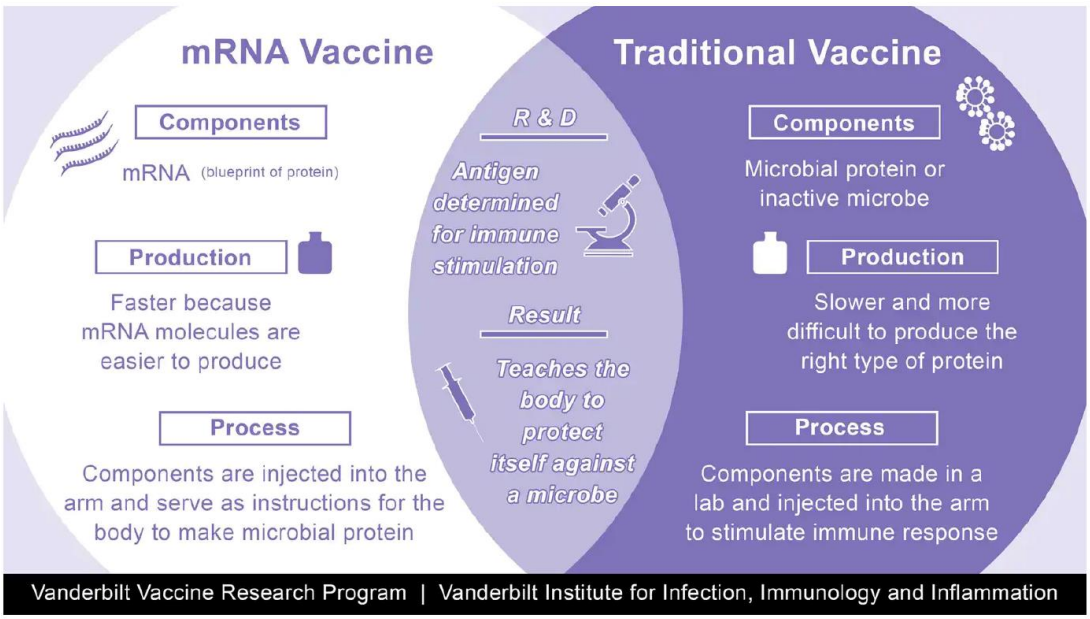
Finally it is important to note that most vaccines have a long life-cycle; some vaccines used today were developed in the 1940s and 1950s and remain essentially unchanged (Plotkin *et al*., 2017).

FIGURE 1.1. DIFFERENT TYPES OF VACCINES

Type of vaccine	Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)	Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism	Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid	Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)	Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle	Human papillomavirus	1986 (hepatitis B)
Outer membrane vesicle	Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate	*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored	Ebola	2019 (Ebola)
Nucleic acid vaccine	SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored	Experimental	–
Antigen-presenting cell	Experimental	–

Source: Pollard and Bijker (2021)

FIGURE 1.2. A COMPARISON OF TRADITIONAL WITH THE NEW mRNA VACCINES



A comparison of traditional with the new mRNA vaccines. @VI4research. CC BY-SA

TABLE 1.1. VACCINES FOR COVID-19 IN DEVELOPMENT AS OF 7TH MAY 2021			
Number of vaccines in pre-clinical development		183	
Number of vaccines in clinical development		97	
Platform		**Candidate vaccines (no. and %)**	
PS	Protein subunit	30	31%
VVnr	Viral Vector (non-replicating)	14	14%
DNA	DNA	10	10%
IV	Inactivated Virus	15	15%
RNA	RNA	15	15%
VVr	Viral Vector (replicating)	3	3%
VLP	Virus Like Particle	5	5%
VVr + APC	VVr + Antigen Presenting Cell	2	2%
LAV	Live Attenuated Virus	2	2%
VVnr + APC	VVnr + Antigen Presenting Cell	1	1%
TOTAL		**97**	
Source: WHO (2021, May 7a)			

TABLE 1.2. BREAKDOWN BY TECHNOLOGY OF VACCINES AGAINST COVID-19 Approved as of 15 July 2021 by FDA, EMA or WHO			
Firm	**Type of Vaccine**	**Approved by**	**Nº of Doses**
Pfizer/Biontech	mRNA	FDA, EMA, WHO	2
Moderna	mRNA	FDA, EMA, WHO	2
U. of Oxford-Astra Zeneca SKBio (Republic of Korea) Serum Institute of India	Non replicating Viral vector (adenovirus)	EMA, WHO	2
J&J/Janssen	Non replicating Viral vector (adenovirus)	FDA, EMA, WHO	1
Sinopharm	Inactivated virus	WHO	2
Sinovac	Inactivated virus	WHO	2
Sources: OECD (2021a), Cañelles and Jiménez (2021), BBC (2021), WHO (2021, 15 July)			

1.2. Research and Development of Vaccines

This section provides an overview of the scientific and technical characteristics and complexities of the R&D of vaccines, the time usually required to develop a new vaccine project, and the risks involved, as well as a few remarks on the recent progress of innovations. In section 3.3.2, we will comment about the costs of R&D.

First, we have to highlight the obligatory stages of these innovative processes[1]. After both the initial discovery research stage and pre-clinical stage are overcome we can consider that there are two interrelated streams of subsequent innovative stages: one is more clinically oriented, clinical development. The second one is more of an industrial nature, bioprocess development.

1. Discovery Research

Discovery research involves laboratory-based research to find ways to induce an immune response at a molecular level. Normally, it takes 2–5 years.

2. Pre-Clinical Stage

[1] This section is a synthesis of information from Douglas and Samant (2017), Plotkin *et al.* (2017), and Wellcome (2021).

The pre-clinical stage involves testing in animals to assess the safety and suitability of potential vaccines for humans, analytical release assays, preclinical toxicology, and immunological assays to evaluate clinical responses. It takes up to 2 years.

3a. Clinical Development

Clinical development involves testing potential vaccines in humans for safety, immunogenicity, and efficacy. It has three phases:

Phase I: Testing for safety and immunogenicity in small numbers takes 2 years and requires 10–50 (usually healthy) volunteers to take part in trials.

Phase II: Understanding the immune response, safety, and dosage takes
2–3 years and requires 200–400 people to take part in randomized trials, including a placebo control group and people with the target disease.

Phase III: This phase involves assessments of a vaccine's protection against a disease, prevention of infections, and related immune responses. It requires thousands of people participating in trials, including a placebo control group. Keys to successful phase III clinical studies are accurate estimates of sample sizes based on disease incidence, low dropout rates, precise clinical endpoint definitions related to future label claims, and rigorous data management. This phase takes 5–10 years.

3b. Bioprocess Development

Process development, as described by Douglas and Samant (2017), involves preparing the test vaccine, including clinical lots, preclinical toxicology testing, analytical assessments, and scale-up methods that lead to a consistent manufacturing process at one-tenth of the full scale. It also includes several steps and can be as costly as clinical development. "Assay development involves the definition of specific methods to test the purity of raw materials, stability and potency of the vaccine product, and immunologic and other criteria to predict vaccine efficacy" (Douglas and Samant, 2017).

The first step involves the development of a small-scale process and the formulation of the phase I clinical study materials.

The second stage completes the product and process definitions before initiating phase II studies. Product definition "includes methods of synthesis/bioprocess steps, number of components, and stability/formulation. Stability, release, and raw material assays must be in place. Immunologic and other assays must be established to support dose-ranging studies" (Douglas and Samant, 2017).

The third step is "to define the clinical dose and arrive at the appropriate manufacturing scale, which may take 2 years or more. It results in the identification, manufacture, filling, and release of clinical-grade vaccine - usually in a pilot plant – demonstration of safety and a dose response in a Phase II clinical study; validation of critical assays to support Phase III clinical studies; consistency of lot manufacture (…); and completion of technology transfer to final site of manufacture of full-scale lots" (Douglas and Samant, 2017).

4. Regulatory Approval

Regulatory authorities, such as the Food and Drug Administration (FDA) in the United States of America (USA) or European Medicines Agency (EMA) in the European Union (EU), extensively review preclinical and clinical data to assess safety, efficacy and quality according to specific and detailed regulations. All vaccines have to be approved before they

are launched for public utilization. The requirements are very stringent and different from those mandated for chemical pharmaceuticals. Under normal circumstances, approval may take up to 2 years. In section 3.3.2, we will return to this point, highlighting the costs arising from regulation.

Developing a vaccine usually takes 10–15 years. A detailed study of all vaccine projects in development from 1998 to 2009, from the pre-clinical development phase and clinical trial phases I–III up to market registration (605 unique human vaccine candidates from 188 individual firms covering over 60 therapeutic areas), found that the average vaccine requires a development timeline of 10.71 years. The more recent vaccine development projects from 1998 to 2009 showed a longer timeline (Pronker *et al.,* 2013). The same authors noted that "vaccine timelines remain significantly shorter when compared to NCE development."

The development of vaccines against SARS-CoV-2 has been extraordinary in this respect. In approximately 10 months since sequencing the virus in January 2020, the Pfizer/BioNTech vaccine was approved by the FDA on December 11 and by EMA 10 days later. FDA approved Moderna's mRNA-based vaccine on December 18 and EMA on January 6, 2021, and the AstraZeneca on January 29. The J&J/Janssen vaccine was approved by the FDA on March 1, 2021, and by EMA on March 11, 2021.[1] The Chinese vaccines by Sinopharm and Sinovac were approved by WHO on May 7 and June 1, 2021.

Pharmaceutical companies are obliged to continue monitoring a vaccine's effectiveness and safety after it has been authorized. In particular, they have to perform post-marketing surveillance, submit risk management plans for approval, and implement them. For instance, EMA has issued a safety monitoring plan and guidance on risk management planning for COVID-19 vaccines (EMA, 2020).

Vaccine development is generally considered **highly risky**, like pharmaceutical development in general. It is estimated that less than 1 in 15 vaccine candidates entering phase II obtains licensure (Douglas and Samant, 2017). The detailed study by Pronker *et al.* (2013) found a market entry probability of 6%. "Unlike pharmaceuticals, vaccines that pass early proof-of-concept studies in humans have a very high probability of achieving licensure" (Douglas and Samant, 2017).

The most notable accomplishment related to vaccines in the past half century was the eradication of smallpox, as verified by the WHO in 1980. The reduction of polio cases by 99.5% since 1988 is also a landmark. Very important achievements were the 1986 approval of the first vaccine based on recombinant technology, a hepatitis B vaccine, the first polysaccharide-protein conjugate vaccine in 1987 (*Haemophilus influenzae*), and the approval of the first two mRNa vaccines at the end of 2021 (Gerberding and Haynes, 2021). The human papillomavirus (HPV) vaccines significantly expanded the field of adolescent vaccines and confirmed the market acceptance of premium pricing (Douglas and Samant, 2017). Table 1.3 gives an idea of the innovation pace, taking into account FDA licensure dates for selected innovative vaccines since 1970.

An important advancement with the mRNA vaccines is that they "can leapfrog the hurdles of developing traditional vaccines such as producing non-infectious viruses, or producing viral proteins at medically demanding levels of purity. In fact, within days of the genetic code of the SARS-CoV-2 virus becoming available, the mRNA code for a candidate vaccine testing was ready. What is most attractive is that once the mRNA vaccine tools become viable, mRNA can be quickly tailored for new variants or future pandemics" (Mishra, 2020).

[1] It is important to clarify that these have been emergency use approvals. It is not full approval. Also, the emergency use authorization is restricted to national use. The process of submitting full dossiers for WHO prequalification has also taken much longer, delaying regulatory approval particularly in developing countries.

1.3. Overview of Vaccine Manufacturing Processes

It is generally acknowledged that vaccine manufacturing requires relatively high technological and organizational levels on the part of the manufacturer, substantial investments in plant and equipment and highly trained technical staff. “Sustaining vaccine manufacturing requires developing a strong base of scientific, technical, product-specific manufacturing and quality control system knowledge” (Plotkin *et al*., 2017). Vaccine production involves a complex range of steps that require significant up-front investment in R&D and also in selecting suppliers of key ingredients, setting up manufacturing processes and quality checks, and sourcing primary and secondary packaging (OECD, 2021b).

The Manufacturing of classic vaccines (e.g. viral vector, protein subunit, inactivated or attenuated viruses) is a slow biologic process involving the production of proteins. It has two stages: bulk manufacturing and fill and finish operations (Douglas and Samant, 2017).

Bulk manufacturing includes cell culture and/or fermentation-based manufacturing followed by a variety of separation processes to purify the vaccine.

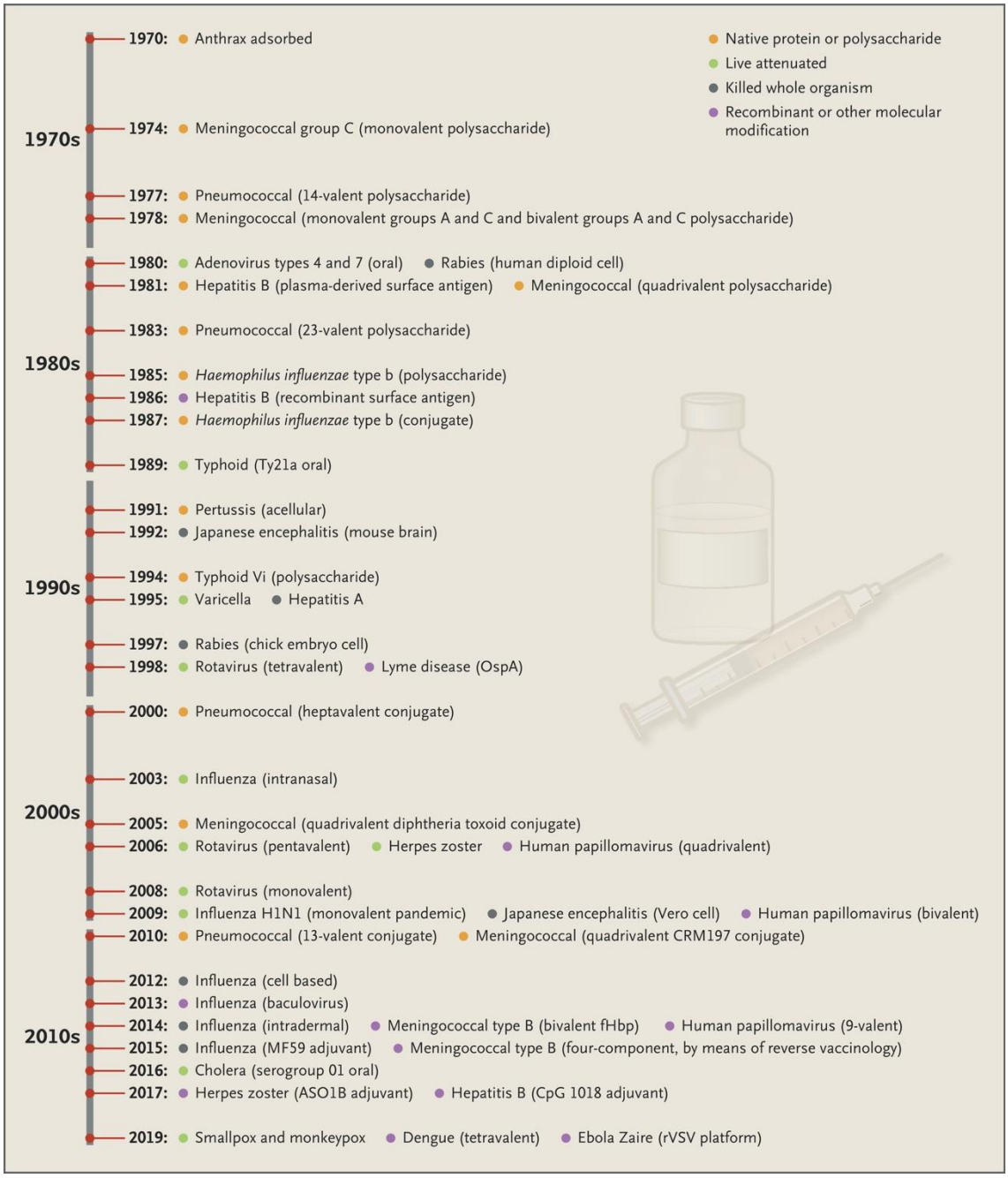
- Upstream: cell culture to produce the drug substance.
- Downstream: the cell culture harvest is purified. (Hatchett *et al.*, 2021)

In the **fill-and-finish** operations (also known as formulation and filling) the drug substance is formulated with other ingredients (or excipients, adjuvants, stabilizers…) to enhance the immune response, where needed, and to ensure product stability. After the inspection it is filled into vials (including lyophilization in the case of live viral vaccines), followed by packaging, labelling, and controlled storage (Douglas and Samant, 2017; Hatchett *et al.*, 2021).

The first and second step of bulk manufacturing and the first two sub-steps of formulation and filling must be conducted under stringent aseptic or sterile conditions. Manufacturing sub-steps differ significantly depending on the respective technology platform.

The production process of **mRNA vaccines** is largely chemical in nature rather than biological and requires specialized equipment. There is the first step via biological fermentation, then chemical reactions, formulation in lipid nanoparticles (LNPs) and finally fill-and-finish as well as quality assurance and quality control in the same manner as the other vaccines (Hatchett *et al.*, 2021; see also Sousa *et al.,* 2021). The novelty of manufacturing mRNA vaccines is therefore a challenge, but it also opens new opportunities. As Mishra (2020) stated, they “eliminate much of the manufacturing process because, as stated in section 1.1, rather than having viral proteins injected, the human body uses the instructions to manufacture viral proteins itself. Also, mRNA molecules are far simpler than proteins. For vaccines, mRNA is manufactured by chemical rather than biological synthesis, so it is much quicker than conventional vaccines to be redesigned, scaled up and mass-produced.”

TABLE 1.3. FDA LICENSURE DATES FOR SELECTED INNOVATIVE VACCINES SINCE 1970



Source: Gerberding and Haynes (2021)

Jackson *et al.* (2020) described the pros of mRNA vaccines in manufacturing:

> "One of the central advantages hinges on rapidity of manufacture. Within weeks, clinical batches can be generated after the availability of a sequence encoding the immunogen. The process is cell-free and scalable. Of paramount advantage, a facility dedicated to mRNA production should be able to rapidly manufacture vaccines against multiple targets, with minimal adaptation to processes and formulation. In addition, new targets requiring multi-antigen approaches will benefit from the speed in which mRNA can render multiple constructs".

Hatchett *et al.* (2021) underline the **operational challenges** of the vaccine manufacturing process:

- Highly specialized equipment and personnel
- Manufacturing consistency and control to guarantee the quality and safety of each vaccine. External regulatory authorities ensure some of these quality controls and review the batch summary protocol before releasing each individual batch for use.
- Lengthy capacity ramp-up and technology transfer timelines. For mRNA vaccine production, the entire supply chain has to be built ex novo.
- Lengthy manufacturing times; 90–120 days are needed for the manufacturing and control of a single batch of COVID-19 vaccines.
- On-time input supply delivery for more than 100 components

The lead **time** to produce a vaccine lot may be long. It ranges from several months (e.g. influenza vaccine) to 3 years (Plotkin *et al.,* 2017).

Manufacturing classic vaccines, which involves biological processes to produce proteins, involves **uncertainty and variability** about yield, performance, and throughput. There are also contamination incidents distributed stochastically over time that we review in section 3.3.2.B. This year, the problems of AstraZeneca to provide the EU with its initial supplies of the SARS-CoV-2 vaccine and the contamination problems of the J&J vaccine at the Emergent vaccine plant in Baltimore are good examples. Plotkin *et al.* (2017) clearly explained the problem and the economic consequences: "Outcomes can vary widely due to the nearly infinite combinations of biological variability in basic starting materials, the microorganism itself, the environmental condition of the microbial culture, the knowledge and experience of the manufacturing technician, and the steps involved in the purification processes." They are of the view that "this is also the main reason why the number of vaccine manufacturers that succeed and thrive remains low despite unmet demand for many vaccines globally …. This compounded risk of biological and physical variability makes vaccine manufacturing more challenging than typical small molecule pharmaceuticals and is a primary root cause of the high proportion of vaccine manufacturing failures and supply shortages" (Plotkin *et al.,* 2017).

Manufacturing requires not only setting up and running the plant but also the organization of a complex **supply chain** and an extensive network of suppliers. Each vaccine has specific active components (the antigen) that generate different immune responses, as we have seen in section 1.1. However, they also contain a range of common ingredients:

- Preservatives prevent contamination of the vaccines, which is especially important when these are stored in multidose vials.
- Stabilizers prevent further chemical reactions from occurring, keeping a vaccine's potency stable while being transported.
- Surfactants ensure that ingredients remain blended, avoiding the clumping of elements in liquid form.
- Adjuvants are sometimes used to enhance the immune response.
- Other substances, including antibiotics, prevent contamination.
- Diluents temper the concentration of vaccines before use.
- In mRNA vaccines, the messenger ribonucleic acid (mRNA) is encapsulated in lipid nanoparticles, microscopic droplets of oily liquid that enclose and protect fragile genetic instructions as they are manufactured, transported, and finally administered (OECD, 2021b).
- Glass vials, syringes, and packing materials are also used.

Table 1.4 provides a list of key ingredients for vaccine manufacturing.

Two special difficulties have arisen in the deployment of manufacturing capacities for SARS-CoV-2 vaccines.

- First, for the new mRNA vaccines the supply chain and the networks of contract manufacturers were non-existent before the pandemic and had to be organized from scratch. It implies the supply of sophisticated components as plasmids (DNA molecules for insertion of the desired RNA sequence) or the already highlighted lipid-based nanoparticles. “Reliably manufacturing consistent LNPs was another challenge, and producing the raw materials needed to make the particles is a limiting factor in the production of COVID-19 vaccines today” (Cross, 2021).
- The second difficulty is the pressure on global supply chains for all kinds of inputs given the enormous volume of vaccines (Wouters *et al.*, 2021).

Another essential idea to understand the manufacturing processes of vaccines against COVID-19 is the deployment of global manufacturing networks to cover global demand for vaccines. Large multinationals and other companies have embarked in collaborations with contract development and manufacturing organizations (CDMOs) to “scale out” manufacturing. Promoting these agreements, collaborations, and networks has been one of the main components of both industry strategy to increase production and government policies to tackle and overcome the pandemic. These agreements, collaborations, and networks are instrumental in increasing global capacity to scale up production and in ensuring affordable prices to support global access.

The question that remains is whether mainly private market arrangements are enough to meet the global needs for vaccination and reverse the present highly inequitable distribution of vaccines, which were abundantly delivered in 2021 to rich countries. This paper does not aim to respond immediately to this crucial question but certainly tries to contribute to find the answer. Section 5 provides some remarks on the subject.

Whatever may be the difficulties and complexities of vaccine R&D and manufacturing, it seems that there is room enough for new actors and increased competition, which will increase supply and access. Towards this goal, appropriately organized **transfers of technology** would be instrumental. WHO is establishing a COVID-19 mRNA vaccine technology transfer hub to scale up global manufacturing (WHO, 2021, April 16). To this end, the first initiative has been advanced by a South African consortium (WHO, 2021, June 21).

The potential for local production in medium and small firms, government research centres, and universities is very high. New opportunities are open with the mRNA vaccines (successfully developed against SARS-CoV-2) since manufacturing processes are easier, quicker, more flexible, and more efficient than in other platforms. Consequently, there are multiple actors that may be involved in the vaccine R&D and manufacturing: multinational pharmaceutical firms, medium and small firms, government research centres and universities are all important sources of innovation. Box 1.1. provides some examples of CDMOs in Spain to manufacture vaccines against SARS-Cov-2.

Two innovative medium-size firms have played an important role in the development of the ground-breaking mRNA vaccines: Moderna in the USA (Garde and Saltzman, 2020) and BioNTech in Germany (Miller and Cookson, 2020; Gelles, 2020). R&D by Oxford University (Neville, 2020) has been fundamental in creating one of the first developed vaccines against SARS-CoV-2 (a nonreplicating viral vector [adenovirus] vaccine), in collaboration with AstraZeneca for the later stages.

TABLE 1.4. LIST OF KEY VACCINE INGREDIENTS

Appendix Table 1: List of vaccine ingredients and specialist distribution items

EU CN code	Ingredient/product name	Type of Ingredient
29061310	cholesterol	Key Ingredients
29232000	1,2-dimyristoyl-rac-glycero3-methoxypolyethylene glycol-2000	Key Ingredients
29239000	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	Key Ingredients
38220000	mRNA	Key Ingredients
39072011	2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide	Key Ingredients
25010099	sodium chloride	Other Ingredients
28272000	potassium chloride	Other Ingredients
28273100	magnesium chloride hexahydrate	Other Ingredients
28352200	dibasic sodium phosphate dihydrate	Other Ingredients
29152100	acetic acid	Other Ingredients
29152900	sodium acetate	Other Ingredients
29221900	Tromethamine	Other Ingredients
29224985	disodium edetate dihydrate	Other Ingredients
29232000	SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate)	Other Ingredients
29332990	L-histidine / L-histidine hydrochloride monohydrate	Other Ingredients
31056000	monobasic potassium phosphate	Other Ingredients
34021300	polysorbate 80	Other Ingredients
40151905	Nitrile Glove	Vaccine Distribution
90183100	Syringes	Vaccine Distribution
70179090	Borosilicate vials	Vaccine Distribution

Source: Ingredients sourced from official regulatory statements concerning the AstraZeneca-Oxford, Moderna, and Pfizer-BioNTech vaccines. Vaccine distribution items identified from specialist industry media sources.

Source: Evenett *et al*. (2021, p. 17)

There are also examples of increasing local production capacity in developing countries. The example of the Serum Institute of India, the world's largest producer of vaccines, is very clear in this respect, though for COVID-19, its role is of CDMO limited to fill and finish for AstraZeneca and Novavax vaccines. Other initiatives to be taken into account are Biovac in South Africa, Butantan Institute in Brazil, and Cuba, which has developed Soberana and Abdala vaccines. **Purely public and private/public collaborative internationally driven new projects** of manufacturing plants in developed and developing countries are also under serious consideration, such as the EU initiative to implement capacity in Africa through the Sustainable Healthcare Industry for Resilience in Africa (SHIRA) (European Commission, 2021) and the proposals of the Rome Declaration of the Group of Twenty (G20) Global Health Summit on May 21, 2020.

When produced locally, consumables (such as raw materials produced by biological production processes, like yeast extract and natural or recombinant enzymes, and materials of animal origin) can be an area of cost savings for vaccine manufacturers in low-resource countries, with prices estimated to be as low as 15% than those in high-resource countries (Plotkin *et al.,* 2017).

Enhancing the role and potential of local producers and medium and small firms can take various forms, including purely public efforts, public/private collaborations, and internationally driven projects. Nevertheless, policies have to be soundly designed to overcome restrictions and barriers rooted in the structure of the industry that will be reviewed in the following sections.

BOX 1.1.
CDMOs IN SPAIN TO MANUFACTURE VACCINES AGAINST SARS-COV-2

ROVI. The Spanish pharmaceutical firm ROVI reached in 2020 an agreement with Moderna to participate in the manufacturing of the mRNA vaccine. First it was a "fill and finish operation" in the San Sebastián de los Reyes factory, near Madrid. Last April the company announced that it was doubling capacity with two new lines for formulation, filling, automatic visual inspection, labelling and packaging of vials. The new lines are expected to be operative at the end of 2021 or beginning of 2022.

The agreement was extended in April 2021 to the production of the active principle (the antigen). Rovi had experience in biotechnology manufacturing (heparine) and sterile injectables.

For this purpose, a new line of production is under construction in the plant owned by the firm in Granada. The amount of the investment is not disclosed but is estimated in 60 M euros. Then expected time for the construction is around six months. The production capacity will be 100 million doses per year.

ZENDAL. The biotechnological firm Zendal, through subsidiary Biofabri, reached an agreement with Novavax to manufacture the antigen.

REIG JOFRE will fill and finish the vaccine of Janssen in Sant Joan Despí (Barcelona), starting in July 2021.

INSUD will fill and finish the vaccine of AstraZeneca in Azuqueca de Henares (Guadalajara, near Madrid).

Sources: 5 Días, 12 and 29 April 2021

1.4. Summary

Vaccines prevent more than 20 life-threatening diseases, saving two to three million deaths every year. As of June 1, 2021, six vaccines against COVID-19 have been approved by WHO, FDA, and EMA. Vaccines are large molecules that are more complex and difficult to handle than small-molecule drugs (chemical pharmaceuticals). As most vaccines are designed for primary prevention and applied to large healthy populations, safety requirements must be reinforced.

Presently, there are many technological platforms for the production of vaccines that can be classified in two broad groups: classic or traditional (live-attenuated, inactivated, and toxoid vaccines) and innovative (subunit, recombinant protein, polysaccharide, and conjugate vaccines; virus-like particles and nucleic acid vaccines). Among the latter, mRNA vaccines have demonstrated high efficacy and safety against SARS-CoV-2 and superior efficiency in manufacturing.

R&D of vaccines is expensive, difficult, long and risky. Manufacturing requires relatively high technological and organizational levels, substantial investments in plant and equipment,

highly trained technical staff and supply chains with networks of suppliers and collaborations with CDMOs. The question that remains is whether mainly private market arrangements are enough to meet the global needs for vaccination and reverse the present highly inequitable distribution of vaccines.

Despite the difficulties and complexities of vaccine R&D and manufacturing, there is room for new actors and increased competition to improve supply and access. Towards this goal, appropriately organized transfers of technology would be instrumental. In the future, it is possible to enhance the role and potential of local producers and medium and small firms as well as purely public, public/private, and international projects. Policies have to be soundly designed to overcome restrictions and barriers rooted in the structure of the industry.

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2. A DESCRIPTION OF THE VACCINE INDUSTRY

2.1. Size and Sales Forecasts

In 2019, the vaccine industry held about 3.6% of the total world market for pharmaceutical products (prescription and over-the-counter (OTC)) (EvaluatePharma, 2020). The vaccine industry is therefore relatively small compared to the pharmaceutical industry as a whole. The total infectious disease vaccine sales in 2019 were estimated at USD 32,500M worldwide. Among 14 therapeutic areas, it is the fifth largest. It is a growing segment expected to reach about USD 56,000M of sales by 2026. Its growth rate is accelerating (expected to reach 8.1% from 2020 to 2026, the fourth fastest area), partly due to developments before the pandemic and also because of the new vaccines against COVID-19 (see Table 2.1).

TABLE 2.1. INFECTIOUS DISEASE VACCINES: WORLD SALES

Year	Million (USD)	Growth (%) CAGR
2013	25,000	
2018	30,500	
2019	32,500	
2024 forecast	44,800	6.6 (24/18)
2026 forecast	56,100	8.1 (26/19)

Sources: Douglas and Samant (2017), EvaluatePharma (2019), EvaluatePharma (2020)
Note: CAGR: Compound annual growth rate

Sales forecasts for vaccines advanced by IQVIA, a leading firm in pharmaceutical markets data mining and analysis, are even higher. Over the next five years, most therapy areas are forecast to grow slower than in recent years. However, vaccines, including COVID-19 vaccines, will grow at 12%–15%, becoming the fastest growing category. According to IQVIA, it likely understates the spending impact of these new vaccines, as spending will have moderated by 2025. Actually, spending on COVID-19 vaccines is expected to reach 157,000 million USD by 2025 (see Figures 2.1. and 2.2.) (IQVIA, 2021).

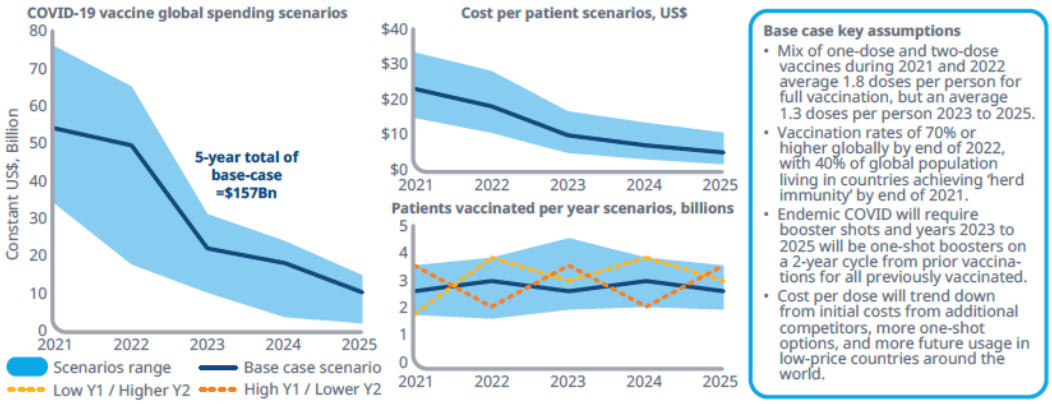
The steady growth of vaccine markets started before the COVID-19 pandemic. The vaccine segment was considered a laggard in the pharmaceutical business, but “in the past 20 years, has shown remarkable growth powered by new innovative vaccines coupled with superior pricing strategies” (Douglas and Samant, 2017). Table 1.3 compiles innovative vaccines developed since 1970. These authors highlighted the following as specifically contributing to this spectacular growth: varicella, hepatitis A, pneumococcal conjugate, shingles, rotavirus, meningococcal conjugate, and HPV vaccines, as well as combination vaccines.

FIGURE 2.1.

IMPACT OF COVID-19 ON THE USE OF MEDICINES

Global spending on COVID-19 vaccines is modeled to be $157 billion over the next five years, though cost and volume estimates vary

Exhibit 7: Estimates of Global Vaccine Spending, Cost per Patient and Patients Vaccinated Globally



Base case key assumptions

- Mix of one-dose and two-dose vaccines during 2021 and 2022 average 1.8 doses per person for full vaccination, but an average 1.3 doses per person 2023 to 2025.
- Vaccination rates of 70% or higher globally by end of 2022, with 40% of global population living in countries achieving 'herd immunity' by end of 2021.
- Endemic COVID will require booster shots and years 2023 to 2025 will be one-shot boosters on a 2-year cycle from prior vaccinations for all previously vaccinated.
- Cost per dose will trend down from initial costs from additional competitors, more one-shot options, and more future usage in low-price countries around the world.

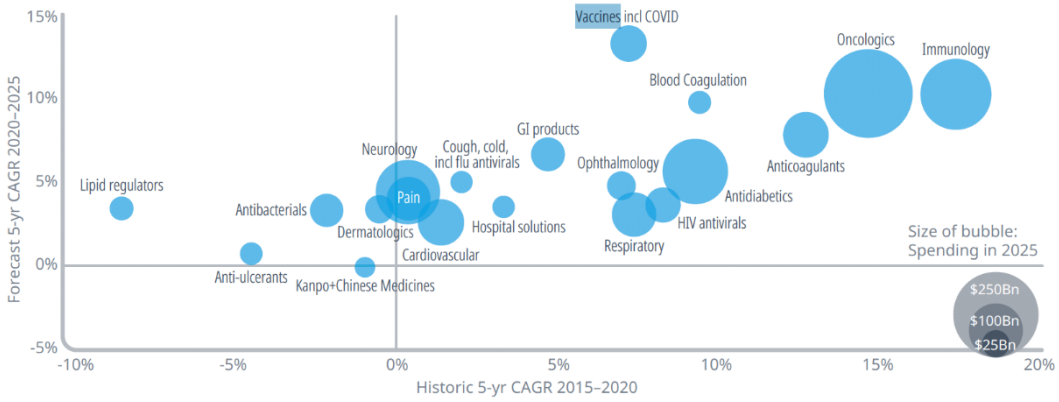
Source: IQVIA Institute, Mar 2021; Pricing information from public disclosures as of Mar 25, 2021; Vaccination trends to date from Ourworldindata.org

FIGURE 2.2.

KEY THERAPY AREAS

Most therapy areas are forecast to grow more slowly over the next 5 years, with the exception of vaccines

Exhibit 33: Global Historic and Forecast Spending Growth for Top 20 Therapy Areas



Source: IQVIA Institute, Feb 2021; Bubble Size represents forecast in 2025; COVID Vaccine estimates based on estimates of periodic booster shots; Neurology includes Nervous system disorders such as epilepsy, Parkinson's, Alzheimer's, other neurological disorders and mental health. Neurology estimate based on risk-adjusted potential for Alzheimer's approval and uptake.

2.2. Geographical Concentration

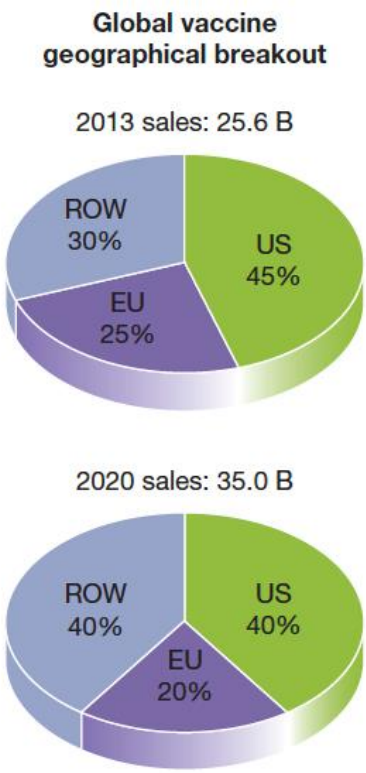
This section describes how manufacturing is distributed geographically (section 3 deals with economic concentration, but both concepts are interrelated). In a detailed study of trade flows and firm ownership, the vaccine industry has been depicted as **"the vaccine production club"** (Evenett *et al.*, 2021), for it is highly concentrated in a small number of multinational companies and plants mostly located in developed countries (European Union and the USA). These companies hold the dominant share of vaccine business on a revenue basis (see Figure 2.3). This geographically concentrated production for vaccines is a long-standing pattern. "The data clearly point to high concentration and self-reliance in COVID-19 vaccine production among a group of 13 countries. These countries are not only where the headquarters of the companies currently producing COVID-19 vaccines are found—they are also where 91% (783 out of 857 subsidiaries worldwide) of the subsidiaries of these companies are located" (Evenett *et al.*, 2021). The OECD also emphasizes the geographical concentration of production. "Developing economies depend on high-income countries for vaccines. The European Union (EU) is the main source of vaccine imports for all regions. In particular, South Asia and Sub-Saharan Africa import more than two-thirds of their vaccines from the European Union" (OECD, 2021).

An accurate idea of the unbalance is given by the WHO's list of prequalified vaccine manufacturers. There are 21 in developed countries (some of them are subsidiaries of the same multinational corporation (MNC)) and 13 in developing countries (medium income and Cuba), 7 of which are in India (1 is a subsidiary of an MNC), 4 are in China, and 1 is in the Russian Federation (WHO, 2021, May 14).

Geographical and firm concentration has been recently documented with new data on potential production capacity for anti-SARS-CoV-2 vaccines. A survey by the Coalition for Epidemic Preparedness Innovations (CEPI) highlights that a few high-income and emerging economies have the manufacturing capacity. The United States, China, and India are the largest potential producers, followed by several economies in the European Union, Australia, Brazil, Canada, the Russian Federation, and the United Kingdom (CEPI, 2020a). CEPI's opinion is that "as reflected by the number of manufacturers with regulatory approvals for their operations, mature manufacturing capacity is available for both drug-substance and drug-product manufacturing in multiple locations around the world" (CEPI, 2020b). "113 manufacturers, from over 30 countries, responded to our survey. 43 were both drug-substance and drug-product manufacturers. 56 were drug-substance manufacturers only. 100 were drug-product manufacturers only." However, only 9 manufacturers had inspection track records from WHO's prequalification scheme, 18 from EMA, and 15 from FDA for drug substances (the unformulated active [immunogenic] substances); and 17, 39, and 38, respectively, for drug products (the finished dosage form of the product, including a final container) (CEPI, 2020a). CEPI concluded that there was, at the moment, potential global capacity to produce at least two to four billion doses of COVID-19 vaccine by the end of year 2021.[1]

[1] This analysis represents a snapshot in time and will have changed dramatically since the data were collected between May and June 2020.

FIGURE 2.3. GLOBAL VACCINE MARKET, PROJECTED GROWTH (BEFORE THE PANDEMIC) FROM 2005 TO 2020



Notes: B: 1,000 Million; EU, European Union; ROW, rest of world; US, United States; USD, U.S. dollars.

Source: Douglas and Samant (2017)

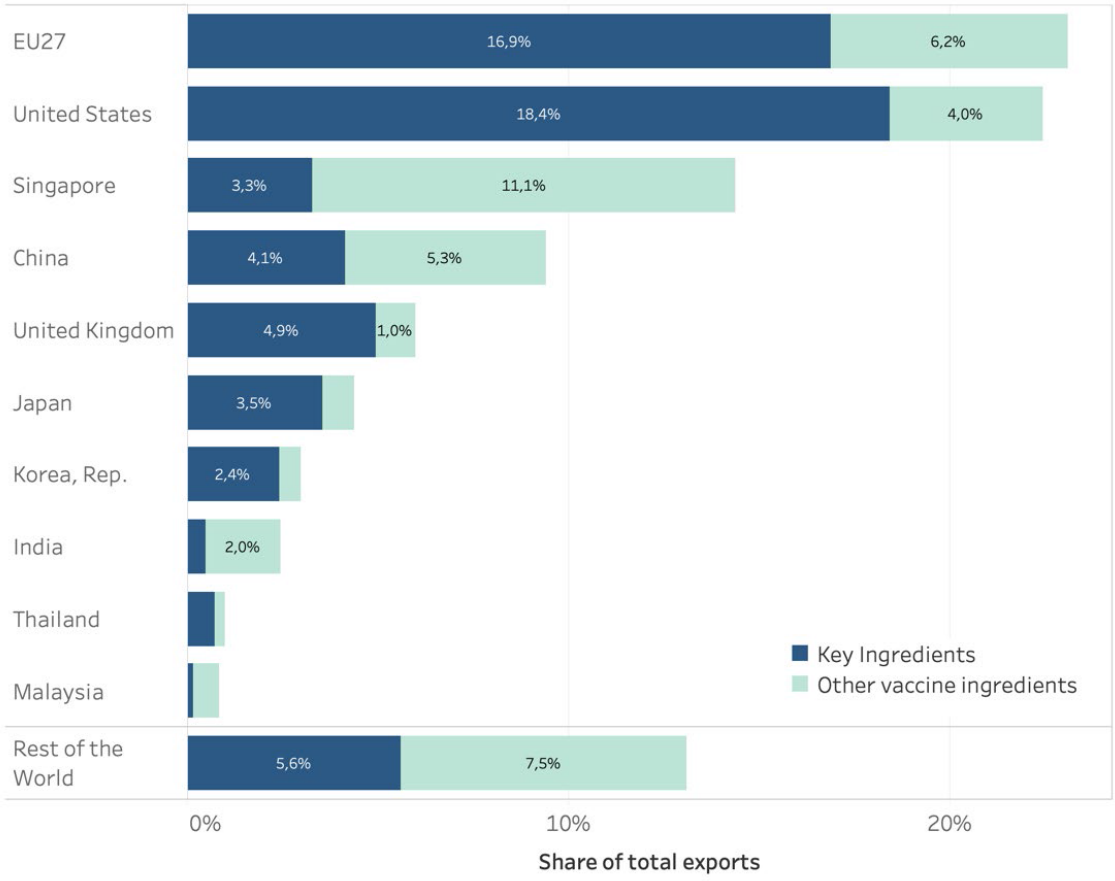
Manufacturing capacities are not the only relevant parameter. The **ingredients** and items needed to manufacture and distribute COVID-19 vaccines are also critical. The detailed study of trade flows and firm-level ownership data by Evenett *et al.* (2021) found that "global markets for COVID-19 vaccine ingredients are highly concentrated. The top-five exporters of these products (the EU, United States, Singapore, China, and United Kingdom) accounted for around three-quarters of total pre-pandemic imports. For the key ingredients the shares of imports from the top exporters were even higher and close to 80 percent, concentrated mainly in the United States, the EU, United Kingdom, China, and Japan. Vaccine producers are both the main source and destination of exports of key ingredients" (Figure 2.4) (Evenett *et al.,* 2021, p. 13).

Figure 2.5 shows that the manufacturers of ingredients used in the preparation of vaccines tend to be located in the countries where final vaccines are manufactured. Specifically, more than 70% of 444 firms identified by the Asian Development Bank (ADB) as manufacturers of ingredients that are relevant for COVID-19 vaccines are located in the European Union (156 firms), the United States (70 firms), China (49 firms), and India (43 firms) (Evenett *et al.,* 2021).

"The interdependence of the Vaccine Club is apparent from the data: vaccine producers sourced 88.3% of key vaccine ingredients from other vaccine producers …. To conclude … a small number of nations are responsible for the lion's share of the production and cross-border supplies of both COVID-19 vaccines and other

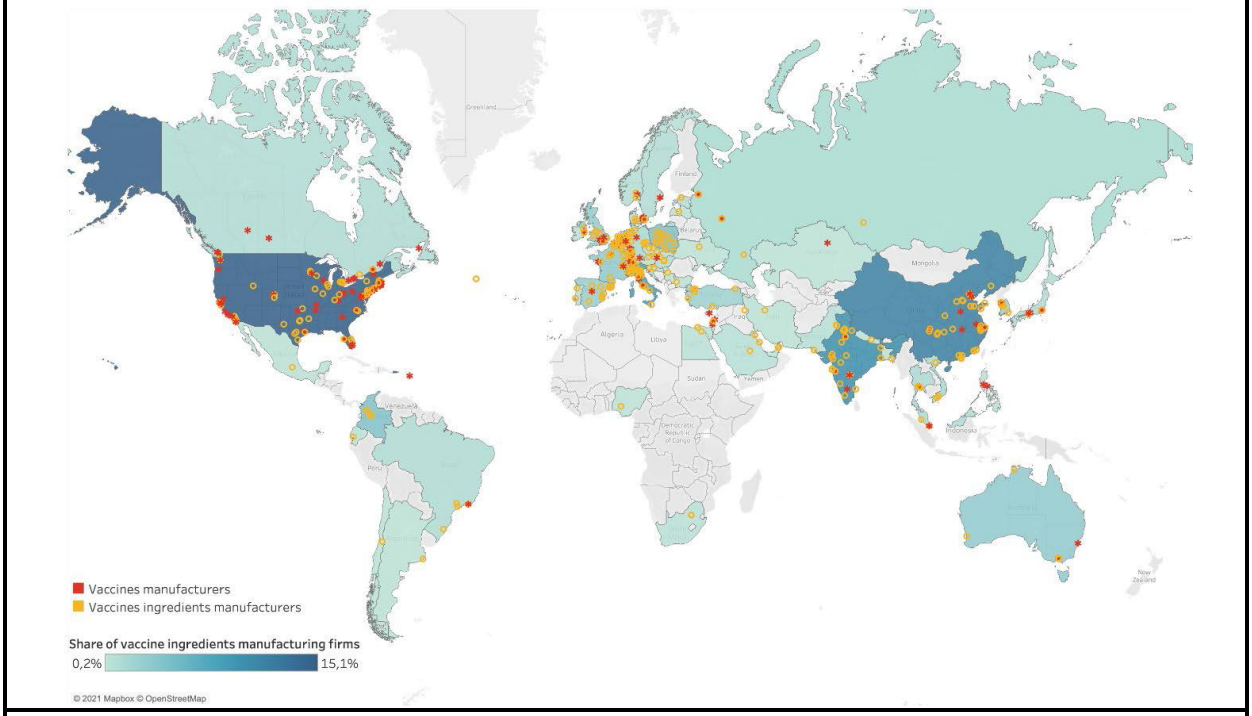
ingredients …. This state of affairs has important policy implications at a time of significant shortages of COVID-19 vaccines" (Evenett *et al.,* 2021, p. 17).

FIGURE 2.4. TOP 10 EXPORTERS OF COVID-19 VACCINE INGREDIENTS



Sources: World Integrated Trade Solution (WITS) for 2017, 2018, and 2019, from Evenett *et al.* (2021)

FIGURE 2.5. DISTRIBUTION OF VACCINE AND VACCINE INGREDIENT MANUFACTURERS



Source: 2021 Asian Development Bank (ADB) supply chain maps for pandemic-fighting products, from Evenett *et al.* (2021)

2.3. The Companies

WHO gives a good description of the firms supplying the global vaccine market:

> About 80% of global vaccine sales come from five large multi-national corporations (MNC) that were the product of various mergers and acquisitions of pharmaceutical companies over the past decades. While maintaining a strong focus on vaccines for industrialized country markets, MNCs also sell their products in developing countries and emerging markets and participate in Global Health Initiatives. To compete in these markets, MNCs will often outsource and participate in joint-development activities and technological transfers.
>
> In the 1980s emerging market manufacturers started entering the vaccine market and have assumed a significant role since. Emerging manufacturers (in India, China, and Brazil), play a critical role in the supply of vaccines of developing countries, particularly basic and some combination vaccines. They now supply about half of UNICEF vaccine procurement in volume of doses, representing about 30% of the value of UNICEF's total vaccine procurement.
>
> The entry of emerging market manufacturers … has resulted in lower vaccine prices due to increased competition and higher production capacities …. A few emerging market manufacturers are also trying to expand their production to newer vaccines. Emerging manufacturers are represented by the Developing Countries Vaccine Manufacturers Network (DCVMN) (WHO 2021, May 13).

Douglas and Samant (2017) estimated that, in 2014, the top four Western suppliers accounted for approximately 85% of global sales; the remainder came from regional vaccine

companies, the largest of which are located in middle-income countries, such as India, China, and Brazil (see Table 2.2). The top four companies are slowly losing market shares in doses to the DCVMN companies.

Hatchett *et al.* (2021) provide another description of producers by continent. It seems that the study units are firms with full capacity in antigen, bulk, and fill-and-finish operations. This description reckons only 13 manufacturing firms across the world, with around 55% of capacity located in East Asia, 40% in Europe and North America, and less than 5% in Africa and South America (Figure 2.6) (Hatchett *et al.*, 2021).

Serum Institute of India is the world's largest producer of vaccines by number of doses, producing 1,300 million a year. Its products are used in more than 140 countries. One out of every two children immunized worldwide get at least one vaccine produced by the Serum Institute. Of the 40 vaccine manufacturers in 14 nations that are part of the Developing Countries Vaccine Manufacturers Network, only one is African: the Biovac Institute based in Cape Town, South Africa, which currently delivers over 25 million doses of vaccines each year for illnesses such as measles, polio, and tuberculosis (UNCTAD, 2020).

TABLE 2.2. MARKET SHARES OF VACCINE COMPANIES, 2014

Company	Year-End Earnings (USD 1000 M)[a]	Market Share (%)
GlaxoSmithKline	5.3	19.7
Merck & Co.[b]	6.2	23.4
Novartis	1.5	5.7
Pfizer	3.5	16.8
Sanofi[b]	5.8	21.9
Others	3.4	12.6
Total	**26.7**	**100**

[a] Company 2014 year-end earnings releases from EvaluatePharma (http://www.evaluategroup.com).

[b] Each includes 50% of revenues from Sanofi Pasteur MSD joint venture.

Source: Douglas and Samant (2017)

FIGURE 2.6. Vaccine producers by continent, with stage 3 products and later, excluding C(D)MOs with no known own contracts with countries / mechanisms

Source: Hatchett *et al.* (2021)

Douglas and Samant (2017) appropriately described the role of large vaccine companies in vaccine R&D mainly focussed in development:

> They engage in some limited basic research and significant amounts of targeted research regarding specific organisms, but the preponderance of activity is in clinical and process development. Sufficient personnel and expertise in process development and chemical engineering reside almost exclusively in these companies; there is no other resource for such development. Clinical development that will satisfy FDA standards is also done mostly by the large companies, performed by academia and contract research organizations.

The role of smaller biotechnology companies engaged in vaccine research is centred in the earlier innovative stages. “They are often started by university scientists, supported by venture capitalists, and are capable of basic research on a vaccine idea. At this early stage, they usually have limited capacity in process development, manufacturing, and clinical development, and none in distribution, sales, or marketing. If research results are favourable, capacity in process engineering, clinical studies, and manufacturing must be enhanced or obtained by partnering. Because of the large cost of adding new capacities and expertise, many biotech companies in advanced product development will opt to partner with large, full-scale companies” (Douglas and Samant, 2017).

“Only a very few, such as MedImmune, have made it to the market … on their own. More have licensed their products or technology platforms to larger companies…. For example … Chiron Corporation succeeded in making hepatitis B surface antigen in yeast … enabling Merck and GlaxoSmithKline to commercialize the … vaccines. In the case of H. influenzae type b (Hib), Praxis Biologics and Connaught Laboratories pioneered the development of Hib polysaccharide and conjugate vaccines … were eventually acquired by Sanofi and Wyeth-Lederle, respectively” (Douglas and Samant, 2017).

The development of mRNA vaccines for SARS-CoV-2 is a superior example of the entry in the market of new firms with biotechnology capabilities. BioNTech in Germany and Moderna in the USA have developed the mRNA technology and are now essential firms in the supply of vaccines. Pfizer-BioNTech is nowadays the main global producer and supplier of vaccines

against SARS-CoV-2, and Moderna operates independently with substantial production and supplies. The mRNA technology is expected to contribute to other therapeutic breakthroughs, for instance, in the treatment of different forms of cancer.

“The greatest contributions of the biotechnology companies have been the introduction of multiple ideas into early vaccine development, and testing them to determine if they should be rejected or carried forward” (Douglas and Samant, 2017).

Is the COVID-19 pandemic changing the landscape of geographical and firm concentrations of production? “COVID-19 vaccine manufacturers ramped up their own manufacturing in parallel to clinical development (‘scale-up’) in response to this challenge. They also formed more than 150 partnerships with CDMOs and other multinational biopharmaceutical companies to transfer their technology and increase their overall production (‘scale-out’)” (Hatchett *et al.,* 2021). Independent information and detailed studies are needed to clarify the extent of the agreements and transfers of technology. It is important to go beyond contract manufacturing for fill-and-finish in developing countries with the limited aims of reducing costs and increasing manufacturing capacity. In the short term, there is an urgent need to enable greater global production of COVID-19 vaccines. In the long term, technical capabilities for R&D and manufacturing have to be significantly increased and distributed to meet global needs and to prevent and respond rapidly to emerging infections and future pandemics.

Table 2.3 and Figure 2.7 provide information on the main vaccine-manufacturing individual companies (circa 2009 and 2018) before the COVID-19 pandemic. Figure 2.7 specifies the number of vaccine subtypes produced. It is evident how the manufacturing landscape evolved throughout these years with the surge of emerging manufacturers (notably, Serum Institute of India). It is also evident that the landscape has changed with the pandemic. Now, small innovative companies introducing mRNA vaccines (BioNTech, Moderna) are leading actors in the market, and the prospects of this technology will probably give them a prominent role in the future. Conversely, of the four “full-scale companies with large vaccine focus” according to Table 2.3, there are three that, as of today, have failed to introduce any significant product to prevent SARS-CoV-2 and “are left playing catch-up to upstarts with new technology” (Kouchler and Abboud, 2021).

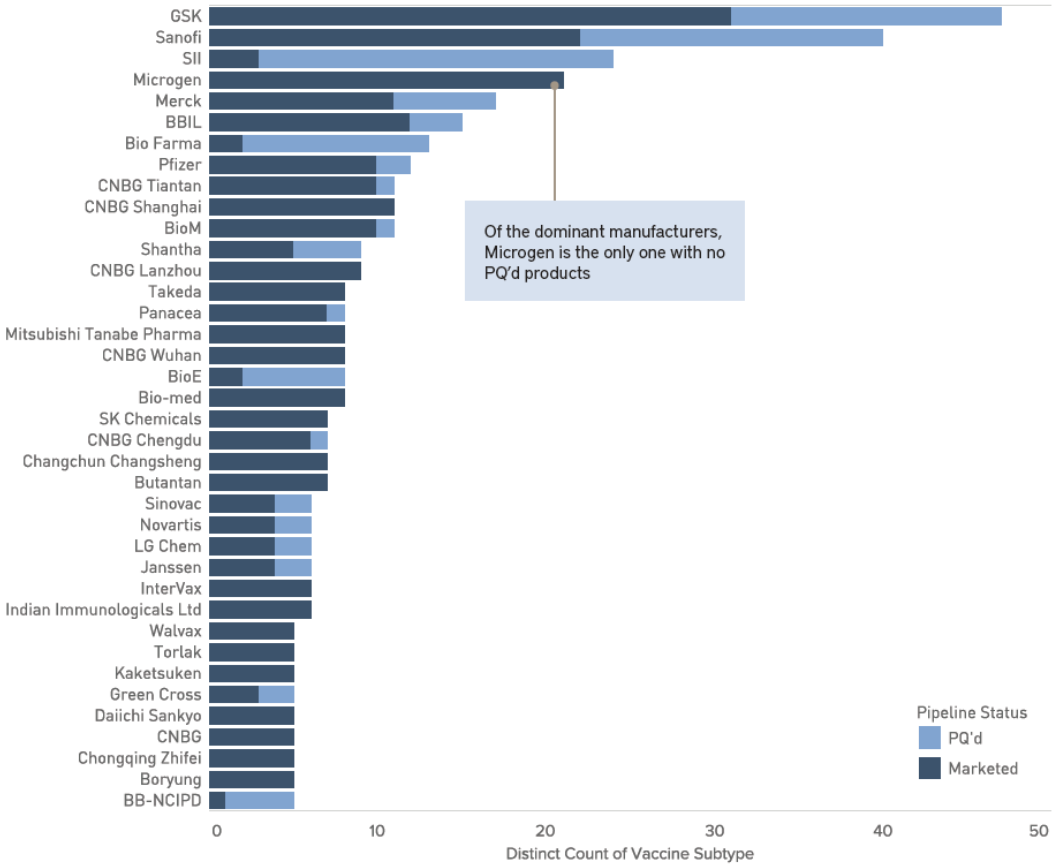
TABLE 2.3. MAIN VACCINE MANUFACTURING COMPANIES, 2009

FULL-SCALE COMPANIES WITH LARGE VACCINE FOCUS (~90% WORLD MARKET SHARE)	
France	Sanofi
United Kingdom	GlaxoSmithKline
United States	Merck Pfizer
OTHER FULL-SCALE COMPANIES WITH VACCINE DIVISION	
Australia	CSL (CSL Biotherapies)
United Kingdom	AstraZeneca (MedImmune)
United States	Johnson & Johnson (Crucell)
BIOTECH VACCINE COMPANIES	
Denmark	Bavarian Nordic
France	Vivalis
United States	Dynavax Emergent BioSolutions Genocea Novavax PharmAthene Protein Sciences Vical
REGIONAL COMPANIES	
Argentina	National Administration of Laboratories and Institutes of Health ANLIS Dr. Carlos G. Malbrán Sinergium Biotech S.A.
Bangladesh	Incepta Vaccine Ltd
Brazil	Ataulfo de Paiva Foundation Bio-Manguinhos–Institute of Technology on Immunobiologicals Butantan Institute Ezequiel Dias Foundation (FUNED)
Bulgaria	BB-NCIPD
Canada	InterVax Medicago
China	Beijing Minhai Biotechnology Co., Ltd Beijing Tiatan Biological Products Co., Ltd China National Biotec Group (CNBG) Hualan Biological Engineering Liaoning Cheng Da Biotechnology Co., Ltd (CDBIO) Sinovac Biotech Ltd. Walvax Biotechnology Co., Ltd Xiamen Innovax Biotech Co., Ltd
Cuba	Center for Genetic Engineering and Biotechnology Finlay Institute
Denmark	Statens Serum Institute
Egypt	The Holding Company for Biological Products & Vaccines (VACSERA)
India	Bharat Biotech International Ltd Biological E. Ltd Cadila Pharmaceuticals Ltd Hafkine Bio-Pharmaceutical Corporation Limited Indian Immunologicals Ltd Panacea Biotec Ltd Serum Institute of India Ltd
Indonesia	Bio Farma
Iran	Pasteur Institute of Iran Razi Vaccines
Israel	BiondVax
Italy	Okairos
Japan	Astellas Pharma Denka Seiken Japan BCG Kaketsuken Kitasato Institute Kyoto Biken Takeda
Korea	Boryung Biopharma Cheil Jedant (CJ Pharma) Dong Shin Pharma EuBiologics, Co., Ltd. Green Cross Corporation Korea Vaccine LG Life Sciences Ltd SK Chemicals
Malaysia	Pharm Malaysia
Mexico	Laboratorios de Biologicos y Reactivos de México, S.A. de C.V. (Birmex)
Netherlands	Netherlands Vaccine Institute
Poland	IBSS Biomed
Russia	Immunopreparat Research productive association, Ufa Products Immunologicals and Drugs, Irkustk RIVS, Saint Petersburg
Senegal	Torlak Institute of Immunology and Virology
Serbia	The Biovac Institute
South Africa	BioNet Asia Co., Ltd
Thailand	The Government Pharmaceutical Organization Queen Saovabha Memorial Institute
Vietnam	Institute of Vaccines and Medical Biologicals (IVAC) The Company of Vaccine and Biological Production No. 1-VABIOTECH
CONTRACT MANUFACTURERS	
Germany	Boehringer Ingelheim IDT
Holland	DSM Biologics
Switzerland	Lonza Biologics
PRODUCT DEVELOPMENT PARTNERSHIPS	
Korea	International Vaccine Institute
United States	Aeras Global TB Vaccine Foundation Dengue Vaccine Initiative International AIDS Vaccine Initiative Malaria Vaccine Initiative Sabin Hookworm Vaccine Initiative

Data from World Health Organization. Influenza vaccine manufacturers. May 13, 2009. Available at http://www.who.int/csr/disease/influenza/Influenza_vaccine_manufacturers2009_05.pdf.

Source: Douglas and Samant (2017)

FIGURE 2.7. MAIN VACCINE MANUFACTURING COMPANIES AND NUMBER OF VACCINE SUBTYPES PRODUCED. CIRCA 2018



Notes:
This figure only lists manufacturers with five or more licensed vaccines in their portfolio.
PQ'd: WHO prequalified products

Source: WHO (2018)

2.4. Trade

As shown in section 2.2, the global markets for COVID-19 vaccines and vaccine ingredients are highly concentrated and vaccine producers, "the vaccine production club", are both the main source and the destination of exports of key ingredients. In fact, there are strong trade interdependencies of the goods needed to produce, distribute, and administer vaccines (active ingredients, other ingredients, bulk product, finished vaccines, vials to move the vaccines, syringes to administer, cold boxes to transport, dry ice to maintain cold temperatures, and freezers to store). Interdependency means access to goods produced across a range of countries is required (OECD, 2021).

Exports of vaccines are significantly concentrated. The top 10 exporters account for 93% of the global export value (80% in volume). Ireland is the top exporter by value, accounting for 28% of global exports,[1] followed by Belgium (which is the top exporter by volume) representing 21%.

[1] This is because Ireland is the location for parent firms due to lower taxation, not for production capacity.

Both value and volume imports are, in relative terms, less concentrated. The top 10 importers still represent 72% of global import values (69% in volume). The United States is the top importer with 24% of global imports, followed by Belgium with 22% (OECD, 2021, p. 3).

In sum, the patterns of trade for vaccines and ingredients respond to the strong trade interdependencies of the goods needed and the concentration of production.

2.5. Summary

The vaccine industry is relatively small compared to the pharmaceutical industry as a whole. The past 20 years has shown remarkable growth, thanks to innovative vaccines, new target population groups (adolescents), and more aggressive pricing strategies. The COVID-19 pandemic is dramatically changing the landscape with an enormous increase in production and sales ("scale-in and scale-out") to respond to the global demand. Therefore, growth is expected to be very high in the forthcoming years, 8.1% from 2020 to 2026.

The "vaccine production club", a small number of nations, concentrates the production and trade of both COVID-19 vaccines and ingredients. Vaccine producers are both the main source and destination of exports of key ingredients. This is a consequence of concentration at the firm level, with a small number of multinational companies and plants mostly located in developed countries. However, East Asia and South Asia are increasingly becoming a source of vaccines for other developing regions.

The deployment of agreements and transfers of technology from multinational companies to CDMOs for the production of vaccines against COVID-19 is impressive, but more studies are needed to know if they do or do not go beyond fill-and-finish for reducing costs and increasing manufacturing. In the short term, there is an urgent need to enable greater global production of COVID-19 vaccines. In the long term, the technical capabilities for R&D and manufacturing have 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.

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3. The Structure of the Vaccine Industry

3.1. Effectiveness and Efficiency of Vaccines

Historically, the effectiveness of vaccines has proved to be very high, leading to spectacular reductions of mortality and morbidity. The best example is smallpox, which was declared to be eradicated from the planet by the WHO in 1980 after a laudable international vaccination effort. Another example is poliomyelitis, which has been eradicated in most regions of the world, the last one being in Africa in October 2020 (WHO Regional Office for Africa, 2020). Section 1.1 of this paper provides a list of selected innovative vaccines since 1970 (Table 1.3).

Many vaccines offer highly favourable cost-effectiveness ratios (Table 3.1). Traditional vaccines, in particular, with research and development investments already paid off and with minimal costs per dose, reach high levels of cost-efficiency with very advantageous cost-effectiveness ratios. Their performance is outstanding. They give highly positive outcomes in terms of health while also reducing the financial burden on health systems.

TABLE 3.1. VACCINES: BENEFIT/COST RATIO

Diphtheria/whooping cough	27/1
Measles	13.5/1
Chicken pox	4.8/1
Streptococcus pneumoniae (Strep. pneumonia)	0.68–1.1
Source: Sloan (2012)	

3.2. Demand

3.2.1. Factors Relevant to Demand

Societies and individuals demand preventive vaccines because they diminish the probability of becoming infected and effectively control or even eliminate the negative health, social, economic, and psychological consequences of illnesses.

Other factors relevant to demand are as follows:

- Preventive vaccines are administered to large healthy populations (not suffering yet from the illness we wish to prevent).
- The administration of vaccines is an infrequent event for most individuals as most people are inoculated only a few times in their lives (in comparison, for instance, to

the use of common analgesics or even medications taken every day for chronic conditions).
- Individual demand depends on the infection rate and virulence of the pathogenic agent, the number of people already infected, the probability of transmission, and thus, the expected incidence of illness.
- Vulnerable populations like children, the elderly, socioeconomically deprived communities
- Availability of effective treatments

The first point is extremely important. It implies that the benefit-risk ratio of the vaccine has to be clearly positive, with very few safety concerns for adverse reactions. It follows that safety requirements have to be very stringent and clinical trials have to enrol larger groups of subjects than is usual in the evaluation of medicines intended for ill people.

It is said that vaccines have a relatively small market compared to pharmaceuticals that would limit incentives to invest in the industry. The use of vaccines is empirically less frequent, and the aim is to prevent illness. So, the use of vaccines is certainly not as recurrent as the utilization of pharmaceuticals for chronic conditions. However, for vaccines against SARS-CoV-2, there is global demand. Even before the pandemic, large countries and the entire world were **not** exactly **a small market** either. If we examine vaccines designed for children alone, the number of births per year worldwide (140.1 million in 2019, of which 7.7 million was in Europe and 4.3 million was in North America (Our World in Data, 2021)), though declining in most developed parts of the world, provides a significant target population. The expected pricing tiers for these vaccines show that the expected sales are not small at all. The influenza vaccine, for example, also has a large potential market.

Developing countries lack the ability to pay and provide limited sales potential to commercial firms. The vicious circle of poverty plays an important role here. Since low-income individuals lack the ability to pay, commercial production is less profitable, further entrenching the illness in poorer countries, which in turn worsens the economic outlook for these developing countries. If social and economic development programmes are introduced via international cooperation, as economies improve, willingness to pay will be higher, providing more incentives for future R&D and for marketing future vaccines. Positive externalities mean that the population will enjoy better health status and, in turn, will push economic growth.

Looking ahead to the future, developing countries are a source of growing demand. Before the pandemic, many were experiencing economic growth and still have high birth rates. International cooperation also provides financial support and technical assistance. The role of United Nations (UN) agencies, such as the WHO and the United Nations Children's Fund (UNICEF), is very important, and nongovernmental organizations and philanthropic bodies, such as GAVI, the Vaccine Alliance, have been very active in the last 25 years.

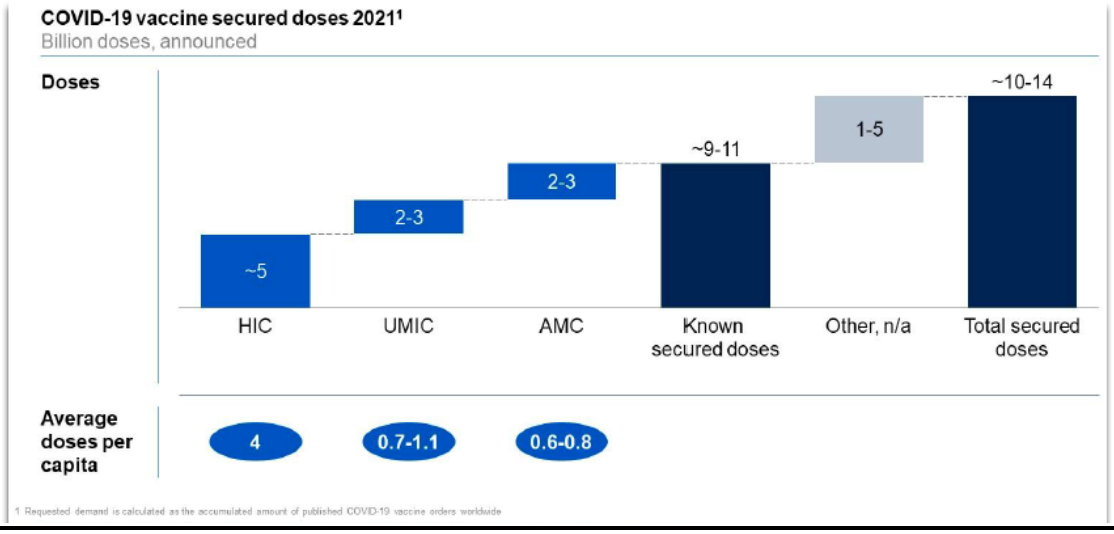
With the **COVID-19 pandemic, the demand for effective vaccines** already available has skyrocketed. "The world now needs more doses of COVID-19 vaccines than it has done for any other vaccine in history to inoculate enough people for global vaccine immunity" (Wouters *et al.*, 2021). We now know effective demand for anti-SARS-CoV-2 vaccines. "As of late February 2021, countries, regional and global mechanisms such as COVAX have announced 9,000-11,000 million secured doses for 2021. Of these, 5,000 million doses are for high-income countries (HICs), 2,000-3,000 million doses for upper-middle income countries (UMICs), and 2,000-3,000 million for the 92 low and middle-income countries that include COVAX Advance Market Commitments (the 'AMC countries')" (Hatchett *et al.*, 2021). These data are shown in Figure 3.1.

The fact that developed countries have ordered or secured doses in amounts more than double their needs and **the unbalance in vaccination rates in developing countries are the most important problems to be solved in 2021**. Many voices are demanding redistribution through different ways. See, for instance, the statement by the Director-General of WHO (Ghebreyesus, 2021).

A final remark on demand size is that it is not a variable to be taken in isolation. "What matters in determining the potential for having multiple viable producers in a product category is the size of the market relative to the volume required to realize most or all economies of scale. … for at least some vaccines, significant economies of scale continue to generate large annual sales volumes. An adverse relationship between market size and scale economies may explain much of the high concentration in vaccine production" (Scherer, 2007). We will return to this important point in sections 3.3.4 and 4.

It is anticipated that COVID-19 will prompt a range of changes in the use of medicines: increased demand for new vaccines and therapeutics and shifts in demand for existing therapies (IQVIA, 2021). Persistent COVID-19, the collateral effects of the pandemic due to postponed demands to address other illnesses, new reinforced efforts to prevent future pandemics, and changes in patient behaviours will be the driving factors.

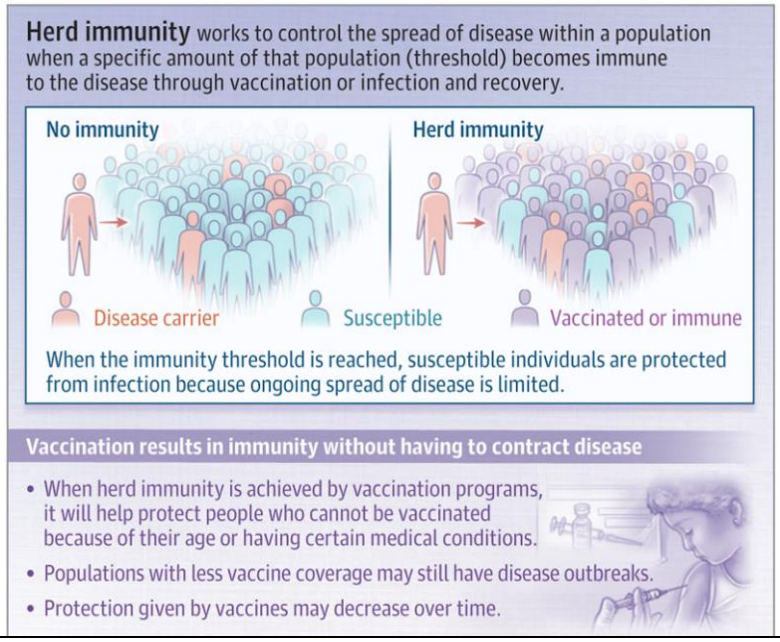
FIGURE 3.1. COVID-19 Vaccine Demand 2021



Note: HIC: high-income countries. UMIC: upper-middle income countries. AMC: low and middle-income countries in COVAX

Source: Hatchett *et al.* (2021)

Figure 3.2. HERD IMMUNITY



Source: Desai and Majumder (2020)

3.2.2. Externalities: Herd Immunity

The demand for vaccines creates both internal and external effects, an important distinction in microeconomics. External effects or externalities arise when the production or consumption of a good affects anyone other than the buyers and sellers. Externalities may be positive (like the ones arising from research and development). The agents profiting from the positive externalities do not have to pay for them, and the producers or consumers generating the positive effect benefiting others have no way to charge for it. That is, they see the consequences of their actions "externalized." On the contrary, externalities may be negative, like the air pollution from a steel mill, domestic violence associated with the consumption of alcohol, or a respiratory illness brought on by passive smoking (second-hand smoke). The polluter, drinker, or smoker does not incur costs for the damage caused to others; that is, he or she "externalizes" his or her costs. In the presence of externalities, the market allocation of the product or good will not show Pareto efficiency. Society will have more negative externalities and less positive externalities than it wishes if no action is taken.

In the case of vaccines, or at least for most of them, there is a peculiar and important externality called "herd or group immunity". The scientific truth is that for pathogens to thrive and propagate an epidemic or pandemic, they need, at any given moment and in a certain community, a minimum threshold of infected carriers who can transmit the infection. If the probability for any susceptible person to contact a carrier is very low, the contagion does not prosper and the infection does not progress (Figure 3.2). One who is vaccinated, at least for some illnesses, will not transmit the infection to others.

"Herd immunity" occurs when a sufficient portion of a population becomes immune to an infectious disease and the risk of spread from person to person decreases. Those who are not immune are indirectly protected because the ongoing disease spread is very small. The proportion of a population who must be immune to achieve herd immunity varies by disease. For example, a disease that is very contagious, such as measles, requires more than 95% of the population to be immune to stop sustained disease transmission and achieve herd immunity (Desai and Majumder, 2020). Theoretically, herd immunity can be reached through

vaccination and naturally if a sufficient number of the population suffer from the infection and become immune. However, this steady state may impose a tremendous price in terms of lives lost and unbearable social and economic costs.[1] In any case, herd immunity means that a portion of people in a community would theoretically not need to be vaccinated; they are afforded indirect immunity due to the decreased risk of infection. This is important if there are people who cannot be vaccinated for medical or other individual reasons.

"The percentage of people who need to be immune in order to achieve herd immunity varies with each disease. For example, herd immunity against measles requires about 95% of a population to be vaccinated. The remaining 5% will be protected by the fact that measles will not spread among those who are vaccinated. For polio, the threshold is about 80%. The proportion of the population that must be vaccinated against COVID-19 to begin inducing herd immunity is not known. This is an important area of research and will likely vary according to the community, the vaccine, the populations" (WHO, 2020a). From an economic point of view, when herd immunity is reached and remains stable, the demand for vaccines will fall to zero.

In sum, the externality in vaccination arises if vaccinated people do not transmit the infection to others. Vaccination has two distinct benefits: achieving individual immunity to a pathogen and not infecting others. Through vaccination, we protect ourselves and also society.

People, according to simple microeconomics, may act self-centredly, focusing only in maximizing their individual utility (individual gains) and taking into account the personal eventual cost of vaccination and setting aside the positive effects to others. Then, incentives to vaccinate may not be enough and the rate of vaccination could fall short of what is needed. This is the "free-rider" problem—people who do not want to vaccinate but expect others to do so and get the benefits of herd immunity.

Accordingly, intervention from the state and regulation is needed to overcome this failure. In some countries, it is standard, especially during epidemics and pandemics to provide vaccines to the public free of charge. Other incentives are also sometimes provided, even payments. Regulations may also require vaccinations for children going to school or adults looking for work or travelling.

3.3. Supply

From the supply side, there are five points to be highlighted: capital requirements, the production function, product specialization in manufacturing, horizontal concentration, and the absence of generics.

3.3.1. Capital Requirements

Douglas and Samant (2017) stressed the fact that the vaccine industry is a capital-intensive business that requires considerable ongoing investment in manufacturing assets, facilities, and people. This is a barrier to new firms and plants undertaking production and an obstacle to competition. It derives from the technology of vaccines and manufacture (Section 1). "Manufacturing plants are very expensive to construct, ranging from USD 50 million to USD 300 million depending on the size (dose

[1] "Can anybody please name a disease where proper herd immunity with elimination of the disease has been achieved through natural infection? Except, perhaps, diseases like the plague where the disease killed off the infection reservoirs. Has herd immunity eliminated measles, TB, polio, smallpox? I might be mistaken but I always thought it was vaccination that eliminated smallpox. For a disease like Covid, it could eventually achieve an equilibrium at tremendous cost with few active cases and slower spread but it would always be there waiting to infect those who had been shielding" (Pickin, 2020).

requirements) and manufacturing complexity, with an additional expenditure of approximately 20% of that cost for cleaning and process validation activities that are now required under the current good manufacturing practices regulations" (Douglas and Samant, 2017).

The WHO also reckons that it costed between USD 50M and USD 500M to set up a facility to produce monovalent vaccines and as much as USD 700M for polyvalent vaccines in 2017 in the USA. Seven years are needed to design, build, validate, and commence commercial manufacturing in a three-product polyvalent vaccine facility. "Smaller manufacturer and manufacturers located in resource poor settings are shut out" (WHO, 2020b).

Another valuation by the United States (US) Department of Defence estimated the 25-year life-cycle cost of a three-product facility to be USD 1,560M (in a developed country) and that 7 years are needed to design, build, validate, and commence commercial manufacturing (Plotkin *et al.,* 2017).

It is worth noting that there is high variation. There are examples now from COVID-19 production showing short time for facility re-purposing and establishment (Lonza for Moderna in Switzerland and J&J in USA). Variations also depend on the vaccine technology. If it is well known and no longer proprietary, capital requirements will be lower. We need additional information to show divergence in potential facility setup costs according to local conditions. As a rule, we can expect lower costs in developing countries (personnel, etc.), though some costs "can be expected to be as high or higher in low resource countries, as many materials may be imported and some key personnel may be hired from other countries as expatriates" (Plotkin *et al.,* 2017).

However, engineers and scientists are developing new methods and technologies to lower capital costs and time. For instance, through process intensification, a method comprising densification (smaller and more efficient equipment) and chaining (leading to continuous processing instead of batch manufacture); high-yield cell substrates to boost output; 'plug and play' production platforms; prefabricated and modular manufacturing facilities[1] (WHO, 2020b). It seems therefore that there is some room for multiple small facilities that could be deployed more broadly and even could be switched on relatively quickly to tackle emergent needs of production in case of a surge of new pathogens.

3.3.2. The Production Function: Costs

Overall, R&D, production, testing, evaluation, and distribution of biological products are complex and costly. The analysis is hindered by the fact that the information available about costs and profits in the pharmaceutical industry and in the segment of vaccines is, in general terms, scarce. This section tries to identify the main sources of complexity and subsequent high costs. We will consider the following cost items: R&D, stochastic risk of batch contamination, regulation, and liability risks.

[1] An interesting project of this sort is described as follows: "Univercells and Batavia spent two years designing a manufacturing process for Sabin inactivated polio vaccine (sIPV) and achieved an estimated cost per dose for 40 million doses for less than USD 0.30. While twice the target set by the foundation, it is a fifth of the current UNICEF price for this vaccine. 'We estimate that the vaccine could be produced in a micro-facility, costing approximately USD 30 million and capable of delivering between 40-50 million trivalent doses per year,' Hamidi says, adding that the investment required to go into production at that scale would typically be between USD 100 – 150 million" (WHO, 2020b).

A. Research and development costs

In section 2, we already discussed the technological aspects of R&D. Here, we focus on the R&D costs. Unfortunately, we have not found in the literature detailed data nor empirically well-founded studies analysing this important question. For the pharmaceutical industry as a whole, we do have a full stream of empirically based literature and a permanent debate on the subject.[1] However, the focus has been in chemical drugs (new chemical entities). Different authors consider that data on costs for chemical pharmaceuticals are transferable to vaccines, but this is not clear since success rates and size of clinical trials are different.

Therefore, there are frequent opinions about R&D costs for vaccines being high, as is the rule in the pharmaceutical industry, although there is controversy about how much high. In 2002 an expert from the industry wrote that developing a human vaccine from the preclinical phase to registration requires an increasing average investment of approximately USD 200M–900M (Andre, 2002), but without any supporting data. Scherer, a leading scholar in the subject, guessed that R&D costs for new vaccines are of the same order of magnitude as new pharmaceuticals, in 2007 hundreds of millions of dollars (Scherer, 2007). Douglas and Samant (2017) gave the following figures: USD 231M in 1991, USD 802M in 2003, USD 1,000 million in 2010, estimates that would consider all costs (including products that fail, post-licensure clinical studies, and improvements in manufacturing processes). The references provided do not support these estimates.[2] A substantial improvement of official data and disaggregate studies for vaccines R&D is badly needed.[3]

We have to expect high fixed costs for new vaccines because there are many unavoidable stages that must be passed during vaccine development, (mentioned in section 2): discovery; pre-clinical research; clinical testing, bioprocess development and regulatory evaluation, including plant certification. For older products these costs are not so significant. These costs are essentially sunk fixed costs once production actually starts. High fixed costs are a barrier to new competitors and encourage market concentration (section 3.3.4.).

Influenza vaccines have to be adapted every season to the mutations of the virus but the costs emerging periodically are not as big as in the case of new vaccines and a substantial part is financed by public laboratories. For the COVID-19 vaccines it seems that periodical updates and booster shots will be needed to guarantee immunity against new variants of the pathogen.

With regard to the **distribution of public and private inputs** leading to the final outcomes of R&D it should be noted that the support of governments, public funding and state laboratories is very important. A substantial part of the funds needed are provided by the public purse. Table 3.2 provides an image of the role of the main actors, notoriously including several branches of government in vaccine R&D in the USA around 1997. Most probably their relative role has not changed substantially in more recent times. In the first decade of the current century it was estimated that in the USA one third of all funds allocated to R&D of vaccines were provided by the National Institutes of Health (NIH) (Scherer, 2007; Institute of Medicine, 2004).

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[1] The works by DiMasi *et al.* (2016), Mestre-Ferrándiz *et al.* (2012), Prasad and Malinkody (2017), and Wouters *et al*. (2020) are well known. Lobo (2019) and Lobo and Rovira (2020) provided summaries of this long and difficult debate.

[2] Gregerson (1997) only gave references to studies on pharmaceuticals at large. DiMasi *et al.* (2003) estimated USD 802M, but this figure was also for pharmaceuticals in general, and they had only one vaccine in their sample of 68 products. Adams and Brantner (2010) made no reference to vaccines but only to pharmaceuticals in general.

[3] In the USA, the National Science Foundation provides comprehensive data on R&D for the Pharma Industry but not detailed by product and not specific for the vaccines segment (NSF, 2021).

The public contribution towards R&D of vaccines against COVID-19 has been outstanding. According to a careful investigation of publicly available data on disbursements by governments and nonprofit organizations into the R&D, and production of advanced COVID-19 vaccine candidates, developers have received approximately USD 10,000M in public and nonprofit funding. The figure includes funding paid upfront or via milestone payments for the late-stage development of an experimental vaccine or the scaling up of production at risk prior to the completion of clinical testing granted in pre-purchase agreements (advance market commitment (AMC)/advance purchase agreement (APA)) between governments and companies. It excludes payments for doses (the actual purchase of the vaccine). These numbers, the authors warn, are probably an underestimation, for the lack of data in some projects (Wouters *et al*., 2021). The top five companies have each received between USD 957M and 2,100M in funding commitments, mostly from the US Government and the CEPI (Wouters *et al*., 2021). Table 3.3 summarises these data. Including all types of funds for all purposes (also actual payments for the product) through Operation Warp Speed, the US federal government has provided more than USD 19,000M in assistance to seven private pharmaceutical manufacturers to develop and produce a vaccine or treatment for COVID-19 (CBO, 2021). Table 3.4 shows the amounts transferred to each individual company and the purpose of the subsidies.

TABLE 3.2. U.S. NETWORK RELATIVE CONTRIBUTION TO VACCINE R&D

TABLE 4.4 U.S. Network Partners' Relative Contributions to Vaccine Research and Development

	Research			Development		
	Basic/Related	Targeted	Process	Clinical	Manufacture	Postlicensure Studies
NIH	+++	+++	—	++	—	—
CDC	—	—	—	—	—	++
FDA	—	+	+	+	—	+
DOD	+	+	+	+	—	+
USAID	—	+	—	+	—	—
Large company	+	+++	+++	+++	+++	+++
Small company	+	+++	±	±	±	—
Academia	+++	+++		+++	—	—
NGOs (PDPs)	—	+	±	+++	±	—

CDC, Centers for Disease Control and Prevention; DOD, Department of Defense; FDA, U.S. Food and Drug Administration; NGO, nongovernmental organization; NIH, National Institutes of Health; PDP, product development partnerships; USAID, U.S. Agency for International Development.
Relative contribution: +++, major; ++, intermediate; +, minor; ±, varies by company.
Modified from Marcuse EK, Braiman J, Douglas RG, et al, for the National Vaccine Advisory Committee. United States vaccine research: A delicate fabric of political and private collaboration. Pediatrics. *1997;100:1015–1020.*

Source: Douglas and Samant (2017)

According to the European Commission, "for the fight against COVID, the Commission pledged €1,400 M under the global response. €1,000 Million comes from H2020, of which €350 million are dedicated to support coronavirus vaccine development. Prior to the dedicated COVID-19 investments, over €650 million had been invested through Horizon 2020 (2014-2020) in vaccine and vaccination research and innovation, also building on efforts from previous research and innovation programs. Overall, the EU spent more than €1,000 Million in vaccine research from Horizon 2020. It is important to make a distinction between funding for research and development of vaccines, investment in the development of production capacities, and the payment of the prices of the vaccines. In addition to the research spending, the Commission is investing €2,900 Million in the development of production capacities on the basis of the Advance Purchase Agreements. And one should also consider the prices paid by Member States to purchase the vaccines, which brings the total amount of support to over €30,000 M" (European Commission, 2021).

What are the implications of the high public funding for COVID-19 vaccines? The high public investments in COVID vaccines were justified to guarantee vaccine development and availability. “The fact is that starting from the early stages of development, most vaccines fail. We cannot afford to fail, so we need to plan for success. To do that, we must think and invest as ambitiously as we can” (Athey *et al.,* 2020). Also, the AMC model was needed to avoid uncertainties and has proved successful. Both high investments and the AMC agreements have substantially reduced private firms risks. Arguably, governments could take a greater role in defining the terms and conditions for vaccine supply (including terms for licensing so it is nonexclusive, conditions to make clinical trial data available, and facilitating Training of Trainers (ToT)).

TABLE 3.3. PUBLIC AND NONPROFIT FUNDING FOR THE R&D AND PRODUCTION OF LEADING ANTI-SARS-CoV-2 VACCINE CANDIDATES

	Technology	Known public and non-profit funding, US$	Funders
Sanofi with GlaxoSmithKline	Protein subunit	$2·1 billion	US Government
Novavax	Protein subunit	$2·1 billion	Bill & Melinda Gates Foundation, CEPI, US Government
AstraZeneca with Oxford University	Non-replicating viral vector	$1·7 billion	CEPI, UK Government, US Government
Johnson & Johnson	Non-replicating viral vector	$1·5 billion	US Government
Moderna	mRNA	$957 million	CEPI, Dolly Parton COVID-19 Research Fund, US Government
BioNTech with Pfizer	mRNA	$445 million	German Government
Clover Pharmaceuticals with Dynavax	Protein subunit	$430 million	Bill & Melinda Gates Foundation, CEPI
CureVac	mRNA	$348 million	CEPI, German Government
Sinopharm with Wuhan Institute	Inactivated virus	$142 million	Chinese Government
Medicago	Virus-like particle	$137 million	Canadian Government
Inovio	DNA	$107 million	Bill & Melinda Gates Foundation, CEPI, US Government
Covaxx with Nebraska University	Protein subunit	$15 million	Taiwanese Government
SK Biosciences	Protein subunit	$14 million	Bill & Melinda Gates Foundation, CEPI
Biological E	Protein subunit	$9 million	Bill & Melinda Gates Foundation, CEPI, Indian Government
University of Hong Kong	Replicating viral vector	$4 million	CEPI, Hong Kong Government
CAMS with IMB	Inactivated virus	$3 million	Chinese Government, Jack Ma Foundation
AnGes with Osaka University	DNA	Unknown	Japanese Government
Anhui Zhifei with CAMS	Protein subunit	Unknown	Chinese Government
Bharat Biotech	Inactivated virus	Unknown	Indian Government
CanSino	Non-replicating viral vector	Unknown	Unknown
Gamaleya	Non-replicating viral vector	Unknown	Russian Government
RIBSP	Inactivated virus	Unknown	Kazakh Government
SII with Max Planck Institute	Live attenuated virus	Unknown	Unknown
Sinopharm with Beijing Institute	Inactivated virus	Unknown	Chinese Government
Sinovac	Inactivated virus	Unknown	Unknown
Vector Institute	Protein subunit	Unknown	Russian Government

Data are as of Feb 3, 2021. The sources and methodology are outlined in appendix 2, which also includes more information about the funding arrangements. In brief, for developers with COVID-19 vaccines that have been approved or authorised for human use in one or more countries, are in phase 3 clinical testing, or are under contract with CEPI or the COVAX Facility, we searched press releases from developers and funders, as well as financial reports filed by developers with regulators in various countries, for information on public and non-profit funding. We did not count funds provided to licensees that produce and distribute vaccines on behalf of lead developers or to contract development and manufacturing organisations, nor did we count loans (ie, debt financing) from international financial institutions (eg, European Investment Bank) or national governments. We included pre-purchase agreements between governments and companies where it appeared as though a substantial portion of the funding went towards late-stage development (ie, phase 1–3 trials) or scaling up production at risk before the completion of clinical testing. CAMS=Chinese Academy of Medical Sciences. CEPI=Coalition for Epidemic Preparedness Innovation. IMB=Institute of Medical Biology (China). RIBSP=Research Institute for Biological Safety Problems (Kazakhstan). SII=Serum Institute of India.

Table: **Public and non-profit funding for the research, development, and production of leading vaccine candidates**

Source: Wouters *et al*. (2021)

TABLE 3.4.

Federal Funding to Support the Development of a COVID-19 Vaccine

BARDA Funding for COVID-19 Vaccines as of March 2, 2021

Sponsor	BARDA Funding (Millions of dollars)	Funding for Research and Clinical Trials?	Funding for Manufacturing?	Funding to Purchase Vaccine?	Type of Vaccine	Date Entered Phase I Clinical Trials	Date Entered Phase II Clinical Trials	Date Entered Phase III Clinical Trials	Date Received EUA	Doses to be Purchased (Millions)
Pfizer and BioNTech	5,973	No	No	Yes	mRNA	4/29/20[a]		7/27/20	12/11/20	300
Moderna and NIAID	5,896	Yes	Yes	Yes	mRNA	3/16/20	5/29/20	7/27/20	12/18/20	300
Sanofi Pasteur and GlaxoSmithKline	2,073	Yes	Yes	Yes[b]	Spike Protein	9/3/20[a]		*	*	100
Johnson & Johnson (Janssen subsidiary)	1,998	Yes	Yes	Yes	Viral Vector	7/15/20[a]		9/7/20	2/27/21	100
Novavax	1,600	No	Yes	Yes[b]	Protein Subunit	5/25/20[a]		12/22/20[c]	*	100
AstraZeneca and Oxford University	1,600	Yes	Yes	Yes[b]	Viral Vector	4/23/20[a]		8/28/20[d]	*	300
Merck and IAVI	143	Yes	Yes[e]	No	Viral Vector	8/27/20[a]		Discontinued 1/25/21		

Data source: Congressional Budget Office, using data from the Department of Health and Human Services. See www.cbo.gov/publication/57025#data.

BARDA = Biomedical Advanced Research and Development Authority; EUA = emergency use authorization; IAVI = International AIDS Vaccine Initiative; mRNA = messenger ribonucleic acid; NIAID = National Institute of Allergy and Infectious Diseases; * = The vaccine has not yet reached this stage.

a. Phase I and phase II clinical trials combined.

b. Contingent upon receiving emergency use authorization.

c. Phase III trials with South African participants began on August 17, 2020; trials with U.K. participants began on September 28, 2020.

d. Phase III trials with U.K. participants began on June 2, 2020.

e. Funding to manufacture the Johnson & Johnson vaccine.

Source: CBO (2021)

B. Stochastic risk of batch contamination

The possibility of vaccine contamination during manufacturing or distribution is a significant entrepreneurial risk. In section 1.3, it was already noted that manufacturing vaccines and the biological processes involved in producing proteins are risky**.** For instance, a contamination incident at a plant in the 2004–2005 influenza season led to the need for implementing a programme of stringent rationing of immunizations in the USA. Chiron Corporation suffered contamination problems in its plant in Liverpool (United Kingdom (UK)) and could not supply nearly half of the 100 million vaccine doses planned (Scherer, 2007). Only one more company was licensed to supply the vaccine and was unable to increase production. In 2021, in a manufacturing subcontractor factory run by Emergent BioSolutions in Baltimore (USA) while manufacturing two coronavirus vaccines, the ingredients were accidentally conflated, ruining up to 15 million vaccine doses from Johnson & Johnson. “Vaccine production is a notoriously fickle science, and errors are often expected to occur and ruin batches” (LaFraniere and Weiland, 2021).

This is why stringent and officially approved current good manufacturing practices (cGMP) have to be followed and enforced. Quality Assurance personnel may be one-half of the number of production workers (Plotkin *et al.,* 2017).

C. Regulation

The production and distribution of vaccines is subject to very stringent regulations apart from cGMP. Rigorous safety requirements are necessary given the facts that vaccines are generally being administered to healthy individuals, adverse effects cannot be ruled out even after large clinical trials and the risks of contamination. Detailed legislation, rules and guidelines regulate all the following items in most jurisdictions, most of which continue all the life of the product:

- Evaluation and licensure of the specific biological entity (already introduced in section 1.2.)
- Certification of plants and processes
- Batch release
- Inspections of the manufacturing facilities
- Annual reporting of specific manufacturing information
- Export and import licenses
- Adverse event data

Regulatory agencies such as FDA or EMA evaluate new vaccines supervising safety and efficacy particularly by means of clinical trials also subject to extensive and detailed regulations. Quality is also carefully appraised. “Failure to gain approval … poses a substantial risk, as successful passage through clinical trials only occurs 6–11% of the time. Regulatory challenges are particularly prominent in emerging infectious diseases vaccine development, as viable candidates are rarely available for distribution during outbreaks, making safety and efficacy testing difficult. As a result, vaccine development … has been reactive and technologically conservative” (Vu *et al.*, 2020).

Regulatory authorities review for approval not only a specific biological entity, but also the plant and the process by which that entity is produced and tested, as well as release (approve) individual production batches for use. A key rule is that commercial plants must be built for phase III trials of vaccines (a mayor difference between vaccines and drugs), implying plant set up several years in advance of product approval. “The fact that vaccine plants are required a number of years earlier in the investment process makes for much higher capitalized plant costs for vaccines” (Grabowski and Vernon, 1997).

In the USA, the Centre for Biologics Evaluation and Research (CBER) of the FDA may require individual production batch release (approval) for every vaccine product made or sold in the United States. Some manufacturers of well-established biological drug products have, through approved license supplements, been granted the alternative to lot release and are on a surveillance programme. Manufacturers on surveillance are still required to submit samples and/or protocols to CBER at specified intervals, but they may distribute the applicable products without receiving prior CBER lot release. Such manufacturers must still complete their own internal lot release process whether on CBER lot release or on a surveillance program (CBER, 2010). Similar regulations apply in the EU and other jurisdictions.

The manufacturing facilities are subject to routine and unannounced regulatory inspections to review conformance with cGMP, maintenance of facilities, manufacturing and quality systems, and performance of the process (Plotkin *et al*., 2017).

To export a product, a specific license must be obtained from the importing country, often requiring country-specific clinical trials. A firm that exports product globally may need to manage scores of unique licenses for each market where the product is licensed, and is

subject to nearly continuous inspection by multiple National Regulatory Authorities. (Plotkin *et al*., 2017).

D. Liability risks

The issue of product liability is extremely important for the vaccines industry as large amounts of people are the target and contaminations, marketing of defective products (with or without fault from the part of the supplier) and adverse events cannot be ruled out. These risks may be difficult to cover by insurance and generate enormous litigation costs. In the USA in 1980–1984, as courts applied more strict liability standards, liability cases filed against manufacturers increased substantially and amounted to USD 3,500M. Claims in court went from four in 1980 to 255 in 1986. As a result, six out of eight manufactures of the diphtheria, tetanus toxoids and pertussis (DTP) vaccine exit the market. In 1986, the stock of DTP vaccines only covered six months of the amount needed (Grabowski and Vernon, 1997; Sloan, 2012, p. 543). “Increased product liability costs were a major factor underlying the rapidly rising prices and falling number of U.S. vaccine suppliers during this period” (Grabowski and Vernon, 1997).

One of the most important cases involving vaccines product liability arose in 1998 with the publication in the UK in the prestigious medical review *The Lancet* of a study linking the Measles, Mumps and Rubella (MMR) vaccine with autism. After years of controversy, it became clear that the study did not comply with scientific and ethical standards. The leading author was declared by the UK General Medical Council not apt for the practice of the profession, and the article was fully retracted from *The Lancet* in 2010 (The Lancet Editors, 2010; Omer, 2020). A related incident developed in the US at the same time. In 1999, the FDA found that thimerosal, a compound used as preservative in vaccines, could cumulate mercury over the recommended level in children and it was subsequently eliminated from the composition. Fake news expanded, linking thimerosal with autism. In 2004, the Institute of Medicine (IOM) concluded there was no proof of such a relation. In 2009, the US Department of Health and Human Services stated that there was no scientific basis for the association between vaccines and autism (US Department of Health and Human Services, 2009; Adamo Idoeta, 2017).

Nevertheless, these incidents boosted **hesitancy** about vaccines and vaccination rates declined in the UK and other countries leaving children unarmed in front of lethal illnesses like measles or diphtheria. There were also product liability claims. In the US alone in 2009, over 5,000 National Vaccine Injury Compensation Program (VICP) claims linking thimerosal to autism had been filed, although no one had been paid (Sloan, 2012, p. 545).

Obviously, the risk of liability claims increases costs and may greatly diminish the incentive to enter the industry and to continue manufacturing. In part 5 we will review policies that have been put in operation in different countries to deal with these problems.

It seems that the liability question was one of the main points in the negotiations of the AMCs for anti-COVID-19 vaccines between the EU Commission and pharmaceutical companies. Apparently, the US negotiators accepted from the beginning the exemption of liability from the part of the companies while the European negotiators were not ready to accept immunity for the producers. It was one of the causes for delay in signing the contracts and subsequent postponement of supplies. There were also problems in the negotiations between India and Pfizer. A balance has to be reached to limit excessive risks to firms—in the exceptional circumstances of a pandemic—on the one side, but maintaining also incentives for companies and executives to act in a responsible manner.

To end this section on the production function, it is worth noting that **manufacturing costs fall once the fixed costs are covered and with higher volumes** of production to satisfy

larger market demand. As noted by WHO, for traditional vaccines of the Expanded Program on Immunization i.e. measles, diphtheria, pertussis, tetanus, oral polio and Bacillus Calmette–Guérin (BCG), these are mature products because the fixed costs of production of these vaccines have been covered long ago, and because their production costs have been lowered due to the learning curve, more competitors in the market and economies of scale, which favors affordable prices (Global Alliance for Vaccines and Immunization, 2000).

In view of all these costs peculiar of the vaccine industry (arising from research and development; stochastic risk of batch contamination; regulation and liability risks) we can conclude that the production function is more complicated than expected in many industries and goes far beyond the usual components of costs (personnel, material supplies, energy…).

3.3.3. Product Specialization in Manufacturing

Product specialization in manufacturing means that plants and equipment are specific for each product and cannot easily be diverted from one production to another. This implies lack of flexibility or elasticity to adapt to shocks in demand and increased risk of shortages and production dead stops. Experts are convinced this is the case. “With few exceptions, each vaccine requires a different plant because of unique manufacturing requirements and the regulatory difficulties associated with changing over to a different product” (Douglas and Samant, 2017). “While there may be common equipment across platforms, such as bio reactors, filtration and chromatography equipment, filling and lyophilization equipment, the sequence of operations and the specific cycles for each product vary. In most cases, each product (or group of products within a product family) has its own dedicated facility and production team” (Plotkin *et al.,* 2017).

3.3.4. Horizontal Concentration, Exit from the Industry, and Economies of Scale

The concept of horizontal concentration means that there is only a small number of suppliers in the market. The relevant market here is not the vaccine industry as a whole, but the market for vaccines that are close substitutes in the sense that they prevent the same illness and can be used alternatively. When horizontal concentration is high, as measured by the sales concentration ratio or the Herfindahl index, there is a high probability that the firms will enjoy market power leading to oligopoly or monopoly. In section 2.2 we documented geographical and firm concentration of supply depicted by some authors as the “vaccine production club”. If the top four Western suppliers accounted in 2014 for approximately 85% of global sales for all vaccines (Douglas and Samant, 2017), it is clear that many relevant markets are extremely concentrated. ”One example is the MMR vaccine, which after 40 years still has no competition in the United States” (Douglas and Samant, 2017). The landscape has now changed as emerging manufacturers (in India, China, and Brazil), play a critical role in the supply of vaccines for developing countries, but they focus in the more classical products.

Concentration has evolved along time as some firms proceed to **exit the market or as a result of mergers and acquisitions**. “The number of firms licensed by the FDA to manufacture vaccines has declined from twenty-six in 1967 to seventeen in 1993, with the greatest decline occurring between 1967 and 1980. In the case of the paediatric market, eleven firms were producing childhood vaccines in 1980, and this number fell to seven by 1993. There was a sole-source manufacturer for ten of the fifteen childhood vaccines” (Grabowski and Vernon, 1997; Sloan, 2012, p. 533; Scherer, 2007). Baxter and Novartis, two leading firms, also discontinued vaccine operations some years ago, “an ominous sign that reflects the continued financial pressure on the remaining four major vaccine makers” (Douglas and Samant, 2017). “The vaccine industrial base has been declining for decades. Between 1966 and 1977, half of all commercial vaccine manufacturers stopped producing vaccines, and the exodus continued in the 1980s and 1990s. More than 25 companies

produced vaccines for the U.S. market 30 years ago; today there are only 5 (Institute of Medicine 2004). Five of the current recommended vaccines have only one producer, and the others have either two or three (Institute of Medicine, p. 5)" (Lichtemberg, 2007). "The supply of paediatric vaccines in the US appears precarious, with a declining number of producers and products. In 1967 there were 26 licensed manufacturers, but only 12 in 2002. Five firms produce almost all routine childhood vaccines, with a sole supplier for five of the eight recommended paediatric vaccines" (Danzon and Pereira, 2011). Baxter and Novartis, two leading firms, also discontinued vaccine operations some years ago leaving four major vaccine makers (Douglas and Samant, 2017. See also Scherer, 2007, Sloan, 2012, p. 533).

The WHO describes the problem as follows:

> There are relatively few vaccine manufacturers that meet international standards of quality established by WHO. Many of the individual vaccine markets are monopolies or oligopolies, either by product or presentation. The limited number of vaccine suppliers and production capacities leads to a tenuous balance between demand and supply in many individual vaccine markets. Constant management and communication between market actors is absolutely required to guarantee sufficient supply of vaccines for each purchaser (WHO, 2021).

"According to the WHO, nearly one third (32%) of vaccines have fewer than four suppliers, while nearly two thirds (63%) have two or fewer prequalified products. 'COVID-19 has shown just how vulnerable medical product supply chains are when relying on a small number of manufacturers for raw materials and final products,' said Emer Cooke, director of the WHO's regulation and prequalification department" (UNCTAD, 2020).

More radically Balasubramanian and Sita (2014) conclude: "The vaccine industry has an oligopoly character in which a handful of companies compete …. The entry barriers to the business are high. As a result, competition is reduced … Not surprisingly therefore, prices are high, as also the profitability of the companies".

Apart from other circumstances, like commercial or pricing policies by firms, there are technical reasons that explain, at least partly, high concentration in the industry. One is the compounded risk of biological and physical variability and contamination already mentioned in sections 1.3. and 3.3.2. These hazards in a highly concentrated markets increase in turn the risks of shortages, since there is not replacement for a factory suffering a contamination.

Another reason is **economies of scale,** a fundamental feature to better understand the structure of any industry. They are related to the underlying technology and in fixed capital-intensive industries such as utilities, petrochemicals or steel they are pervasive. From an economic point of view, economies of scale imply average costs decreasing with increasing levels of production. Operating at a large scale firms can produce at lower cost per unit. The relation between the size of the market and the level of production fully realizing all economies of scale (the minimum average cost) is critical. When it equals 1, a "natural monopoly" exists and it is common to observe markets with only one supplier, a large firm in terms of market size, charging prices above marginal costs and without competition to drive prices lower. Therefore, economies of scale explain market concentration since the most efficient company in terms of lower costs will turn into a monopoly. In this situation, policies to promote competition—for instance, by splitting a big company into smaller companies—are self-defeating, and state intervention is needed whether through regulation or public ownership.

Are economies of scale observed in the vaccine production industry? The information on costs and other variables is scarce, but some evidence can be found at least for conventional vaccines. In the first place we have the opinion of engineers. "Some processes are scalable,

such as bacterial or yeast fermentation, so that increasing the size of the manufacturing unit (i.e., fermenter) will greatly increase the yield; unit cost will decrease with volume increase. Other manufacturing processes, for example, those dependent on viral growth in embryonated hen eggs or cell lines, are not scalable. Additional plants or modules within plants must be built to increase the throughput, so unit costs do not appreciably decrease with volume increases" (Douglas and Samant, 2017).

Second, Scherer gave substantial reasons to conclude that economies of scale are present at least also for conventional vaccines. Scherer found three signs of economies of scale at plant level (with data available since around the beginning of the 21st century): 1) A high level of investment (USD 100–150M per plant). 2) Production is more capital-intensive than small-molecule pharmaceutical manufacturing. 3) The gross book value of manufacturing plants and equipment was 61.9% of sales compared to 29.7% for pharmaceuticals in 2002 and 40% (in 1997) for all manufacturing according to US Census reports (Scherer, 2007). Product-specific economies of scale are significant for new vaccines since the route from development to market has to pass through stages of preclinical research, product development, clinical testing, and regulatory evaluation, that are lengthy and costly, with important fixed costs involved.

Research and development costs are high, as high as for conventional pharmaceuticals, always under the uncertainties of limited information. There is some possibility of reducing private costs through public cooperation, as mentioned in section 3.3.2.A, and clinical trials entail less risk in the case of vaccines. But "it seems clear that front-end research, product development, clinical testing, and regulatory evaluation costs for a new vaccine may be measured in the hundreds of millions of dollars. These are essentially sunk fixed costs once production actually commences" (Scherer, 2007). Furthermore, testing and regulatory evaluation costs are also important even for older drugs. Plant facilities have to be certified or pre-qualified by the regulatory agencies, including the inspection and testing of samples from actual production processes. These requirements are very rigorous and tend to become more and more stringent over time. It has been estimated that fixed production costs (excluding R&D) account for up to 60% of total costs (Scherer, 2007).

The conclusion by Scherer is that "significant economies of scale exist in the development, qualification, and production of vaccines… The strongest scale economies, compelling natural monopoly at low to middling demand levels, exist for completely new vaccines" (Scherer, 2007). Of the same opinion are Evenett *et al*. (2021): "Given the complexity of vaccine manufacture, the evident need to meet demanding regulatory requirements, and economies of scale (reflecting not least high set up costs for manufacturing facilities), there were strong incentives to concentrate production in a limited number of locations."

A similar explanation of concentration is given by Danzon and Pereira (2011): Concentration reflects the interaction of high fixed costs with concentrated, price-sensitive demand and dynamic quality competition in which product superiority is reinforced by government recommendation. These conditions result in price and quality competition leading to the exit of all but one or very few producers per vaccine. In such a setting "there is no incentive to introduce 'me-too' vaccines, which could not plausibly compete with established firms unless they offer some clear quality or cost advantage. Consequently, new vaccine R&D targets improved technologies for existing vaccines or new vaccine categories. Entry of superior products in turn leads to exit of the now obsolete inferior products".

Nevertheless, there are other technological forces driving in the opposite direction, favouring more diversity of actors in R&D and manufacturing, less concentration and more competition. In section 1.3. we noted that multinational pharmaceutical firms, medium and smaller firms, government research centers and universities are all or may be important sources of innovation and production. New opportunities are open with the Messenger RNA vaccines. It

is possible to enhance the role and potential of local producers and medium and smaller firms, in various forms: purely public, public/private collaborations and new projects internationally driven.

Horizontal concentration in the vaccine industry is therefore mainly explained by technical reasons: the compounded risk of biological and physical variability and contamination and economies of scale. Concentration and monopoly would be the "natural state" for the industry. However, other technological forces favour more diversity of actors and competition. Given the inefficiencies of monopoly in terms of welfare loss (less vaccines available tan society would like) and particularly the risk of shortages and supply breakdowns governments and international organizations have to deploy remedial policy instruments and take advantage of the new technological opportunities for competition. The problem is extremely pressing in view of a pandemic requiring greater capacity and flexibility to scale up production. Breaking with concentration and more even distribution of production facilities is a necessary condition for appropriate preparedness. We will turn to this question in chapter 4.

3.3.5. Limitations to Generic Competition

The structure of the pharmaceutical industry fundamentally changed when in the USA generics were allowed to enter the market with simplified regulatory requirements and compete with original trademark products in the late 80s of the twentieth century. Generics are medicines equivalent to the original product, with patents already elapsed and marketed by firms competing with the originator usually under a generic name (WHO International Non Proprietary Name). Changes in regulation decisively lowered the barriers to entry raised by the obligation to perform clinical trials to get the marketing approval even for products with elapsed patents and therefore with safety and efficacy long established in the market. With no patent obstacles and simpler procedures to obtain marketing approval the door was opened to price competition in a large segment of the industry. The impact of generics in drug markets was enormous enhancing competition and driving prices down, which is very positive for access from a public health perspective (see for instance Danzon, 2012). In the last 30 years generics have expedited access to safe and effective medicines all over the world as much as any other public policy. More recently a parallel development has taken place with biosimilars particularly in the EU. Though regulatory requirements are not as much expedited as is the case with generics, vigorous competition and substantial price reductions have taken place in EU countries (Lobo and Del Río, 2020).

In the case of vaccines, the barriers to entry cannot be moved away to implement a market for "generic" vaccines in the same way as for chemical pharmaceuticals. For follow-on vaccine manufacturing, the impediment raised by patents has to be removed, and the know-how to perform the manufacturing processes has to be developed or transferred. Moreover, detailed tests and clinical trials are generally required even in the case of the same vaccines if manufactured by a firm other than the first licensee by the regulatory national authority, at least if the technology is not exactly the same, i.e. if there has not been voluntary transfer between the two firms. In principle the rational is potential biological variability. "Because vaccines are biologics, generics have not been able to use the abbreviated new drug application (ANDA) process which enables generic equivalents of chemical drugs to get approval by showing bioequivalence to the originator product (in the USA). Thus, follow-on versions of existing vaccines are treated as originators and must undertake de novo clinical trials to demonstrate safety and efficacy" (Danzon and Pereira, 2011).

In the context of the COVID-19 emergency, debates are going on in relation to the extent of the tests needed to prove safety, efficacy and quality (see for instance Gopakumar *et al.*, 2021, advocating for full disclosure of information including trade secrets). It is not known as of today the impact that new technologies such as mRNA may have in this respect.

3.4. Summary

In sum, a fundamental fact is that the effectiveness of vaccines has proved to be very high and vaccines offer highly favourable cost-effectiveness ratios. In the structure of the vaccine industry demand is different to most pharmaceuticals insofar as consumers are usually large, healthy populations, implying very stringent safety standards and large clinical trials raising upfront costs. Externalities like “herd immunity” give rise to “free-riders” pushing the rate of vaccination short of what is needed, in itself a market failure obliging government action to foster vaccination. In the supply side we see a capital-intensive business but with variations and lower capital entry requirements conditional upon technologies and local conditions that may lower costs of capital and time giving more room for multiple production facilities. The production and cost function has unique characteristics but lack of reliable information hinders any analysis. R&D costs, risks of batch contamination, detailed regulations, even more stringent than usual for pharmaceuticals, are generally considered to raise costs. The problems of product liability and product specialization in manufacturing are also barriers to competition from new firms encouraging market concentration. Manufacturing costs fall once the fixed costs are covered, with higher volumes of production and economies of scale, progress in the learning curve and more competitors, as is the case with traditional vaccines that can sustain affordable prices.

Due to geographical and horizontal firm concentration of supply the vaccine industry has been depicted as the “vaccine production club”. Many relevant markets are extremely concentrated. Top four Western suppliers accounted in 2014 for 85% of global sales for all vaccines, but emerging manufacturers already play a role. Supply chains are also vulnerable when relying on a small number of manufacturers for raw materials and final products. Apart from commercial or pricing policies by firms high concentration roots in technical reasons, mainly economies of scale leading to “natural monopoly”. Concentration, monopoly or oligopoly would be the “natural state” for the industry. This is surely the main reason to explain shortages before and along the COVID-19 pandemic. However, other technological forces favour more diversity of actors and competition that could be exploited by governments and international organizations in deploying remedial policy instruments.

Finally, given the technical background of the industry, generics are not an opportunity to introduce a competitive segment as is the case with other pharmaceuticals.

To overcome all these market failures governments and international organizations must implement a full array of policies to guarantee supply and access to vaccines breaking concentration and favouring competition and a more dense and even distribution of manufacturing facilities. Section 5 offers a summary of policies related to vaccines.

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4. INCENTIVES FOR VACCINE INNOVATION AND TO BOOST PRODUCTION. ECONOMIC CONCENTRATION, EXIT, UNDERINVESTMENT, SHORTAGES AND PROFITABILITY

After discussing the structure of the industry, we now turn to consider directly the problem of incentives. Are there insufficient incentives to innovate and boost production of vaccines? Is this a problem deep-rooted in the structure of the industry leading to systematic market failures? Is there a need for equally systematic public interventions and regulations to guarantee optimal supply of vaccines in the short and in the long term? Are there other alternative means for vaccine production including government production and public-private partnerships? To answer these questions, we will rely on previous findings in this paper.

We have extensively documented high levels of market **economic concentration** and provided some data on **industry exit**. We concluded that concentration is embedded in the technical characteristics of the industry: the compounded risk of biological and physical variability and contamination as well as economies of scale. Concentration and monopoly would be the "natural state" for the industry. The risk of concentration is that supply may not be able to satisfy effective demand giving rise to shortages.

When the market is not able to deliver an available product and supply does not satisfy demand, even if society is willing and able to pay the price, we encounter shortages. Shortages are a clear sign of market failure. Historically, **shortages** have been relatively frequent in vaccine supply. "Immunization programs in the United States have repeatedly experienced vaccine production failures that have led to shortages, rationing, and black markets. During the 1980s, there were significant shortages of the diphtheria-tetanus-pertussis vaccine administered to children. Between 2000 and 2002, supplies of tetanus-diphtheria and pneumococcal conjugate vaccine were short by 40 percent, of varicella (chickenpox) vaccine by 26 to 29 percent, and of measles-mumps-German measles vaccine by some 15 percent. (Institute of Medicine, 2004). A survey of state immunization programs in early 2002 reported 52 cases in which there were shortages of two or more vaccines and 31 cases in which five or more vaccines whose supply was inadequate. In nine cases, shortages of one or more vaccines persisted for a year or longer" (Scherer, 2007). More recently, the Centers for Disease Control and Prevention (CDC) stockpiled paediatric vaccines to alleviate critical shortages in case of supply interruptions (Douglas and Samant, 2017).

In Spain, with extensive vaccination programmes carried by the National Health System, the newspaper La Vanguardia in 2017 described the situation in the following points. In recent years, there have been recurrent scarcities of vaccines for varicella, pneumococcus, pertussis, and tetanus. Health authorities routinely have to reorganize their plans to cover what is more essential and delay booster shots for the future. This year we will lack supplies for tetanus and diphtheria. Hepatitis A vaccines for children will not arrive until April or May; for adults, they will be unavailable throughout the year. Pneumonia vaccines for people over 65 will be unavailable until May. The same for hepatitis B for newborn babies. Representatives of the industry explained to the journalists that low prices in Spain, high demand in other countries and incidents with quality control were responsible for the shortages (Macpherson, 2017).

Experts of the industry warned about the "industry's vulnerability because dependence on single-sourced vaccines continues to be an unresolved concern. The regulators and the industry must proactively develop a solution to this critical challenge and avoid any future public health crisis resulting from vaccine shortages during a pro- longed supply interruption" (Douglas and Samant, 2017). They nevertheless considered that the vaccine industry in the

United States and Europe has in more recent years considerably improved its reliability as a supplier. Primarily by modernization of vaccine manufacturing and distribution infrastructure supported and funded by the profitability of the business.

Underinvestment in R&D and manufacturing of vaccines is often considered one of the reasons for the industry's underperformance (e.g. Wouters *et al.,* 2021). Grabowski and Vernon signalled that in the last quarter of the twentieth century the proportion of total private pharmaceutical R&D devoted to biologicals and vaccines declined significantly (1997).

What reasons may explain concentration, industry exit, underinvestment and shortages? Grabowski and Vernon (1997) enumerated as potential explanations different dimensions of market structure: increased number of liability suits, increased regulation, rising R&D costs, and lower risk-adjusted expected returns for vaccines as compared with other pharmaceutical businesses. We have already considered demand (externalities) and supply factors (capital requirements, R&D costs, risk of batch contamination, regulation, liability risks, product specialization in manufacturing, and concentration) that contribute to market failure, underinvestment, and shortages. Xue and Ouellette (2020) explain "the economics of underinvestment in vaccines R&D" with two specific reasons that help account for what they call the "anaemic development pipeline" of vaccines: (1) They are preventatives rather than treatments. (2) They are generally durable goods with long-term effects rather than products purchased repeatedly.

Wouters *et al.* (2021) argued that underinvestment is not the issue in the COVID-19 pandemic, as demonstrated by the high number of R&D projects undertaken to find new vaccines. In section 3.3.2.A, we reviewed the figures on funds provided by governments and nonprofit organizations for R&D and manufacturing of advanced COVID-19 vaccine candidates, received by developers amounting to around USD 10,000M. No doubt private investors and firms on their own would have not been at all able to develop vaccines in less than one year.

Underinvestment in R&D and manufacturing is related to a lack of incentives—for all the aforementioned reasons—and the main incentive is profitability. **Reduced profitability** is often signalled as the main cause for underinvestment and shortages. Vu *et al.* (2020) analysed the economic returns of a portfolio of emerging infectious disease vaccine assets and find that under realistic financing assumptions, the expected returns are significantly negative, implying that the private sector is unlikely to address this need without public-sector intervention. "While governments and international agencies have striven to create incentives to attract additional private sector investment in vaccine development, these efforts have so far failed in attracting sufficient capital to enhance preparedness against the world's most deadly emerging pathogens."

In a more informal and less rigorous way, Douglas and Samant (2017) argued that profit margins can be high. First, costs tend to diminish: "Despite the complexity of bulk vaccine manufacturing, 3 to 5 years post–product launch, the fully burdened bulk cost of production for most of the older vaccines declines to as little as USD 0.50 to USD 1.00 per dose, and significant elements of product cost are primarily driven by activities related to filling, vialing, and packaging" (Table 4.1). Second, established vaccines with a limited number of suppliers can generate very high profit margins over the product life cycle. Third, old vaccines continue to be profitable (for the absence of generics competition; because access to know-how, such as proprietary cell lines, virus strains, and internally developed processes, is far more valuable than patent protection; and everlasting demand since birth cohort is renewable).

Reduced profitability may be explained at least partly by an additional reason—heterogeneity of demand. Vaccine consumers have variable risks of becoming infected in comparison with ill patients seeking treatment for specific illnesses. Therefore, it is difficult for the supplier to

identify the customer's expected willingness to pay, and thereafter exert price discrimination and appropriate the surplus (Kremer and Snyder, 2006; Kremer and Snyder, 2020; Sloan, 2012; Lakdawalla, 2018). Public purchases and tenders could also reduce profitability. It is argued that public purchases and tenders would drive prices to low levels insofar as governments are a large part of demand and may exercise monopsony power. In the USA more than 50% of the children's market is driven by government purchases. Tenders certainly push price competition towards marginal costs. Older vaccines out of patent protection are depicted by industry representatives as "low-margin" commodities. However, Scherer attests that US prices, and probably European prices, leave margins above marginal production costs insofar as prices quoted in international tenders organized by UNICEF are significantly lower.

TABLE 4.1. VACCINE PRODUCT COST

TABLE 3.2 Vaccine Product Cost

	USD/Dose
Bulk[a]	0.20–3.00
Fill/finish[b]	1.00–1.50
Syringe fill (optional)[c]	1.00–2.00
Total cost[d]	2.20–6.50

[a]Bulk range reflects older vaccines such as measles-mumps-rubella (MMR) and hepatitis B, at the low end, to newer vaccines such as shingles and live attenuated influenza at the high end.
[b]Fill/finish range reflects differences in speed, volume, and efficiency of operations.
[c]Syringe-filled product reflects cost of syringe and reduced line efficiency.
[d]Estimated fully burdened manufacturer's cost for U.S.-based operations in 2012.

Source: (Douglas and Samant, 2017)

Danzon and Pereira (2011) give empirical support to the hypothesis that government purchasing is not the driver for exit from the industry. The reason – as we reviewed in chapter three – in recent years before the COVID-19 pandemic, is that high fixed, sunk costs and relatively concentrated demand result in price and quality competition leading to the exit of all but one or very few producers per vaccine.

In any case it is worth remembering the argument by Scherer (2007): profitability is an empirical question**.** Unfortunately, data is lacking to reach solid conclusions, but 2002 data on "price-cost margin" from the US Census of Manufactures show a margin of 56.4 % for the sector of Vaccines, toxoids and antigens and 62.3 % for Pharmaceuticals vs 28 % for Manufacturing Industries as a whole. According to these figures "low profitability would not be expected nor accounted for".

In **conclusion**, **two theories would explain** underinvestment, shortages and exit of firms from the market, both highlighting demand and supply factors in the structure of the industry. The first underlines economic concentration and oligopoly and monopoly all compatible with high profitability, shortages and exit of smaller firms. The second theory directly focuses on lack of profitability, although there are some partial data challenging this assumption. The point is that both theories lead to the same conclusion: market failures are pervasive and prevent the industry from satisfying effective demand, triggering shortages of products that are essential for public health and economic development.

Most economists, therefore, recommend extensive government or international regulations, subsidies, design of new “push” and “pull” mechanisms and other interventions. “Unless these market challenges are addressed, the global population will remain vulnerable to substantial human and economic losses when epidemics and pandemics arise”; the private sector is unlikely to address this need without public-sector intervention (Vu *et al*. 2020). “… if the private sector lacks sufficient incentives, because the prospect for profits is bleak, it would be appropriate, given the existence of substantial externalities, for the government to subsidize…” (Scherer, 2007).

Though the objective of this paper is not an in-depth examination of policy options, the next chapter, as an invitation for future research and discussion, very briefly summarizes the remedies enforced or proposed to solve market failures in the vaccine industry.

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5. A BRIEF INVENTORY OF POLICIES TO STIMULATE R&D AND MANUFACTURING

After reviewing in the two preceding chapters market structure and market failures we turn now to outline a very brief summary of policies that have been used by governments in recent years, before the COVID-19 pandemic, to stimulate R&D, production, distribution and access to vaccines. It is also stressed that after the COVID-19 pandemic these policies will certainly have to be reformulated and extended including a profound overhauling of the industry.

5.1. "Supply Push" Policies

"Supply push" policies try to stimulate R&D and manufacturing mainly by reducing upfront costs. Patents, or more broadly intellectual property rights (IPRs) are the standard policy across all markets to stimulate R&D. Patents allow the originator producer to fence off competition for a limited period of time, thus strengthening the appropriability of knowledge-based inventions that increases profit maximization. In the pharmaceutical market patents are nowadays accompanied by other exclusive rights (data protection) and specific regulations for some segments (orphan drugs…). It is common knowledge that IPRs offer lights and shadows insofar they create a tension between incentives to innovate (long term dynamic goal) and access to medicines, particularly for developing countries and destitute social groups (short term goal) and because the empirical evidence on their actual ability to foster innovation historically is not clear. A variety of proposals and mechanisms to reform IPRs have been advanced in the last 20 years, but with little success. On the contrary, the period of exclusivity from IPR protection and other provisions have been reinforced by national and international regulations, although countries have some scope to apply flexibilities under the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). (On this complicated subject, see, for instance, Correa, 2016; Lobo, 2017).

For vaccines, the value of patents is moderate. "Patent barriers to entry of competitors are weak for most vaccines, which often rely on propriety strains of the virus and sometimes process patents. These do not preclude other firms from using different strains to supply competing products during the life of any patents" (Danzon and Pereira, 2011). (The judgement seems to refer to traditional vaccines only) "Access to knowhow, such as proprietary cell lines, virus strains, and internally developed processes, is far more valuable than patent protection" (Douglas and Samant, 2017). One evidence is that "individual vaccine prices do not always decline, even after the patents expire, in contrast to pharmaceutical products." Another is that "process patents may present a more significant barrier to entry than the patent on the vaccine composition itself" (Plotkin *et al.,* 2017).

Though it is not under the focus of this report mention should be made to the effort of the WHO COVID-19 Technology Access Pool (C-TAP) mechanism for vaccine manufacturers to share intellectual property (IP) and know-how, to no avail, and the proposal for a waiver to IPRs under TRIPS proposed at WTO. This proposal is one of the main initiatives to promote equitable and expedited global access to vaccines and response to the COVID-19 pandemic being the object of controversies and discussions at all levels including the highest national and international organizations (see, for instance, Danaiya Usher, 2020; Zoracostas, 2021).

There are also various **policies to reduce upfront costs**, such as

- Subsidies to private R&D
- Subsidies to reduce quality control costs

- Government financed or directly executed basic and development R&D
- Public-private partnerships in R&D, quality control, and manufacturing

We have provided notorious examples for these strategies in the previous sections particularly those related to R&D of vaccines anti-COVID-19.

Collaboration among firms to increase capacity and production is primarily organized through private agreements. However, it can be also fostered with government support and stimuli. The issue is extremely important in the first part of 2021 for the need to increase production of vaccines anti-SARS-CoV-2 rapidly. The industry prefers this policy and underlines that numerous agreements of this sort have been signed and implemented (Hatchett *et al.*, 2021). "A successful solution to the production bottleneck would probably require widespread technology transfer to enable the expansion of manufacturing capacity. Currently, few countries have the domestic capacity to rapidly produce COVID-19 vaccines on their own and instead will need companies to actively share knowledge, technology, and data with domestic manufacturers" (Wouters *et al.*, 2021). As stated in section 1.3, the question that remains is how to expedite the technology transfer. What instruments would be more effective to reaching this goal and what would be the right combination of private market voluntary agreements and government and international action to foster production and distribution and meet the global needs for worldwide vaccination. This paper does not envisage to respond immediately to this crucial question but has given some background to clarify the subject.

Direct involvement of government in manufacturing is very uncommon in market economies but in the case of vaccines and given effectiveness and externalities it is a possibility. In small countries the market is likely too small to sustain private vaccines production and "run the risk of being cut off essential vaccines supplies during times of shortages, particularly in the case of pandemics. Public production of vaccines may be the desirable albeit second best, alternative." The US National Vaccine Authority Act envisages the development and production of vaccines by government (Sloan, 2012, p. 542).

5.2. "Demand Pull" Policies

To expand demand is another way to stimulate R&D and manufacturing apart from obviously increasing access and vaccination of populations. There are different possibilities:

- Information and education
- Subsidies at the level of the immunization point
- Direct provision by the public sector, vaccination campaigns
- Recommendations by health authorities to get vaccinated
- Legal obligation to be vaccinated
  - ✓ General
  - ✓ For certain activities: nurseries, schools, universities, health services personnel, firms
- Philanthropic initiatives, voluntary work

Advance market commitments are a recently devised and implemented mechanism "one kind of pull program, a purchase commitment in which sponsors would commit to purchase a specified number of doses at a specified price if a vaccine meeting certain specifications were developed" (Kremer, 2002, p. 83). AMCs are intended to tackle static (monopoly deadweight loss) and dynamic distortions (R&D incentives) in the vaccine market, encouraging innovation and production of the vaccine once developed, as they reduce uncertainties and ensure a solvent and reliable demand for the developer (Kremer and Glennerster, 2004; Glennerster *et al.,* 2006). AMCs have been extremely successful. Vaccines against pneumococci and Ebola were developed in the last ten years under contracts of this kind.

However, there are more critical opinions, for instance that of Medicins Sans Frontières (2020).

When the COVID-19 pandemic started, AMCs had the advantage that they were not only formulated according to sound economic theory, they had been successfully tested. The COVID-19 Vaccines Global Access (COVAX) mechanism, the EU and the USA have agreed contracts of this kind with potential developers/manufactures giving them a strong incentive to develop and manufacture vaccines. The success of developing a number of vaccines against SARS-CoV-2 in less than one year is to be credited not only to science and entrepreneurial determination but also to AMC. No doubt the mechanism has to be developed in the future while attention has to be given to design issues, with more transparency on costs and open consultation on methodologies for establishing adequate prices.

To note that an AMC implies a preferential right of the purchaser vis á vis third parties, as any purchasing contract. If the amount of vaccines so committed by the first country is over the needs of the respective population other countries may be left behind without supplies and groups not at risk in the first jurisdiction may get vaccinated before groups at risk in the latter country. This is the present global situation in the Spring of 2021. A more equitable solution has to be found by moral and practical reasons in a global world where exposure to pandemics and emerging infections is a risk for all populations until the disease is not under control globally. Once the vaccines are developed and available they have to be redistributed to guarantee access in favour of all populations at risk in the world through international cooperation. The optimal solution for the future would be full multilateralism with global AMCs covering all populations at risk from the beginning.

5.3. Policies Influencing Both Demand and Supply

There also policies touching simultaneously supply and demand. An outstanding example are special civil liability regulations, like “no tort liability” and limits to compensations. As we have already mentioned in section 3.3.2, product liability is extremely important for the vaccines industry since the costs of litigation from claims for injuries (adverse reactions) may be extremely high for suppliers (because the number of healthy vaccinated persons tends to be large) and for consumers (due to procedural difficulties). For manufacturers liability high costs may limit incentives to developing and manufacturing a steady flow of vaccines. To the consumer in many countries legal and procedural difficulties and costs may discourage action (demand side). A system of “**no tort liability”** has been introduced to avoid or limit these problems. The central idea is that the supplier of a product is responsible for the damages that may arise insofar as it has put the good in the market. No tort or negligence from his part is required nor has to be proved.

The European Union introduced this system in 1985 by Directive 85/374/CEE for all consumer products including pharmaceuticals and vaccines. In the USA in 1986 the National Childhood Vaccine Injury Act created the VICP introducing also no-fault compensation for childhood vaccines (Grabowski and Vernon, 1997; Finkelstein, 2004; Sloan, 2012). Medicare in 1993 started providing insurance coverage for influenza vaccines (Sloan, 2012). In some jurisdictions the law also sets a limit to the amount of the compensation. We have seen in previous sections that liability was a strong disincentive and a number of manufacturers exit the market. There is evidence that “no tort liability” legislation in the USA was positively associated with fostering R&D, investments, and manufacture (Finkelstein, 2004).

All these policies may encourage manufacturers to develop and supply new vaccines. Finkelstein (2004) found that increases in the development of new vaccines in the USA were associated with previous policies such as the establishment of the Vaccine Injury

Compensation Fund in 1986, recommendations in 1991 to vaccinate infants against hepatitis B and expanded coverage of Medicare to include influenza vaccination in 1993.

5.4. International Cooperation with Developing Countries

International cooperation with developing countries to facilitate immunization for their populations is a form of "demand pull" policy at the global level that merits especial consideration. We can only give here a very short inventory of possibilities and practices. There are important bilateral activities in the form of donations and technical assistance. But even more important is international cooperation. Since its very beginning WHO developed a full array of programmes (prequalification of products and manufacturers, technical assistance…). UNICEF has a successful and extensive programme of cooperation in acquisitions by tenders. There also extremely significant philanthropic and private-public initiatives contributing to develop and distribute vaccines and treatments for tuberculosis, human immunodeficiency virus (HIV), malaria, and now COVID-19. The main actors are GAVI, CEPI, Unitaid, The Global Fund and the Gates Foundation (BMGF). Nowadays, the main global cooperation international programme for vaccines against COVID-19, particularly for developing countries (low and low-middle income economies), is the COVAX Facility. In the Spring of 2021 it seems that the strategy of COVAX is an appropriate road-map but in practice financing, timing and implementation are not satisfactory, as evidenced by the sharp unbalance in vaccination rates between developed and developing countries. COVAX has to be expedited now with determination and political will from partners and in the future in the face of new pandemics and emerging infections much more resolute and overarching strategies have to be deployed.

5.5. Summary

To conclude this brief inventory of policies to stimulate R&D and manufacturing it has to be stressed that after the COVID-19 pandemic these policies – and particularly international cooperation - will certainly have to be reformulated and extended. Future pandemics and emerging infectious diseases have to be prevented on the basis of universal cooperation for R&D, manufacturing and immunization, considering not only solidarity among human societies but also the fact that in front of very contagious pathogens in a world of global and fast interrelations no one is safe until everyone in the Earth is safe. A grand goal must be pursued: to distribute evenly across the world preventive and curative measures including increased capacity to develop and manufacture vaccines in all regions, paying particular attention to less developed countries. Actions in fulfilment of this goal have to encompass as an instrumental target a profound overhauling of the industry to overcome the market failures afflicting the sector we have reviewed in this report. Box 5.1 provides some suggestions for this profound reform.

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BOX 5.1. GLOBAL RESTRUCTURING OF THE VACCINE INDUSTRY. CRITERIA

- Access: Vaccines for all. Reformulate more ambitiously the Sustainable Development Goals (SDGs) by 2030. Good health and well-being.
- Target 3.b. Support research, development, and universal access to affordable vaccines and medicines. Support the research and development of vaccines and medicines for the communicable and noncommunicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines.
- In relation to targets 3.2, end all preventable deaths under 5 years of age. Concerning 3.3, fight communicable diseases.
- Access: Expansion of demand towards full global coverage for all recommended vaccines.
- Access: Increase global access in the short run. Increase international cooperation aid and WHO resources.
- Access: Increase global access in the long run. Reform of intellectual property rights. Design of new mechanisms.
- R&D: Increase incentives to R&D for the research community.
- R&D: Increase public and private investments.
- R&D: Ensure steady and flexible communication and cooperation among R&D institutions globally.
- Industrial: Public sector leadership and involvement.
- Industrial: Profit from market potentialities.
- Industrial: Public-private cooperation. Win-win solutions.
- Industrial: Profit from the expansion of demand as a big opportunity for businesses and all stakeholders.
- Industrial: Maintain incentives to R&D and manufacturing for the industrial community. Advanced market commitments and others.
- Industrial: Increase entry in the industry. New firms. New mechanisms. Public sector involvement. Increase competition. Apply anti-trust regulations if needed.
- Industrial: Geographical de-concentration of the industry. Expand plants and facilities for the manufacture and quality control to all regions.
- Technology Transfer: Expand and regulate international and company cooperation and agreements for transfer of technology.

- Technology Transfer: Expand international and company cooperation and agreements for training in industrial, chemical, biotech engineering and quality control.
- Evaluation and Regulation: Fully coordinate and standardize regulations for evaluation and approval of vaccines through the International Conference of Drug Regulatory Authorities (ICDRA).
- Evaluation and Regulation: Coordinated global evaluation of vaccines. Better coordination of regulatory national and international agencies.
- Evaluation and Regulation: Organize international coordination for vaccine clinical trials with advanced mechanisms to rapidly launch tests and studies for new pathogens and antigens and vaccines. Pre-planification of universal sampling representativeness.
- Evaluation and Regulation: Introduce systematic economic evaluation of vaccines.

CONCLUDING REMARKS

The report has provided elements for the understanding of the economics of the vaccine industry. It has also briefly described the range of policies that have been used to address problems in the functioning of vaccine markets, and to drive vaccine innovation efforts towards meeting needed immunization programmes and pandemic situations, such as COVID-19. The expectation is that the paper can contribute to the policy debate.

Market failures are pervasive in the vaccine industry, an essential industrial sector that is far away from the competitive market paradigm, both in national and international terms. High levels of market economic concentration limit “the vaccine production club” to a handful of firms and countries. Consequently, performance of the industry is below the needed level, notwithstanding important successes in development of new vaccines and manufacturing before and after the pandemic of COVID-19. However, shortages and stockouts in developed and developing countries, exit of firms from the industry, underinvestment in R&D and manufacturing, even an “anaemic development pipeline”—all signs of market failure and most probably compatible with high profitability (see section 4)—are the factors associated with underperformance in the vaccine industry. Furthermore, the noncompetitive and concentrated structure of the industry is one of the reasons explaining continuing insufficient access to vaccines in less developed countries, in spite of recent progress powered by national economic development, public health advancements and a number of meritorious actions carried under the auspices of international cooperation. The sharp unbalance in vaccination rates to prevent COVID-19 between developed and developing countries at the mid of 2021 is a clear demonstration. Vaccine deprivation is not only due to deficient health systems, lack of economic development and finance but also to the configuration of the industry.

The COVID-19 pandemic has demonstrated the need to drastically reformulate and extend policies to stimulate R&D, manufacturing, distribution, and access to vaccines. The private sector is not enough, although public/private cooperation particularly in industrial endeavours will be the most efficient orientation. There is a need to implement a profound overhauling of the industry with the goal of universal access of all populations to all vaccines. Box 5.1 provides some suggestions for this profound reform. The present and future pandemics and emerging infectious diseases have to be prevented and treated on the basis of universal cooperation and multilateralism for R&D, manufacturing, immunization, and distribution, including increased capacity to develop and manufacture new vaccines in all regions, paying particular attention to less developed countries. This is mandated not only by solidarity among human societies but also by the fact that, in front of very contagious pathogens in a world of global and fast interrelations, no one is safe until everyone in the Earth is safe.

Lastly, there is the need for reliable, comprehensive, and detailed data and statistics as well a whole battery of studies on the industrial economics of the vaccine industry. Increasing our knowledge of the vaccine segment of the pharmaceutical industry is essential to planning and achieving profound reforms.

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