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FROM LAB TO JOB

Improving Asia and the Pacific's Readiness to Produce and Deliver Vaccines



Edited by Rupa Chanda, Pralok Gupta, and Matthias Helble



From Lab to Jab: Improving Asia and the Pacific's Readiness to Produce and Deliver Vaccines

Edited by

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2

The Economics and Actors in Vaccine Research and Development

Antonio Postigo

2.1 Introduction

Despite great progress over the recent decades, millions of people in developing countries die each year from infectious diseases—in particular communicable diseases—most commonly caused by viruses, bacteria, and parasites, because of the lack of effective vaccines and/or treatments.¹ Infectious diseases not only cause disability and cost lives, but also affect livelihoods, hamper social and economic development, and affect global security. In 2019, several countries in Asia and the Pacific were among those with the highest “burden of disease” from infectious diseases (GBD-CN 2020; GBDI-2019C 2020).² Although there are no figures on the overall “cost of illness” from infectious diseases in Asia and the Pacific (Shah et al. 2020), eliminating malaria alone would save more than 400,000 lives and generate economic benefits totaling almost \$90 billion (Shretta et al. 2019).³ In this context, vaccine

¹ As detailed later, most vaccines are used to prevent infectious diseases (prophylactic or preventive vaccines), but some are used to treat diseases (therapeutic vaccines) like cancer and chronic diseases. This report focuses primarily on the research and development (R&D) of preventive vaccines for infectious diseases and, therefore, refers to biological or synthetic products designed to generate an immune response in the recipient to prevent an infection.

² The “burden of disease” quantifies the impact of living with illness and injury and dying prematurely. It is often expressed as disability-adjusted life years, which indicate the years of healthy life lost from death and illness.

³ The “cost of illness” measures the medical and other costs that result from a specific disease or condition.

development has become a key component of any multipronged strategy to control the spread of infectious diseases and combat their impacts. Once available, vaccines are also among the most cost-effective public health interventions. They have contributed to reducing mortality and morbidity from infectious diseases and generated significant cost savings for health systems.

The composition and participants encompassed in the research and development (R&D) ecosystem vary among authors (Keusch and Lurie 2020). Keusch and Lurie (2020) describe R&D as a “series of non-linear mini-ecosystems, each with particular characteristics, business needs, and incentives, pathways, problems, barriers, and proponents, each influencing one another.” In its broadest sense, R&D comprises the set of activities, actors, and institutions that begins with upstream research (fundamental discovery research in fields like microbiology and immunology), continues with preclinical research, and concludes with clinical research. Some scholars also include in the R&D ecosystem the regulatory approval and manufacturing stages; still others expand R&D to global access to newly developed drugs, vaccines, and diagnostic kits, as well as the global financing mechanisms to ensure access for those who cannot afford them.

2.2 R&D in Vaccines: Vaccine Technologies, Stages, and Main Actors

2.2.1 Main Types of Vaccines and Technology Platforms

Most vaccines contain two components: the antigen (all or part of the infectious pathogen) or a precursor of the antigen (the genetic component of the pathogen: DNA or RNA), and the adjuvant (a product that stimulates the immune system in the person receiving the vaccine to generate a stronger response) (reviewed in Ahmed, Ellis, and Rappuoli 2018; Iwasaki and Omer 2020). In addition, the vaccine solution contains preservatives and stabilizers to extend the shelf life of the product. Vaccine R&D is mainly focused on identifying the most appropriate antigen (or its precursors) and adjuvants to include in the vaccine preparation (Ahmed, Ellis, and Rappuoli 2018).

Recent advances in genome sequencing and bioinformatics approaches have reduced the time and costs of vaccine design and development. In addition, gene synthesis and automation technologies now allow a part or the whole genetic code of pathogens to be synthesized rapidly and relatively inexpensively. For instance, in the context of the COVID-19 pandemic, these technologies have been used to synthesize in the laboratory the most antigenic parts of the genome of SARS-CoV-2

(those that were predicted to generate the strongest immune response)—and of any variants arising over time—and use the synthetic material as a source of viral particles instead of having to rely on clinical samples.

There are different types of vaccines with different implications for the complexity of their R&D and manufacturing (Iwasaki and Omer 2020; Pollard and Bijker 2021) (Table 2.1). Vaccines containing live attenuated and/or inactivated or killed versions of the pathogen or an inactive version of a toxoid produced by the pathogen were first introduced more than a century ago. Vaccines that contain a subunit of

Table 2.1: Main Types of Vaccines and Vaccine Platforms

Type of Vaccines	First Time Used	Advantages	Challenges
Live-attenuated pathogen	1798	Long-lasting protection Most do not require an adjuvant	Safety and stability issues
Killed pathogen	1896	Most do not require an adjuvant	
Toxoid	1923		
Subunit (protein, peptide, polysaccharide)	1970	Can be tested quickly	Require an adjuvant
Virus-like protein	1986		Require an adjuvant
Viral vector	2019	Strong protection Do not require an adjuvant Replicable manufacturing	Preexisting immunity against vector Potential challenges still not completely known
Nucleic acid (DNA, RNA)	2020	Strong protection Do not require an adjuvant Replicable manufacturing	Potential challenges still not completely known Unstable and easily degraded
Antigen-presenting cells (dendritic cells), T cells		Approved by the United States Food and Drug Administration for therapeutic use in cancer	Potential challenges still not completely known
Bacterial vector		Lasting protection Stability	Not yet approved for use in humans

Sources: Ahmed, Ellis, and Rappuoli (2018); Iwasaki and Omer (2020); and Pollard and Bijker (2021).

the pathogen (e.g., a protein or a fragment of a protein, either purified or synthetically produced) or a virus-like particle (viral proteins that resemble a native virus but lack the viral genome that allows virus replication) became available in the 1970s and 1980s. Gene synthesis and automation technologies have made it possible to develop and manufacture viral vectors and nucleic acid-based (RNA, DNA) vaccines much faster than traditional vaccines. The COVID-19 pandemic has spurred the introduction of mRNA vaccines for the first time for use in humans (Iwasaki and Omer 2020; WHO 2021) (Table 2.1). Instead of introducing the pathogen or fractions of it, mRNA and DNA vaccines induce the recipient to produce the viral proteins on their own. Except for some live-attenuated vaccines that generate live-lasting protection, most vaccines require additional booster shots.

The production of classical vaccines (e.g., live attenuated, killed, subunits) is not only slower than for nucleic acid-based vaccines but also involves a biological process rather than a chemical one, which entails greater variability in yield and performance from one batch to another.⁴ The manufacturing of classical vaccines is also more prone to batch contamination compared to the production not only of therapeutic drugs but also of viral vector-based and nucleic acid-based vaccines (Douglas and Samant 2018). The greater biological variability in the yield and performance of vaccines compared to therapeutic drugs also means slower approval by regulatory authorities and, as detailed later, precludes a market for generic vaccines such as the existing one for therapeutic drugs. As discussed in the following sections, these technical challenges create uncertainty for potential vaccine developers and manufacturers and are important economic disincentives that can lead to fewer (or no) firms interested in vaccine R&D and manufacturing, and to manufacturing failures and supply shortages.

In contrast, mRNA vaccines can be designed more rapidly once the genetic code of the pathogen is available and can be more easily updated and redesigned to take into account new variants of the pathogen. Although the manufacturing of mRNA vaccines requires advanced gene synthesis technologies and expertise—which are still lacking in many countries—their production is largely a chemical process that does not depend on the growth of the pathogen or the culture of cells, so their production is easier to scale up and can be performed more consistently (Jackson et al. 2020). These features of mRNA vaccines explain why they were the first to be developed and approved for COVID-19 (WHO 2021). They also have other advantages relative to traditional platforms. First,

⁴ For instance, *inter alia*, variability in the degree of pathogen attenuation, the stability of the pathogen, or in the environmental conditions of the culture of the pathogen.

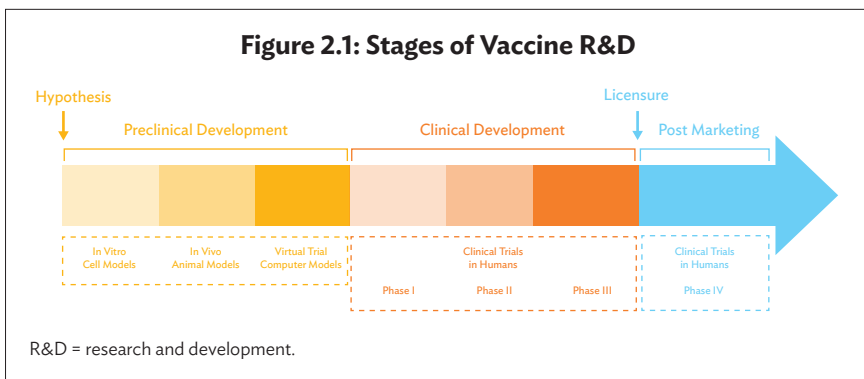
mRNA vaccines are safer because their production does not require the inactivation of the infectious pathogen. Second, in mRNA vaccines, a fragment of the pathogen is produced by our cells, thus promoting a more effective immune response and without the need of adding an adjuvant. Third, mRNA vaccines are easier to redesign to account for new variants of the pathogens. And fourth, once the technology is set up, the high consistency in the production process and the trend toward lower costs as the technology progresses mean low marginal costs of R&D and manufacturing (Pardi et al. 2018; Knezevic et al. 2021). The World Health Organization (WHO) has played a key role in setting standards regarding the quality, safety, and efficacy of traditional vaccines; different initiatives are currently being considered to reach a similar consensus in the manufacture and regulation of mRNA vaccines (Knezevic et al. 2021). One of the drawbacks of mRNA vaccines relative to traditional vaccines is that they are more labile and require cooler storage conditions, which are not always available in remote and/or low-income settings.⁵ In any case, mRNA vaccines are opening a new era in vaccinology whose implications in the fight against infectious diseases, as well as other diseases and conditions (e.g., anti-cancer vaccines), are still unforeseen.

Vaccine developers across Asia and the Pacific have successfully developed candidates and commercial vaccines for COVID-19 using most of the existing technologies, including new platforms such as viral vector vaccines, and several companies in the region are now working toward developing and manufacturing mRNA-based vaccines (see Chapter 3).

2.2.2 Stages of Vaccine R&D

Although the vaccines for Ebola virus disease were developed in around 5 years and several of the vaccines for COVID-19 in less than a year, for most vaccines, it can take up to 10–15 years to obtain a safe and efficient candidate. Vaccine development comprises several stages (Figure 2.1), most overlapping with the stages involved in developing therapeutic drugs (Leroux-Roels et al. 2011; Douglas and Samant 2018; Artaud et al. 2019).

⁵ Being a newer platform, mRNA vaccines also raise new issues regarding intellectual property rights protection that are addressed in Chapter 5 of the book. WHO, the Medicines Patent Pool initiative, and several African international partners have established an mRNA Vaccine Technology Transfer Center for the production of mRNA vaccines for Africa, and WHO plans to establish similar centers in other regions (Medicines Patent Pool 2021).



The first step in vaccine R&D is the discovery stage (2–4 years), which involves basic research in a laboratory to define an appropriate vaccine technology and identify what elements (antigen targets) in the infectious agent can best trigger an immune response in the individual receiving the vaccine.⁶ Recent technological advances (compound library screening, bioinformatics, spectrometry, crystallography, artificial intelligence, etc.) can predict which regions in the pathogen interact with human antibodies for structure-based vaccine design. The second is the preclinical stage (1–2 years) when laboratory animals are subjected to an early version of the vaccine to assess in vivo both its safety and immunogenicity potential. The third is the clinical trials stage, during which vaccine candidates are administered to humans to test that they are safe and provide effective protection in different human populations (different cohorts by age, sex, ethnic group, etc.). Clinical trials are lengthy (8–10 years), costly, and subject to strict regulatory and ethical standards that are set by the corresponding regulatory authorities and vary from country to country. In turn, clinical trials comprise several phases: Phase I (around 2 years), in which vaccine candidates are tested for safety and immunogenicity in 10–50 healthy volunteers; Phase II (2–3 years), during which 200–500 individuals participate in randomized trials where some individuals receive a placebo while others receive vaccine candidates to monitor their effective dosage, safety, and immunogenicity; Phase III (5–10 years) involves thousands of people in randomized placebo and vaccine cohorts and in which a selected vaccine

⁶ Also called immunogenicity: production of antibodies and/or a cellular response against the antigen.

candidate is assessed for triggering an immune response and preventing infection in the context of an outbreak. Unlike with drugs, vaccines that pass phases II and III have a high probability of achieving licensure. Phase III requires rigorous analysis and management and constitutes the mainstay over which regulatory authorities approve or deny the use of the vaccine in a specified target population. In most cases, vaccine manufacturers scale up production only after licensure. Even after the vaccine is on the market, manufacturers must continuously conduct pharmacovigilance of the vaccine (Phase IV) to evaluate its safety, the degree of long-term protection it provides, and investigate potential new indications (different schedules, the need for boosts, etc.). Likewise, the competent authority will continue to monitor vaccine production facilities and review testing processes.

In contrast to therapeutic drugs, which are designed to treat a person who is already ill, most vaccines aim at preventing a particular disease and are administered to large populations of healthy people.⁷ Consequently, the threshold to accept adverse secondary effects in preventive vaccines must meet more stringent safety requirements to gain regulatory approval, requiring longer and more expensive clinical trials. In this chapter, the term “vaccine” is used to refer to preventive vaccines.

Basic preclinical-clinical R&D of vaccines must be closely integrated with **manufacturing R&D**, which includes process and assay development. **Process development** involves the manufacture of vaccine samples that comply with regulatory requirements for use in humans, preclinical toxicology testing, analytical assessment, and technological transfer for consistent manufacturing and scale-up from a pilot plant to final locations for large-scale batches (Douglas and Samant 2018). **Assay development** refers to the definition of benchmarks regarding the purity of vaccine components, stability, consistency of production batches, and tests to predict vaccine efficacy. Since Phase III clinical trials are expensive, lengthy, and require large numbers of people, certain analytical correlates of vaccine immunogenicity and disease protection (e.g., blood levels of antibodies) have been proposed as possible alternatives or complements to Phase III trials of some vaccines (Plotkin 2010). Nevertheless, the adoption of these correlates requires approval by the corresponding regulatory authorities.

⁷ In this particular aspect, therapeutic vaccines to fight cancer, allergies, and certain chronic diseases are similar to therapeutic drugs.

2.2.3 Main Actors in Vaccine R&D

In recent years, vaccine and drug R&D has witnessed the emergence of new actors and new forms of interactions between them. The actors involved through the different stages of vaccine R&D are relatively similar to those in R&D for therapeutic drugs:

- (i) **Discovery research.** This is typically carried out in basic research laboratories at universities, research institutes, and, increasingly, in small start-up biotechnology companies.
- (ii) **Preclinical research.** Automation in sequencing and small-molecule synthesis has allowed basic research laboratories and biotech firms to become increasingly involved not only in vaccine design but also in the production of small samples of pathogen subunits or adjuvants to test in preclinical animal models. Alternatively, once a proof of concept has been designed, vaccine samples for preclinical trials are produced by pharmaceutical firms or in collaborations with basic research laboratories.
- (iii) **Clinical trials and pharmacovigilance.** Pharmaceutical firms are responsible for carrying out phases I–IV of clinical trials through agreements with clinics and hospitals, or, increasingly, outsourcing to contract research organizations (CROs).

In many countries, particularly high- and upper middle-income economies, **government agencies** are the major source of direct funding for discovery and preclinical research for drug and vaccine development (Viergever and Hendriks 2016), which increasingly implies partnerships with private firms. In the case of vaccines for diseases that affect primarily the developing world, governments in developed economies fund health R&D directly, through official development assistance, or via partnerships with philanthropic foundations and international organizations. For instance, product development partnerships (PDPs)—nonprofit organizations that coordinate public and private stakeholders—are now one of the main players in vaccine and drug R&D for endemic, neglected, and emerging infectious diseases.

Within the **private sector**, the landscape of actors involved in vaccine R&D is changing because of the mergers and consolidations among the largest multinational pharmaceutical firms (MNPFS), the proliferation of biotech companies and CROs, and the increased participation of pharmaceutical firms in developing countries. During the 15 years before the COVID-19 pandemic, the number of new vaccines developed by MNPFS remained stagnant, while those developed by small biotech

firms doubled and those developed by emerging-market pharmaceutical firms experienced a 13-fold increase (Aars, Clark, and Schwalbe 2021). MNPFs are often feeding their pipelines through licensing and/or acquisitions of smaller biotech firms.

Most **multinational pharmaceutical firms** that conduct R&D for vaccines also do so for therapeutic drugs. The largest MNPFs have within the firm all the required expertise in clinical R&D, data and project management, and regulatory affairs (Douglas and Samant 2018). Since some of these tasks are now carried out by CROs, MNPFs are focusing their expertise and financial efforts on vaccine design, process and assay development, registration, and manufacturing.

Many **small biotech companies** involved in vaccine R&D began as start-ups that academic scientists established with funding from venture capitalists often matched by government programs, with the vast majority based in developed countries. As most of these small biotech firms have limited expertise in process and clinical development and manufacturing, they often partner with and/or license their vaccines and/or technology platforms to MNPFs (Douglas and Samant 2018). Some of the recent advances in vaccinology have been introduced by small biotech firms. For example, technological innovations in vaccines for hepatitis B and *Haemophilus influenzae* type b were developed by small biotech companies that later became associated or acquired by larger MNPFs (Douglas and Samant 2018). In 2018, BioNTech AG, a biotech company specializing in mRNA technologies, partnered with Pfizer to jointly conduct R&D for mRNA-based influenza vaccines, with Pfizer taking sole responsibility for clinical development and commercialization. More recently, during the COVID-19 pandemic, BioNTech, along with Moderna emerged as key players in mRNA vaccines.

A total of 41 public and private pharmaceutical firms in developing countries are part of the **Developing Countries Vaccine Manufacturers Network** (DCVMN). In 2019, companies in the network had an estimated capacity of 3.5 billion doses for more than 50 vaccines, 13 of them prequalified by WHO and eligible for procurement by United Nations agencies (Hayman and Pagliusi 2020; Hayman, Suri, and Prasad 2021; DCVMN website). Although most of these firms have relatively limited financial and expertise capabilities, some have been able to develop second-generation vaccines without formal technology transfer (Aars, Clark, and Schwalbe 2021). Many DCVMN firms conduct vaccine R&D through partnerships, including PDPs (as discussed later), with philanthropic foundations and larger pharmaceutical companies. During the pandemic, several DCVMN members have developed

COVID-19 vaccines on their own and/or manufacture them through partnerships with MNPFs—for instance, the Serum Institute of India teamed up with AstraZeneca for the manufacturing of COVID-19 vaccines in India. Nevertheless, a recent survey among DCVMN firms regarding their R&D capabilities indicated that most require funding and/or technical transfer for the newest mRNA vaccines (Hayman, Suri, and Prasad 2021).

The first **contract research organizations** emerged in the 1940s, but their number, size, and roles have expanded enormously since the 1990s (Dimachkie-Masri et al. 2011; Balconi and Lorenzi 2017; Gad, Spainhour, and Serota 2020). Initially, MNPFs only outsourced to CROs their clinical research activities to enhance the cost benefits and to expand the geographical reach of clinical trials. Most of the major CROs are now taking on new tasks, from participating in preclinical vaccine research stages to preparing applications for ethical committees, institutional review boards, and regulatory authorities. In 2018, the global CRO market stood at \$38.4 billion, but this number has likely increased significantly since then, as many of the COVID-19 vaccines were developed with support from CROs. The involvement of CROs in health R&D goes often unnoticed, because contract relationships between pharmaceutical firms and CROs are confidential since the former, particularly the largest MNPFs, rarely acknowledge the participation of CROs in their clinical trials.

In the context of health emergencies, **global and regional intergovernmental organizations** can coordinate the policies and actions of governments, strengthen disease surveillance, and share information and best strategies. But intergovernmental organizations also have important functions in vaccine R&D. In May 2015, in the aftermath of the 2014 Ebola virus disease epidemic, WHO convened a group of experts to develop the *R&D Blueprint for Action to Prevent Epidemics* (WHO 2016, 2017). The initiative aims to strengthen R&D preparedness (before a health threat) and R&D response (during an outbreak) with the ultimate goal of reducing the time between a disease outbreak and the approval of efficient vaccines, drugs, and diagnostic tools. To that effect, the WHO R&D Blueprint prioritizes diseases with the greatest epidemic potential and/or for which no or insufficient diagnostic, preventive, and curative solutions exist and develops an R&D road map for each of these diseases (WHO 2016, 2017; Mehand, Al-Shorbaji, et al. 2018; Mehand, Millett, et al. 2018; WHO 2021). Diseases with ongoing R&D programs or product pipelines are not included in the priority list. Among the prioritized diseases is the so-called Disease X, which refers to a serious international epidemic caused by a pathogen currently unknown to cause human disease. The

R&D Blueprint aims at developing crosscutting R&D preparedness that also covers Disease X.

The emergence and proliferation of **product development partnerships** has transformed the R&D landscape for diseases affecting the developing world. PDPs are nonprofit, legally independent partnership organizations that were introduced in the late 1990s as a form of private–public partnership to address failures in the vaccine and drug markets and the lack of economic incentives for pharmaceutical firms to undertake R&D for neglected diseases affecting developing countries (as discussed in section 2.3) (Widdus 2001; Hayter and Nisar 2018; Taylor and Smith 2020; Bulc and Ramchandani 2021).⁸ PDPs channel funding from high-income countries and philanthropic foundations and engage academic research laboratories and pharmaceutical firms in conducting vaccine and drug R&D to develop at affordable costs vaccines, drugs, and diagnostic tools for diseases in developing countries. For instance, one of the first PDPs was established to develop a meningococcal conjugate vaccine by the Serum Institute of India with funding from the Bill & Melinda Gates Foundation and technical assistance from PATH. PDPs use management practices in their R&D activities and coordinate partners through R&D stages, allocate financial resources to the most promising vaccine development projects, and manage the project portfolio. Most PDPs have in-house R&D capabilities, conduct capacity building and technological transfer, and carry out advocacy, and some have manufacturing capacities. To minimize risks in vaccine R&D, they use a portfolio approach and simultaneously develop multiple vaccine candidates for a single disease. PDPs focus on one or several diseases, though some do not aim at any particular disease. Rather, they promote R&D that can accelerate vaccine and drug R&D on several diseases—for instance, new mouse models for preclinical research, diagnostic tools, benchmarks for clinical trials, and harmonized biological standards and assays (Aars, Clark, and Schwalbe 2021). In 2018, R&D funding for emerging infectious diseases reached \$886 million, with 65.2% for vaccine development and 95.7% directly from the funders to vaccine and drug developers (Policy Cures Research 2021a). In contrast, 23% of the \$3.9 billion global investments in R&D for neglected diseases were channeled through PDP and non-PDP intermediaries (Policy Cures Research 2021b).

⁸ There are three main types of health-related private–public partnerships (PPPs): (i) access PPPs that aim to expand access to existing products but for which there is limited demand or ability to pay; (ii) systems-based PPPs, whose goal is to improve the capacity of health systems; and (iii) PDPs (Taylor and Smith 2020).

PDPs can be distinguished from other **non-PDP intermediaries**—often referred to as “virtual companies” or “social capital venture funds”—that also direct funding for R&D in poverty-related diseases to vaccine and drug developers. In contrast to PDPs, they rely on external partners for R&D. The largest of these non-PDP intermediaries is the Coalition for Epidemic Preparedness Innovations (CEPI) that channels funding for vaccine R&D for priority diseases identified in the WHO R&D Blueprint.

The *Global Research Collaboration for Infectious Disease Preparedness* (GLOPID-R) is a global alliance of 32 funding organizations (government agencies, philanthropic foundations, and non-PDP intermediaries) that finance R&D to develop vaccines, drugs, and diagnostic tools for new or reemerging infectious diseases. Its goal is to facilitate an effective R&D response within 48 hours of a significant outbreak. GLOPID-R itself does not fund R&D; instead, it promotes the sharing of information and addresses scientific, logistical, legal, regulatory, ethical, and financial challenges that underpin an international R&D response. WHO, CEPI, the European & Developing Countries Clinical Trials Partnership, and ESSENCE on Health Research⁹ are observers in the global alliance.

2.3 The Economics of Vaccine R&D

Vaccine production is a highly capital-intensive industry, which represents a barrier to new entrants and competition. A WHO study calculated that the cost for setting up a plant to produce monovalent vaccines in a high-income country stands at between \$50 million and \$500 million and rises to \$700 million for polyvalent vaccines (Lobo 2021). Projecting the costs and profits in vaccine R&D and manufacturing is also more difficult than in other industry sectors (Aars, Clark, and Schwalbe 2021). The cost of progressing a vaccine through the end of Phase II of clinical trials has been estimated at \$112 million to \$469 million (Gouglas et al. 2018). R&D costs for newer technology vaccines are higher at all stages, as developers must recover discovery and/or preclinical research investments, as well as obtain regulatory approvals and plant certifications. In contrast, for traditional technologies, older vaccines, and modifications of existing vaccines (e.g., influenza variants), many fixed costs have been recouped (Lobo 2021).

⁹ ESSENCE on Health Research is an initiative of TDR, the Special Programme for Research and Training in Tropical Diseases, cosponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme, the World Bank, and WHO.

Liability risks are also higher for newer vaccines and technologies. The biological nature of most vaccines with the corresponding variability in yields, the larger size of clinical trials, and the stricter regulatory requirements make vaccine R&D more lengthy and costly than R&D for therapeutic drugs. On average, the time to develop a traditional vaccine, from the preclinical stage to its entry into the market, is 10.7 years and the market entry probability of a vaccine candidate is 6% (Pronker et al. 2013).

As noted, the R&D, manufacturing, and sales of new vaccines are highly concentrated in a few large MNPFs located in high-income countries, the so-called vaccine production hub (Evenett et al. 2021). In 2013, around 70% of global vaccine sales were in the United States (US) and the European Union (Douglas and Samant 2018). Historically, MNPFs have shown more interest in developing new therapeutic drugs than in new vaccines. In 2019, global vaccine sales totaled \$35.2 billion, just 3.5% of the entire pharmaceutical market (Evaluate 2020; Lobo 2021). Nevertheless, vaccine sales are growing faster, having tripled since 2005—compared to an 80% growth of drug sales—owing to the introduction of new vaccines with high volumes and margins (e.g., hepatitis B, multivalent diphtheria–tetanus–pertussis [DTP], pneumococcal, human papillomavirus [HPV], and zoster) and many low-income countries gaining access to vaccines funded through official development assistance, philanthropic foundations, and international organizations (Evaluate 2020; Douglas and Samant 2018). The COVID-19 pandemic has increased these figures; some market studies estimated that in 2021 the COVID-19 vaccine market alone in the US, Japan, and the five largest European economies amounted to \$13.1 billion and that in 2024 may reach \$25 billion for the entire world (GlobalData 2021; Market Study Report 2021).

The economics behind vaccine R&D and manufacturing are influenced by supply and demand factors (Sloan 2012; Lobo 2021). On the **supply side**, pharmaceutical firms must consider the opportunity cost of investing their financial, human capital, and manufacturing assets in the R&D of a particular vaccine compared to doing so in therapeutic drugs (or other vaccines) with higher prospects of success and/or returns on investment. As noted earlier, compared to therapeutic drugs, developing a new vaccine involves stricter safety requirements, which increase the costs and time of clinical trials. Additionally, since most vaccine and drug candidates eventually fail, pharmaceutical firms usually wait to collect data on safety and efficacy before scaling up manufacturing (which requires specific sunk investments), also delaying the eventual availability of vaccines and drugs. For instance, most COVID-19 vaccine candidates will never reach the market.

While the availability of multiple vaccines and platforms ensures that several of them will be safe and effective, simultaneous investment in too many candidates can have diminishing returns.

On the **demand side**, some factors are common between vaccines and therapeutic drugs, and some are different. The demand for vaccines and therapeutic drugs is affected by disease prevalence and pathogen infectiveness, as well as people's willingness and ability to pay, which are reduced in socioeconomically vulnerable populations in developing countries. However, unlike therapeutic drugs, particularly those for treating chronic conditions, preventive vaccines are administered only once or a few times during a lifetime. Evidence also indicates that individuals—and often government health programs—are more willing to pay for treatment than for prevention (Kremer and Snyder 2015). The lack of predictable demand for a vaccine, particularly in resource-scarce developing countries, creates uncertainty about returns on investment, precluding or delaying the development of vaccines. While some vaccines (e.g., pediatric vaccines, influenza, COVID-19) are in high demand, vaccines for many neglected infectious diseases affecting developing countries have relatively low demand, a factor that is compounded by the lower ability to pay by those that need them. Similar economic factors apply when it comes to outbreaks of emerging infectious diseases, which tend to start in low-income countries and are also plagued by unpredictability and uncertainty regarding their nature, geographical location, and potential spread and duration—thus, the incentives of firms to invest in R&D preparedness (Nuzzo et al. 2019).

Although most analyses conclude that the economic incentives to develop new vaccines are low, the incentives should be assessed on a case-by-case basis and there are also arguments pointing to high profit margins for vaccines (Douglas and Samant 2018; Lobo 2021). First, many vaccines are produced by a limited number of manufacturers—36 vaccines have two or fewer suppliers prequalified by WHO¹⁰—thus generating higher margins. Second, in contrast to therapeutic drugs, yield and batch variability in biological vaccines force new entrants to conduct new clinical trials and obtain regulatory approvals, so the vaccine market is not amenable to the production of generics. Consequently, the holders of vaccine intellectual property rights enjoy monopoly rents for a longer period than for therapeutic drugs. Third,

¹⁰ This concentration is the result of the business structure of the vaccine market with high fixed costs, price-sensitive demand, and dynamic quality competition (Danzon and Sousa Pereira 2011). New pharmaceutical firms in Brazil, India, and the People's Republic of China have increased the sources of vaccines for developing countries, particularly for traditional vaccines (WHO 2021).

vaccines that have been on the market for a long time have low marginal costs per dose and high cost-effectiveness ratios. Empirical evidence indicates that stronger protection of intellectual property rights does not necessarily promote public–private partnerships for vaccine R&D if stakeholders are not prepared to cooperate (da Veiga et al. 2016). Likewise, linking tax reductions to R&D investments may be more attractive for pharmaceutical and biotech firms than grants.

Unlike most therapeutic drugs, vaccine R&D and manufacturing generate benefits (**positive externalities**) for the population at large, even globally, because most vaccines prevent contagion and also protect unvaccinated individuals (Gersovitz and Hammer 2003; Endarti and Riewpaiboon 2016; Younes et al. 2020). As with any externality, individuals that have not received the vaccine do not pay for this additional benefit and pharmaceutical firms have no way to charge for this societal benefit, thus creating a gap between private (pharmaceutical firms) and social (society) rates of return (Younes et al. 2020; Endarti and Riewpaiboon 2016).

Some of the abovementioned factors reduce the profitability of many vaccines (particularly those for diseases afflicting populations in low-income countries), the incentive for MNPFs to invest in such vaccine R&D, and ultimately the overall supply of vaccines (below the socially optimal amount), thus creating a **market failure**. Cost–benefit analyses of investment in vaccine R&D must take into account (internalize in economic terms) the positive social benefits of vaccines (Vu et al. 2020). Like downstream investments in free immunization programs, upstream investments in vaccine R&D must consider the impacts of immunization beyond its health benefits. When the broader societal impacts of immunization (e.g., long-term disability burden, economic productivity, education) are considered, the estimated net return to vaccination programs ranges from \$16 to \$44 for every dollar spent in free vaccination programs (Bärnighausen et al. 2014; Ozawa et al. 2016).

2.4 Strengthening Incentives for Vaccine R&D

2.4.1 Prioritization of Targets in the Vaccine R&D Pipeline

To build and strengthen R&D preparedness, national governments, as well as regional and subregional intergovernmental organizations, should first identify which infectious diseases to prioritize for vaccine R&D. The **vaccines included in most national immunization programs** have been around for a long time, can be procured from multiple

sources, and can be produced at relatively low marginal costs. Countries with vaccine manufacturing capacity should aim to conduct R&D and produce these vaccines domestically or coordinate their production at the regional and/or subregional level. Similar recommendations apply to other vaccines with large target populations even if they are not included in national immunization programs (e.g., influenza vaccines).

Prioritization is particularly important in **emerging infectious diseases with high epidemic potential**. As no single country, including high-income economies, can invest in R&D for all potential emerging pathogens, regional cooperation is particularly important for these infectious diseases. Disease prioritization is not always straightforward and requires establishing clear criteria. The WHO R&D Blueprint has developed a **comprehensive methodology of R&D prioritization** to ensure that its list of selected diseases best reflects targeted global health needs and focuses on the most pressing threats based on their epidemic potential and for which there are no, or insufficient, countermeasures. This methodology used by WHO is readily available and draws on established best practices and national and regional experience. It is similar also to the methodology that CEPI uses to prioritize its vaccine R&D targets (WHO 2016; Mehand, Al-Shorbaji, et al. 2018; Mehand, Millett, et al. 2018; Gouglas and Marsh 2019; Jonkmans, D'Acremont, and Flahault 2021; Kojom and Singh 2021). In developing countries lacking the expertise to implement this methodology, WHO, through its regional offices, donor countries, PDPs and non-PDP intermediaries, and/or international organizations (e.g., United Nations Economic and Social Commission for Asia and the Pacific [UN-ESCAP], scientific associations), can provide technical assistance and capacity building of policymakers responsible for health and science, technology, and innovation.

For **existing diseases of predominantly domestic or subregional and regional prevalence**, which disease to prioritize should be guided by several parameters: (i) prevalence and burden and cost of illness of each disease (e.g., case fatality, disability-adjusted life years, economic impacts) in the country, the region (e.g., Asia and the Pacific), or subregions; (ii) its infectiveness and potential for epidemic and pandemic spread; (iii) the global status of R&D for each disease; (iv) the existence, availability, and cost of other vaccines; (v) other qualitative, intangible, or subjective criteria depending on the stakeholders; and, importantly, (vi) the financial viability and R&D capacity to generate new vaccines (Andre 2002; WHO Regional Office for South-East Asia 2003; Mehand, Millett, et al. 2018; Gouglas and Marsh 2019; Jonkmans, D'Acremont, and Flahault 2021; Sharma 2021).

The prioritization of R&D investments should also include **building preparedness for still-unknown pathogens (Disease X)**. Most of

the newly emerging human infectious diseases are caused by viruses that jump from other animals (zoonotic diseases). Of the estimated 1.6 million viruses affecting animals, only a small number can infect humans. Identifying in advance and including in prioritization lists pathogens in animals with a high risk of infecting humans is key to develop R&D preparedness for the next zoonotic threat. Advances in genomic sequencing, bioinformatics, and artificial intelligence are being used to assess the risk of human infection by viruses that have not yet jumped to humans (Mollentze, Babayan, and Streicker 2021).

2.4.2 Overcoming Market Failures in Vaccine R&D

The possibility of a market failure supports external interventions and/or regulation of the vaccine market. Prospective vaccine buyers (usually, governments, PDPs and non-PDP intermediaries, or international organizations) can bear part of the risk and incentivize firms to invest in R&D and/or scale up vaccine production before R&D and regulatory approval are completed by subsidizing the cost of R&D and/or new production facilities and stimulating the supply of vaccines (supply side or push strategies). Alternatively, potential buyers can stimulate vaccine demand by introducing regulations that increase vaccine uptake and/or by committing to purchase doses after regulatory approval (demand side or pull strategies). As with other global common goods, individual countries have an incentive to free ride on the vaccine R&D investments of other countries. Although this additional market failure also occurred in the context of the COVID-19 pandemic, many governments—including middle-income countries—have funded R&D programs for COVID-19 vaccines, and their willingness to pay has been high as countries compete to gain early access to vaccines (Younes et al. 2020).

Multiple **supply-side approaches** are used to address potential failures in the vaccine market. The most common strategy is funding vaccine R&D through public and/or philanthropic sources. Governments can incentivize vaccine R&D by increasing funding for basic and preclinical research in universities and public research institutes. While there may be a case for government intervention and regulation to address market failures in R&D and manufacturing of vaccines for some diseases, establishing the optimal level of public funding and support for R&D is not straightforward (Younes et al. 2020). Targeted funding for vaccine R&D can potentially result in diminishing returns and overinvestment, as well as the diversion of resources to other diseases. Most low-income countries lack the financial resources to invest in vaccine R&D and/or the physical infrastructure and/or human capital required for R&D investments to be productive and effective. As noted earlier, for countries

with limited economic resources to address other social and economic challenges, it is neither possible nor sensible to invest in the early stages of vaccine R&D or to develop an advanced vaccine pharmaceutical industry. PDPs and other non-PDP intermediaries have proliferated as an innovative mechanism to fund vaccine R&D. In situations where it is deemed important to involve developing countries in later stages of vaccine R&D (e.g., clinical trials) and/or because of other factors (e.g., size of the country, geography, epidemiological status), WHO, regional intergovernmental organizations, regional scientific societies, and PDPs can provide technical training and/or financial resources to these countries to develop and strengthen vaccine R&D through improvements in the physical infrastructure and human capital.

Other supply-side mechanisms to encourage pharmaceutical firms to invest in vaccine R&D include **regulatory, policy, tax, and direct financial incentives**. For instance, **milestone subsidies**—for when companies successfully complete an R&D stage—have been applied successfully. Governments can also explore other supply mechanisms short of grants like **tax incentives** for investing in vaccine R&D. Strengthening intellectual property right protection can also incentivize firms to invest in vaccine R&D and manufacturing, though this can result in higher prices and generate equity problems with lower access for low-income countries (see Chapter 5). Policy reforms to ensure a **fast-track review of vaccine candidates** by regulatory authorities in the context of health emergencies also ease uncertainty for firms to invest in vaccine R&D by accelerating the time and reducing the cost of clinical trials, particularly of Phase III trials that involve large numbers of people. For instance, in several vaccines, efforts have been made to validate analytical parameters as proxy measurements of immune protection, thus reducing the number of people required in clinical trials (Plotkin 2010; Aars, Clark, and Schwalbe 2021). However, any potential relaxation of the regulatory framework of clinical trials should ensure the safety and effectiveness of approved vaccines. Other supply-side strategies include public–private partnerships in R&D at the national or international level (see Chapter 3), and technology transfer from multinational corporations to indigenous start-ups and small and/or medium-sized private firms.

Demand-side approaches that increase the final demand for vaccines also incentivize firms to invest in R&D. One way to address market failures and de-risk and incentivize vaccine R&D investment by pharmaceutical firms—and, in some cases, directly fund R&D—is through the use of a financial commitment—advanced market commitments (AMCs) and advanced purchase agreements (APAs)—to subsidize the future purchase of a vaccine that is not yet available,

at an agreed-upon price and contingent upon the development of an efficient and safe vaccine. APAs are contracts between a pharmaceutical manufacturer and buyers (governments, international organizations, philanthropic foundations, PDPs, and non-PDP intermediaries) whereby buyers commit to purchasing a product once the product is developed, approved, and brought to the market, thus guaranteeing that there will be a market for the product even before the product is available (Turner 2016; Boulet et al. 2021). Buyers benefit both from speeding up vaccine R&D and securing doses at a predictable price. APAs do not only de-risk R&D investment, but they can also fund capacity building for scaling up manufacturing and directly finance R&D. AMCs can also be supply-side approaches when they directly finance R&D and/or the scale-up of manufacturing. The terms of reference of APAs vary widely by contract and are usually confidential. Increased production capacity remains a permanent benefit for the firm, and late-stage (e.g., clinical trials) R&D costs, when the APA covers these, do not have to be refunded if a product is not successful or approved by the regulatory authorities (Boulet et al. 2021). At the same time, APAs do not require the intellectual property generated by the firms to be shared, licensed, or co-owned with the buyer. In return, APAs impose conditions on pharmaceutical firms regarding the number of doses and time line of the delivery. AMCs were first used in 2009 when Gavi, the Vaccine Alliance; UNICEF; and the World Bank pledged \$1.5 billion to incentivize the development and supply of pneumococcal vaccines in low-income countries. Since then, APAs/AMCs have been used to accelerate the development and supply pandemic influenza and Ebola vaccines (Turner 2016). APAs are part of global pandemic influenza preparedness, and some countries pay an annual “pandemic preparedness fee,” which cost is not publicly available, to the manufacturer to maintain the contract (Turner 2016). APAs have become even more popular during the COVID-19 pandemic with many high-income and upper middle-income countries signing APAs with vaccine developers to procure COVID-19 vaccines (Pharmaceutical Technology 2021). PDPs and non-PDP intermediaries have also used AMCs successfully to incentivize R&D for neglected and emerging diseases.

Overall, APAs have proven successful in de-risking investments by pharmaceutical firms in R&D and building manufacturing capacity, thus accelerating the ultimate development of vaccines. Ahuja et al. (2021) found that early at-risk investments yield large benefits for countries across all levels of income, including low-income countries that would be otherwise priced out of the market. Buyers should diversify vaccine candidates and platforms and provide both supply-side approaches like payments for only part of the total cost—to ensure that firms have

a stake in the risk and success of vaccine development—and demand-side approaches structured in ways to incentivize speed. On the other hand, pharmaceutical firms may be discouraged from investing in R&D when governments and PDP and non-PDP intermediaries, as the main purchasers of vaccines, use their bargaining power and often the government's regulatory prerogative to bring prices down to levels close to the marginal cost of manufacturing and distribution which does not cover vaccine R&D (Sloan 2012).¹¹ In addition, as firms have to fulfill their delivery commitments to buyers—most often developed countries—before producing doses for countries without APAs, such agreements can impact equity in access to vaccines in developing countries. This highlights the need for international organizations and initiatives (e.g., CEPI, COVAX, Gavi) to engage in APAs/AMCs to serve low-income countries.

Other demand-side strategies include increasing vaccine uptake through information campaigns, free vaccination programs, and/or mandatory vaccinations. In most countries, vaccines included in recommended or mandatory national immunization programs, as well as those required during epidemics and pandemics, are administered free of charge by the government. The impact of mandatory vaccinations on vaccine uptake is still open to debate, and countries need to consider whether compulsory programs can be effectively implemented and enforced or whether recommendations and incentives work better.

¹¹ The prices paid by high-income countries tend to be above the prices offered in tenders organized by UNICEF and other organizations purchasing vaccines for distribution in low-income countries.

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From Lab to Jab

Improving Asia and the Pacific's Readiness to Produce and Deliver Vaccines

The coronavirus disease (COVID-19) pandemic highlighted the complexities and challenges associated with the development, production, and distribution of vaccines and the consequent risks and vulnerabilities arising from the lack of affordable and equitable access to essential vaccines and other health products.

This book identifies the challenges across the entire vaccine value chain from “lab to jab”—from research and development to the production and cross-border delivery of vaccines and their related inputs involving trade, transport, logistics and regulatory approvals, and finally to the distribution and administration of vaccines. These challenges include market failures, financing gaps, barriers to technology transfer, tariff and non-tariff barriers, transport and logistical constraints, lack of regulatory harmonization across countries, and limitations in the capacity of national health systems.

From Lab to Jab: Improving Asia and the Pacific's Readiness to Produce and Deliver Vaccines underscores the need for unilateral and collective measures, such as coordinated efforts for financing, procurement, capacity building, needs assessments, and technology transfer. These can be implemented by leveraging trade and investment agreements, ensuring greater regulatory coordination, facilitating investments in national health systems, and sharing data, knowledge, and good practices across the region. The timely discussions call on vaccines to be viewed as a global public good. Hence, a combination of national, regional, and global mechanisms and platforms will be needed to ensure affordable and equitable access to vaccines in preparation for future pandemics.

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