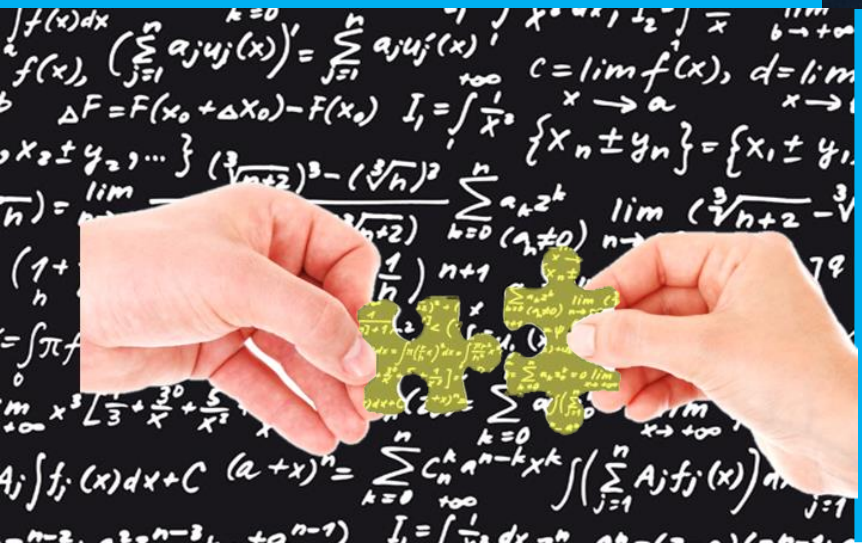
ARTNeT

UNITED NATIONS ESCAP
Economic and Social Commission for Asia and the Pacific

Special Series on Trade and Health

Vaccine Research and Development (R&D) in the Asia-Pacific: The economics of vaccine R&D and policy recommendations to overcome market failures and promote R&D cooperation



Antonio Postigo

ASIA-PACIFIC RESEARCH AND TRAINING NETWORK ON TRADE

Working Paper

No. 216 | 2022

The Asia-Pacific Research and Training Network on Trade (ARTNeT) is an open regional network of research and academic institutions specializing in international trade policy and facilitation issues. ESCAP, WTO and UNCTAD, as key core network partners, and a number of bilateral development partners, provide substantive and/or financial support to the network. The Trade, Investment and Innovation Division of ESCAP, the regional branch of the United Nations for Asia and the Pacific, provides the Secretariat of the network and a direct regional link to trade policymakers and other international organizations.

The ARTNeT Working Paper Series disseminates the findings of work in progress to encourage the exchange of ideas about trade issues. An objective of the series is to publish the findings quickly, even if the presentations are less than fully polished. ARTNeT Working Papers are available online at http://artnet.unescap.org. All material in the Working Papers may be freely quoted or reprinted, but acknowledgment is requested together with a copy of the publication containing the quotation or reprint. The use of the Working Papers for any commercial purpose, including resale, is prohibited.

Disclaimer:

The designations employed and the presentation of the material in this Working Paper do not imply the expression of any opinion whatsoever on the part of the Secretariat of the United Nations concerning the legal status of any country, territory, city or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries. Where the designation “country or area” appears, it covers countries, territories, cities or areas. Bibliographical and other references have, wherever possible, been verified. The United Nations bears no responsibility for the availability or functioning of URLs. The views expressed in this publication are those of the author(s) and do not necessarily reflect the views of the United Nations. The opinions, figures and estimates set forth in this publication are the responsibility of the author(s) and should not necessarily be considered as reflecting the views or carrying the endorsement of the United Nations. Any errors are the responsibility of the author(s). The mention of firm names and commercial products does not imply the endorsement of the United Nations.

ASIA-PACIFIC RESEARCH AND TRAINING NETWORK ON TRADE

WORKING PAPER

Vaccine Research and Development (R&D) in the Asia-Pacific: The economics of vaccine R&D and policy recommendations to overcome market failures and promote R&D cooperation

Antonio Postigo[1]

Please cite this paper as:

Antonio Postigo (2022). "Vaccine Research and Development (R&D) in the Asia-Pacific: The economics of vaccine R&D and policy recommendations to overcome market failures and promote R&D cooperation", **ARTNeT Working Paper Series** No. 216, October 2022, Bangkok, ESCAP.

Available at http://artnet.unescap.org

[1] Department of International Development, London School of Economics (LSE), London, UK. E-mail: a.postigo-angon@lse.ac.uk and postigoa@yahoo.com. This paper was written for and funded by the ESCAP-WHO research initiative "From Lab to Jab: Improving Asia-Pacific's Readiness to Produce and Deliver Vaccines". The author is grateful to the ARTNeT secretariat for the support in preparing this paper for dissemination.

Abstract

The COVID-19 pandemic has highlighted both the strengths and weaknesses of national, regional, and global vaccine research and development (R&D) systems. Translating public and private R&D efforts into effective vaccines in a timely manner requires not only sufficient financial and scientific resources but also a policy-driven R&D ecosystem that fosters innovation, public-private partnerships, and international cooperation. This paper outlines several supply-side and demand-side factors behind vaccine R&D that generate economic disincentives for pharmaceutical firms to invest in vaccine R&D and can lead to a market failure for vaccines targeting diseases in low-income countries. Most developing countries in Asia-Pacific not only lack the financial and technological resources to invest in vaccine R&D, but it is also not sensible to develop and replicate R&D capabilities in each country. Consequently, low-income countries are dependent on vaccines researched, developed, and manufactured by other nations that they must obtain through trade and international cooperation. The Asia-Pacific region accounts for the largest share of global R&D spending and large shares in publications and patents on vaccine R&D. The region is home to dozens of state-owned and private pharmaceutical firms and contract research organizations that conduct vaccine R&D. Global pharmaceutical firms have not only offshored part of their vaccine manufacturing to Asia-Pacific but also transferred some of their R&D activities. Countries in Asia-Pacific have used several supply-side and demand-side approaches to incentivize investments in vaccine R&D. For instance, high-income countries are major contributors to product development partnerships and philanthropic foundations and have launched programs to boost university-industry R&D ties. During the COVID-19 pandemic, many high- and middle-income countries in the region established advanced market commitments for vaccine doses. The COVID-19 pandemic also showed the possibilities and challenges of international cooperation in vaccine R&D. Pharmaceutical firms in some developing countries built their vaccine R&D capabilities through technological transfer from high-income countries. Regional institutions and intergovernmental organizations in Asia-Pacific have also helped promote and coordinate regional cooperation in vaccine R&D. This paper proposes policy actions to stimulate investments in vaccine R&D and promote regional cooperation along four dimensions, namely a) on the prioritization of targets in the vaccine R&D pipeline; b) on how to overcome market failures in vaccine R&D; c) on fostering partnerships between relevant stakeholders at the national and regional levels; and d) on increasing the preparedness and response of national and regional vaccine R&D systems.

Keywords: COVID-19, vaccines, medical products, R&D, regional cooperation, Asia-Pacific

JEL Codes: F15, F21, I18

Table of Contents

List of Tables

List of Figures

List of abbreviations

AAS	African Academy of Sciences
AASSA	Association of Academies and Societies of Sciences in Asia
ACPHEED	ASEAN Centre for Public Health Emergencies and Emerging Diseases
AESA	Alliance for Accelerating Excellence in Science in Africa
AMC	Advanced market commitments
APA	Advanced purchase agreements
APASTI	ASEAN Plan of Action on Science and Technology
APHECS	ASEAN Public Health Emergency Coordination System
ASEAN	Association of Southeast Asian Nations
BIRAC	Biotechnology Industry Research Assistance Council
CEPI	Coalition for Epidemic Preparedness Innovations
CNBG	China's National Biotechnology Group
COVAX	COVID-19 Vaccines Global Access
CRADLE	Collaborative Research and Development to Leverage Philippine Economy
CRO	Contract research organization
DELTAS Africa	Developing Excellence in Leadership, Training, and Science in Africa
EDCTP	European & Developing Countries Clinical Trials Partnership
GHIT Fund	Global Health Innovative Technology Fund
GLOPID-R	Global Research Collaboration for Infectious Disease Preparedness
GPO	Government Pharmaceutical Organization [Thailand]
GSK	GlaxoSmithKline

IVI	International Vaccine Institute
MNPF	multinational pharmaceutical firm
MSD	Merck Sharp
NAFOSTED	National Foundation for Science and Technology Development
NNSF-China	National Natural Science Foundation of China
ODA	Official Development Assistance
PCOST	Permanent Committee on Science and Technology
PDP	Product development partnership
R&D	Research and development
SAARC	South Asian Association for Regional Cooperation
SARS	Severe Acute Respiratory Syndrome
SDG	Sustainable Development Goal
SEAMO	Southeast Asian Ministers of Education Organization
SII	Serum Institute of India
SKBP	Shenzhen Kangtai Biological Products
SSTC	South-South triangular cooperation
ST&I	Science, Technology and Innovation
UNDP	United Nations Development Programme

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—caused by viruses, bacteria, and parasites, due to the lack of effective vaccines and/or treatments.[2] Infectious diseases not only cause disability and cost lives, but also affect livelihoods, hamper the development process, and affect global security. In 2019, several countries in Asia-Pacific were among those with the highest "burden of disease" from infectious diseases (GBD-CN, 2020; GBDI-2019C, 2020; GBD Website).[3] Although there are no figures on the overall "cost of illness" from infectious diseases in Asia-Pacific (Shah et al., 2020), eliminating malaria alone would save more than 400,000 lives and generate economic benefits of almost US$ 90 billion (Shretta et al., 2019).[4] In this context, vaccine development has become a key component of any multi-pronged 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 and have contributed to reducing mortality and morbidity from infectious diseases and have generated significant cost savings for health systems.

The 65th World Health Assembly held in May 2012 endorsed the *Global Vaccine Action Plan* for 2011-2020, which was declared the Decade of Vaccines with the goal of a world in which all individuals and communities enjoy lives free from preventable diseases through vaccines (WHO, 2013). The Plan has five goals and six strategic objectives. Goal number 5 is to develop and introduce new vaccines and technologies and Strategic Objective number 6 is to promote national, regional and global research and development (R&D) innovations that maximize the benefits of immunization. The Plan aims to make progress toward effective vaccines for HIV, tuberculosis, malaria, and influenza through R&D.

But first, what is R&D? As Keusch and Lurie (2020) pointed out, there are different perspectives on who and what is included in the R&D ecosystem. In its broadest sense, R&D comprises the set of activities, actors, and institutions (public, private, third sector, etc.) that, in a more or less linear progression manner, start from the upstream research (fundamental discovery research in microbiology and immunology), advances through preclinical research and concludes with the clinical research. For some authors, R&D also includes regulatory approval and manufacturing. For others, R&D expands all the way to global access to the newly developed drugs, vaccines and diagnostic kits as well

[2] As detailed below, most existing vaccines are used to prevent diseases (prophylactic or preventive vaccines), but some vaccines are used to treat diseases (therapeutic vaccines). Also, although most vaccines have been developed to prevent infectious diseases, some vaccines target cancer and chronic diseases. This report focuses primarily on the R&D of preventive vaccines for infectious diseases vaccines and, therefore, refers to biological or synthetic products designed to generate an immune response in the recipient to prevent an infection.

[3] The "burden of disease" quantifies the impact of living with illness and injury and dying prematurely and is often expressed as "disability-adjusted life years" (DALY) which measures the years of healthy life lost from death and illness.

[4] The "cost of illness" measures the medical and other costs that result from a specific disease or condition.

as the global financing mechanisms to ensure access for those who cannot afford them. Keusch and Lurie (2020) argue that the R&D ecosystem can also be envisioned 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." These different conceptualizations have implications for how to identify R&D challenges (organization and coordination versus scientific) and how to address them. In this research paper, we will use the traditional linear model of vaccine R&D from discovery science to clinical research. Subsequent stages (regulatory approval, global access, etc.) are explored in other papers of the Project.

The importance of R&D in biomedical and healthcare innovation has been always widely recognized, but this realization has been heightened by the COVID-19 pandemic, which has highlighted the strengths and weaknesses of national, regional, and global drug and vaccine R&D systems. The development cycle of a preventive vaccine in humans is between 5 and 12 years; therefore, when the genetic sequence of the SARS-Cov-2 virus that causes COVID-19 was published in February 2020, the prospects of having a single effective vaccine within less than 5 years were slim. However, the global scientific community, governments, pharmaceutical companies, international organizations, regulatory agencies, and many other stakeholders have worked together in an unprecedented way and several vaccines received emergency use authorization in less than a year. Although significant challenges remain with respect to the scaling up of vaccine production and its equitable distribution, the R&D response to COVID-19 represents a milestone in vaccine development that demonstrates that efficient and safe vaccines can be developed in a relatively short time. The COVID-19 pandemic has emphasized the need not only for sufficient economic and scientific resources but also for policy-driven R&D ecosystems that can translate public and private R&D efforts into effective countermeasures (vaccines, therapeutic drugs, diagnostic tools) to health emergencies in a timely manner.

Developing strong vaccine R&D preparedness and response will also be essential to achieving Sustainable Development Goal 3 (SDG 3) (Ensure healthy lives and promote well-being for all at all ages) and other SDGs that depend on healthy people and populations. Specifically with regard to SDG targets 3.3 and 9.5, the resolution adopted by the UN General Assembly on Work of the Statistical Commission pertaining to the 2030 Agenda for Sustainable Development (A/RES/71/313) includes several indicators that highlight the importance of ending communicable diseases and enhancing R&D through investment and capacity building (Table 1).

Table 1: Vaccines and the SDGs		
SDGs	**Targets**	**Indicators**
Goal 3. Ensure healthy lives and promote well-being for all at all ages	3.3: By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases	3.3.1 Number of new HIV infections per 1,000 uninfected population, by sex, age and key populations 3.3.2 Tuberculosis incidence per 1,000 population 3.3.3 Malaria incidence per 1,000 population 3.3.4 Hepatitis B incidence per 100,000 population 3.3.5 Number of people requiring interventions against neglected tropical diseases
Goal 9. Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation	9.5: Enhance scientific research, upgrade the technological capabilities of industrial sectors in all countries, in particular developing countries, including, by 2030, encouraging innovation and substantially increasing the number of research and development workers per 1 million people and public and private research and development spending	9.5.1 Research and development expenditure as a proportion of GDP 9.5.2 Researchers (in full-time equivalent) per million inhabitants
Source: UN-DESA (2018)		

Vaccine R&D, manufacturing and sales are all highly concentrated. In 2019, just four multinational pharmaceutical firms (MNPFs) based in the United States of America and Europe (GSK, MSD, Pfizer, and Sanofi) accounted for 90% of the value of the global vaccine market, in monetary terms (global sales in US$) (WHO, 2021). The vaccine market is also highly concentrated in terms of volume with 44% of all vaccine doses being manufactured in India. This discrepancy in global sales in monetary terms and in the number of doses is explained by the fact that, as indicated below, most of the vaccines sold by multinationals are still protected by patents and have a high value per dose, while most vaccines manufactured by Indian firs are off-patent and have a low cost per dose. Vaccine development is becoming more complex and most of the R&D on new vaccines is conducted in developed economies (Douglas and Samant, 2018); for instance, the vaccines for COVID-19 using the newest technologies were all developed in the United States and Europe. Few developing countries in Asia-Pacific and elsewhere can engage in conducting cutting-edge vaccine R&D. Developing countries not only have limited resources—economic and know-how—to invest in R&D and/or manufacturing for new vaccines but also many of the diseases afflicting developing countries in Asia-Pacific are not deemed as economically or politically priorities for MNPFs. The COVID-19 pandemic has reignited the debate about how to scientifically stimulate and economically incentivize vaccine R&D for many neglected and regionally endemic infectious diseases that would benefit from vaccines but that continue to be out of the R&D pipelines of MNPFs.

The concentration of vaccine R&D and manufacturing in Western countries has been compounded by the widespread prevalence of “vaccine nationalism” with vaccine-producing countries restricting the export of vaccines until they have ensured they have

enough doses for several times their size populations. The possibility of similar vaccine shortages in future pandemics and the existence of diseases of regional importance without efficient vaccines represent a call for all stakeholders in Asia-Pacific to improve regional preparedness and response to future health emergencies and prevalent neglected diseases by the strengthening of national and regional vaccine R&D systems and regional cooperation mechanisms.

2. Understanding R&D in vaccines

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 et al., 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 (Ellis et al., 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 allow now to rapidly and relatively inexpensively synthesize a part or the whole genetic code of pathogens. For instance, these technologies have been used to synthesize in a laboratory the most antigenic parts of the genome of SARS-Cov-2 virus (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). Vaccines containing live attenuated/inactivated or killed versions of the pathogen or an inactive version of a toxoid produced by the pathogen were firstly introduced a century ago. Vaccines that contain a subunit of the pathogen (for instance, 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 not only brought most vaccine types to clinical trials and many into the market but it has also spurred the introduction of mRNA vaccines for the first time for use in humans (Iwasaki and Omer, 2020; (R&D Blue Print-WHO, 2021) (Table 2). 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.[5] The manufacturing of classical vaccines is also more prone to batch contamination compared to the manufacturing of therapeutic drugs, but also in relation to viral vector and newer nucleic acid-based vaccines (Douglas and Samant, 2017). The greater biological variability in the yield and performance of vaccines compared to therapeutic drugs also means slower approval by regulatory authorities and, as also detailed below, precludes a "generic vaccines" market such as the existing 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 none) 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 largely a chemical process that does not depend on the growth of the pathogen or the culture or cells, so their production is easier to scale up and can be performed more consistently (Jackson et al., 2020). These distinguishing features of mRNA vaccines explain why they were the first to be developed and approved for COVID-19 (R&D Blue Print-WHO, 2021). mRNA vaccines also have other advantages relative to traditional platforms: first, mRNA vaccines are safe 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 own 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 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. Nevertheless, mRNA vaccine developers are making progress toward new formulations that improve their stability (Crommelin et al., 2021;

[5] For instance, variability in the degree of attenuation, the stability of the pathogen, in the environmental conditions of the culture of the pathogen, etc.

Ramachandran et al., 2022).[6] In any case, mRNA vaccines are opening a new era in vaccinology whose implications in the fight against infectious diseases but also of other diseases and conditions (e.g., cancer) is still unforeseen.

Vaccine developers across the Asia-Pacific region have successfully developed vaccine candidates and commercial vaccines for COVID-19 using most of the existing technologies, including new platforms like viral vector vaccines and several Asia-Pacific companies are now working toward developing and manufacturing mRNA-based vaccines (Table 2, and below in Section 3)

Table 2: Main types of vaccines and vaccine platforms and their availability in Asia-Pacific

Types of vaccines	First used	Advantages	Challenges	Produced by firms in Asia-Pacific during the COVID-19 pandemic
Live attenuated pathogen	1798	Long lasting protection Most do not required an adjuvant	Safety and stability issues	China (CoronaVac, VeroCell BBIBP-CorV/Sinopharm-Beijing, Sinopharm-Wuhan) India (BBV152 (Covaxin) Iran (Islamic Republic of) Shifa Pharmamed vaccine Kazakhstan (QazCovid-in) Russian Federation (CoviVac) Turkey (Turkovac)
Killed pathogen	1896	Most do not required an adjuvant	No need for adjuvant	
Toxoid	1923			
Subunit (protein, peptide, polysaccharide)	1970		Can be tested quickly. Require adjuvant	Australia (Spikogen, CpG 1018) Iran (Islamic Republic) and Australia (CinnaGen) China (ZF2001/RBD- Dimer, West China Hospital vaccine) Russian Federation (EpiVacCorona)
Virus-like protein	1986		Require adjuvant	
Viral vectored	2019	Strong protection Do not required an adjuvant	Pre-existing immunity against vector Still not completely known	China (Ad5-nCoV/Convidecia) Russian Federation (Sputnik V)

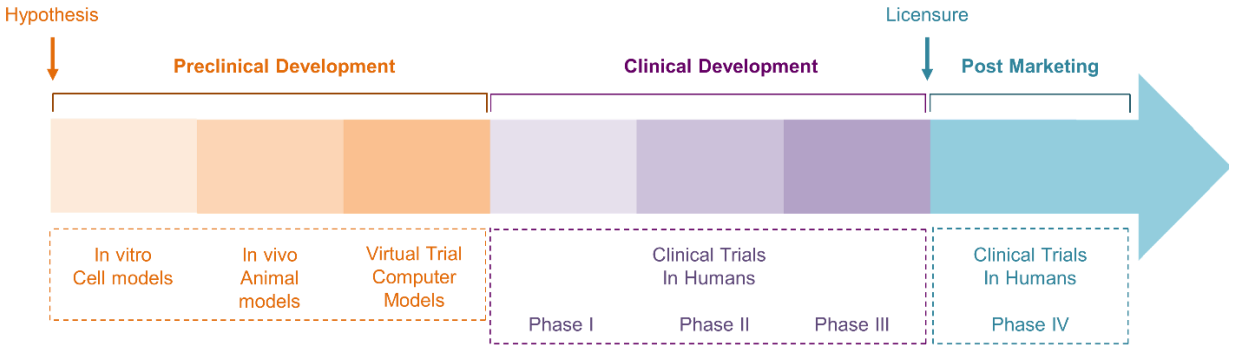
[6] Being a newer platform, mRNA vaccines also raise new issues with respect to IPR protection, which is addressed in detail in a companion paper in the From the Lab to Jab Project. The WHO, the Medicines Patent Pool initiative, and several African international partners have established an mRNA Vaccine Technology Transfer Center for the production of mRNA vaccines for Africa and the WHO plans to establish similar centers in other regions (Medicines Patent Pool, 2021).

		Replicable Manufacturing		
Nuclei Acid (DNA, RNA)	2020	Strong protection Do not required an adjuvant Replicable Manufacturing	Still not completely known	Several Asia-Pacific firms are currently working toward mRNA vaccines for COVID-19
Antigen presenting cells (dendritic cells) T cells		Approved by USA FDA for therapeutic used in cancer		
Bacterial vectored		Lasting protection Stability	Not yet approved for use in humans	
Source: Iwasaki and Omer (2020), Pollard and Bijker (2021)				

2.2 Stages of vaccine R&D

Although the vaccines for Ebola took around 5 years and several of the vaccines for COVID-19 were developed in less than a year, the development of most vaccines takes 10 to 15 years. Vaccine development comprises several stages, most of them overlapping with the stages involved in developing therapeutic drugs (Leroux-Roels et al., 2011; Douglas and Samant, 2017; Arnaud et al., 2019).

Figure 1: Stages of vaccine R&D



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 (immunogenicity: production of antibodies and/or a cellular response against the antigen) in the individual receiving the vaccine. Recent technological advances (e.g., compound library screening, bioinformatics, spectrometry, crystallography, artificial intelligence, etc.) permit the prediction of which regions in the pathogen interact with human antibodies for structure-based vaccine design.

The second stage is the pre-clinical stage (1-2 years) where laboratory animals are subjected to an early version of the vaccine to assess in vivo both its safety and immunogenicity potential.

The third stage is the clinical trials stage, during which vaccine candidates are administered to humans to test that it is safe and provides effective protection in different human populations (e.g., different cohorts by age, sex, ethnic group, etc.). Clinical trials are lengthy (8-10 years), costly, and subject to strict regulatory and ethical standards set by the corresponding regulatory authorities that 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 its 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 candidate is assessed for triggering an immune response and preventing infection in the context of an outbreak. In contrast to drugs, vaccines that pass Phase II-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, it is only after licensure that vaccine manufacturers scale up production. 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 (e.g., 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 that 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. Hereafter, and unless otherwise noted, throughout this report, 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, 2017). Assay development refers to the definition of benchmarks regarding the purity of vaccine components, stability, consistency of

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

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) has been proposed as possible alternatives or complements to Phase III trials for some vaccines (Plotkin, 2010). Nevertheless, the adoption of these correlates requires approval by the corresponding regulatory authorities.

2.3 Main stakeholders 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, namely: a) Discovery research. It is typically carried out in basic research laboratories at universities, research institutes, and, increasingly, in small start-up biotech companies; b) Preclinical research. Automation in sequencing and small-molecule synthesis have 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; c) Clinical trials and pharmacovigilance. Pharmaceutical firms are responsible for carrying out phases I to IV of clinical trials through agreements with clinics, hospitals, or, increasingly, outsourced to contract research organizations (CROs) (see below).

In many countries, particularly high-income economies, government agencies are the major source of direct funding of discovery and preclinical research for drug and vaccine development (Viergever et al., 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 (ODA), or via partnerships with philanthropic foundations and international organizations. For instance, as detailed below, product development partnerships (PDP)—non-profit 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 due to the consolidation among the largest MNPFs through mergers and consolidations, the proliferation of biotechnology companies and CROs, and the increased participation of pharmaceutical firms in developing countries. During the last 15 years before the COVID-19 pandemic, the number of new vaccines developed by MNPFs remained stagnant, while those developed by small biotech firms and emerging-market pharmaceutical firms doubled and experienced a 13-fold increase, respectively (Aars et al., 2021). MNPFs are often feeding their pipelines through licensing and/or acquisitions of smaller biotechnology firms.

Most of the MNPFs that conduct R&D for vaccines also do so for therapeutic drugs. MNPF's vaccine R&D focuses primarily on chemical engineering, clinical R&D, and process development. 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 biotechnology companies involved in vaccine R&D began as start-ups established by academic scientists with funding from venture capitalists often matched by government programs, the vast majority of them in developed countries. As most of these small biotech firms have limited expertise in process and clinical development and manufacturing, they often partner and/or license their vaccines and/or technology platforms to MNPFs (Samant and Douglas, 2018). In fact, some of the recent advances in vaccinology have been introduced by small biotech firms. For example, technological innovations in vaccines for hepatitis B and H. influenzae type b viruses were developed by small biotech companies that later became associated or acquired by larger NMFs (Samant and Douglas, 2018). In 2018, BioNTech AG, a biotechnology company specializing in mRNA technologies, partnered with Pfizer to jointly 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, DCVMN companies 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 UN agencies (Hayman and Pagliusi, 2020; Hayman et al., 2021, DCVMN website). Despite the fact that 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 et al., 2021). Many DCVMN firms conduct vaccine R&D through partnerships, including product development partnerships (PDP, see below), with philanthropic foundations and larger pharmaceutical companies. During the COVID-19 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 of them require funding and/or technical transfer for the newest mRNA vaccines (Hayman et al., 2021).

The first CROs 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 et al., 2020). Initially, MNPFs only outsourced to CROs their clinical research activities due 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 US$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 inter-governmental organizations also have important functions in vaccine R&D. In May 2015, in the aftermath of the 2014 Ebola virus epidemic, the WHO convened a group of experts to develop the WHO R&D Blueprint for Action to Prevent Epidemics (WHO, 2016; WHO, 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 R&D Blueprint prioritizes diseases with the greatest epidemic potential and/or for which there is no or insufficient diagnostic, preventive and curative solutions exist, and develops a R&D roadmap for each of them (WHO, 2016; WHO, 2017; Mehand et al., 2018; WHO R&D Blueprint website). Diseases for which there are ongoing R&D programs or product pipelines are not included in the priority list. One of the prioritized diseases is the so-called "Disease X " that refers to a serious international epidemic caused by a pathogen currently unknown to cause human disease. The R&D Blueprint aims at developing cross-cutting R&D preparedness that also covers "Disease X ".

The R&D landscape for diseases affecting the developing world has been transformed by the emergence and proliferation of product development partnerships (PDPs). PDPs are non-for-profit legally independent partnership organizations that were introduced in the late 1990s as a form of private-public partnership (PPP) 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 (see below in section 2.4) (Widus, 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 (Table 3). For instance, one of the first PDPs was established to develop a meningococcal A conjugate vaccine by the Serum Institute of India with funding from the Bill and Melinda Gates Foundation and technical assistance from the Program for Appropriate Technology in Health (PATH). PDPs use management practices in their R&D activities and coordinate

[8] PDPs are one of the three types of health PPPs, namely: a) access PPPs that aim to expand access to existing products but for which there is limited demand or ability to pay; b) systems-based PPPs, whose goal is to improve the capacity of health systems; and c) PDPs (Taylor and Smith, 2020).

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, advocacy tasks and some have manufacturing capacities. To minimize risks in vaccine R&D, PDPs use a portfolio approach and simultaneously develop multiple vaccine candidates for a single disease. PDPs focus on one or several diseases but some do not aim at any particular disease but rather to 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 essays, etc (Aars et al., 2021).

Table 3: Non-profit intermediaries funding vaccine R&D

PDP Intermediaries	Main target disease(s)	Website
Drugs for Neglected Diseases Initiative (DNDi)	Malaria, Kinetoplastids	https://dndi.org/
European Malaria Vaccine Initiative	Malaria	https://www.euvaccine.eu/
Foundation for Innovative New Diagnostics (FIND)	Tuberculosis, malaria, sleeping sickness	https://www.finddx.org/
International AIDS Vaccine Initiative (IAVI)	HIV/AIDS (also TB and other)	https://www.iavi.org/
Infectious Disease Research Institute (IDRI)	HIV/AIDS, Tuberculosis, leishmaniasis, leprosy	http://www.idri.org/
International Partnership for Microbicides (IPM)	HIV/AIDS	https://www.ipmglobal.org/
International Vaccine Institute (IVI)	Diarrhoeal diseases, dengue, bacterial pneumonia and meningitis, typhoid, paratyphoid fever	https://www.ivi.int/
Malaria Vaccine Initiative (MVI)	Malaria	https://www.malariavaccine.org/
Dengue Vaccine Initiative (DVI)	Dengue	http://www.denguevaccine.org/
One World Health (OWH)	Kinetoplastids: Drugs Diarrhoeal diseases: Drugs Malaria: Drugs Core funding	http://www.oneworldhealth.org/
Sabin Vaccine Institute	Helminth diseases (Hookworm and Schistosomiasis)	https://www.sabin.org/
TB Alliance	Tuberculosis	https://www.tballiance.org/
International Partnership for Microbicides		https://www.ipmglobal.org/
Program for Appropriate Technology in Health (PATH)	H HIV/AIDS, malaria, rotavirus and other Diarrhoeal diseases, Streptococcus pneumoniae, Influenza	https://www.path.org/
Pediatric Dengue Vaccine Initiative	Dengue	
Meningitis Vaccine	Meningitis	
Non-PDP Intermediaries	**Main Target disease(s)**	**Website**
Coalition for Epidemic Preparedness Innovations (CEPI)	WHO R&D Blueprint priority diseases	https://cepi.net

European and Developing Countries Clinical Trials Partnership (EDCTP)	Tuberculosis	https://www.edctp.org/
ISGlobal Barcelona	Chagas, Malaria	https://www.isglobal.org/en/
Global Health Innovative Technology (GHIT) Fund	Malaria, tuberculosis, Chagas, Leishmaniasis, Dengue, Schistosomiasis	https://www.ghitfund.org/
German Center for Infection Research (DZIF)	Gastrointestinal Infections, Tuberculosis, Hepatitis, HIV, Malaria, Emerging Infections	https://www.dzif.de/en
Clinton Health Access Initiative, Inc. (CHAI)	Tuberculosis, Hepatitis, HIV, Malaria,	https://www.clintonhealthaccess.org
African Academy of Sciences (AAS)	COVID-19, emerging and re-emerging infectious threats	https://www.aasciences.africa/
RIGHT Fund	Cholera, Hepatitis A, Tuberculosis, COVID-19, polio	https://rightfund.org
Aaron Diamond AIDS Research Center (ADARC)	HIV/AIDS, COVID-19	https://www.adarc.cuimc.columbia.edu
The Union	Tuberculosis, COVID-19	https://theunion.org/
Sources: Huzair et al (2011), Moran et al (2010). PDP and non-PDP intermediaries websites		

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 but that, in contrast to PDPs, rely on external partners for R&D (Table 3). 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 re-emerging infectious diseases. Its goal is to facilitate an effective R&D response within 48 hours of a significant outbreak. GOLPID-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 (GOLPID-R website). The WHO, CEPI and the *European & Developing Countries Clinical Trials Partnership* (EDCTP) and ESSENCE on Health Research Initiative (WHO/TDR, Special Programme for Research and Training in Tropical Diseases) are observers in GOLPID-R).

2.4 Vaccine R&D preparedness and response

The lack of effective vaccines and therapeutic drugs during the 2014-2015 West African Ebola epidemic acted as a catalyst in the effort to develop and improve global R&D readiness for future health threats. The Ebola outbreak prompted the launch of initiatives such as the WHO R&D Blueprint, CEPI and the Global Preparedness Monitoring Board and a great deal of progress had been made in epidemic preparedness since then. WHO R&D Blueprint has identified future pandemic threats and CEPI has been channeling funding to develop countermeasures against those threats. CEPI also funds R&D

preparedness through the development of platform technologies that can be used against different pathogens and allow rapid vaccine development against unknown pathogens like Disease X in the WHO R&D Blueprint. Among its strategic objectives for 2019-2022, CEPI aims to build R&D preparedness for future epidemics and pandemics by advancing three vaccine candidates for three WHO R&D priority diseases through the end of Phase II so they can be ready to progress to Phase III when an outbreak strikes (CEPI, 2021). CEPI also seeks to strengthen R&D response to future outbreaks and plans for having at least two vaccine platform technologies that can be rapidly adapted to develop vaccines against Disease X pathogens by 2022.

The COVID-19 pandemic has revealed that most countries, including high-income economies, were unprepared to fight it on their own. Before the COVID-19 pandemic, the Global Preparedness Monitoring Board, a group convened by the WHO and the World Bank concluded in its 2019 Annual Report that most countries were underprepared for a pandemic, including for a respiratory pathogen as it eventually materialize in the COVID-19 pandemic (GPMB, 2019). At the time of the COVID-19 outbreak, there were major research gaps in the biology of the virus and no vaccines, antiviral drugs, or rapid point of care diagnostic tests for COVID-19 were available. As the COVID-19 pandemic has also made evident, the cost of preparedness for health emergencies is cost-effective compared to the human loss and economic costs of dealing with a pandemic once it strikes (Amaya et al., 2021b). On 11-12 February 2020, just four weeks after the sequence of SARS-Cov2 was first released and a month before the WHO declared the COVID-19 pandemic, WHO and GLOPID-R organized a Global Research Forum on research and innovation for COVID-19 that convened 450 experts and funders from 48 countries to identify research gaps, develop a prioritized research agenda, and accelerate the discovery and production of diagnostics, vaccines, and therapeutics for SARS-Cov2 (WHO Blueprint 2020).

Developing effective vaccines and therapeutic drugs for emerging infectious diseases within a reasonable time countries need to develop and sustain R&D preparedness. R&D preparedness requires the existence of adequate basic research infrastructure and funding before an outbreak to then support a rapid and effective translational R&D response to develop vaccines and drugs once an outbreak emerges. R&D preparedness involves sustained commitment over time for basic and discovery research and investment on R&D beyond immediate emergencies and specific pathogens. Despite SARS-Cov2 being a new virus, the rapid R&D response in the COVID-19 pandemic was only possible because traditional and innovative vaccine platforms were already set up and ready to be used. Even countries with strong R&D preparedness will have to mobilize new resources to respond to a major health outbreak. Weaker health R&D and healthcare systems in most low-income countries not only reduce their capacity to build preparedness for epidemics but these countries also face greater challenges to mobilize financial resources to mount a rapid and adequate R&D response to health emergencies.

2.5 The economics of vaccine R&D

Vaccine production is capital intensive and represents a barrier to new entrants and competition. A study by the WHO calculated that setting up a plant to produce monovalent vaccines in a high-income country stands at between US$ 50-500 million and raises to US$ 700 million for polyvalent vaccines (Lobo, 2021). Projecting costs and profits in vaccine R&D and manufacturing are also more difficult to assess than in other industrial sectors (Aars et al., 2021). The cost of progressing a vaccine through the end of Phase II of clinical trials has been estimated at US$ 112-469 million (Gouglas et al., 2018). R&D costs for newer technology vaccines are higher at all stages as developers must recover discovery/preclinical research investments, 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). 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 stands at 6% (Pronke et al., 2013).[9]

As noted above, 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 of America and the European Union (Samant and Douglas, 2018). Historically, MNPFs have shown more interest in developing new therapeutic drugs than on new vaccines. In 2019, global vaccine sales amounted to US$ 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—thanks to the introduction of new vaccines with high volumes and margins (e.g., Hepatitis B, multivalent DTP, pneumococcal, HPV and zoster) and many low-income countries gaining access to vaccines funded through ODA, philanthropic foundations, and international organizations (Evaluate 2013; Evaluate, 2020; Samant and Douglas, 2018). The COVID-19 pandemic has obviously increased these figures; some market studies estimated that in 2021, only the COVID-19 vaccine market in the United States, Japan and the five largest European economies amounts to US$ 13.1 billion and that in 2024 may reach US$ 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

[9] Technological advances in biomedicine and related fields have the potential of reducing the cost and time of developing new vaccines.

therapeutic drugs (or other vaccines) with higher prospects of success rate and/or returns to investment. As noted above, compared to therapeutic drugs, developing a new vaccine involves stricter safety requirements increasing 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, as of January 2022, there were 329 vaccine candidates for COVID-19, of which 111 are in clinical trials (Vaccine Tracker-LSHTM website; Shrotri et al., 2021). Most of these vaccine candidates will never reach the market and 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 and the willingness and ability to pay, which are reduced in socioeconomically vulnerable populations in developing countries. However, unlike therapeutic drugs, particularly those treating chronic conditions, preventive vaccines are administered only once or a few times during life. Evidence also indicates that individuals—and often government health programs—are more willing to pay for treatment than for prevention (Kremer 20005). 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 economies apply to emerging infectious diseases; whose outbreaks not only tend to start in low-income countries but that 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).

Nevertheless, and although most analyses conclude that the economic incentives to develop new vaccines are low, these should be conducted on a case-by-case basis and there are also arguments pointing for 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 WHO (WHO, 2021)[10]—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 making the vaccine market not amenable for the production of generics. Consequently the holders of vaccine intellectual property rights enjoy monopoly rents for a longer period than for therapeutic drugs. Third, vaccines that have been on the market for a long time have low marginal costs per dose and high cost-effectiveness ratios. Empirical evidence in some countries (e.g. Brazil) indicates that

[10] New pharmaceutical firms in India, China, and Brazil have increased the sources for vaccines for developing countries, these firms focus on traditional vaccines (WHO, 2021). This concentration is the result of the business structure of the vaccine market with high fixed costs, price-sensitive demand and dynamic quality competition (Dazon and Sousa Pereira, 2011).

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, evidence shows that 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 in 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 above factors reduce the profitability of many vaccines (particularly those for diseases afflicting low-income countries), the incentive for MNPFs to invest in R&D for them, and ultimately the overall supply of vaccines that can fall below the socially optimal amount, thus creating a market failure.

In the context of pandemics, accelerating stages and conducting R&D and scale up manufacturing for multiple vaccine candidates simultaneously have a social value that exceeds the commercial value of the vaccine and does not necessarily accrue to the pharmaceutical firm. Consequently, 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 research and development must consider the impacts of immunization beyond its health benefits. It has been estimated that when the broader societal impacts of immunization (e.g., long-term disability burden, economic productivity, education) are considered, the net return to vaccination programs ranges from US$16 to US$44 for every US$ spent in free vaccination programs (Bärnighausen et al., 2014; Ozawa et al., 2016). 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 is 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 committing to purchase doses after regulatory approval (demand side or pull strategies).

Multiple supply/push side approaches have been used to address potential failures in the vaccine market. The most common strategy is funding vaccine R&D through public and/or philanthropic sources. PDPs and other non-PDP intermediaries have proliferated as an innovative mechanism to fund vaccine R&D. In 2018, funding of R&D for emerging infectious disease reached US$ 886 million, 65.2% for vaccine development and 95.7%

directly from the funders to vaccine and drug developers (PCR, 2021a). In contrast, 23% of the US$ 3.9 billion global investments in R&D for neglected diseases was channeled through PDP and non-PDP intermediaries (PCR, 2021b). As it occurs in other global common goods, individual countries have the incentive to free-ride in 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 (Rassenfosse et al., 2020). Another supply side measure to incentivize investments in vaccine R&D by pharmaceutical firms is the strengthening of property right protection; however, this can result in higher prices and generate equity problems with lower access for low-income countries. The streamlining of regulatory systems or the use of correlates of protection to reduce the need for large Phase III clinical trials can reduce the time and cost of vaccine R&D for pharmaceutical firms but any relaxation of the regulatory framework 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 below in Section 3.4), and technology transfer from multinationals to indigenous start-ups and small/medium private firms.

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. Thus, demand/pull side approaches that increase the final demand for vaccines incentivize firms to invest in R&D. One way to address market failures in the vaccine market and de-risk and incentivize R&D investment by pharmaceutical firms, and, in some cases, directly fund it is through the use of advanced market commitments (AMCs) and advanced purchase agreements (APAs). 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 comes 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 making possible vaccine R&D at a faster rate and securing doses at a predictable price. APAs do not only de-risk R&D investment, but they can also fund building up capacity for manufacturing scale-up and they can also directly finance R&D. The terms of reference of APAs vary widely from contract to contract and are usually confidential. Increased production capacity remains a permanent benefit for the firm and, when the APA covers late-stage (e.g., clinical trials) R&D costs these do not have to be refunded if the 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 timeline of the delivery. AMCs were first used in 2009 by GAVI The Vaccine Alliance, UNICEF and the World Bank that pledged US$1.5 billion to incentivize the development and supply of pneumococcal vaccines in poorer countries. Since then, APAs have been

used to accelerate and supply vaccines for pandemic influenza and Ebola (Turner, 2016). APAs are part of the pandemic influenza preparedness and contracts are maintained by states paying an annual 'Pandemic Preparedness Fee' to the manufacturer whose costs are not publicly available (Turner, 2016). APAs have become even more popular during the COVID-19 pandemic with many high-income and high-middle income countries signing APAs with vaccine developers to procure COVID-19 vaccines (Pharmaceutical Technology, 2021).

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) have modeled how many vaccine candidates should be supported and how much capacity should be procured in advance. They concluded 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 candidates and platforms and provide push payment for only part of the total cost—in order to ensure that firms have a stake in the risk and success of vaccine development—and pull incentives structured to incentivize speed. However, governments and PDP and non-PDP intermediaries, as the main purchasers of vaccines, can use their bargaining power and often government's regulatory prerogative to keep prices down and close to their marginal cost of manufacturing and distribution that do not cover the cost of vaccine R&D, thus discouraging pharmaceutical firms to invest in R&D in the first place (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, APAs can have an impact on equity in access to vaccines in developing countries. This highlights the need for international organizations and initiatives (e.g., CEPI, COVAX, GAVI-The Vaccine Alliance, etc.) to engage in APAs to serve low-income countries. Although it was not an APA, because of its novelty as supply side mechanism, it is worth mentioning the R&D funding contract between the United States Health and Human Services department and Moderna that provided financial support for the development of the latter's vaccine without any commitment to purchase (Boulet et al., 2021).

Other demand/pull strategies include regulations and policies that increase vaccine uptake, like information campaigns, free vaccination programs (funded by local governments, philanthropic organizations, international organizations, ODA), and/or mandatory vaccinations. In most countries, vaccines included in recommended or mandatory national immunization programs, and those required during epidemics and pandemics are administered free of charge by the government. In some cases, governments offer incentives for people to get vaccinated; in other cases, regulations require vaccinations for attending to school or going to the workplace. There is still an open debate on whether or not mandatory vaccination increases vaccine uptake. The impact of demand-side strategies depends on the type of vaccines. For developing

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

countries that can produce vaccines locally and for vaccines in national immunization programs, demand-side approaches can help local pharmaceutical firms to invest in vaccine R&D and manufacturing. However, in the case of vaccines for neglected diseases and in countries without vaccine manufacturing capacity that depend on imported vaccines, these approaches may have more limited effects on the incentives of MNPFs.

3. Vaccine R&D in Asia-Pacific

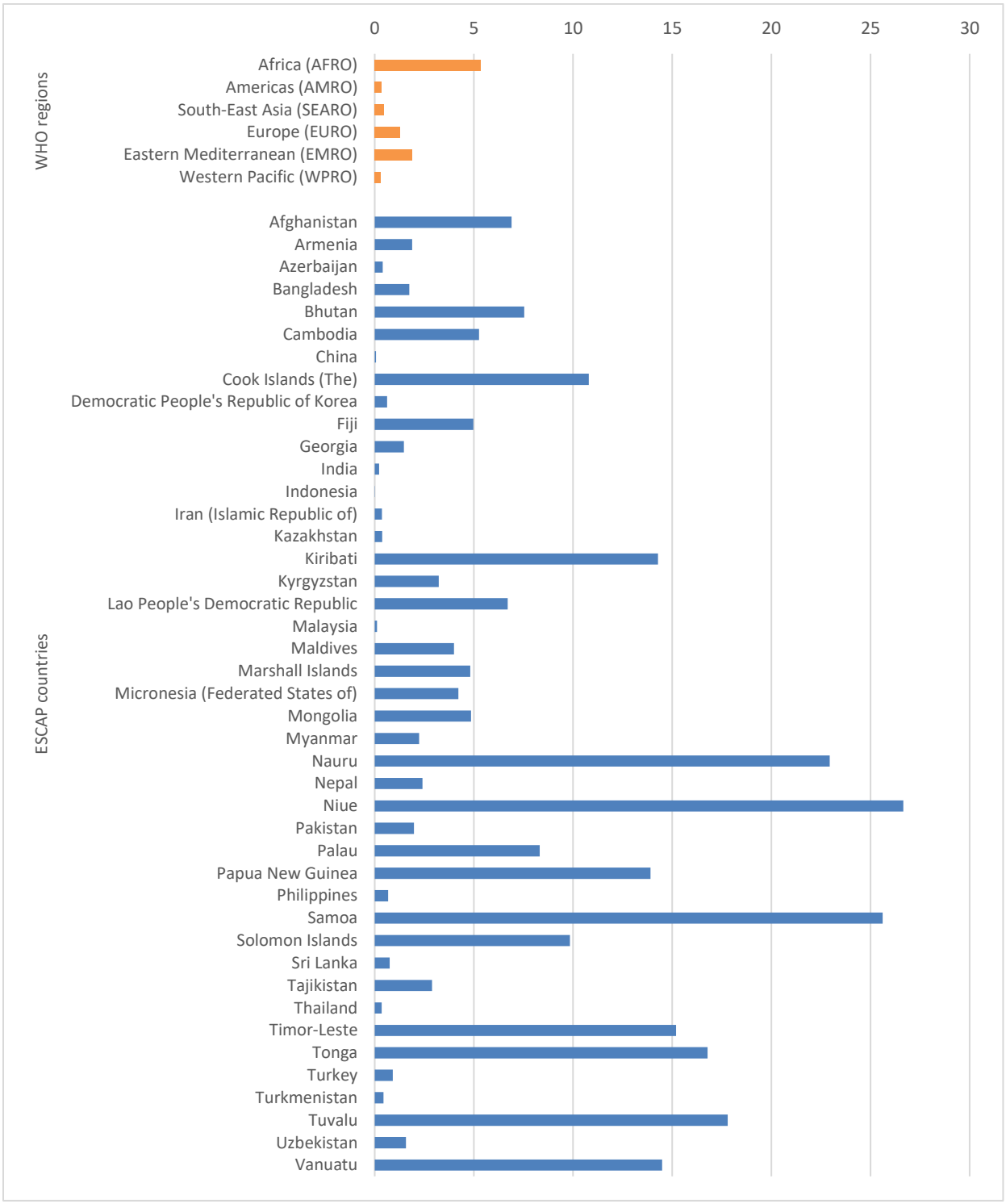
3.1 Main indicators in the biomedical and vaccine R&D in Asia-Pacific.

Current status of SDG targets and indicators related to health and biomedical R&D

As noted in Table 1, several SDG targets and indicators are related to R&D in health. A total of 44 countries in the UN-ESCAP region are recipients of official development assistance (ODA) for medical research and basic health sectors (SDG indicator 3.b.2) (Figure 2) (WHO website); in fact, of all WHO regions, the WHO Western Pacific region has the highest per capita average for indicator 3.b.2.

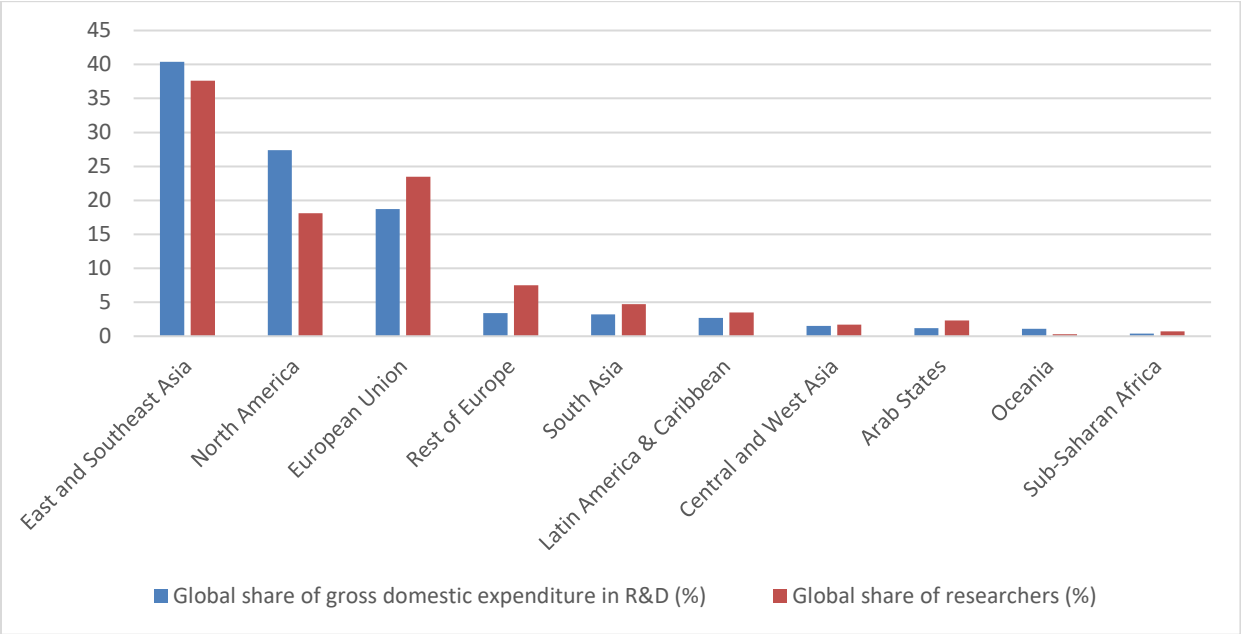
At the same time, Asia-Pacific accounts for the largest share of global R&D spending; just the East and Southeast Asia UNESCO region—led by China, Japan, and the Republic of Korea—represents 40.4% of global R&D expenditures, followed by North America (27%) and the European Union (19%) (Figure 3) (UNESCO, 2021; UIS website). Four countries/provinces in Asia-Pacific are among the world's top 15 territories with the highest R&D spending as a percentage of GDP (SDG indicator 9.5.1)—namely, Republic of Korea (4.5%), Taiwan-Province of China (3.3%), Japan (3.2%), and China (2.14%)—and are ahead of the corresponding figure in the UK and the average in Europe (UNESCO, 2021) (Figure 4). Taking into account only the 75 countries in the world for which data is available, during 2015-2019, six countries in Asia-Pacific invested on average more than 15% of their total spending on R&D in the medical and healthcare sectors (Myanmar, Brunei Darussalam, Macao-China, Cambodia, Singapore and Hong Kong-China) (UIS Website; WHO-GOHR&D website). Health R&D as a percentage of GDP in Singapore (0.37%) and the Republic of Korea (0.21%) is higher than in other high-income countries with a strong biomedical sector like the United Kingdom (0.13%) (WHO's Global Observatory on Health R&D).

Figure 2: SDG indicator 3.b.2: Total net ODA to the medical research and basic health sectors per capita (US$), by recipient country (where available) in 2019 (or latest year available



Source: WHO's Global Health Observatory website

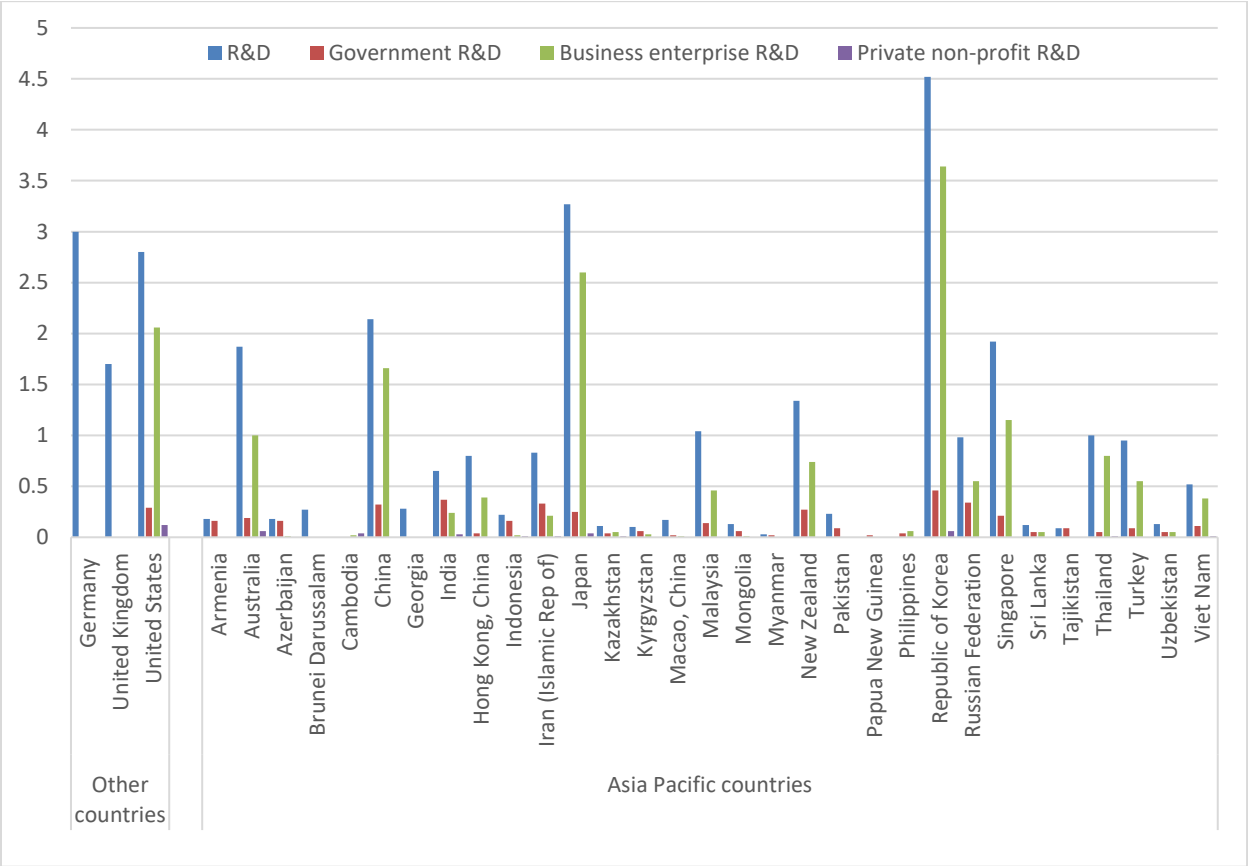
Figure 3: Global shares of gross domestic expenditure in R&D (%) and researchers (%) in 2018, by region



Source: UNESCO Science Report 2020

In countries with high total R&D spending, the private sector tends to be a major, often the largest, contributor to R&D expenditures. For instance, in 2018, the business enterprise sector funded 78% of R&D spending in Japan and 76% in the Republic of Korea (Figure 4) (UNESCO, 2021; UN-DESA website; UNESCO Institute of Statistics website). Furthermore, while in the past, basic and preclinical research was funded almost exclusively by governments, this distinct division of labor is fading, with up to one-third of corporate R&D spending in some high-income countries now going to basic science (UNESCO, 2021).

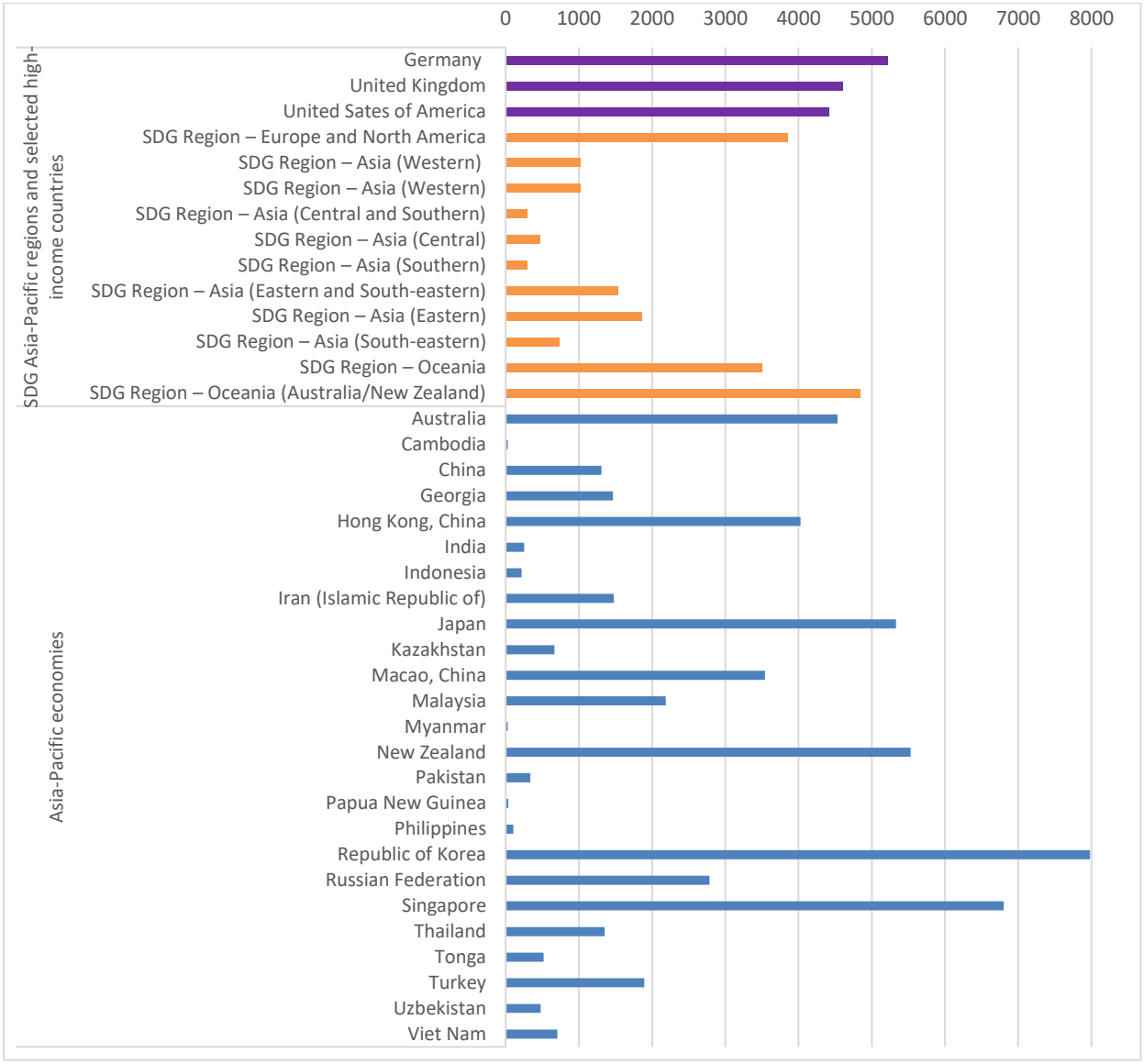
Figure 4: SDG indicator 9.5.1: R&D expenditures in 2018 as a percentage of GDP (by sector) in 2018 (or latest year) in Asia-Pacific countries for which data are available



Source: UNDESA website, UNESCO Institute of Statistics website

With regard to human resources in R&D, the East and Southeast Asia UNESCO region had 37.6% of the world's researchers in 2018 (Figure 5) (UNESCO, 2021; UIS website). China alone accounts for around a third of the increase in the global number of researchers between 2014 and 2018 (UNESCO, 2021). In 2018, the number of researchers per million inhabitants in full-time equivalents (SDG indicator 9.5.2) in Asia-Pacific was the highest in the Republic of Korea, Singapore, Japan, New Zealand, where this indicator was higher than in the United States of America, the United Kingdom, and Germany (Figure 5).

Figure 5: SDG Indicator 9.5.2: Researchers per million inhabitants in full time equivalents in 2018 (or latest year for which data are available)



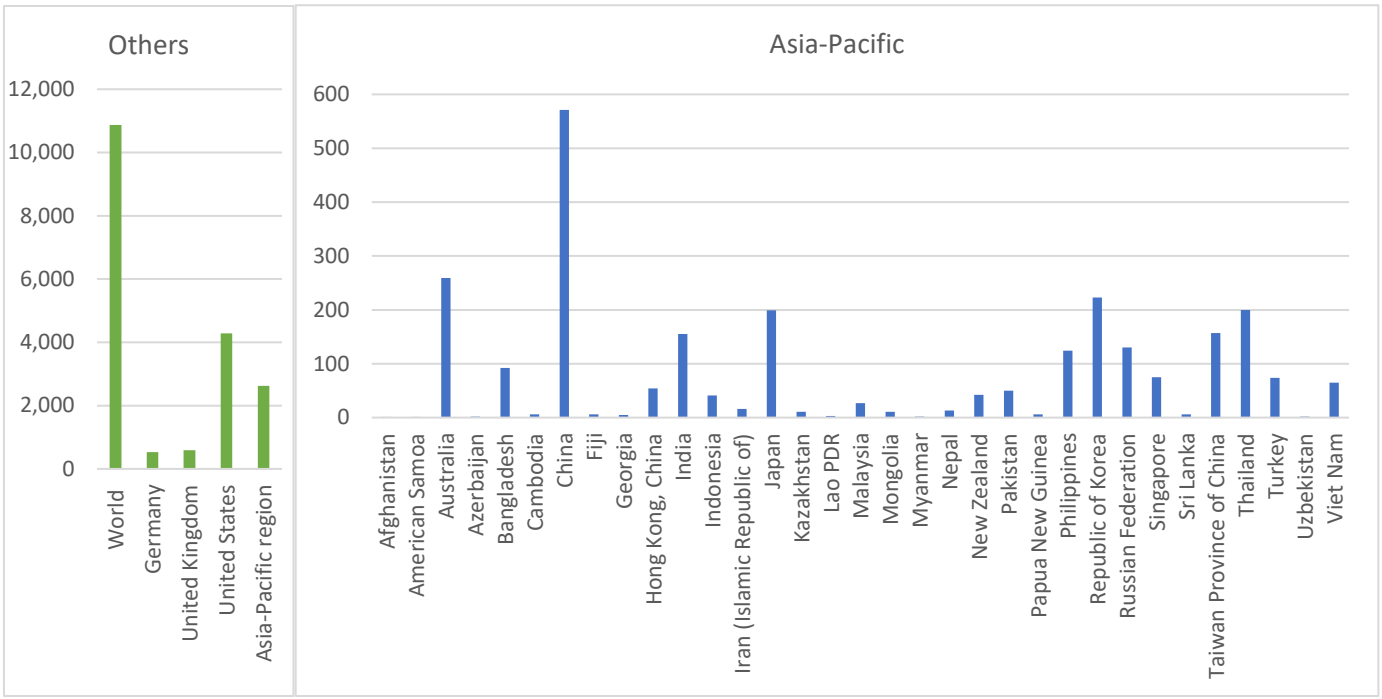
Source: UNESCO Institute of Statistics website, UNESCO SR website, World Bank Open Data website

R&D output indicators: Clinical Trials and Patents on vaccines in Asia-Pacific

As of March 2022, Asia-Pacific had conducted 24.1% of all vaccine clinical trials in the world, led by China (with a fifth of all clinical trials on vaccines conducted in Asia-Pacific and 5.25% in the world), Australia, and the Republic of Korea (Figures 6 and 7). As of March 2022, Asia-Pacific had conducted 24.1% of all vaccine clinical trials in the world, led by China (with a fifth of all vaccine clinical trials conducted in Asia-Pacific and 5.25 % globally), Australia, and the Republic of Korea (Figure 7). It should be noted that many developing countries in the region have participated in clinical trials of vaccines. As the success of typhoid and cholera vaccine clinical trials in Nepal and Viet Nam conducted with the support of the International Vaccine Institute attests, carrying out clinical trials in low-income countries can have many positive side effects (Kim and McCann, 2021; Saluja et al., 2021), namely: 1) it ensures that the safety and efficacy of vaccines have been tested in populations of different ethnic and socioeconomic origins; 2) it

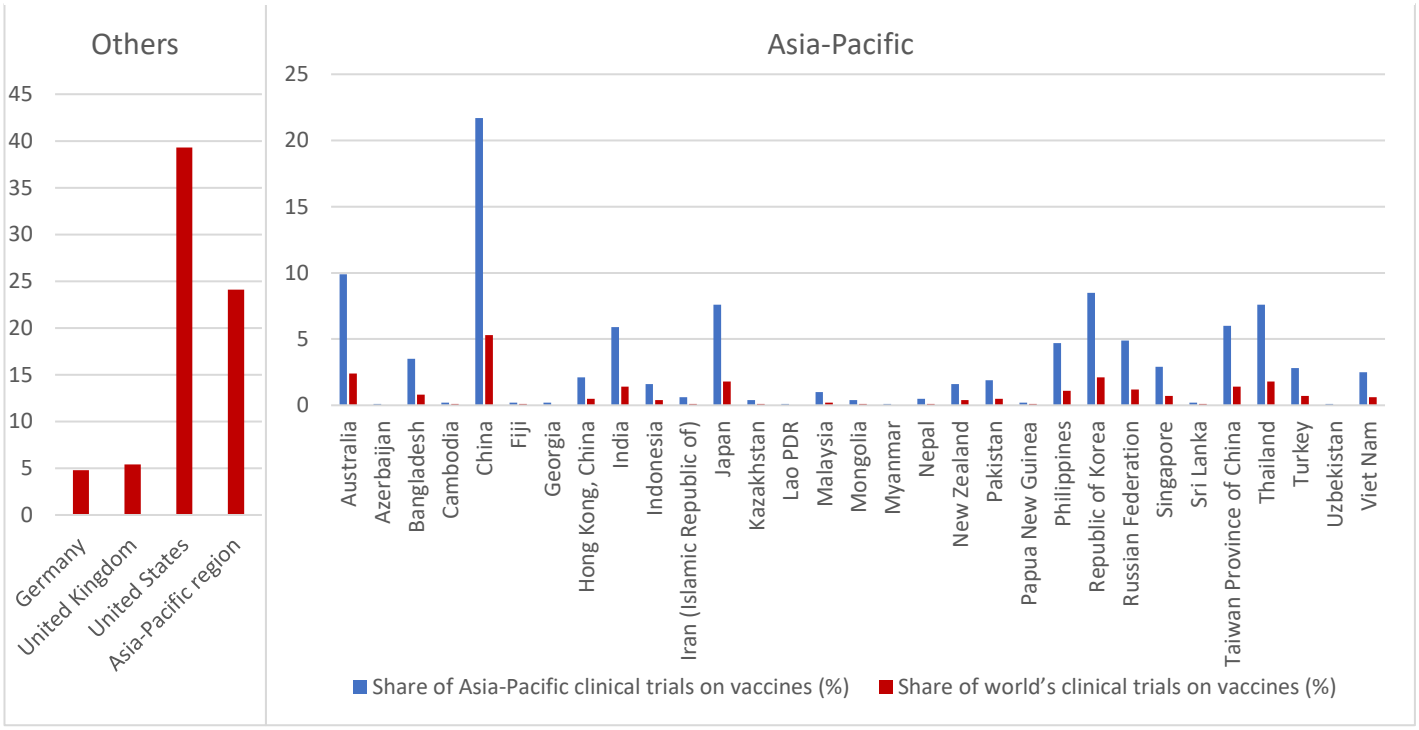
not only strengthen research capacities in low-income countries but it can also improve the quality of medical care, and 3) it helps to base R&D and health policy decision-making on locally generated data.

Figure 6: Number of clinical trials for vaccines, as of March 2022



Source: ClinicalTrials.gov website

Figure 7: Share of world's and Asia-Pacific's clinical trials on vaccines (%), as of March 2022



Source: ClinicalTrials.gov website

One of the pillars for scientific progress and the eventual translation of basic and preclinical research into new drugs, vaccines, and diagnostic tools is the timely dissemination of scientific results through peer-reviewed journals.[12] The COVID-19 pandemic has witnessed an unprecedented increase in scientific production, in both quantity and speed, on all aspects of the disease, from basic research on the virus to data on clinical trials and therapeutic strategies. Notably, a larger share than usual of articles on COVID-19 has been open access through waivers of subscription fees, open access journals, and public repositories of articles before peer review. The free dissemination of scientific data during the pandemic has been instrumental for improvements in clinical management approaches. As of March 2022, scientists in Asia-Pacific countries have contributed to a fifth of all scientific publications on vaccine research at all stages—with China, Japan, and India as the largest contributors—on par with the share of publications by scientists in the United States (Figures 8 and 9; PubMed Database).

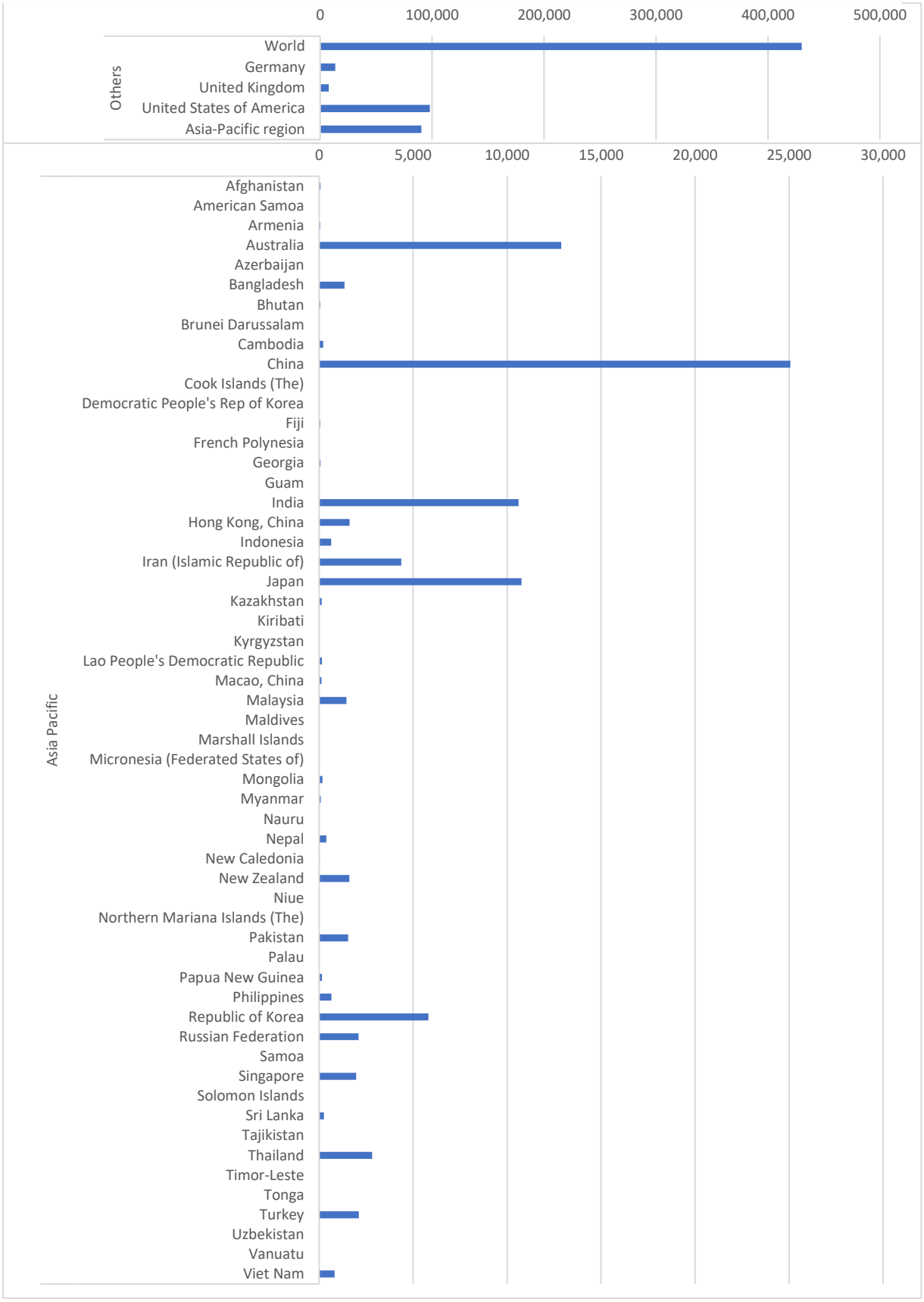
Research can generate new knowledge, but it does not necessarily generate economic value; for that to happen, R&D must result in the creation of innovative products and processes. An indicator of a country's ability to innovate is the number of granted patents, which maintains a positive correlation with its R&D spending (Hassan and Tucci, 2010). In 2019, China, Japan, and the Republic of Korea ranked first, third and fourth in the world in the number of patents filed (WIPO, 2021:9).

Other ESCAP countries like the Russian Federation, India, the Islamic Republic of Iran, and Turkey stood among the top 15. In the biotechnology and pharmaceutical sectors, China, Japan, and the Republic of Korea have the largest number of patents granted and together have as many as the United States of America (Figure 10) (Patentscope website).

Before 2019 and the COVID-19 pandemic caused by the coronavirus SARS-Cov2, only six coronaviruses were known to cause illness in humans. A recent analysis of the patents granted on new countermeasures for coronavirus found a total of 3,660 patents; notably, 79.8% of the patent holders were from Asia-Pacific, of which 82.9% were Chinese inventors (Liu et al., 2021).

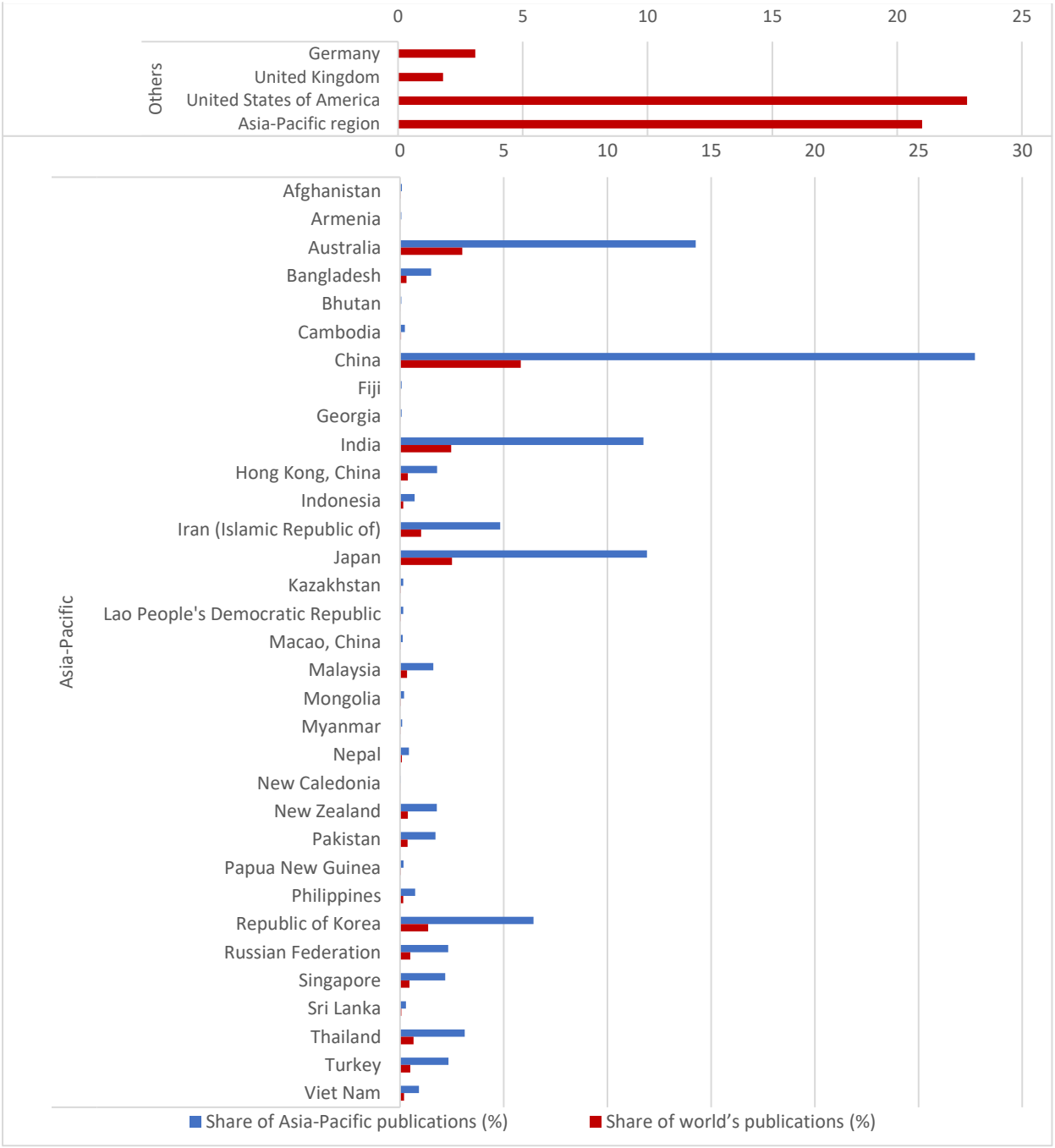
[12] Although the number of open access journals, whose content is available online at no cost, has grown rapidly over the last decade, it is estimated that 72% of all medical and biomedical research articles require a personal or institutional paid subscription, which creates a barrier to the access of knowledge for many scientists and doctors in resource-poor countries (Piwowar et al., 2017; Kruesi et al., 2020).

Figure 8: Scientific journal publications on vaccines, as of March 2022



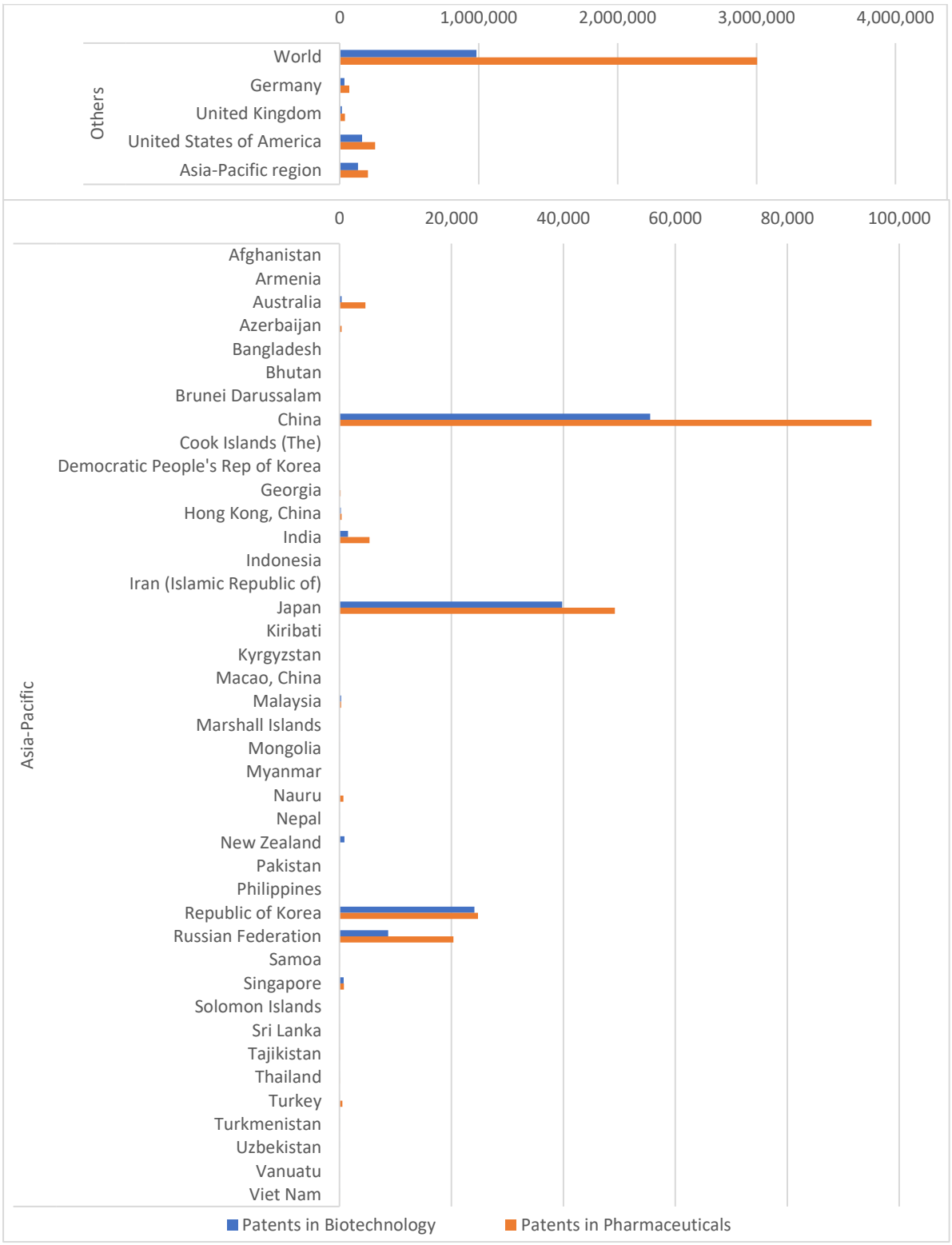
Source: PubMed database

Figure 9: Share of world's and Asia-Pacific's scientific journal publications on vaccines, as of March 2022



Source: PubMed database

Figure 10: Patents granted in biotechnology and pharmaceuticals, as of 2019



3.2 Landscape of the main actors in vaccine R&D in selected Asia-Pacific countries

Like elsewhere in the world, many high- and middle-income countries in Asia-Pacific have specialized research funding government agencies—most often within the organizational structure of the ministries of health, of education or science—that offer grants for early stages of biomedical research (discovery and preclinical stages) at universities and research institutes (see below in Section 3.4).

In a large and diverse region like Asia-Pacific, the vaccine pharmaceutical industry varies greatly from country to country. Many pharmaceutical companies in high-income Asia-Pacific countries are world leaders in vaccine R&D and manufacturing. In a number of Asia-Pacific countries, state-owned vaccine manufacturers control a significant share (in some instances, the largest) of the domestic vaccine market and conduct R&D and production of high-quality vaccines, some of which are prequalified by the WHO as safe and effective vaccines for purchase by UN agencies (Table 4). The state-owned vaccine firms from several Asia-Pacific countries deserve a special mention. China's National Biotec Group (CNBG), (a subsidiary of Sinopharm) accounts for half of the vaccines produced in the country and is very active in R&D using both traditional and newer technologies. India has 13 state-controlled (public sector undertakings) pharmaceutical companies, of which at least five (Haffkine Institute, Central Research Institute Kasauli, and Pasteur Institute of India, BCG Vaccine Laboratory, and Bharat Immunologicals and Biologicals Ltd) are involved in vaccine R&D and production. In Indonesia, state-owned PT Bio Farma (Persero), the country's only vaccine manufacturer, is engaged in advanced R&D for new vaccines and technologies in partnership with academia. As of March 2022, PT Bio Farma is in talks with the WHO to become one of the global manufacturing hubs for mRNA vaccines. Thailand's state-owned General Pharmaceutical Organization manufactures vaccines for the domestic market and other ASEAN countries.

Many Asia-Pacific countries have a vibrant domestically-owned private pharmaceutical industry that is involved not only in vaccine manufacturing, but in many cases also conduct their own vaccine R&D. Selected domestic vaccine manufacturers are included in Table 4. Of the 41 manufacturers that form the DCVMN—which includes both private and state-owned vaccine producers—34 are based in Asia-Pacific, most of them private companies. Around half of all WHO prequalified vaccines are produced by DCVMN manufacturers, of which virtually all (96%) are located in Asia-Pacific (WHO Prequalification website). As of February 2022, of the 259 presentations for 163 vaccines that have been prequalified by the WHO, 61.7% are developed by manufacturers in Asia-Pacific (WHO Prequalification website).

Table 4: Vaccine companies involved in R&D in Asia-Pacific					
Country	**Company**	**Website**	**WHO PQ (# of vaccines)**	**DCVMN**	**Private/ State-owned**
Bangladesh	Incepta Vaccine Ltd	http://inceptavaccine.com/		Yes	PV
China	Beijing Minhai Biotechnology Co., Ltd	https://en.biominhai.com/		Yes	PV
	Beijing Tiatan Biological Products Co., Ltd	www.btbp.com.cn			SO
	BravoVax Co. Ltd	http://www.bravovax.com/		Yes	PV
	Changchun BCHT Biotechnology Co	http://www.bchtpharm.com/		Yes	PV
	China National Biotec Group (CNBG)	https://www.cnbg.com.cn/##	Yes (2)	Yes	SO
	Chongqing Zhifei Biological Products Co., Ltd.	http://en.zhifeishengwu.com/about/zfgk/		Yes	PV
	Hualan Biological Engineering	http://english.hualanbio.com/	Yes (1)		PV
	Institute of Medical Biology Chinese Academy of Medical Sciences	http://www.imbcams.ac.cn/Category_2143/Index.aspx		Yes	PV
	Liaoning Cheng Da Biotechnology Co., Ltd.	http://www.cdbio.cn/		Yes	PV
	Sinovac Biotech Ltd.	http://www.sinovac.com/	Yes (2)	Yes	PV
	Walvax Biotechnology Co., Ltd	http://www.walvax.com/		Yes	PV
	Xiamen Innovax Biotech Co., Ltd	http://www.innovax.cn	Yes (1)	Yes	PV
India	Bharat Biotech International Ltd	https://www.bharatbiotech.com/	Yes (10)	Yes	PV
	Bharat Immunologicals and Biologicals Ltd	https://www.bibcol.com/			SO
	Biological E. Ltd	https://www.biologicale.com/	Yes (12)	Yes	PV
	Cadila Pharmaceuticals Ltd	https://www.cadilapharma.com/			PV
	CPL Biologicals Pvt Ltd	http://cplbio.com/			PV
	Green Signal Bio Pharma Pvt Ltd	http://www.gsbpl.com/	Yes (5)	Yes	PV
	Haffkine Bio-Pharmaceutical Co. Ltd	https://www.vaccinehaffkine.com	Yes (3)		SO
	Indian Immunologicals Ltd	https://www.indimmune.com/		Yes	PV
	Panacea Biotec Ltd	https://www.panaceabiotec.com/en	Yes (3)	Yes	PV
	Pasteur Institute of India	https://pasteurinstituteindia.com/		Yes	SO
	Serum Institute of India Ltd	https://www.seruminstitute.com/	Yes (62)	Yes	PV
	Vins Bioproducts Ltd	https://vinsbio.in/		Yes	
	Zydus Cadila	https://www.zyduscadila.com/		Yes	PV
Indonesia	Bio Farma	https://www.biofarma.co.id/	Yes (15)	Yes	SO
Japan	Astellas Pharma	https://www.astellas.com/en/			PV
	Denka Seiken	https://www.denka.co.jp/eng/			PV
	Japan BCG	https://www.bcg.gr.jp/en/			PV
	Kaketsuken	https://www.kaketsuken.org			PV
	Kitasato Institute	https://www.kitasato-u.ac.jp/en/about-kitasato/institute.html			PV
	Kyoto Biken	https://www.kyotobiken.co.jp/en/			PV
	Takeda	https://www.takeda.com/			PV
Malaysia	Pharmianaga Life Sci	https://pharmaniaga.com/			PV
	Solution Biologics	http://solutionbiologics.com.my/			PV
Pakistan	Amson Vaccines & Pharma	http://amson.org.pk/		Yes	PV
Republic of Korea	Boryung Biopharma	http://www.boryung.co.kr/eng/index.do			PV
	Cheil Jedant (CJ Pharma)				PV
	Dong Shin Pharma				PV
	EuBiologics, Co., Ltd.	http://www.eubiologics.com/kor/	Yes (2)	Yes	PV

	GC Pharma	http://www.globalgreencross.com/eng/index.do		Yes	PV
	Korea Vaccine	http://www.koreavaccine.com/eng/main/main.php		Yes	PV
	LG Life Sciences Ltd	https://innovation.lgchem.com/	Yes (7)	Yes	PV
	SK Bioscience Co.,Ltd	https://www.skbioscience.co.kr/en/ir/info_01	Yes (5)	Yes	PV
Russian Federation	Immunopreparat Research productive association, Ufa	https://www.microgen.ru/en/			SO
	Products Immunologicals and Drugs, Irkustk RIVS				SO
	LLC Nanolek	https://www.nanolek.ru/en/		Yes	PV
	St. Petersburg Research Institute of Vaccines and Serums	https://www.istc.int/en/institute/9983		Yes	SO
Thailand	BioNet	https://www.gpo.or.th/?lang=en	Yes (1)		PV
	The Government Pharmaceutical Organization	https://www.gpo.or.th/?lang=en		Yes	SO
	Queen Saovabha Memorial Institute	https://www.saovabha.org/		Yes	SO
Taiwan, Province of China	Medigen Vaccine Biologicals Co.	https://www.medigenvac.com/public/en		Yes	PV
Viet Nam	The Company of Vaccine and Biological Production No. 1-VABIOTECH	https://www.vabiotech.com.vn/?lang=en		Yes	SO
	Da Lat Pasteur Vaccines Company Ltd (DAVAC)	http://davac.com.vn/			SO
	Institute of Vaccines and Medical Biologicals (IVAC)	http://en.ivac.com.vn/			SO
	Center for Research and Production of Vaccines and Biologicals (POLYVAC)	http://www.polyvac.com.vn/		Yes	SO

Abbreviations: PV: private; SO: state-owned; WHO PQ: prequalification by WHO
Source: Tsai et al (2018), DCVMC website, companies websites

With Asia-Pacific being the world's second-largest market for pharmaceuticals, all MNPFs have a presence in the region. MNPFs have not only offshored part of their vaccine and drug manufacturing to Asia-Pacific but have also transferred some of their R&D activities, directly (to subsidiaries, opening new R&D centers) and/or indirectly (through partnerships with academic institutions or local firms). Most of the largest MNPFs have R&D centers and manufacturing centers not only in the larger economies (e.g., China, India, Japan and the Republic of Korea) but also in the ASEAN subregion. The offshoring of R&D from global vaccine MNPFs to developing countries in Asia-Pacific can potentially enhance technology transfer to domestic biotechnology firms.

In developed countries, stricter ethical standards and regulatory environments make conducting clinical trials more difficult and expensive. As a result, most MNPFs have outsourced various stages of vaccine and drug R&D to CROs with a presence in developing countries (Sayal and Angal, 2020). Nevertheless, weaker and more unpredictable regulatory environments in developing countries can also be an obstacle to offshoring of clinical trials and R&D. All global CROs now have a presence in Asia-

Pacific, particularly, in India, China, and Japan (Table 5). Leading international CROs also carry out early stages of R&D (e.g., discovery of targets, small molecule synthesis, toxicology services, manufacturing of advanced intermediates and active pharmaceutical ingredients, cell banking services) at their Asia-Pacific locations. The expansion of the international CRO market has led to the emergence of dozens of domestically-owned CROs in Asia-Pacific countries, especially China and India (Table 5). Although the world's largest CROs by revenue are headquartered in developed countries, particularly the United States, some Asia-Pacific CROs have gained global reach; for instance, the Chinese CRO WuXi AppTec Group ranked seventh in the world by revenue in 2021.

Conducting clinical trials for new vaccines and drugs in developing countries faces significant challenges including lack of a research environment, ethical and regulatory hurdles, logistical barriers, and competing demands (Alemayehu et al., 2018). On the one hand, carrying out clinical trials in developing countries is essential to ensure not only that vaccines are safe and protective across different human populations and ethnic groups, but also that vaccine formulations can be easily administered in low-income settings. Nevertheless, the increasing outsourcing of clinical trials to developing countries has also raised some ethical concerns (Glickman et al., 2009; Kamat, 2014). The booming of the Indian CRO industry is due not only to changes in the patent legislation, more relaxed regulatory and lower labor costs for the professionals involved (physicians, nurses, clinical trial coordinators), but also to the availability of a large pool of volunteers and weaker liabilities in case of adverse effects (Glickman et al., 2009; Kamat, 2014).

Table 5: CROs in Asia-Pacific involved in clinical R&D

Country	Locally headquartered CROs	Global CROs
Australia	Avance Clinical / Datapharm Australia / GreenLight Clinical	Charles River Laboratories / Covance / Factory-CRO / ICON / IQVIA / Novotech / Parexel / PPD / Syneos Health
Bangladesh		Dokumeds
China	Acrovan / Gene Company / Hangzhou Tigermed Consulting Co / H&J CRO International / Pharmaron / PHDS Healthcare Research / PPC group / Proswell Medical Company / SLG / WuXi AppTec Group	Aastrom Research International / ACM Global Laboratories / Bioclinica / Charles River Laboratories / Covance / CrownBio / Dicentra / EAG Laboratories / Fountain Medical Development (FMD) / GenScript / GreenLight Clinical / ICON / IQVIA / MakroCare / Medidata / Novotech / Parexel / PPD / Proswell Medical Company / Syneos Health
Georgia	"Medconsult-Geo" LLC	Comac Medical / Cromos Pharma / Dokumeds / MB Quest / OCT Clinical / Parexel / SanaClis / X7 Research
Hong Kong, China	Acadechem Company / Advanced Technology & Industrial Co / Chinese University of Hong Kong / Gene Company / Groken Bioscience / Hong Kong Institute of Biotechnology	ACROSS Global / Covance / ICON / Medpace / Parexel / PPD /Syneos Health
India	Abiogenesis Clinpharm / Accutest Global / Actimus Bio / Asiatic Clinical Research / BioAxis / Catalyst Clinical Services / Cliantha Research / Cliniminds / CliniRx / D2L / DIL Limited / Dishman Group / Divi's Laboratories Limited / Dubar Research Foundation / Eurofins Advinus / Global Drug Development Experts (GDDE) / Hi Tech Bio Laboratories / Indus	Aagami / Accelsiors / ACM Global Laboratories / ACROSS Global / Actimus Bio / APCER Life Sciences / Aris Global / Astron Research / AXIS Clinicals / Bioclinica / Bio Reliance Corporation / Charles River Laboratories / Clinical Site Services (CSS) / Covance / Endpoint / eResearchTechnology, Inc (ERT) / Fountain Medical Development (FMD) / GCT (Global Clinical Trials) / GVK Biosciences / ICON / IntrexTest / IQVIA / Jai Research

	Biotherapeutics / International Pharma Trials / Intox Lab / Kemwell Biopharma / KPS Clinical Services / Labnetworx / Laxai / MakroCare / Max India / Metropolis / Ocimum Biosolution / Pharmaffiliates / Premas Biotech / ProRelix Research / RCC Laboratories / Reliance Life Sciences / Sai Life Sciences / Spectrum Clinical Research / Strand Strides Pharma Science Limited / SyMetric / Symphony Pharma Life Sciences / Syngene / TCG Lifesciences Private Limited / The Sanmar Group / The SIRO / Vedic Lifesciences / Veeda House / VIMTA / Vivo Bio Tech	Foundation (JRF Global) / JSS Medical Research / Lambda Therapeutic Research Limited / Maya Clinicals / MMS Holdings / Navitas Life Sciences / Novotech / Orphan Reach / PPD / Quanticate /Quest Diagnostics, Inc / Syneos Health / TAKE Solutions / Tech Observer
Indonesia	Prodia The CRO	IQVIA / Syneos Health
Iran (Islamic Republic of)	Farzan Clinical Research	
Japan	A2 Healthcare Corporation / Asklep / Biotoxtech CRO / CMIC Group / FALCO Biosystems / InCROM / KRI Inc. (Kansai Research Institute)	ACROSS Global / Alcami / Aris Global / BBK / Bioclinica / Bio Reliance Corporation / Charles River Laboratories / ChemDiv / Clinlogix / EAG Laboratories / eResearchTechnology, Inc (ERT) / Fountain Medical Development (FMD) / GenScript / ICON / IQVIA / MakroCare / MedidataPPD / Proswell Medical Company / SNBL / Syneos Health
Kazakhstan		ACROSS Global / Documeds / IQVIA / MB Quest
Malaysia	Info Kinetics Sdn Bhd	ACROSS Global / Covance / ICON / IQVIA / Parexel PPD / Syneos Health
New Zealand	P3 Research	Covance / Green light Clinical / ICON / IQVIA / Novotech / PPD / Syneos Health
Pakistan	Dimension Research / Metrics Research	DRK Pharma Solutions / IQVIA
Philippines		ACROSS Global / Clinitude / Covance / Dokumeds / Fountain Medical Development (FMD) / ICON / Novotech / Parexel / PPD / Syenos Health
Russian Federation	Avinex / Ipharma LLC	Accell Clinical Research / ACROSS Global / Biocard Reseach / Carpathian Research Group / Congenix / Covance / Chromos Pharma / Dokumeds / Emergo Group / GCT (Global Clinical Trials) / Harrison Clinical / ICON / Intertek / IVQIA / MB Quest / OCT Clilnical / PPD / Sana Clis / Syneos Health
Singapore	Syncare	ACM Global Laboratories / ACROSS Global / Bio Reliance Corporation / Celerion / Charles River Laboratories / Clinitude / Covance / EAG Laboratories / ICON / IQVIA / MakroCare / Novotech / Parexel / PPD / Syneos Health / TAKE Solutions
Korea, Republic of	LSK Global PS	ACROSS Global / Celerion / Charles River Laboratories / Covance / Green Light Clinical / ICON / IQVIA / Medidata / Novotech / Parexel / PPD / Syenos Health / WuXi App Tech Group
Sri Lanka		ACROSS Global / IQVIA
Taiwan, Province of China	ScinoPharm	ACROSS Global / Clinipace / Covance / Crown Bioscience / EAG Laboratories / FAVORGEN Biotech / ICON / Novotech / Parexel / PPD / Syneos Health / Veristat
Thailand	Aclires / Asia Global Research (AGR)	Covance / ICON / IQVIA / Novotech / Parexel / PPD / Synchron / Syneos Health
Turkey	CRM-CRO / Klinar CRO / Mene Research / Monitor Medical Research Consulting	Covance / ICON / IQVIA / Parexel / PPD / Syneos Health / ZEINCRO
Viet Nam		Dokumeds / IQVIA / Parexel / PPD
Source: ICH-GCPN website, websites of companies		

3.3 R&D preparedness and the vaccine R&D pipeline in Asia-Pacific

On the one hand, economic growth in all subregions of Asia-Pacific has contributed to slowing the growth of most infectious diseases, including neglected and newly emerging infectious diseases. On the other hand, increasing urbanization, food insecurity, and/or political instability operate in the opposite direction. Thus, while many neglected tropical diseases have been declining in Asia-Pacific in recent decades, others such as Echinococcosis or Dengue have increased (Hotez, 2020; Sripa et al., 2021).

The 2019 Global Preparedness Monitoring Board Annual Report predicted that the economic loss from a pandemic was between 1% and 2% for all countries in Asia-Pacific with the exception of Australia, Japan, New Zealand, and the Republic of Korea, where losses were estimated at below 1% (GPMB, 2019). In most countries of the world, national preparedness plans to deal with epidemics and pandemics have focused primarily on influenza. Still, 99 countries in the world have no preparedness plans for influenza outbreaks (Nuzzo et al., 2019; WHO-SPHSEP website), of which 13 are in Asia-Pacific, namely Afghanistan, Armenia, Democratic People's Republic of Korea, the Islamic Republic of Iran, Kazakhstan, Kyrgyzstan, Nepal, Pakistan, Russian Federation, Tajikistan, Turkey, Turkmenistan, Uzbekistan (WHO-SPHSEP website).

Many of the vaccines used today in the Asia-Pacific and worldwide have been researched, developed and/or manufactured by firms in the region, especially, in Japan, China, India, and Australia, but also in smaller economies like Viet Nam. Some developing countries in Asia-Pacific that until recently only hosted vaccine fill-and-finish manufacturing operations are now also engaged in vaccine R&D for new vaccines.[13] Vaccines researched and developed in Asia-Pacific for diseases of regional importance include those for severe acute respiratory syndrome (SARS), Japanese encephalitis, the Hantaan and Seoul viruses causing hemorrhagic fever with renal syndrome, Russian spring–summer encephalitis, Kyasanur Forest Disease, cholera, and Q fever (Tsai et al., 2018). Manufacturers in Asia-Pacific have also developed for national or regional distribution newer vaccines for measles, mumps, hepatitis A, rotavirus, and intranasally-delivered pandemic H1N1 virus. Some new vaccines developed in the region have been distributed globally like those for hepatitis E, enterovirus A71, and COVID-19 (Tsai et al., 2018).

As of December 2021, the vaccine R&D pipeline in Asia-Pacific includes new vaccines for tuberculosis, malaria, HIV, Kinetoplastids (e.g., Chagas disease, sleeping sickness, leishmaniasis), diarrhoeal diseases, Hepatitis C, Salmonella, bacterial pneumonia and meningitis, rheumatic fever, and COVID-19 (Tables 2 and 6). In fact, 100% of the world's new vaccine candidates for Salmonella, 66.8% for bacterial pneumonia and meningitis, 43.8% for tuberculosis and 36.8% for diarrhoeal diseases are being researched and developed in Asia-Pacific (Table 6 and R&D Pipeline Tracker website). Several countries

[13] When technological and/or manufacturing capacities are limited or when production volumes are small, vaccine manufacturers do not conduct upstream stages of vaccine manufacturing (e.g., bioprocessing and formulation), but rather limit their activity to downstream steps where the vaccines are filled into vials and packaged for distribution (fill, finish, and packaging).

in the region have been at the forefront of R&D for COVID-19 (Table 2). Notably, clinical trials for China's Cansino Biologics COVID-19 vaccine started in March 2020, at the same time as Moderna's clinical trials in the United States of America (Chakraborty et al., 2021).

Table 6: Vaccine candidates in the pipeline of Asia-Pacific firms				
Disease	**Disease**	**Vaccine Candidate**	**Pharmaceutical Firm**	**Country**
Tuberculosis	Preclinical	CysVac2/A	TBVI Univ of Sydney	International Australia
	Phase I	Ad5Ag85A	CanSino Biologicals Inc McMaster Univ	China Canada
		AEC/BCO2	Anhui zhifei longcom biopharmaceutical co. ltd	China
		GamTBVac	Gamaleya Research Institute of Epidemiology and Microbiology	Russian Federation
	Phase II	TB-FLU-04L	Kazakhstan Ministry of Health Research Institute for Biological Safety Problems	Kazakhstan
	Phase III	MIP	Cadila Pharmaceuticals	India
		Vaccae	anhui zhifei longcom biopharmaceutical co. ltd & Institute of Microbiology, Chinese Academy of Sciences	China
		VMP1002	Serum Institute of India Vakzine Projekt Management Gmbh	India & Germany
Malaria	Discovery	Pfs230 fragments	Ehime University & PATH	Japan International
	Phase I	ChAd63/MVA PvDBP	International Centre For Genetic Engineering And Biotechnology & Okairos	India Switzerland
		PlasprotecT	Griffith Univ	Australia
		PvDBPII	Syngene International Limited & International Centre For Genetic Engineering And Biotechnology	India
HIV/AIDS	Phase I	SeV-G (NP), Ad35-GRIN	DNAVEC Corporation & International AIDS Vaccine Initiative	Japan International
	Phase II	HIV DNA-rTV	Beijing Bioproduct Research Institute & Beijing You Ann Hospitals	China
Kinetoplastids (Chagas disease, sleeping sickness, leishmaniasis)	Preclinical	LmCen-/-	Gennova Biopharmaceuticals & McGill University	India Canada
	Phase I	LEISH-F3+GLA-SE	Gennova Biopharmaceuticals & Infectious Disease Research Institute	India USA
Diarrhoeal Diseases	Preclinical	34kDa OMP	Indian National Institute of Colera and Enteric Diseases	India
		Heat-killed multisertope Shighella	Indian National Institute of Colera and Enteric Diseases	India
	Phase I	Hexavalent BRV vaccine	Wuhan Institute of Biological Products Co Ltd	China

			& Hebei Province Center for Disease Prevention and Control	
		S Flexneriz – S Sonei Bivalent Conjugate vaccine	Beijing Zhifei Lvzhu Biopharmaceutical Co. Ltd.	China
		VP V2/6/7	Mitsubishi Tanabe Pharma Corporation	Japan
	Phase II	Heat Stable rotavirus (HSRV)	Hilleman Laboratories & MSD (Merck)	India & Germany
		RV3-BB	Biofarma & Gadjah Mada University	Indonesia
	Phase III	BRV-TV	Shantha Biotechnics (Sanofi Group)	India
		P2-VP8-P[8]	SK Chemicals & PATH	ROK International
Hepatitis C	Preclinical	HepSeeVax	Burnet Institute	Australia
Salmonella	Preclinical	OSP-rEPA	Abasyn University & Canadian NRC	Pakistan Canada
		Ryavlent typoid/iNTS glycoconjugate vaccine	Bharat Biotech & University of Maryland, Baltimore	India USA
		Vi-CRM197+O:2-CRM197	Biological E. Limited & Novartis Vaccine Institute for Global Health	India Switzerland
	Phase I	Live oral PA vaccine (CVD 1902)	Bharat Biotech & University of Maryland, Baltimore	India USA
	Phase II	O:2-TT	Lanzhou Institute of Biological Products & USA NIH	China USA
		Vi-CRM197	Biological E. Limited & Novartis Vaccine Institute for Global Health	China Switzerland
		Vi-DT	Biofarma & SK Chemicals	Indonesia & ROK
		vi-rEPA	Lanzhou Institute of Biological Products & USA NIH	China USA
Bacterial pneumonia & meningitis	Preclinical	23-valent pneumococcal PS vaccine	Sinovac Biotech Ltd	China
	Phase I	A, C, Y, W135 meningococcal LPS conjugate vaccine	China Air Force Medical University & Chinese National Insitute for Food and Drug Control	China
		ASP3772	Astellas Pharma Affinivax	Japan USA
		GBP411	SK Chemicals Sanofi	ROK France
		Tetravalent meningococcal conjugate vaccine	Wuhan Institute of Biological Products & Lanzhou Institute of Biological Product	China
	Phase II	Biological E 14-valent PCV	Biological E Ltd	India
		LBVE013 (multivalent)	LG Life Sci	ROK
		Pentavalent Meningoccocal Vaccines	Serum Institute of India & PATH	India International

	Phase III	MCV4	Cansino Biologicals	China
		MCV-ACYW135	Beijin Minhai Biotechnology	China
		NBP606	SK Chemicals	ROK
		Pneumosil	Serum Institut of India & MRC Unit The Gambia	India Gambia
Rheumatic Fever	Phase I	MJ8VAX (J8-DT)	Ausralian Centre for Health Service Innovation & Q-Pharm	Australia
Source: R&D Pipeline tracker and email communications with individual companies				

3.4 National strategies for the financing, capacity building and management of vaccine R&D in Asia-Pacific

Countries in Asia-Pacific have used several of the supply- and demand-side approaches described in Section 2.4 to incentivize investments in vaccine R&D and manufacturing by pharmaceutical firms. The biomedical R&D ecosystem—with a particular focus on vaccine R&D—in China, India, and the Association of Southeast Asian Nations (ASEAN) countries is highlighted in **Boxes 1, 2** and **3**, respectively.

a) Supply-side approaches: On the supply side, governments of many Asia-Pacific countries offer grants to universities and research institutes to carry out early stages of biomedical R&D (Table 7). In 2013, only the Australian National Health and Medical Research Council and the National Natural Science Foundation of China (NNSF-China) were among the world's top 10 public funders of biomedical and health research, ranking seventh and ninth, respectively. Reflecting the rapid growth in biomedical and health R&D expenditures and the number of researchers in Asia-Pacific (Figures 4 and 5; UNESCO, 2021), by 2021, the NNSF-China, Japan Science and Technology Agency, and the Korean National Research Foundation ranked second, third, and fourth in the world for the amount of funds disbursed (Table 7). In 2018, the Russian Federation and the Republic of Korea ranked second and fourth in the world in direct government funding and tax support for business R&D as a percentage of GDP (OECD, 2021). Of the 32 public and private research funding organizations included in GOLPID-R, five are from Asia-Pacific countries, namely the Indian Council of Medical Research (India), the Agency for Medical Research and Development (AMED), the National Health and Medical Research Council (Australia), the National Institute of Health-Department of Medical Sciences (Thailand), and the National Research Foundation of Korea (Republic of Korea).

Table 7: Government agencies funding health and biomedical R&D in Asia-Pacific

Funding Agency	Country	Value (in US$ 2020)	Website
Outside Asia-Pacific (included in the top 10)			
National Institutes of Health	United States	41.7 bil (2020)	https://www.nih.gov/grants-funding
Congressionally Directed Medical Research Programs (CDMRP)-US Department of Defense	United States	1.3 bill (2020)	https://cdmrp.army.mil/default
European Commission	European Union	1.2 bill (2021)	https://ec.europa.eu/info/research-and-innovation_en
Medical Research Council	UK	1.1 Bill (2021)	https://mrc.ukri.org/

National Institute of Health and Medical Research (INSERM)	France	967 mill (2021)	https://www.inserm.fr/en/home/
Asia-Pacific			
National Natural Science Foundation of China	China	4.8 bill (2019)	http://www.nsfc.gov.cn/english/site_1/index.html
Japan Science and Technology Agency	Japan	2.1 bil (2021)	https://www.jsps.go.jp/english/
Korean National Research Foundation	ROK	2.0 bil (2021)	https://www.nrf.re.kr/eng/index
Australian National Health and Medical Research Council	Australia	1259.6 (2019) 497.7 (2020)	https://www.nhmrc.gov.au/
Singapore National Medical Research Council	Singapore	243.51 mill (2017)	https://www.nmrc.gov.sg/home
Indian Council of Medical Research	India	140.3 mill (2013)	https://www.icmr.gov.in/index.html
Japan Science and Technology Agency	Japan	100 mill (2019)	https://www.jst.go.jp/EN/
Health Research Council of New Zealand	New Zealand	87.47 mill (2020)	https://www.hrc.govt.nz/
Korea National Institute of Health	ROK	N/A	https://nih.go.kr/index.es?sid=a5
Russian Foundation for Basic Research	Russian Federation	N/A	https://www.rfbr.ru/rffi/eng
Biomedical Research Council of the Singapore Agency for Science, Technology and Research	Singapore	N/A	https://www.a-star.edu.sg/
Ministry of Science and Technology of China	China	N/A	http://en.most.gov.cn/
Indian Department of Biotechnology	India	N/A	https://dbtindia.gov.in/
Indian Department of Science and Technology	India	N/A	https://dst.gov.in/
Lipi Indonesian Research Council	Indonesia	N/A	http://lipi.go.id/
Ministry of Healthcare of the Russian Federation	Russian Federation	N/A	https://minzdrav.gov.ru/en
Tubitak / Scientific and Technological Research Council of Turkey	Turkey	N/A	https://www.tubitak.gov.tr/en
Turkish Academy of Sciences (TUBA)	Turkey	N/A	http://www.tuba.gov.tr/
Source: Websites of funding agencies, Viergever et al (2016), Aars et al (2021)			

Beyond funding for R&D in COVID-19 vaccines, the share of public funding for health R&D that countries in Asia-Pacific earmark for vaccine R&D is either unavailable or only fragmentary, especially in middle- and low-income countries. As part of its US$ 5.2 billion science and technology budget for 2021, the Republic of Korea will spend US$ 37 million on developing new vaccines and drugs for emerging infectious diseases (Sharma, 2021). In China, public and private funding play different but complementary roles in pharmaceutical R&D and, as in other large countries, private sources of R&D are higher in more developed provinces, while in less developed provinces the government is the main, if not the only, source of funding for pharmaceutical R&D (Qiu et al., 2014).

PDP and non-PDP intermediaries are, together with governments, one of the main sources of funding for R&D of vaccines on neglected and/or emerging infectious diseases. As in the case of public funding, data on the share of R&D expenditures funded by philanthropic foundations in Asia-Pacific are incomplete (Table 6). As illustrated in several of the case studies highlighted in Boxes 1 to 3, PDPs and non-PDP intermediaries, and global philanthropic foundations have funded projects for vaccine

and drug R&D in developing countries in Asia-Pacific. A total of twenty countries and territories in Asia-Pacific have benefited from vaccines for infectious diseases purchased by GAVI The Vaccine Alliance (GAVI Website). CEPI has created economic incentives to bring vaccine candidates from the discovery to the end of Phase II for various regionally prevalent diseases such as Chikungunya and Nipah viruses.

Governments in several high-income countries in the Asia-Pacific region are major contributors to PDP and non-PDP intermediaries and philanthropic foundations. The Japanese Ministry of Health, Labour and Welfare (with US$ 51 million) and Australia's Ministry for Home Affairs and Department of Foreign Affairs and Trade (with US$ 7.2 million) were among the top 10 donors to PDP and non-PDP intermediaries that funded vaccine and drug R&D for emerging infectious diseases during 2017-2019 (PCR 2021a). Australia (in sixth position, with US$ 38 million) and Japan (in seventh place, with US$ 33 million) are also among the largest donors to PDP and non-PDP intermediaries that financed R&D for neglected infectious diseases in 2019 (PCR 2021b). The Japanese government is also the largest contributor to the Global Health Innovative Technology (GHIT) Fund, a non-PDP intermediary headquartered in Japan that, in collaboration with the Bill & Melinda Gates Foundation, the Wellcome Trust, and the United Nations Development Programme (UNDP), mobilizes the Japanese pharmaceutical industry, academia, and research institutes to create new vaccines, drugs, and diagnostics for malaria, tuberculosis, and neglected tropical diseases (PCR 2021b).

A review of the impact of public spending in R&D on private R&D expenditures found that public investment is not only complementary but also encourages private investment (David et al., 2000). In many Asia-Pacific countries, particularly those with expenditures in R&D greater than 0.5% of GDP, the private sector tends to be the largest contributor to R&D. For instance, in 2018, businesses funded more than three-quarters of all R&D expenditures in the Republic of Korea (80.5%), Thailand (80.0%), Japan (79.5%), and China (77.5%) (Table 6) (UNESCO, 2021; UIS Website). Among Asia-Pacific countries with R&D greater than 0.5% of GDP, public funding of R&D is higher in India and the Islamic Republic of Iran. As noted above, basic and preclinical research is no longer funded exclusively from public sources, and up to one-third of business R&D expenditures in some high-income countries now go to basic science (UNESCO, 2021).

A UNESCO survey in 53 countries around the world found that most pharmaceutical firms have relatively low interest in establishing R&D collaborations with universities (UNESCO, 2021). In fact, most firms in developed and developing countries indicate that they prefer to maintain their core R&D activities in-house rather than outsource them to academic researchers (UNESCO, 2015). Less than 2% of scientific publications in New Zealand and China involved co-authorship between universities and businesses. In the Republic of Korea (3.9%), academic-business co-authorship was higher (3.9%) and more similar to the levels found in Germany (4.4%) and France (4.5%) (UNESCO, 2021). To promote knowledge transfer and accelerate innovation, many Asia-Pacific government agencies that fund biomedical R&D have launched programs to

boost university-industry R&D ties. For example, Malaysia's Collaborative Research in Engineering, Science and Technology Centre (CREST) provides funding to universities and companies for market-driven collaborative research projects. In Pakistan, the World Bank-supported Technology Transfer Support Fund offers grants for collaborations between academic researchers and businesses when the latter matches government funding (HEC, 2021). In the Philippines, the Collaborative Research and Development to Leverage Philippine Economy (CRADLE) programme offers government funding for projects in which a company partners with a tertiary education institution to conduct R&D and the company contributes at least 20% of total financing (DOST, 2021). Armenia has also implemented a similar funding scheme for academia-industry R&D collaborations where the private partner must finance at least 15% of the project (UNESCO, 2021). In Sri Lanka, the government offers tax breaks of more than 50% to firms conducting R&D in collaboration with government institutions (UNESCO, 2021).

b) Demand-side approaches: The impact of demand side strategies to incentivize vaccine R&D depends on the type of vaccines and the structure of the pharmaceutical industry. In many developing countries, vaccines included in national immunization programs are researched, developed, and manufactured by state-owned pharmaceutical firms that supply most of the doses needed. In developing countries where private firms also conduct R&D and manufacturing for vaccines in national immunization programs, demand-side approaches can incentivize local private pharmaceutical firms to invest in vaccine R&D. However, in the case of vaccines for neglected infectious diseases and in countries without vaccine R&D and manufacturing capacity that rely on imported vaccines, demand-side approaches by governments may have only limited effects on the structure of economic incentive structure for pharmaceutical firms abroad, especially for MNPFs.

Governments can create demand for vaccines by providing free vaccination, offering incentives for people to get vaccinated or through mandatory vaccination to attend school or go to the workplace. In most countries in the region, the vaccines included in national immunization programs and those required during epidemics and pandemics are administered free of charge by governments. Legislation on vaccination varies across Asia-Pacific countries. Several Asia-Pacific countries have compulsory vaccination for their national immunization programmes and/or for school enrollment, although many low-income countries have limited capacity to implement (e.g., supply, delivery and access issues) and enforce programs (Vanderslott and Marks, 2021). In addition, there is still an open debate on whether mandatory vaccination increases vaccine uptake. Singapore has mandatory childhood vaccinations against diphtheria and measles through the Singapore Infectious Diseases Act 1977, which also covers mandatory vaccination of people at risk during disease outbreaks (Vanderslott and Marks, 2021). In June 2019, the National People's Congress of China adopted the Vaccine Administration Law under which all citizens who reside in China are entitled and obliged to be immunized with national immunization program vaccines, which the government provides free of charge (NPC-PRC, 2019). In 2019, Pakistan made all vaccines in its mandatory schedule

for children within the capital. In Afghanistan, polio vaccination is mandatory, but access is not universal. In Iran, children must get vaccinated to enroll in schools and it is mandatory for polio. Indonesia has made vaccination mandatory for children under the age of five, primary school students, and women of reproductive age. Following an outbreak, Samoa made measles, mumps, and rubella vaccination mandatory in 2019. In India, mandatory vaccination policies vary from state to state being compulsory in Tamil Nadu and Kerala for children attending school. Bhutan has mandatory vaccination for school enrollment. In Nepal, vaccination is only mandatory in the context of epidemics. Malaysia has been debating whether or not to introduce mandatory vaccination for children (Khan and Zulkipli, 2018). Other Asia-Pacific countries have eliminated mandatory vaccinations. For example, New Zealand, Japan, and the Republic of Korea previously had mandatory childhood immunisation schedules but were later superseded by voluntary vaccination by guardians along with strong recommendations. Australia offers tax incentives and childcare benefits for parents that vaccinate their children (Vanderslott and Marks, 2021).

As discussed in Section 2.4, a commonly used mechanism by which final purchasers of vaccines can incentivize investment by pharmaceutical firms in vaccine R&D and production is through AMCs. While APAs signed by high-income countries with pharmaceuticals can lead to higher prices and negative externalities for low-income countries if vaccine supply is inelastic, they can also foster global capacity expansion and accelerate R&D and manufacturing creating positive externalities for third countries (Ahuja et al., 2021). APAs are part of pandemic influenza preparedness plans with signatory countries paying an annual fee to the manufacturer and committing to purchase a specified number of annual doses (Turner, 2016). To ensure equity in vaccine supply, WHO encourages developing countries to use APAs and some MNPFs such as GSK have pledged to supply vaccines at tiered prices to developing via APAs based on the country's gross domestic product (WHO, 2011; Turner 2016). Nevertheless, in Asia-Pacific, APAs have been almost exclusively used by high-income countries (Turner, 2016; Pharmaceutical Technology, 2021). For instance, during the 2009-H1N1 pandemic, New Zealand was the only country in Asia-Pacific that held an APA for H1N1 vaccines.

During the COVID-19 pandemic, some Asia-Pacific pharmaceutical firms have signed APAs with the COVID-19 Vaccines Global Access (COVAX) facility; namely, the Gamaleya Institute (Russian Federation), Sinovac (China), Cansino Biologicals (China), Bharat Biotech (India), and the Serum Institute of India (India) (Pharmaceutical Technology, 2021). As part COVAX, GAVI-The Vaccine Alliance has established an AMC by pooling up to US$ 2.4 billion from the financial contributions of high-income countries to support R&D and manufacturing for several COVID-19 vaccines before they have been approved (Phelan et al., 2020). Higher-income countries participating in the COVAX AMC only pay for the cost of the doses they receive. Thirteen Asia-Pacific countries have signed self-financing agreements to the COVAX AMC (Armenia, Australia, Azerbaijan, Brunei Darussalam, China, Georgia, Iran, Japan, Nauru, New

Zealand, Palau, Singapore, and the Republic of South Korea). COVID-19 vaccine doses for the 92 lower-income economies eligible to benefit from the COVAX AMC are paid through ODA and contributions from the private sector and philanthropy. Of them, thirty Asia-Pacific countries (Afghanistan, Bangladesh, Bhutan, Cambodia, Democratic People's Rep. of Korea, Fiji, India, Indonesia, Kiribati, Kyrgyzstan, Lao PDR, Marshall Islands, Maldives, Micronesia (Fed. Sts), Mongolia, Myanmar, Nepal, Pakistan, Papua New Guinea, Philippines, Samoa, Solomon Islands, Sri Lanka, Tajikistan, Timor-Leste, Tonga, Tuvalu, Uzbekistan, Vanuatu and Vietnam) (GAVI Website).

During the COVID-19 pandemic, many high-income countries, including some in the Asia-Pacific region such as Japan and Australia, contracted directly from the vaccine manufacturers vaccine doses several times higher than their populations and across different platforms (DGHIC, 2021a; DGHIC, 2021b). Their investments eventually accelerated R&D for COVID-19 vaccines, which has also benefited other countries. Middle-income countries made advanced purchases for fewer doses than their populations and for fewer candidates, while COVAX made purchases of COVID-19 doses for low-income countries.

BOX 1: VACCINE R&D IN CHINA

In the last decade, China's gross expenditures in R&D as a percentage of GDP increased by more than a third to reach 2.23% in 2019 (UNESCO, 2021). In 2018, public and business funding of R&D accounted for 20.2% and 76.6% of total R&D expenditures, respectively (UIS Website). The distribution of R&D spending among basic research, applied research, and experimental development was 5.5%, 11.1%, and 83.3%, respectively. Between 2013 and 2018, the number of researchers in China increased by 22.6%, surpassing all other countries in the world (UIS Website; UNESCO, 2021).

The *Made in China 2025 Strategy* aims at reducing China's dependence on foreign technology through government subsidies, the mobilization of state-owned enterprises, and the acquisition of intellectual property (UNESCO, 2021). To incentivize knowledge transfer from academia to industry, between 2000 and 2016, China introduced policies that allow academic scientists to own patents arising from government-funded projects. Preliminary evidence indicates that these changes have increased the number of patent approvals (Yi and Long, 2021). China's 14th Five-Year Plan (2021-2025) for National Economic and Social Development and Vision 2035 projects that R&D expenditures will grow at an annual rate of 7%. The government will upgrade national research and innovation centers and promote the sharing of resources between universities, research institutes, and businesses. Public funding for basic research will increase to account for more than 8% of total R&D spending; in addition, the government will offer preferential tax treatment to companies engaging in basic research. New tax incentives will be introduced for small- and medium-sized scientific and technological enterprises. The Five-year Plan aims that the growth of spending on R&D by state-owned enterprises exceeds the national average. The government will strengthen the protection of foreign capital to encourage foreign investment in high-tech manufacturing and support international firms that set up R&D centers. China also pledges to accelerate the evaluation and approval mechanisms for new drugs and vaccines.

Since 2000, when the Chinese pharmaceutical industry began to target higher-end drugs and vaccines, investment in the industry has grown, albeit less than in other high-tech industrial sectors (Qiu et al., 2014). Data on the sources of private investment in pharmaceutical R&D are scarce, but private equity is larger than venture capital (Qiu et al., 2014). Both public and private investments in pharmaceutical R&D are highly concentrated in eastern and southern China (Qiu et al., 2014). The Zhangjiang Hi-Tech Park in Shanghai is the pharmaceutical hub of China. Other areas with high public and private investments in pharmaceutical R&D are the Tianjin district and Guangdong Province. In turn, half of the top 10 provinces with the highest public investments in pharmaceutical R&D are less developed areas like Gansu, Yunnan, Hainan, and Guizhou Provinces.

Beyond COVID-19 vaccines, there is no publicly available data on the percentage of public or private R&D investment dedicated to vaccine research. In any case, increased funding has led to a rapid increase in the number of vaccine publications, clinical trials, and patents, setting China as one of the world's leading vaccine R&D centers (Figures 6 to 10 and Table 4). Before the COVID-19 pandemic, Chinese vaccine production was primarily oriented to the domestic market with average annual exports of just US $ 79 million during 2015-2019 (UN Comtrade website). In 2019, China stood as the world's largest producer and consumer of vaccines, with an estimated annual capacity of 1 billion doses of 55 different vaccines for 28 infectious diseases (Ghosh, 2020a). As in other countries, vaccines represent a small share of the entire pharmaceutical market; in 2018, 2.6% of the US$ 134.6 billion Chinese pharmaceutical market. There are two categories of vaccines in China. Category I includes vaccines against 17 infectious diseases included in the Expanded Program of Immunization that the government provides free of charge; Category II vaccines cover 11 diseases and must be paid by consumers (Zheng et al., 2018). Category I and II vaccines account for 40% and 60% of the Chinese vaccine market, respectively. Category I vaccines have low-profit margins and are supplied mostly by state-own pharmaceutical firms while Category 2 vaccines are mainly researched and produced by private manufacturers and MNPFs (Ghosh, 2020a). Some Category II vaccines are still under patent and are only produced by the MNPFs holding the patents and are, therefore, more expensive.

Vaccine R&D and manufacturing in China is conducted by 46 firms, distributed in three categories: the state-owned China's National Biotech Group (CNBG, a subsidiary of Sinopharm Group Co., Ltd.), 23 domestic private firms, and the subsidiaries of four MNPFs (Ghosh, 2020a, 2020b, 2020c). The National Vaccine and Serum Institute focuses on the development of polyvalent vaccines and new vaccine technologies and processes. Sinopharm dominates the cheaper Category I vaccines while Category II vaccines, with higher profit margins, are manufactured by all three categories of pharmaceutical firms.

Sinopharm (China National Pharmaceutical Group Corporation) owns more than 1,000 subsidiaries and six listed companies in health-related firms in China. Vaccine R&D and production within the Sinopharm Group is undertaken by CNBG and its six affiliated institutes (Changchun Institute of Biological Products, Chengdu Institute of Biological Products, Lanzhou Institute of Biological Products, National Vaccine and Serum Institute, Shanghai Institute of Biological Products, and Wuhan Institute of Biological Products) (Ghosh, 2020a). CNBG supplies more than 50% of all vaccine doses administered in the country and over 85% of the doses for government-sponsored free vaccines under China's Expanded Program of Immunization. In addition to R&D at each of these institutes, CNBG has a large R&D center in Beijing. A vaccine for Japanese encephalitis developed by the Chengdu Institute in collaboration with the PDP

PATH has been prequalified by the WHO (WHO Prequalification Website). The Changchun Institute was the first in China to develop a recombinant DNA-based vaccine against a subunit of the Hepatitis B virus.

Of the 23 private vaccine manufacturers, only the larger companies conduct R&D (Ghosh, 2020b). Eleven of them are members of the DCVMN and three (Hualang Biological Engineering, Sinovac Biotech Ltd., Xiamen Innovax Biotech Co. Ltd.) have developed vaccines prequalified by the WHO, (Table 4). Some private companies have succeeded in developing modern technologies vaccines; for instance, CanSino Bio has produced adenovirus-based vector vaccines against tuberculosis and Ebola. Beijing Minhai Bio has three vaccines registered in a dozen countries and Sinovac exports its vaccines to the Philippines, Mongolia, and Nepal. Before its acquisition by Novartis in 2011, Zhejiang Tianyuan BioPharmaceutical has exported its vaccines to Macao-China, Eastern Europe, South America, and India. Xiamen Innovax Biotech developed the first vaccine approved in the world against the Hepatitis E virus.

Finally, there are four global MNPFs with R&D and manufacturing presence in China (Ghosh, 2020c), namely, GlaxoSmithKline (GSK), Sanofi Pasteur, Pfizer, and MSD. The R&D center of GSK in China is the third-largest R&D center in the world and it is primarily dedicated to degenerative diseases. The acquisition of Novartis vaccine business (except influenza vaccines) by GSK in 2015, included Zhejiang Tianyuan BioPharmaceutical vaccine pipeline. GSK China focuses on influenza vaccines for sales in mainland China, Hong Kong, and Macao. Sanofi Pasteur has its world's third-largest presence in China with three manufacturing sites (one of them for vaccine production in Shenzhen), four domestic R&D sites (including a Biometrics Center in Beijing), the headquarters of its Asia-Pacific R&D, one of the only three global R&D operations hubs, and the first global research institute. Sanofi Pasteur China invests more than US$ 95 million annually. The company collaborates on more than 60 projects with China's top research institutions, including the Chinese Academy of Sciences, and has a Scholarship Program to recognize and train Chinese scientists in pharmaceutical R&D in the fields of structural chemistry, biology, and pharmacology. Pfizer has its main R&D center in Shanghai with satellite R&D centers in Wuhan, and Beijing employing more than 1,500 researchers in clinical product development, medical, regulatory, and safety. The R&D center in Shanghai acts as the Asia-Pacific R&D hub. Pfizer R&D centers in China have established collaborations with leading academic institutions and universities in China, including Peking University, Tsinghua University, Fudan University, and the China Academy of Sciences. MSD has three manufacturing facilities in China, R&D centers in Shanghai and Guangdong, its Asia Research & Development (R&D) headquarters in Beijing, and a life sciences center in Jiangsu Province. Back in 1994, the Chinese government foster a partnership between MSD and Shenzhen Kangtai Biological Products (SKBP) for the production of 20 million doses annually of recombinant DNA-based Hepatitis B vaccines. Chinese scientists from SKBP received training in an MSD facility in the United States, and the entire R&D and production module was then transferred to the SKBP factory. In 2012, MSD signed a 6-year agreement with Chongqing Zhifei Biological Products for the marketing of most MSD vaccines in China.

Some Chinese private pharmaceutical firms have established partnerships with foreign MNPFs. For instance, Chongqing Zifei Bio has partnered with MSD for the sale of vaccines developed by the latter; Beijing Vigoo Bio, Sinovac Bio, and the Institute of Medical Biology have jointly partnered with the Chinese Academy of Medical Sciences (Kunming Institute) to develop a vaccine against inactivated enterovirus 71; and Hualan Bio has partnered with the Chinese Academy of Sciences (Ghosh, 2020b).

An analysis of the effectiveness of public funding for vaccine and drug R&D in China in response to the 2014 Ebola epidemic concluded that increase funding resulted in a large and rapid increase in scientific publications and patent applications; however, the number of drugs and vaccines in later stages of R&D was small compared to basic and preclinical research outputs suggesting insufficient and fragmented incentives to translate basic research into advanced product development and immature public and private partnerships (Li et al., 2020). Some of these weaknesses were bridged during the COVID-19 pandemic. China was not only one of the first countries to research and develop vaccines for COVID-19 but it is also one of the largest manufacturers of these vaccines. China's vaccine R&D preparedness to respond to COVID-19 was possible through a collaboration between the Chinese government, Chinese academic institutions, and Sinopharm (Hu and Chen, 2021). One day before Wuhan's lockdown and three months before the United States launched its Operation Warp Speed, a task force led by the Chinese Ministry of Science and Technology sponsored 12 vaccine candidates with five different technologies to be developed by Sinopharm and some Chinese private companies. Thanks to a long-standing relationship between the Ministry of Science and Technology, academic institutions, and pharmaceutical firms, the task force was able to rapidly allocate the animal models required for preclinical research across the Chinese Academy of Sciences, universities, the army, and state-owned enterprises and also to identify which firms were best positioned to develop vaccines for COVID-19 (Hu and Chen, 2021). Hu and Chen (2021) refer to this partnership as a "*state-driven collaborative approach*" that differs from the market-oriented model of COVID-19 vaccine development in the United States and the government-oriented approach in the Russian Federation. For instance, the central government collaborated with vaccine companies to facilitate international phase 3 clinical trials in Brazil, Turkey, and Indonesia. The Beijing municipal government funded Sinovac's acquisition of a vaccine manufacturing plant.

Vaccine R&D by both state-owned and domestic private pharmaceutical firms in China has allowed the development of vaccines using traditional platforms as well as more modern technologies like viral-vectored vaccines. During the COVID-19 pandemic, China has developed inactivated vaccines (CoronaVac, VeroCell BBIBP-CorV/Sinopharm-Beijing, Sinopharm-Wuhan), recombinant subunit vaccines (ZF2001/RBD- Dimer, West China Hospital vaccine), and adenoviral-vectored vaccines (Ad5-nCoV/Convidecia) (Table 2). Most of the almost 2 billion doses of vaccines for COVID-19 administered in China have been inactivated vaccines developed by state-owned Sinopharm/CNBG and privately-owned Sinovac that have shown around 75% efficacy, received WHO approval for emergency use, and that China has exported to more than 100 countries (Riordan and Langley, 2021). mRNA vaccines have proved superior efficacy than inactivated vaccines. BioNTech and Pfizer have established an agreement with China's Fosun Pharma to distribute its mRNA vaccine. However, several Chinese firms are conducting R&D to develop mRNA vaccines for COVID-19. The first candidate is being developed by Suzhou Abogen Biosciences that raised US$ 700 million from investors—including Singapore's state investment firm Temasek Holdings, and Hillhouse-backed GL ventures—and has partnered with China's Academy of Military Sciences and Walvax Biotechnology (Reuters, 2021). Walvax has obtained approval from the governments of Mexico and Indonesia to conduct phase III trials for its mRNA vaccine candidate. The second candidate is being developed by Sinopharm, which is in the preclinical stages to develop an mRNA vaccine as well as a broad-spectrum recombinant protein vaccine that has already reached clinical trials (Riordan and Langley, 2021).

BOX 2: VACCINE R&D IN INDIA

Government expenditures on health in India in 2020 amounted to US$ 46.0 billion (IBEF, 2021). Between 2008 and 2019, overall gross R&D spending in India has decreased by 17% (UNESCO, 2021). Unlike most other large countries in Asia-Pacific, the contribution of the Indian government to R&D in 2018 as a percentage of GDP (0.35%) is larger than that of companies (0.24%) (Figure 4) (UIS database). Although the government has reduced tax incentives for firms conducting R&D, foreign multinationals have increased their R&D investments in India that reached US$ 738.1 million in 2018; most of these investments have been directed to the finance and banking sector and only 3.5% went to the pharmaceutical sector (UNESCO, 2021).

In the last decade, scientific publications in the biotechnology field have increased by 46%. Between 2016 and 2019, the number of startups multiplied by 34, but only 2.5% of them corresponded to the life sciences and health sector (UNESCO, 2021). In the last 15 years, the number of patents granted to foreign residents in India increased 7 times compared to those of Indian residents, which only doubled; pharmaceuticals and software are the two largest sectors by the number of patents granted. The number of researchers per million inhabitants (252.7 in 2018)—14.8 of which are in the health sciences sector—is lower than that in other large Asia-Pacific economies (Figure 5), and is among the lowest of the BRICS countries. India is experiencing a scientist drain and Indian nationals accounted for 23% of all foreign-born working in the United States of America in 2017 with a higher degree in science and engineering (UNESCO, 2021).

The Indian pharmaceutical market is currently valued at US$ 42.0 billion with exports of US$ 24.4 billion compared to US$ 16.9 billion in 2016. There are at least 25 research institutes involved in vaccine research. Of the 21 vaccine manufacturers in India, 14 are private and 7 are state-owned (public sector undertakings and government organizations) (Department of Science and Technology, 2021a; 2021b). Investment in R&D by most of the domestic vaccine manufacturers is relatively low as a percentage of sales compared to peers in other countries (Douglas and Samant, 2018). The largest pharmaceutical firms involved in vaccine R&D and manufacturing are the privately-owned Serum Institute of India, Bharat Biotech, Biological E., and Panacea Biotec. In fact, the Serum Institute of India (SII) is the world's largest producer of vaccines by the number of doses (1.3 billion doses per year) and also the cheapest with an average price of US$ 0.50 per dose. The SII has developed 23 vaccines for 14 diseases that are exported to 165 countries and its R&D and manufacturing facilities in India are considered on par with the best in the United States of America. It is estimated that half of all the immunized children worldwide have received at least one dose produced by the SII (Douglas and Samant, 2018). The SII has acquired several smaller firms in other countries, including in high-income countries; for instance, in 2021, it invested GBP 240 million to expand operations in the United Kingdom. The SII focuses its R&D on vaccines aimed at improving vaccination in low- and middle-income countries.

In March 2019, prior to the COVID-19 pandemic, the Department of Biotechnology (Indian Ministry of Science and Technology) launched the 5-year program Ind-CEPI Mission with the following objectives: 1) develop at least 2-3 vaccines for potential outbreak threats, 2) building coordinated preparedness in the Indian public health system, 3) create an interface between academia and industry to support vaccine R&D, 4) support capacity building, 5) strengthen inter-ministerial coordination for rapid vaccine development and testing to address known and unknown infectious disease threats, and strengthening of development frameworks, surveillance

and logistics for use of new vaccines. The Ind-CEPI Mission is implemented through the Biotechnology Industry Research Assistance Council (BIRAC), a not-for-profit entity, set up by India's Department of Biotechnology (BIRAC, 2019). In its first year of existence, Ind-CEPI has provided financial support for the following initiatives: 1) Global Chikungunya Vaccine Clinical Development Program, a collaboration between the Indian biotechnology firm Bharat Biotech International Ltd and the PDP International Vaccine Institute to advance a new vaccine (BBV87) for Chikungunya virus, which was in Phase II/III as of August 2021; 2) Gennova's mRNA-based COVID-19 vaccine (HGCO19), see below; 3) the Translational Health Science and Technology Institute was one of the seven laboratories recognized globally to measure the immune response to COVID-19 vaccines, under a CEPI call; and 4) in collaboration with India's Clinical Development Services Agency, Ind-CEPI launched the initiative "Partnerships for Accelerating Clinical Trials" that offers e-courses for more than 2,400 researchers across 14 countries (BIRAC, 2020).

During the COVID-19 pandemic, they Indian regulatory authorities have authorized clinical trials for six COVID-19 vaccines, namely: 1) Covaxin, the first indigenous COVID-19 vaccine developed by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV); 2) AstraZeneca's Covishield developed by the SII and Indian Council of Medical Research; 3) ZyCoV-D is a plasmid DNA vaccine developed by Zydus Cadila; 4) Dr. Reddy Laboratories reached an agreement with Russian Direct Investment Fund to produce 100 million of Gam-COVID-Vac (Sputnik) vaccine; 5) a COVID-19 vaccine produced by Biological E; and 6) Gennova Biopharma has teamed up with United States' biopharma company HDT Biotech Corporation to develop a COVID-19 vaccine using mRNA technology (HGCO19 vaccine). Gennova received a grant from Ind-CEPI mission and in August 2021 received approval from Indian regulators to start Phase II and III clinical trials.

Vaccine manufacturers in India have developed scientific and financial partnerships with universities and research institutes in India to develop new vaccines and/or commercialize them (Madhavi 2009). Bharat Biotech has collaborated with the All India Institute of Medical Sciences (AIIMS) to develop a vaccine for rotavirus, and with the International Centre for Genetic Engineering and Biotechnology (an intergovernmental organization established by UNIDO with laboratories in Italy, India, and South Africa) and the Medical Research Council to develop a recombinant vaccine for malaria. Jawaharlal Nehru University transferred the technology to develop an anthrax vaccine to Panacea Biotec. Indian Immunologicals Limited partnered with the Indian Institute of Science to develop an anti-rabies vaccine. The National Institute of Immunology developed a vaccine for leprosy that was then transferred for manufacturing and marketing to Cadila Pharmaceuticals. Hyderabad's Centre for Cellular and Molecular Biology transferred the technology for the Hepatitis B vaccine to Santha Biotech (Chakma et al., 2011).

Several Indian vaccine manufacturers have received technology transfer from Western pharmaceutical firms and these partnerships have intensified during the COVID-19 pandemic. For example: 1) Zydus Cadila partnered with research teams in India and Europe; 2) The SII partnered with Cadagenix, an American biotech firm, to develop COVID-19 vaccines and with the British Oxford Vaccine Group to manufacture them. Additionally, the SII invested US$ 250 million and teamed up with Astra-Zeneca to develop, manufacture and stockpile vaccine dosis before the completion of trials. The Bill and Melinda Gates Foundation donated US$ 150 million to the SII, channeled through GAVI, to produce 100 million vaccines in collaboration with the PDP International Vaccine Institute (IVI); 3) Bharat Biotech has partnered with the American biotech firm FluGen Inc and with virologists at the University of Wisconsin to produce COVID-19

vaccines; 4) Indian Immunological has collaborated with Australia's Griffith University to develop a COVID-19 vaccine using a new technology platform; 5) Lastly, it is worth noting the financial mechanism used by Mynvax to fund its R&D and manufacturing of COVID-19 vaccines. Before the COVID-19 pandemic, Mynvax, an Indian vaccine startup with incubation funding from the Institute of Science and the Society for Innovation and Development, developed influenza vaccines. For its COVID-19 vaccine, Mynvax has raised venture capital from Accel, LetsVenture and 1Crowd, and other early-stage angel investors with the support from the Indian government (BIRAC), and Kotak Investment Advisors.

India is home to the largest number of foreign and domestic CROs. The rapid growth of the Indian CRO market, which in Asia ranks second in market value after China, has been driven by changes in intellectual property rights legislation (Table 5). Many Indian-owned CROs have been expanding abroad and most of their clients are Western pharmaceutical companies (Zainzinger, 2021).

BOX 3: VACCINE R&D IN ASEAN COUNTRIES

Diversity in the levels of economic development among the countries of the Association of Southeast Asian nations (ASEAN) is also reflected in the great regional variability in terms of R&D intensity. In 2017, gross expenditures on R&D relative to GDP ranged from 1.9% in Singapore, 1.4% in Malaysia, or 1.0% in Thailand to 0.12% in Cambodia and 0.03% in Myanmar (UNESCO, 2021). The sources of R&D funding also vary across ASEAN countries; in the latest year for which data was available for the 2015-2017 period, business represented the largest source of R&D in Thailand (80.8%), Viet Nam (64.1%), Malaysia (56.9%), and Singapore (52.2%); in contrast, the government was the largest source of R&D funding in Brunei Darussalam (97.0%), Indonesia (87.7%), Myanmar (77.4%), and the Philippines (49.4%) (UIS database). During the same period, Singapore ranked first in the number of researchers per million inhabitants with 6,803 and almost tripled and quintupled the following countries—Malaysia with 2,397 and Thailand with 1,350; at the other end of the spectrum, Myanmar and Cambodia had 29 and 30 researchers per million inhabitants (UNESCO, 2021).

In 2019, Indonesian scientists not only published more articles than scientists in any other ASEAN country, but Indonesia has also been the country where the output of scientific publications has grown the fastest since 2013, 13 times. This surge has been largely driven by reforms introduced in 2017 that linked career progression to the number of publications in international peer-reviewed journals (UNESCO, 2021). Malaysia and, by some distance, Singapore were the next countries in the absolute number of scientific articles in 2019. Singapore leads ASEAN in the number of scientific publications per million inhabitants with around a third of all articles in health sciences. An analysis of the articles published by scientists from ASEAN that year revealed that the most common collaborators were scientists from the United States of America and Australia, more than from other ASEAN countries (UNESCO, 2021). In 2019, Singapore (3,468), Malaysia (1,016), and Thailand (480) were the ASEAN countries with the most patents granted (UIS database).

The stakeholder meetings hold in 2013 by the Southeast Asian Ministers of Education Organization (SEAMO) with health policymakers, researchers, and the pharmaceutical industry on the status of health R&D identified the development of new vaccines for Dengue, HPV, HIV, malaria, Japanese encephalitis, Leptospirosis, and influenza as the main R&D priorities for

vaccines in ASEAN (SEAMO, 2015). Meetings of vaccine experts from all ASEAN members and the WHO held in 2014 and 2015 emphasized the importance of resource pooling to support vaccine R&D for regional specific needs and identified four areas for regional collaboration and integration, namely: system development for vaccine security, human resource development, ASEAN price policy for vaccine and pooled procurement, and communication and coordination for ASEAN vaccine security and self-reliance (Siripitayakunkit, 2017).

The *2016-2020 Vaccine Strategic Plan* for the Southeast Asia WHO region, which also includes ASEAN countries, established as its Strategic Objective 6 that all its member countries should aim to conduct clinical trials for vaccines and develop Good Clinical Practices standards (WHO-SEARO, 2017). As of March 2022, all ASEAN countries except Brunei Darussalam have conducted clinical trials for vaccines; Thailand and the Philippines accounted for the largest share of clinical trials on vaccines among ASEAN countries, with 36.5% and 22.6%, respectively (ClinicalTrials.gov) (Figure 7). Vaccine R&D and manufacturing in ASEAN have been largely focused on traditional vaccines included in national pediatric immunization programs. As the R&D and production capabilities of many ASEAN vaccine manufacturers have improved and some of their vaccines have obtained WHO prequalification status, ASEAN-made vaccines have reached donor-funded markets not only in the region but also in other developing countries.

Because of its population, **Indonesia** is one of the largest and fastest-growing vaccine markets in Asia-Pacific, which is estimated at US$ 10.1 billion. Although Indonesia is the biggest vaccine exporter in ASEAN (US$ 96.0 million in 2019), its vaccine industry is still relatively small compared to other countries of similar size. The state-owned company PT Bio Farma (Persero) is the only vaccine manufacturer in the country and focuses on large volumes of pediatric vaccines included in the National Immunization Program for which the firm is the only provider (Table 4). PT Bio Farma was the first domestic vaccine manufacturer in ASEAN to get some of its vaccines prequalified by the WHO. WHO prequalification made Bio Farma vaccines eligible for UNICEF procurement and also fostered international partnerships. For example, Bio Farma has developed influenza vaccines thanks to technology transfer from the Biken Institute in Japan and a rotavirus vaccine through its partnership with Australia's Murdoch Children Research Institute (Tull, 2021). In the past, most of the R&D conducted by Bio Farma was funded by ODA. As a middle-income country in the World Bank classification (although it was downgraded to lower-middle-income in July 2021), Indonesia is no longer a priority country for global donors—funding from GAVI ended in 2018—and has to self-finance its state-owned vaccine industry (Tull, 2021).

As of March 2022, Indonesian regulators have authorized five clinical trials for COVID-19 vaccines, namely, a locally developed vaccine by PT Bio Farma (SARS-CoV-2 Protein Subunit), two Chinese vaccines (Anhui Zhifei Longcom's ZF2001 and West China Hospital's Sf9 cell vaccine), and two from Western firms (Aivita Biomedical Inc's AV-COVID-19 and ReiThera's GRAd-COV2). PT Bank HSBC Indonesia financed the purchase of Astra Zeneca and Sinovac COVID-19 vaccines for fill-and-finish by PT Bio Farma. Besides developing its recombinant protein subunit vaccine, PT Bio Farma aims at being chosen by the WHO as one of the few global mRNA vaccine manufacturer hubs to be set up outside the United States of America and the European Union.

In 2019, **Thailand** as ASEAN's second-largest exporter of vaccines after Indonesia, mainly influenza vaccines for export to other ASEAN countries (UN Comtrade database). The main government agencies in Thailand involved in setting the R&D agenda and allocating research

funds are the Thai National Institute of Health (Department of Medical Sciences, Ministry of Health), the National Research Council of Thailand, the National Science and Technology Development Agency, the National Science Technology and Innovation Policy Office, and the Thailand Centre of Excellence for Life Sciences. The Thai National Institute of Health is one of the only five Asia-Pacific R&D funding organizations included in GLOPID-R.

Various organizations within the Thai Ministry of Health are involved in early stages of R&D for vaccines; namely, the Food and Drug Administration, the National Vaccine Institute, and the Department of Disease Control. Among its organizational objectives, the National Vaccine Institute aims to strengthen the national vaccine R&D infrastructure, train and capacity build national vaccine R&D and manufacturing, and conduct technology transfer through its training center.

The main players in vaccine R&D and manufacturing in Thailand are the state-owned Government Pharmaceutical Organization (GPO), the Queen Saovabha Memorial Institute-Thai Red Cross, and the private firm BioNet Asia (Table 4). Nevertheless, other smaller firms and research organizations participate in vaccine R&D, either by themselves or in partnership with foreign players. For instance, the Thailand Ministry of Public Health has also established a partnership with the United States of America's National Institutes of Health and the United States Military HIV Research Program to conduct clinical trials for an HIV vaccine. The Thai Armed Forces Research Institute of Medical Sciences also conducts R&D on vaccines for enteric diseases, malaria, and HIV-AIDS. Biovalys markets vaccines from different manufacturers (SEAMEO, 2013). Siam Bioscience was selected by Astra-Zeneca to produce its COVID-19 vaccine for ASEAN countries and obtained WHO approval. French MNPF Sanofi Pasteur established in 2013 a joint venture with GPO—the Government Pharmaceutical Organization-Merieux Biological Products (GPO-MBP)—to conduct process development and finish-and-fill for new vaccines at the regional level. Under the arrangement, Sanofi Pasteur transfers supplies of the vaccine as bulk and GPO-MBP formulate and release finished forms. Sanofi Pasteur has also entered into a collaborative licensing agreement with Mahidol University to develop a Dengue vaccine. BioNet Asia is one of the most active and innovative ASEAN firms in vaccine R&D. It has developed low-cost vaccines for Haemophilus influenzae type b (Hib) using high-yield fermentation and conjugation technologies and, in collaboration with the National Science and Technology Development Agency and several research institutes, has patented processes for the development of a dengue vaccine. In collaboration with the National Science and Technology Development Agency and Mahidol and Chiang Mai universities, BioNet has developed a dengue vaccine, which was later improved through a partnership with the Pasteur Institute and biotech firm In-Cell-Art in France. In collaboration with Thailand's National Science and Technology Development Agency and scientists in South Africa, BioNet has developed a pentavalent vaccine covering diphtheria, tetanus, pertussis, hepatitis B, and meningitis (NSTDA, 2012; WHO-SEARO, 2017).

Singapore's Economic Development Board identified biopharmaceuticals as a higher value-added sector with a competitive advantage. This has resulted in the proliferation of science parks and biopharmaceutical incubators that along with the National University of Singapore and Nanyang University have placed Singapore as a world-class biopharma research hub. Many of the world's largest MNPFs have manufacturing and/or R&D facilities in Singapore and some have established regional corporate headquarters in the country. In 2009, GSK built a vaccine plant although it has been primarily involved in bulk production. In April 2021, Sanofi announced a US$ 450 million investment over five years to produce innovative vaccines on a massive scale for

Asia. The German firm BioNTech, a pioneer in mRNA vaccines, will build a new plant that from 2023 onwards will produce COVID-19 vaccines for ASEAN and beyond.

Viet Nam's National Foundation for Science and Technology Development (NAFOSTED), affiliated with the Ministry of Science and Technology, was founded in 2008 with the goal of implementing funding to develop the research capacity of scientists, promoting academic exchange, and international cooperation with funding agencies in the UK, Germany, Australia, and Belgium. NAFOSTED concentrates its resources on basic research funding, allocating resources for applied research and translating research results into practice. Viet Nam is approaching self-sufficiency in most vaccines for the 10 diseases included into its Expanded Program on Immunization 2016-2020. Vaccine R&D and manufacturing take place in four state-owned companies (VABIOTECH, DAVAC, POLYVAC, IVAC) (Table 4). Viet Nam aims to acquire full capabilities in the production of traditional vaccines and its development portfolio matches national needs, based on fill-finishing of bulk vaccines. The four manufacturers have received technical and financial support for clinical trials and vaccine product and process development from ODA, foreign pharmaceutical firms, and PDPs. For instance, the Japan International Cooperation Agency (JICA) provided financial support for a 5 year-project to transfer technology from Japan's Kitasato Daiichi Sankyo Vaccine Co., Ltd. to POLYVAC to produce a measles-rubella vaccine in conformity with WHO-current Good Manufacturing Practices (JICA, 2018). POLYVAC (Center for Research and Production of Vaccines and Biologicals) conducted R&D on vaccines for rotavirus in collaboration with Vietnam's National Institute of Hygiene and Epidemiology and the support of PDP PATH. Eventually, POLYVAC succeeded in developing a new rotavirus vaccine that is stable at fridge temperatures--and more suitable for use in low- to middle-income settings--and that a recent study found to be as effective as other vaccines prequalified by WHO (Thiem et al., 2021). The PDP PATH and the WHO have also supported IVAC to develop seasonal and pandemic influenza vaccines. PATH also helped VABIOTECH with technical training, development of the cell-based Good Manufacturing Practices process, and funding to improve their production capabilities (Tull, 2021).

The Philippines, **Malaysia**, and **Brunei** do not have significant vaccine R&D and production and import most of the vaccines for their national immunization programs. Nevertheless, the first two are increasingly participating in clinical trials by CROs. **Lao PDR, Cambodia**, and **Myanmar** rely mostly on vaccines provided by donors.

Several scientific associations spanning across several ASEAN countries promote scientific collaborations. Seven science and technology societies from six ASEAN countries (Indonesia, Malaysia, the Philippines, Singapore, Thailand, and Viet Nam) are integrated in the Association of Academies and Societies of Sciences in Asia (AASSA) (see section 3.5). In addition, the Southeast Asia Infectious Disease Clinical Research Network (SEAICRN) is a partnership between hospitals and research institutions in Thailand, Viet Nam, and Indonesia with the goal of developing clinical research collaborations on emerging infectious diseases of public health relevance. It receives technical support from the National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIH-NIAID) (United States of America) and the Wellcome Trust (United Kingdom) and has the WHO as an observer. SEAICRN is funded by the NIH-NIAID and Wellcome Trust with in-kind support from the governments of Thailand, Viet Nam, and Indonesia. The ASEAN Network for Drugs, Diagnostics, Vaccines and Traditional Medicines Innovation (ASEAN-NDI) was constituted in 2010 and it was the initiative of the Philippines government, endorsed by the ASEAN Committee on Science and Technology and has the support of WHO's Special Programme for Research and Training in Tropical Diseases (TDR).

ASEAN-NDI maps the overall research capacity of ASEAN countries in vaccines, drugs, traditional medicines, and diagnostics and their ability to respond to local public health needs. Among its stated goals, ASEAN-NDI aims at: 1) strengthening cooperation of ASEAN member states in health R&D: sharing of information on infectious diseases; transfer of knowledge and/or technology, facilitate collaboration in R&D initiatives; 2) Development of programs and projects which address public health concerns in ASEAN: Improve disease surveillance, develop research projects to prevent and/or mitigate the spread of diseases through innovative countermeasures; and 3) Development of strategies to strengthen ASEAN member states' capacity and competitiveness in the development and delivery of health-related products and services: Facilitate research and cross-country exchange of experience, products, and resources, establish regional support systems and networks to narrow the gap among ASEAN member states.

3.5 Regional cooperation in vaccine R&D in Asia-Pacific

Vaccine R&D and production is concentrated in a few middle- and high-income countries. Some vaccine companies in developing countries like India have become regional and global manufacturers ahead of larger MNPFs in high-income countries. However, not only do most developing nations lack the financial and technological resources to invest in vaccine R&D but it is also not sensible to develop and replicate R&D capacities in each country. Since most vaccines are biological products with variability in yields, even when there is technology transfer from more advanced firms, the manufacturing of vaccines requires not only more time than therapeutic drugs but also need to conduct new clinical trials and obtain new regulatory approvals. Consequently, most developing countries depend on the vaccines researched, developed, and manufactured by other nations that they have to obtain through trade as well as global/regional cooperation.

Regional cooperation in health during an epidemic or pandemic can help contain its spread and optimize the utilization of medical infrastructures and supplies within the region. This is particularly important for developing countries with weak health systems and limited resources in regard to hospital capacity, supplies, number of healthcare workers and management systems. Regional cooperation in vaccine R&D can take many forms, from informal cooperation between scientists in joint R&D projects to the coordination of activities among all stakeholders—governments, regional intergovernmental organizations, or region-wide private associations—in the pooling of R&D funding or the prioritization of diseases for vaccine R&D pipelines.

The COVID-19 pandemic has highlighted the possibilities of international cooperation but also its potential fragility. On the one hand, the pandemic has also made evident how beggar-thy-neighbor policies with export restrictions on medical protective equipment and vaccines can impact production networks of these products. Vaccine nationalism already took place during the H1N1 epidemic and has reemerged during the COVID-19 pandemic. Attempts to waive intellectual property rights on COVID-19 vaccines have been blocked by pharmaceutical firms owning them. These inward-looking strategies are not an option for many middle- and low-income countries that depend on the vaccines

produced elsewhere. On the other hand, the COVID-19 pandemic has shown that international cooperation between countries in Asia-Pacific and beyond was essential for accelerating the timeline of COVID-19 vaccine development (Chakraborty et al., 2021). International cooperation in R&D during the COVID-19 was in part possible due to previously existing informal networks and formal institutional linkages between the different stakeholders involved. For instance, the sharing of data and knowledge by the scientific community, international PDPs and other non-PDP intermediaries channeling funding from governments and philanthropic foundations to companies and institutes capable of developing vaccines, and international organizations and regional intergovernmental associations coordinating the activities of public and private stakeholders. The global nature of the COVID-19 pandemic has fostered unprecedented levels of investments in R&D not only within countries but also across borders. Organizations created before the pandemic like CEPI and GAVI created along with the COVAX facility to accelerate R&D and production of vaccines for COVID-19.

a) Pharmaceutical firms in developing countries can build their vaccine R&D capabilities through technological transfer from PDPs and/or pharmaceutical firms from high-income countries. But pharmaceutical firms in developing countries have also gained technological expertise through South-South and South-South Triangular (SSTC) cooperation. For instance, Kim and McCann (2021) and Saluja et al., (2021) showcased the SSTC for R&D on a new typhoid conjugate vaccine; the Nepal Health Research Council with help from the International Vaccine Institute, Republic of Korea's SK Bioscience, and Indonesia's Bio Farma, and funding from the Bill and Melinda Gates Foundation, and International Vaccine Institute member states conducted phase III clinical trials in Nepal for this vaccine. Another example of successful SSTC in vaccine R&D was the oral cholera vaccines developed by Santha Biotechnics Ltd. (India), VABIOTECH (Viet Nam), and EuBiologics Co. Ltd. (Republic of Korea) (WHO, 2017; Odevall et al., 2018). Viet Nam’s regulators were not certified yet by the WHO and locally-made vaccines could not be prequalified for procurements by UN agencies. Since the Indian regulatory authority is fully certified by WHO, the International Vaccine Institute established a PDP project with VABIOTECH with funding from the Republic of Korea and Sweden and the Gates Foundation and facilitated technology transfer from Shantha Biotechnics to VABIOTECH. The new vaccine was tested in clinical trials and licensed in India and Viet Nam. The International Vaccine Institute then worked with Shantha Biotechnics vaccine to get its vaccine prequalified by WHO (WHO, 2017; Odevall et al., 2018). Shantha Biotechnics could not meet global demand and the International Vaccine Institute established another PDP with EuBiologics. After the technology transfer, the International Vaccine Institute and EuBiologics initiated R&D for fed batch production. Following successful clinical trials in the Philippines, EuBiologics improved its temperature stability, and the vaccine was eventually prequalified by WHO for global distribution by UN agencies.

b) Regional institutions and intergovernmental organizations can help promote and coordinate regional cooperation. Regional intergovernmental organizations can play

multiple roles in the context of R&D to address health emergencies. Amaya and De Lombaerde (2021) have proposed four major functions of intergovernmental organizations before and during health emergencies: 1) First, they can bridge global and national levels; vertically, by translating global agreements to national policies and targets; and horizontally, by supporting and coordinating actions by countries in addressing cross-border policy challenges. Regional organizations also coordinate countries' responses with WHO regional offices (EMRO, WPRO, SEARO), support epidemiological surveillance and encourage sharing of information. They can also advocate for their members' interests at international forums like the World Health Assembly; 2) Second, they can facilitate the cross-border mobilization of medical supplies, vaccines and their intermediates, encouraging maintaining open borders for good while controlling the spread of the disease. Regional intergovernmental organizations can pool strategic supplies or manage them across the region; 3) Third, they can facilitate the joint procurement of medical supplies, drugs, and vaccines through pooled purchasing, ensuring a lower price for low-income countries; 4) Fourth, they can coordinate the work of donors and partners to support countries.

During the Severe Acute Respiratory Syndrome (SARS) epidemic, the ASEAN Secretariat issued recommendations and supported member countries in their responses to contain its spread, a strategy that was praised by the WHO (Amaya and De Lombaerde, 2021). ASEAN has established a *Permanent Committee on Science and Technology* (PCOST) to promote cooperation in science, technology, and innovation (ST&I) among ASEAN members and to raise the level of scientific and technological advancement in member states. The ASEAN *Plan of Action on ST&I* (APASTI) *2016-2025* aims, inter alia, to intensify R&D collaboration between the public and private sector to address common problems in ASEAN, develop ST&I human resource, network ST&I centers of excellence across ASEAN, strengthening ST&I infrastructure, and create closer cooperation in R&D with ASEAN Dialogue partners (Australia, Canada, China, European Union, India, Japan, Republic of Korea, New Zealand, Russia, and the United States of America) (ASEAN, 2017). In April 2020, the United States of America launched the U*S-ASEAN Health Futures Initiative* to strengthen public health in ASEAN through three areas: R&D, health system capacity, and developing human capital in health. In the first area, joint R&D in ASEAN includes more than 300 active joint research projects between ASEAN members and more than 20 institutes of the US National Institutes of Health, more than US$ 30 million in research grants to universities and government research institutions in ASEAN over the last 10 years, and support for clinical trials for treatments of infectious diseases (US-ASEAN, 2020). The United States' ODA (USAID) collaborates with the ASEAN Secretariat to develop APHECS. Likewise, the United States Centers for Disease Control and Prevention has established the U*S-ASEAN Infection Prevention and Control Task Force*.

ASEAN had a very active profile during the COVID-19 pandemic with at least 11 new health initiatives, including the establishment of the ASEAN Centre for Public Health Emergencies and Emerging Diseases (ACPHEED) to manage and coordinate resources

in health response and the ASEAN Public Health Emergency Coordination System (APHECS) program to improve and harmonise the preparedness and response to health emergencies. As of June 2021, the United States of America and the European Union have committed to donating 500 and 100 million doses of vaccines for COVID-19, respectively, to low- and middle-income ASEAN countries through the COVAX initiatives (ASEAN, 2021; US-DoS, 2021).

Although the South Asian Association for Regional Cooperation (SAARC) organization had been relatively inactive for several years, during the COVID-19 pandemic, SAARC created a health emergency fund of US$ 18 million to pool human resources and supplies and sharing of knowledge (UNESCAP, 2021, LSE-DIR, 2021). In addition to sharing medical supplies, SAARC countries planned the creation of mechanisms for the coordination of R&D activities and disease surveillance. The World Bank lauded SAARC short-term collaboration on COVID-19 for its potential longer-term spillovers to increase regional integration (LSE-DIR, 2021).

UNESCAP can act as a catalyst for these type of collaborative R&D initiatives at the Asia-Pacific level by bringing together all stakeholders—member states, sub-regional organizations such as ASEAN or SAARC, multilateral development banks, companies, philanthropic foundations and civil society—and harnessing its substantive and management expertise in regional cooperation.

c) Regional collaboration on R&D can also be channeled and coordinated through scientific associations and research networks. The Association of Academies and Societies of Sciences in Asia (AASSA) was constituted in 2012 as a non-profit organization that ecompasses the scientific and technological academies and science societies in Asia and the Pacific. Currently, it includes 32 national academies and societies of sciences from 30 countries. AASSA organizes 4-6 seminars every year and publishes a similar number of reports on ST&I issues. However, AASSA activity has been relatively low compared to counterparts elsewhere. For instance, in the context of the COVID-19 pandemic, AASSA held a one-day webinar aimed at identifying the key activities and recommendations of member academies in response to COVID-19 Pandemic. In comparison, the Africa Academy of Science has a wide range of activities, like funding scholarships and research grants, strengthening R&D infrastructure in research institutes across Africa, fostering and funding joint R&D projects and networks between African scientists, and establishing partnerships with world leading scientific organizations and research funding agencies for capacity (Box 4).

In the last two decades, several regional and subregional research networks connecting research institutions across Asia-Pacific have been established. Although they can play important roles in promoting vaccine R&D in the region, some of these initiatives have exhibited relatively low levels of activity since their creation. At the subregional level, the Southeast Asia Infectious Disease Clinical Research Network (SEAICRN) facilitates clinical research collaborations between hospitals and research institutions in Thailand, Viet Nam, and Indonesia (Box 3) (SEAICRN website). WHO-SEARO has proposed the

creation of Regional Vaccine Research Networks that bring together governments, research institutions, manufacturers (including firms in the DCVMN) and the WHO to promote sharing of information, regional R&D and address ethical guidelines and intellectual property rights issues (WHO-SEARO, 2003). It is also worth highlighting the ASEAN Network for Drugs, Diagnostics, Vaccines and Traditional Medicines Innovation (ASEAN-NDI), which was launched in 2010 (Box 3) (ASEAN-NDI website). Other initiatives are disease-specific; for instance, the AIDS Vaccine for Asia Network (AVAN), was launched in 2011 to facilitate the development of a regional strategy that accelerates R&D of an HIV/AIDS vaccine through government advocacy, improved coordination, and harmonization of research; develops clinical trial and manufacturing capacity; supports ethical and regulatory frameworks, and ensures community participation.

BOX 4: AFRICAN ACADEMY OF SCIENCES

The African Academy of Sciences' (AAS) mission is recognizing excellence in science and technology through fellowship and award schemes, providing advisory functions for shaping national and regional ST&I policies and implementing key African-wide ST&I programs.

The Alliance for Accelerating Excellence in Science in Africa (AESA) is a partnership between the AAS, the African Union Development Agency, WHO, United Nations Commission for Africa, and regional and global partners, including ODA, philanthropic foundations, universities and research funding agencies in the United States of America and the United Kingdom. AESA's main mission is contributing to R&D agenda setting, mobilizing R&D funding, and managing regional ST&I programs that promote scientific excellence, mentor emerging research leaders, and translate R&D into new products and processes that improve lives in the continent. AESA offers competitive grants that support African scientists to produce quality research that addresses Africa's health and developmental challenges, to target critical gaps toward creating R&D environments that support a vibrant R&D culture and leadership development, and the development of an innovation and entrepreneurial culture. AESA also works with partners in and outside Africa to ensure ST&I programs are adequately funded.

One of the flagship projects implemented by AESA is DELTAS Africa (Developing Excellence in Leadership, Training, and Science in Africa), which is funded with US$ 100 million and has supported 11 research programs in 54 African institutions and 24 European partners with training fellowships and research infrastructure. DELTAS' goal is to strengthen, sustain, attract and retain researchers with the capacity to publish and lead high-quality research that is relevant to the health research agenda in Africa. The first DELTAS program covered the period 2015-2020 with financial support from the Wellcome Trust and the UK's Department for International Development and the New Partnership for Africa's Development (NEPAD). DELTAS Africa funds four strategic areas: a) Scientific quality to produce world-class scientific research that addresses African health and research priorities through collaborations with leading universities, research institutions, and think tanks; b) Research training by providing tertiary and postgraduate science students and professionals with the academic support, training, and research facilities needed to develop into world-class researchers. c) Scientific citizenship by fostering the communication of research findings to policymakers to ensure that research findings inform policy. In addition, engage the public to raise awareness about scientific advances, increase the uptake of new health policies, and strengthen relationships with local communities; and d) Research

management and environment: Creating professional environments that develop and support research capacity.

Directly related to vaccine and drug R&D, AESA has also implemented a capacity-building program and a clinical trial database. First, the Johnson & Johnson-AESA R&D Fellowship funded by the Johnson & Johnson Foundation trains physicians, pharmacists, epidemiologists and/or public health specialists for two years in public health and tropical medicine modules—at the Institute of Tropical Medicine (Antwerp, Belgium)—, in leadership, communication, project management, and drug development. Fellows are then assigned to late-stage development programs at plants/offices of the company working on infectious diseases, neglected tropical diseases, and vaccines. The ultimate goal of the fellowship is to address shortcomings in R&D knowledge and experience in many African countries so, upon return of the fellow, she/he will contribute to the creation of qualitative clinical development centers of excellence in Sub-Saharan Africa. A second AESA program relevant to vaccine and drug R&D is the Clinical Trials Community, a database of African clinical trials sites and their capabilities funded by the Bill & Melinda Gates Foundation and built with the feedback of all stakeholders in vaccine R&D, namely, African clinical trial researchers, biopharmaceutical sponsors, PDPs, representatives from African regulatory and ethics entities, CROs, and community participants. The goal of the database is to increase clinical trial investments in Africa and make accessible the information on regulatory procedures across countries.

Other initiatives sponsored by the AAS are: 1) The AAS Open Research, an innovative open-access peer-reviewed publication for researchers supported by the AAS to disseminate their results; 2) The Global Grant Community is a digital platform aiming to reduce the cost and time taken to connect funders and grant receivers; 3) The Coalition of African Research and Innovation is a platform set to achieve the SDGs through resource mobilization, advocacy, and partnership development; 4) Human Heredity and Health in Africa (H3Africa) that aims to understand how human genes and the environment influence disease in African populations; 5) Grand Challenges Africa is funded by the African Union Development Agency and the Bill & Melinda Gates Foundation and awards seed and full grants to Africa-led scientific innovations to help countries better achieve the SDGs. It supports big, bold impactful innovative ideas that have a potential for impact, scale, and sustainability. GC Africa builds on the previous successes of local Grand Challenges programs and a strong base of African Grand Challenges grantees.
In 2017, the African Union launched the African Center for Disease Control and Prevention (Africa CDC) as a pan-African institution to support and strengthen the capacity and preparedness of the public health institutions of member states to detect, prevent, control, and respond to health threats and outbreaks based on data-driven interventions and programs. At the start of the COVID-19 pandemic, AAS-AESA, Africa CDC, the African Union Development Agency/New Partnership for Africa's Development, and WHO-Africa Regional Office established a COVID-19 Task Force that engaged 1,400 African scientists to define African research priorities for the pandemic that supplement the WHO Roadmap and that can also serve as a roadmap for future health emergencies. The Task Force identified six key research priority areas where more scientific knowledge is needed for African R&D to be ahead of the pandemic; one of the priorities was to develop a coordination mechanism for pan-African clinical trials on drugs and vaccines.

4. Policy recommendations

4.1 Policy recommendations on the prioritization of targets in the vaccine R&D pipeline

To build and strengthen R&D preparedness, national governments, and regional and subregional inter-governmental 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, they can be procured from multiple sources, and can be produced at relatively low marginal costs. Countries with vaccine manufacturing capacity should aim to R&D and produce these vaccines domestically or coordinate their production at the regional/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. The methodology of prioritization used by WHO is readily available and draws on established best practice and national and regional experience and is similar to the methodology used by CEPI to prioritize its vaccine R&D targets (WHO, 2016; Mehand et al., 2018a; Mehand et al., 2018b; Gouglas and Marsh, 2019; Jonkmans et al., 2021; Kojom and Singh, 2021). Of the multiple prioritization methods, three meet the criteria established by WHO R&D Blueprint, namely: 1) a semiquantitative Delphi process to narrow the list; 2) multicriteria decision analysis to rank them; and 3) questionnaires to standardize information gathering from participating experts. As most emerging infectious diseases originate from zoonotic threats, a One Health approach should be used convening experts in animal health. To reduce expert bias, it is recommended that members in the prioritization committee change periodically (Mehand et al., 2018b). In the case of developing countries and subregions lacking the expertise to implement this methodology, WHO and WHO regional offices, donor countries, PDPs and non-PDP intermediaries, and/or international organizations (e.g., UN-ESCAP, scientific associations) can provide the technical assistance and capacity building of health and ST&I policymakers.

For existing diseases of predominantly domestic or subregional and regional prevalence, the choice of which diseases to prioritize should be guided by several parameters, particularly: a) prevalence and burden and cost of illness of each disease (e.g., case fatality, DALYs, economic impacts) in the country, Asia-Pacific region or subregions, b) its infectiveness and potential for epidemic and pandemic spread, c) the global status of

R&D for each disease, the existence, d) availability and cost of other vaccines, e) other qualitative, intangible, or subjective criteria depending on the stakeholders; and, importantly, e) the financial viability and R&D capacity to generate new vaccines (Andre 2002; WHO-SEARO, 2003; Mehand et al., 2018b; Gouglas and Marsh, 2019; Jonkmans et al., 2021; Sharma, 2021).

The prioritization of R&D investments should also include the building of preparedness for still unknown pathogens (see below in Section 4.5). Most of the newly emerging human infectious diseases are caused by viruses that jump from other animals (zoonotic diseases). It is estimated that there are 1.6 million of viruses affecting animals of which only a small number can infect humans. Identifying in advance and including in prioritization lists pathogens in animals with high-risk to infect humans is key in developing R&D preparedness for the next zoonotic threat. Advances in genomic sequencing, bioinformatics, and artificial intelligence are now being used to assess the risk of human infection upon exposure to infected animals or animal samples. Machine learning has been recently used to identify 41 zoonotic threats by viruses that have not yet jumped to humans but that based on their genome relatedness to previously known animal-infecting viruses capable of infecting humans are of high-risk (Mollentze et al., 2021).[14] This new genome-based zoonotic risk assessment provides a rapid and low-cost approach to virus surveillance and targeting of vaccine and drug R&D for Disease X.

4.2 Policy recommendations on approaches to overcome market failures in vaccine R&D.

As reviewed in Sections 2.4 and 3.4, vaccines are domestic, regional and/or global public goods whose value exceeds their R&D and manufacturing costs and commercial value. To improve the incentives for pharmaceutical firms to invest in vaccine R&D, public health priorities should be aligned with private economic incentives. Insufficient incentives to innovate in vaccines and the possibility of market failures in vaccine R&D open the door for targeted external interventions (supply- and/or demand-side strategies) to stimulate vaccine R&D and manufacturing when there are no effective vaccines, they are not supplied at adequate levels, their costs are too high, and/or their formulation (e.g., temperature requirements, form of administration) are not suited for the prevailing conditions in the country.

On the supply side, governments can incentivize vaccine R&D through increasing funding for basic and preclinical research in universities and public research institutes. 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 above, 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

[14] Retrospectively use of this approach would have identified COVID-19 among these viruses in animals with high-risk of infecting humans.

pharmaceutical industry. In situations where it is deemed important the involvement of developing countries in later stages of vaccine R&D (e.g., clinical trials, see below) and/or because of their size or other factors (e.g., geography, epidemiological status), the WHO, regional intergovernmental organizations, regional scientific societies, and PDPs can provide technical training and financial resources to develop and strengthen vaccine R&D physical and human capital infrastructure. The distribution of labor among stakeholders in increasing funding for R&D can include the following activities:

a) At the national level, governments can mobilize national financial and scientific resources for R&D on prioritized vaccines. To ensure sustained support for health R&D, ST&I policy plans should be aligned with national priorities and national agencies and strategies for R&D funding should be insulated from changes in the political leadership.

b) PDPs can not only act as financial intermediaries, channeling resources from ODA and philanthropic foundations, but they can also facilitate technical transfer from advanced to less advanced pharmaceutical firms and assist national regulatory authorities to achieve WHO certification, which is required for prequalification of vaccines for United Nations procurement. At the same time, governments in developing countries should facilitate and foster PDP activities in their territories by strengthening the regulatory framework related to intellectual property rights and clinical trials.

c) Regional intergovernmental organizations and forums can play a more active role in coordinating public and private efforts on vaccine R&D targeting diseases of regional prevalence and emerging infectious diseases. UNESCAP and subregional organizations like ASEAN (as well ASEAN+3, ASEAN Regional Forum), SAARC, the Pacific Islands Forum, East Asia Summit (EAS), Shanghai Cooperation Organisation (SCO) or the Asia-Pacific Economic Cooperation (APEC) forum can coordinate pooling mechanisms to finance vaccine R&D. The creation of an intergovernmental Asian-wide R&D funding agency (or subregional agencies) should be considered (see below)

d) Regional scientific societies like AASSA can expand their mandate (and/or new organizations can be created) to fund basic and translational research on vaccines, provide human capital training, and coordinate R&D activities to avoid overlapping of projects and the wasting of financial resources. The success of AAS carrying out these activities offers an interesting model for Asian countries

Other supply-side mechanisms to incentivize vaccine R&D by pharmaceutical firms include regulatory, policy, tax, and direct financial incentives. Robust, consistent and transparent regulatory processes can also help reduce investment risks for pharmaceutical firms. Policy and regulatory reforms, especially those relating to

intellectual property rights, can have an important impact in the R&D investment decisions of pharmaceutical firms. The role of intellectual property rights in the vaccine industry is the subject of another report in this UNESCAP-WHO project and it will be mentioned only briefly here. No country can build a vaccine industry completely autonomous and self-sufficient from intellectual property rights generated elsewhere (da Veiga et al., 2016). International technology transfer and partnerships with MNPFs important for national capacity-building requires a secure intellectual property rights framework. Intellectual property rights protection can help to de-risk and incentivize investment in vaccine R&D by pharmaceutical firms. Regulations that provide predictable protection of intellectual property rights can incentivize firm R&D investments, facilitate exports, and foster technology transfer and capacity-building from advanced MNPFs to local firms in third countries. However, strengthening intellectual property rights can also increase the final costs of vaccines and create inequity in their distribution, issues that are subject of another report in this UNESCAP-WHO project. Policy reforms to ensure fast tracking review of vaccine candidates by regulatory authorities in the context of health emergencies also ease uncertainty for firms to invest in vaccine R&D. Likewise, regulatory changes that accelerate the time and reduce the cost of clinical trials, particularly of Phase III that involve large numbers of people. There are currently analytical parameters that can serve as proxies of protection for a number of vaccines (Plotkin, 2010; Aars et al., 2021). Regulatory reforms allowing the use of these parameters of protection to complement (not to substitute) the need for lengthy and costly Phase III clinical trials can also incentivize firm investments in R&D.

Other direct incentives, like as milestone subsidies once companies have successfully completed an R&D stage can be used. As illustrated in the case studies, governments can reduce costs for pharmaceutical companies by offering free or subsidized land or contributing to building for them physical infrastructure.

Governments can also explore other push mechanisms short of grants like tax incentives for pharmaceutical firms investing in vaccine R&D. As shown in countries outside Asia-Pacific (da Veiga et al., 2016), tax reductions linked to R&D investments may be more attractive for pharmaceutical firms than grants when applying and securing the latter involves bureaucratic processes and uncertainty about the consequences of receiving public funding for their ownership of intellectual property rights.

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, and diversion of resources from other diseases.

In addition, since basic discovery and preclinical research in general, and vaccine R&D in particular are prone to high rates of failure, it is important to simultaneously undertake different approaches. Consequently, investments and capacity-building by governments and PDP and non-PDP intermediaries should target multiple vaccine candidates and

technology platforms. A mechanism to maximize the utility of R&D funding is to promote the sharing of data and results. In that line, research funding agencies can require that researchers and academic institutions funded with public resources publish their results in open access journals and platforms.

While not every country in the Asia-Pacific region can be (or should be) involved in early stages of vaccine R&D, many low-income developing countries are currently participating in clinical trials through CROs, in some cases by domestically-owned CROs (Tables 4 and 5). Increased involvement of developing countries in clinical trials is one of the goals established by WHO regional offices (e.g., SEARO, WPRO). Conducting clinical trials in low-income countries has a number of positive spillovers and the successful experiences of the International Vaccine Institute with R&D for typhoid and cholera vaccines in Nepal and Viet Nam supports increasing these efforts for the future.

Unpredictable demand for vaccines, particularly for emerging infectious diseases and diseases afflicting low low-income countries with limited ability to pay, creates uncertainty for firms regarding returns to their R&D investments. Advanced purchase commitments and agreements are important demand-side strategies not only to de-risk R&D investment by pharmaceutical firms. AMCs can also be supply-side approaches when they directly finance R&D and/or the building up of manufacturing scale-up. As reviewed above, AMCs have been mostly directly established between high-income countries and pharmaceutical firms. Nevertheless, AMCs have also been successfully used by PDPs and non-PDP intermediaries to incentivize R&D for neglected and emerging diseases. Ahuja et al. (2021) found that AMCs also benefit low-income countries that would be otherwise priced out of the market.

Prospective buyers of vaccines should diversify candidates and platforms and provide push payment for only part of the total cost—in order to ensure that firms have a stake in the risk and success of vaccine development—and introduce pull incentives structured to incentivize speed. Since pharmaceutical firms have to fulfill their commitments to countries that signed APAs—most of them high-income countries—before selling doses to other countries, APAs can reduce access to vaccines in developing countries. Donor countries, PDP and non-PDP intermediaries should engage in APAs to produce vaccines for low- and middle-income countries, not only to ensure vaccine availability but also to collectively bargain for cheaper prices on their behalf.

Policies and regulations increasing the uptake of vaccines among the target population like free vaccination programs (funded by local governments, philanthropic organizations, international organizations, ODA), information campaigns, and other incentives can also increase the incentives of firms to invest in R&D. The impact of mandatory vaccinations on vaccine uptake is still open to debate and countries should consider whether compulsory programs can be effectively implemented and enforced or whether recommendations and incentives can work better.

4.3 Policy recommendations on fostering partnerships between relevant stakeholders at the national and regional and/or subregional levels.

As noted in previous sections, and in practically all countries, regardless of their level of development and/or geographical location, the transfer of knowledge from academia to the pharmaceutical industry faces constraints. Fundamental research conducted at universities may be either not easily transformed in innovation and inventions with market value or academic scientists and industry lack the communication channels to do so. Even in settings where academic scientists are encouraged to file patents, the industry is not always interested or lacks the information about the patents generated in the country.

Governments can promote academic-industry ties through a number of interrelated policies and regulations that can include: a) strengthening R&D funding programs for joint projects between universities and public research institutes and companies; b) introduce legislation and promote financial management rules of universities to foster university-industry partnerships; c) encourage innovation at the discovery/preclinical stage by defining intellectual property rights for researchers and institutions funded by public grants; d) promote greater flexibility in universities to allow academic researchers to conduct projects in pharmaceutical companies; e) define and protect the intellectual property rights of pharmaceutical firms and academic institution in the context of knowledge sharing and technology transfer; e) assist university staff in business model development for technology transfer; f) establish business incubators at universities and strengthen R&D funding for the establishment of start-up at universities and public research institutes; and g) facilitate the membership of academic researchers in boards of companies and the participation of industry leaders to participate in university committees.

Partnerships between scientists in Asia-Pacific should be encouraged, facilitated and, when possible, funded. The international sharing of scientific knowledge and data among scientists, universities and research institutes across countries most often takes place through informal networks. Although the institutionalization of these informal networks may not necessarily improve scientific collaboration (and can even potentially hamper it), national governments and intergovernmental organizations and scientific societies can promote it by offering travel grants for scientific meetings and research grants for international collaborative R&D projects. The creation of regional and subregional Vaccine Research Networks can bring together WHO, national governments, research institutions, and the private sector to promote sharing of data and knowledge for vaccine R&D and serve as platforms for advocacy, establishing research priorities, promoting joint research projects, and coordinating funding initiatives.

Although several regional and subregional scientific societies and research networks connecting research institutions have been institutionalized and they can play important roles in promoting vaccine R&D in the region, some of these initiatives have exhibited relatively low levels of activity since their creation. The activities of the existing regional

and subregional scientific societies and research networks described above (e.g., AASSA, SEAICRN, ASEAN-NDI, AVAN) should be increased and expanded in their goals to promote joint R&D projects, fellowships to fund short-term visits and exchanges of scientists between research institutes in Asia-Pacific. The creation of new research networks spanning more Asian countries--SEAICRN only includes research institutions in four ASEAN countries--should be considered.

Regional and subregional intergovernmental organizations in Asia-Pacific can play a more active role in coordinating the policies and actions of their members in vaccine R&D in several areas (e.g., prioritizing pipelines, promoting R&D preparedness and response, coordinating the mobilization and pooling of resources). They can map regional and subregional needs and elaborate, in collaboration with regional offices of WHO and other stakeholders, R&D action plans for prioritized diseases. They can also optimize national efforts in vaccine R&D by promoting the sharing of scientific knowledge and data, helping to distribute and coordinate a division of labor in vaccine R&D among countries according to the strengths and weaknesses of each country. WHO can provide technical support to regional and subregional intergovernmental organizations in all these activities.

Regional and subregional intergovernmental organizations in Asia-Pacific can also play a key role in advocacy for R&D for vaccines and drugs at the global level. For instance, they can provide collective support for a new international treaty for pandemic preparedness and response, as called for in the 2021 World Health Assembly, that covers not only disease surveillance but also R&D preparedness and response and that has attached a financial mechanism(s) to fund it. Asia-Pacific countries that are part of the G7 and G20 grouping can also advocate for these initiatives at these intergovernmental forums.

As noted above, the creation of an Asia-Pacific-wide (or subregional) R&D funding agency (Asia-Pacific Research Council) to offer grants for research projects on infectious diseases of regional importance, fellowships to promote on-site capacity building, scientific exchanges and collaborative scientific partnerships between research institutes and universities in Asia-Pacific. This regional R&D funding agency can be modeled upon the European Research Council launched by the European Commission or AESA-AAS launched by the African Union. This Asia-Pacific Research Council would not only maximize investments but also prevent unnecessary overlapping in R&D funding. National contributions to the Asia-Pacific Research Council can be adjusted by GDP per capita. Alternatively, the already existing AASSA can potentially expand its mission to take on these new roles. UN-ESCAP and WHO regional offices (EMRO, WPRO, SEARO) can play an important role bringing together all relevant stakeholders.

4.4 Policy recommendations on how to increase the preparedness and response of national and regional vaccine R&D systems in Asia-Pacific.

a) Vaccine R&D preparedness. Building R&D preparedness for existing infectious diseases within a reasonable time before an outbreak requires first to prioritizing those with the highest epidemic threat for R&D to develop drug and vaccine candidates from

fundamental research to Phase II of clinical trials (Section 4.1). Individual countries and the Asia-Pacific as a whole should develop and strengthen their national and regional vaccine R&D preparedness.

R&D preparedness should strengthen platform technologies that can be used for developing vaccines for different pathogens, including still unknown diseases (Disease X). Despite SARS-Cov2 being a new virus, the rapid vaccine R&D response was only possible because the R&D preparedness for traditional as well as newer mRNA vaccine platforms was in place in several countries and ready to be used from the outset. All stakeholders involved in vaccine R&D should sustain their commitment beyond immediate outbreaks and specific pathogens. R&D preparedness requires countries and regions to fund, build and maintain adequate research infrastructure before an outbreak that is not simply "epidemic specific" but mainly "epidemic sensitive" (Keusch and Lurie, 2020). Preparing for an unknown pathogen (Disease X) needs equipping research centers with fundamental research infrastructure and technological platforms, having a critical mass of scientists, developing newer cell and mouse models for testing, and making use of newer technologies (sequencing, artificial intelligence, machine learning).

Funding for R&D preparedness should be sustained over time. To better target funding for R&D preparedness and avoid unnecessary R&D funding overlaps, it is essential that the status of funded roadmaps for specific diseases and Disease X are made publicly available. Monitoring of funding for different pathogens can be carried out by the WHO's Global Observatory on Health R&D. Other organizations like Policy Research Cures through its G-Finder survey can also monitor financial flows for R&D, the source of funding, the identity of intermediaries, and the firms that will eventually develop vaccines. WHO's Global Observatory on Health R&D and Policy Research Cures can facilitate information sharing to help identify R&D gaps and priorities and opportunities for vaccines and drugs.

b) Vaccine R&D response. Only a strong R&D preparedness can then support a rapid and effective translational R&D response to develop vaccines and drugs once an outbreak emerges. Vaccine R&D responsiveness during an outbreak demands the rapid sharing of data and developing technology systems for rapidly identifying antigens and assessing the efficacy and safety of vaccine candidates. For already known pathogens for which adequate R&D preparedness has brought vaccine candidates to Phase II, R&D response will allow Phase III to commence as soon as an outbreak begins. For previously unknown Disease X pathogens, the R&D response will have to begin from the fundamental and preclinical research but, as shown with COVID-19, R&D preparedness will accelerate the different stages of vaccine development.

Even countries with strong R&D preparedness will have to mobilize new resources to respond to a major health outbreak. The search for financial resources to fund a rapid and effective R&D response cannot start at the time of the outbreak as this will delay the development of vaccines, drugs and diagnostics. Funding for an R&D response should be readily available at short notice. Different financial mechanisms can be explored,

including the creation of a permanent special pandemic fund that can be mobilized and disbursed immediately to the WHO, CEPI and other R&D funding intermediaries to finance a rapid R&D response. The GloPID-R network can coordinate funding flows into such a permanent fund that can be modeled upon the Pandemic Emergency Financing Facility (PEF) that was created and managed by the World Bank between July 2017 and April 2021 to help the low-income countries to finance their response to epidemics and pandemics (World Bank, 2019). A similar mechanism can be established specifically to finance a rapid R&D response to major health outbreaks (WHO R&D Blueprint, 2016).

Stakeholders in vaccine R&D should concomitantly fund a range of vaccine candidates and platforms. Traditional vaccine platforms are set up in several Asia-Pacific countries, including developing countries but the development of vaccines through traditional technologies is lengthy and prone to batch variability. RNA- and DNA-based vaccines can potentially accelerate vaccine development and efforts to implement these technologies are currently underway in several Asia-Pacific countries and should be strengthened. The sharing of specimens (new pathogens or new strains/variants of recognized pathogens) should be facilitated through informal and formal research networks. In addition, efforts should be made to develop regional capacities in new technologies—e.g., sequencing, bioinformatics, and big data, artificial intelligence and machine learning analysis—for rapid identification of new pathogens and new variants of known pathogens, and identifying what are the best targets in pathogens for rapid vaccine design and development. These platforms do not need to be available in each country and can be shared at a regional location.

Epidemics and pandemics are a clear case for regional cooperation in preparedness and response, not only in disease surveillance and health system strengthening but also in vaccine R&D. Regional and subregional intergovernmental organizations in Asia-Pacific as well as cross-regional intergovernmental forums like the G7 and the G20 can coordinate the pooling of funding for R&D preparedness and response plans for emerging infectious diseases within their own membership and beyond.

5. Policy checklist

5.1 Issue of consideration #1: Prioritization of targets in the national and regional vaccine R&D pipelines

Context:

The number of pathogens (known and unknown) with epidemic potential is very large. However, even in high-income countries, the financial and scientific resources available for vaccine R&D are limited. Adequate vaccine R&D preparedness and response requires the prioritization of diseases and the national and regional optimization of financial and scientific resources.

Guiding Questions

- What diseases should be prioritized for vaccine R&D?
- Which stakeholders should be involved in the prioritization of vaccine R&D?
- How stakeholders prioritize which diseases should be targeted for vaccine R&D?

Potential Challenges

- The lack of a strong strategy on which diseases should be prioritized for vaccine R&D investments may result in some diseases being orphaned from suitable vaccines and/or financial and scientific resources being wasted.
- The lack of a standardized method for prioritizing diseases for vaccine R&D can lead to inconsistent strategies for financing and implementing vaccine R&D.
- If left exclusively to the initiative of pharmaceutical companies, the prioritization of diseases worthy of investment in vaccine R&D can be limited to those diseases and vaccines with the greatest potential economic benefits.
- Although some level of overlap in vaccine R&D is desirable and can be beneficial, the absence of national and/or regional governance and coordination among stakeholders can lead to excessive duplication of R&D efforts.

Recommended Actions

See Sections 2.3, 2.4, and 4.1, as well as references therein.

❖ No single country, even high-income economies, can invest in vaccine R&D for all existing and potential newly emerging pathogens. For countries with limited economic resources to address other social and economic challenges, it is neither possible nor sensible to finance the early stages of vaccine R&D or to develop their own vaccine pharmaceutical industry.

❖ National governments and intergovernmental organizations must first identify which infectious diseases to prioritize for vaccine R&D. Stakeholders at the national and Asia-Pacific level should take advantage of the comprehensive methodological and analytical framework for vaccine and drug R&D prioritization developed by the WHO R&D Blueprint initiative. The Blueprint established a framework for building and strengthening R&D preparedness and response at the national, regional, and global levels and allowing the rapid launching of R&D activities during epidemics. The R&D Blueprint has built a governance and coordination framework to define and update the prioritization methodology, estimate funding needs and identify funding options. For each prioritized disease, leading experts and other stakeholders—inter alia, basic researchers, clinical experts, governments, businesses, non-profit and philanthropic entities, communities, and other relevant organizations—develop R&D roadmaps and target product profiles through broad and open consultations.

❖ Prioritization is particularly important in emerging infectious diseases with high epidemic potential as well as for neglected diseases with high morbidity and/or mortality. In line with the prioritization criteria established by the WHO R&D Blueprint, R&D efforts should be focused on the most pressing threats based on: a) the disease prevalence and burden, the cost of illness, and potential social impact of each disease in the country, Asia-Pacific region or its subregions, b) its human transmissibility, the human/animal interface, and potential for epidemic and pandemic spread, and c) the regional and global status of R&D for each disease, d) the public health context of the affected areas, e) the lack of efficient medical countermeasures and the availability and cost of other vaccines within the region or globally, and f) the possibility of the pathogen to evolve to more aggressive forms. The prioritization of R&D investments should also include the building of preparedness for still unknown pathogens (see below in Issue of Consideration #4). See Sections 2.3, 2.4, 3.3, and 4.1, as well as references therein.

❖ In the case of countries lacking the expertise to implement the vaccine R&D prioritization methodology defined by the WHO R&D Blueprint initiative, the WHO and WHO regional offices, donor countries, R&D funding intermediaries (PDPs and non-PDP), and/or international organizations (e.g., UN-ESCAP, scientific associations) can provide the technical assistance and capacity building of health and policymakers.

❖ To reduce expert bias, it is recommended that members in R&D prioritization committees are changed periodically.

❖ For essential vaccines in national immunization programs, countries should assess their vaccine security, namely, the timely, sustained, uninterrupted supply of affordable vaccines of assured quality. These essential vaccines in national immunization programs have been around for a long time and are mostly produced using traditional technologies at relatively low marginal costs of R&D and manufacturing. For these vaccines, the governments of countries with existing vaccine R&D and/or manufacturing capacity may consider supporting the vaccine R&D of private firms or directly engage in it (through public research institutes and government pharmaceutical companies) to strengthen their vaccine security.

5.2 Issue of consideration #2: Overcoming market failures in vaccine R&D

Context:

Several constraints on the supply and demand for vaccines discussed in Section 2.5 reduce the profitability of many vaccines (particularly those for diseases that affect low-income countries), the incentives for private pharmaceutical companies to invest in R&D, and ultimately the overall vaccine supply which may fall below the socially optimal amount.

Guiding Questions

◆ How can government and prospective vaccine buyers incentivize private pharmaceutical firms to invest in vaccine R&D?

◆ What supply-side (push) strategies are most effective to incentivize private pharmaceutical firms to invest in vaccine R&D?

◆ What demand-side (pull) strategies are most effective to incentivize private pharmaceutical firms to invest in vaccine R&D?

Potential Challenges

❖ High costs and rate of failure of vaccine R&D create supply constraints for private pharmaceutical companies and uncertainty regarding returns to their investments that may lead them to underinvest in vaccine R&D and manufacturing and to undersupply vaccines (market failure)

❖ Unpredictable demand for vaccines—particularly for neglected infectious diseases afflicting low-income countries with limited ability to pay or newly

emerging diseases—creates demand constraints for private pharmaceutical companies and uncertainty regarding returns to their investments that may lead them to underinvest in vaccine R&D and manufacturing, and to undersupply vaccines (market failure).

- Market failures in vaccine R&D occur when there are no effective vaccines, they are not supplied at adequate levels, their costs are too high, and/or their formulation are not suited for the prevailing conditions in the country/community.

- A market failure in vaccine R&D occurs when there is a gap between the private (accrued to pharmaceutical firms) and social (accrued to society) rates of return to R&D investments and, as a result, vaccine supply falls below the socially optimal amount because of the lack of effective vaccines, they are not supplied at adequate levels, their costs are too high, and/or their formulations is not suited for the prevailing conditions in the country/community.

Recommended Actions

See Sections 2.5, 3.2, 3.4, and 4.2, as well as reference therein.

- Public health priorities should be aligned with private economic incentives. Many vaccines can be considered national, regional and/or global public goods whose value can exceed their R&D and manufacturing costs and commercial value. To avoid or correct market failures in vaccine R&D, prospective vaccine buyers (national governments, international organizations, PDPs and non-PDP intermediaries, philanthropic foundations, etc.) can improve the incentives for private firms to invest in vaccine R&D through supply-side and/or demand-side strategies.

- Supply-side strategies: increasing government funding for basic and preclinical research. When a country has the capacity to develop its own vaccine R&D (see Issue of Consideration #1), as is the case in many middle- and high-income countries, governments can incentivize vaccine R&D by private firms through increasing funding for basic and preclinical research in universities and public research institutes. At the national level, governments can mobilize national financial and scientific resources for R&D on prioritized vaccines. To ensure sustained support for health R&D, policies should be aligned with national priorities and national agencies and strategies for R&D funding should be insulated from changes in the political leadership.

- Supply-side strategies: government subsidies and incentives to private firms. Direct incentives like milestone subsidies once companies have successfully completed an R&D stage can be used. As illustrated in the case studies, governments can reduce R&D costs for private firms by offering free or subsidized

land or contributing to building physical infrastructure. In some instances, tax incentives have been shown to be more effective than grants to incentivize vaccine R&D by private firms.

❖ Supply-side strategies: use of the regulatory and policy framework by governments. A robust, consistent, and transparent regulatory process helps reduce investment risks for private firms. Policy reforms to ensure fast-tracking review of vaccine candidates by regulatory authorities in the context of health emergencies, without compromising vaccine safety and efficiency, also ease uncertainty for firms to invest in vaccine R&D. On the one hand, regulations that provide predictable protection of intellectual property rights can incentivize R&D investments, and foster technology transfer and capacity-building from multinational firms to local firms in developing countries. On the other hand, strengthening intellectual property rights can also increase the final costs of vaccines and create inequity in their distribution, issues that are the subject of another report in this UNESCAP-WHO project.

❖ Supply-side strategies: fostering the participation of PDP and non-PDP intermediaries. Governments in developing countries should facilitate and foster PDP activities in their territories by strengthening the regulatory framework related to intellectual property rights and clinical trials. PDP and non-PDP intermediaries can not only act as financial intermediaries, channeling resources from ODA and philanthropic foundations, but they can also facilitate technology transfer from advanced to less advanced pharmaceutical firms and assist national regulatory authorities to achieve WHO certification.

❖ Supply-side strategies: strengthening the role of regional scientific societies and networks in the financing of basic and preclinical research. The mandate of the *Association of Academies and Societies of Sciences in Asia* (AASSA) can be expanded (and/or a new organization can be created) to finance basic and translational research on vaccines, provide human capital training, and coordinate R&D activities. The success of the *African Academy of Sciences* (AAS) in carrying out these activities offers an interesting model for Asian countries. The creation of an intergovernmental Asian-wide R&D funding agency (or subregional agencies) should be considered (see below)

❖ Supply-side strategies: the role of intergovernmental organizations. Regional intergovernmental organizations and forums can play a more active role in supporting and coordinating the activities of national governments. UNESCAP and subregional organizations like ASEAN (as well ASEAN+3, ASEAN Regional Forum), SAARC, the Pacific Islands Forum, East Asia Summit (EAS), Shanghai Cooperation Organisation (SCO), or the Asia-Pacific Economic Cooperation (APEC) forum can help coordinate the pooling of financial and scientific resources for vaccine R&D.

❖ Supply-side strategies: Maximize the utility of R&D funding. Since vaccine R&D is prone to high rates of failure, it is important to simultaneously undertake different approaches. Consequently, investments and capacity-building by governments and PDP and non-PDP intermediaries should target multiple vaccine candidates and technology platforms. At the same time, to avoid wasteful duplications, funding agencies can require that researchers share data and results. Establishing the optimal level of government and/or intermediaries funding for R&D is not straightforward as targeted funding for vaccine R&D can potentially result in diminishing returns and overinvestment, and diversion of resources from other diseases.

❖ Demand-side strategies: use of advanced purchase commitments (AMCs) by PDPs and non-PDP intermediaries. Although AMCs have been mostly used by high-income countries, AMCs have also been successfully used by PDPs and non-PDP intermediaries to incentivize R&D for neglected and emerging diseases and benefited low-income countries that would be otherwise priced out of the market. Donor countries, philanthropic foundations, and intermediaries should engage in AMCs to produce vaccines for low-income countries, not only to ensure vaccine availability but also to collectively bargain for cheaper prices on their behalf. Prospective buyers of vaccines should diversify candidates and platforms and provide push payment for only part of the total cost—in order to ensure that firms have a stake in the risk and success of vaccine development—and introduce pull incentives structured to incentivize speed.

❖ Demand-side strategies: policies and regulations increasing the uptake of vaccines. Free vaccination programs (funded by local governments, philanthropic organizations, international organizations, ODA), information campaigns, and other incentives can also increase the incentives of firms to invest in R&D. The impact of mandatory vaccinations on vaccine uptake is still open to debate, and countries should consider on a case-by-case basis whether compulsory programs can be effectively implemented and enforced or whether recommendations and incentives can work better.

5.3 Issue of consideration #3: Fostering partnerships and cooperation between relevant stakeholders at the national and regional and/or subregional levels

Context:

Infectious diseases know no borders and no country, not even high-income countries, can conduct R&D on vaccines for all potentially infectious diseases. On the one hand, preclinical research at universities funded by many middle- and upper-income governments does not necessarily translate into the creation of new vaccines and drugs by private pharmaceutical companies. At the same time, developing countries,

particularly low-income ones, rely on vaccines researched, developed, and manufactured by other nations that they must obtain through trade and regional/global cooperation. Epidemics and pandemics are a clear case for regional cooperation in preparedness and response, not only in disease surveillance and health system strengthening but also in vaccine R&D. Hence, successful vaccine R&D requires partnerships and cooperation between all relevant stakeholders within and between countries.

Guiding Questions

- How can governments ensure that biomedical knowledge generated in universities thanks to government funding is subsequently translated into new vaccines and drugs?

- How can technology transfer and capacity-building from multinational firms to local firms in developing countries be fostered?

- How can developed countries in the Asia-Pacific region cooperate on vaccine R&D with developing countries in the region? How can developing countries in Asia-Pacific cooperate with each other in vaccine R&D?

- What role can international organizations, scientific associations, and PDPs play in regional cooperation on vaccine R&D?

Potential Challenges

- In practically all countries, regardless of their level of development and/or geographical location, the transfer of knowledge from academia to the pharmaceutical industry faces constraints. Research conducted at universities is often not easily transformed into inventions with pharmaceutical market value.
- Networks of international cooperation in vaccine R&D need to be in place and operational before an epidemic outbreak hits. Academic scientists and small pharmaceutical firms, particularly in developing countries, may lack the communication channels between each other and with counterparts in other countries.
- A regulatory framework that provides strong protection for intellectual property rights can promote but also hinder technology transfer from advanced pharmaceutical firms in developed countries to those in developing countries.

Recommended Actions

See Sections 3.5, and 4.3, as well as references therein.

- ❖ Promoting academic-industry partnerships. Governments can enact policies and regulations to promote these ties through inter alia: a) R&D funding programs that specifically finance joint research projects between universities and companies; b) financial management rules of universities that foster university-industry partnerships, including allowing academic researchers funded by public grants to conduct projects in pharmaceutical companies and hold intellectual property rights; c) protect the intellectual property rights of pharmaceutical firms and academic institutions in the context of knowledge sharing and technology transfer; d) establish business incubators at universities and strengthen R&D funding for start-up at universities; and e) facilitate the membership of academic researchers in boards of companies and the participation of industry leaders to participate in university committees.

- ❖ Promote partnerships between and among research institutes and pharmaceutical firms in developed and developing countries. Pharmaceutical firms in developing countries can build their vaccine R&D capabilities through technological transfer from PDPs and/or pharmaceutical firms from high-income countries. As illustrated in the report, pharmaceutical firms in developing countries have also gained technological expertise from counterparts in other developing countries through South-South and South-South Triangular cooperation, which can be facilitated by PDPs.

- ❖ Facilitate, promote and fund research partnerships between scientists in Asia-Pacific. The international sharing of scientific knowledge among scientists and universities across countries often takes place through informal networks. Although the institutionalization of these informal networks may not necessarily improve scientific collaboration (and can potentially hamper it), national governments, intergovernmental organizations, and scientific societies can promote it by offering travel grants for scientific meetings and research grants for international collaborative R&D projects. The creation of regional and subregional Vaccine Research Networks can bring together research institutions, the private sector, and national governments with facilitation by WHO with the goal of data and knowledge sharing for vaccine R&D and serve as platforms for advocacy, establishing research priorities, promoting joint research projects, and coordinating funding initiatives.

- ❖ Regional cooperation in vaccine R&D at the clinical trials stage. Support the participation of developing countries in vaccine R&D at the clinical trials stage. While not every country in the Asia-Pacific region can be (or should be) involved in the early stages of vaccine R&D, many low-income developing countries are currently participating in later stages of vaccine R&D like clinical trials. Increasing

the involvement of developing countries in clinical trials is one of the goals established by WHO regional offices. As testified by the successful experiences reviewed in the report, conducting clinical trials in low-income countries has a number of positive spillovers. In developing countries where it is deemed important for their involvement in clinical trials, the WHO, regional intergovernmental organizations, regional scientific societies, and PDPs can provide technical training and financial resources to develop and strengthen vaccine R&D physical and human capital infrastructure.

❖ Strengthening regional and subregional scientific societies and research networks. Several scientific associations and research networks in the Asia-Pacific region well placed to promote scientific cooperation across borders have exhibited relatively low levels of activity compared to counterparts elsewhere. For instance, AASSA, SEAICRN, ASEAN-NDI, AVAN can increase and expand their goals to promote joint R&D projects, travel grants, and exchanges of scientists between research institutes in Asia-Pacific. The creation of new research networks spanning more Asian countries—SEAICRN only includes research institutions in four ASEAN countries—should be considered.

❖ Expanding the roles and activities of regional and subregional intergovernmental organizations in Asia-Pacific. Intergovernmental organizations in Asia-Pacific can play a more active role in coordinating the policies and actions of member states in mobilizing financial resources, research infrastructure, and human capabilities for vaccine R&D, prioritizing pipelines, promoting R&D preparedness for future health emergencies, and establishing plans for R&D response to outbreaks. They can map regional and subregional needs and elaborate, in collaboration with regional offices of WHO and other stakeholders, R&D action plans for prioritized diseases. They can also optimize national efforts in vaccine R&D by promoting the sharing of scientific knowledge and data, helping to distribute and coordinate a division of labor in vaccine R&D among countries according to the strengths and weaknesses of each country. Regional and subregional intergovernmental organizations in Asia-Pacific can also play a key role in advocacy for R&D for vaccines and drugs at the global level, as well as to provide collective support for a new international treaty for pandemic preparedness and response, as called for in the 2021 World Health Assembly. Asia-Pacific countries that are part of the G7 and G20 grouping can also advocate for these initiatives at these intergovernmental forums. WHO can provide technical support to regional and subregional intergovernmental organizations in all these activities. In countries with limited vaccine R&D and/or manufacturing capacity, governments should ensure the adequate supply of these vaccines from other countries, from international organizations, and/or donors.

❖ Creation of an Asia-Pacific-wide (or subregional) R&D funding agency—for instance, the Asia-Pacific Research Council—to offer grants for research projects on health issues of regional importance, fellowships to promote on-site capacity building, scientific exchanges, and collaborative scientific partnerships between research institutes and universities in Asia-Pacific. This regional R&D funding agency can be modeled upon the European Research Council launched by the European Commission or AESA-AAS launched by the African Union. This Asia-Pacific Research Council would not only maximize investments but also prevent unnecessary overlapping in R&D funding. National contributions to the Asia-Pacific Research Council can be adjusted by GDP per capita. Alternatively, the already existing AASSA can potentially expand its mission to take on these new roles. UN-ESCAP and WHO regional offices (EMRO, WPRO, SEARO) can play an important role in bringing together all relevant stakeholders.

5.4 Issue of consideration #4: Increasing the preparedness and response of national and regional vaccine R&D systems in the Asia-Pacific region

Context:

Despite SARS-Cov2 being a previously unknown pathogen, the rapid vaccine R&D response to the COVID-19 pandemic in many countries, including several in the Asia-Pacific region, was only possible because vaccine platforms were already set up and ready to be used (vaccine R&D preparedness) before health threat. But even countries with strong R&D preparedness need to mobilize new financial and scientific resources to mount a quick and efficient vaccine R&D response once a major epidemic outbreak has hit.

Guiding Questions

◆ How can countries build and strengthen their vaccine R&D preparedness for future epidemics?

◆ How can countries build and strengthen their vaccine R&D response in the context of an outbreak?

Potential Challenges

❖ The development cycle of a vaccine using traditional platforms is between 5 and 12 years. Although this cycle can be shortened in the case of the newest vaccine technologies (e.g., mRNA vaccines), most countries lack the technological know-how and R&D preparedness to research and develop new vaccines using these platforms.

- ❖ Many of the recent epidemics and pandemics have been newly emerging infectious diseases caused by previously unknown pathogens that jumped to humans from other animals. It is estimated that there are 1.6 million viruses affecting animals of which only a small number have so far affected humans.
- ❖ The financial and scientific resources required to mount an effective R&D response need to be readily available at short notice and their search cannot start at the time of the outbreak as this will delay the development of vaccines.

Recommended Actions

Sections 2.3, 2.4, and 4.4, as well as references therein.

- ❖ Building and strengthening R&D preparedness for existing infectious diseases before an epidemic outbreak. Individual countries and the Asia-Pacific region as a whole should develop and strengthen national and regional vaccine R&D preparedness for existing infectious diseases. R&D preparedness requires first to prioritize diseases with the highest epidemic potential (see above). It also demands to fund, build and maintain adequate research infrastructure, equipping research centers with fundamental research infrastructure and technological platforms, and having a critical mass of scientists. It also requires conducting the preliminary stages of R&D to develop vaccine candidates from the fundamental research stage to Phase II of clinical trials.

- ❖ Building and strengthening R&D preparedness for still unknown infectious diseases (so-called Disease X). Individual countries and the Asia-Pacific region as a whole should develop and strengthen national and regional vaccine R&D preparedness for Disease X. This requires strengthening biomedical research capabilities and setting up vaccine platform technologies that can be used for developing vaccines for different pathogens, including still unknown diseases. R&D preparedness should not simply be “epidemic specific” but mainly “epidemic sensitive”, beyond immediate outbreaks and specific pathogens. Since most of the newly emerging human infectious diseases are caused by pathogens that jump from other animals (zoonotic diseases), Identifying in advance and including in prioritization lists pathogens in animals with high risk to infect humans is key in developing R&D preparedness for the next zoonotic threat.

- ❖ Funding for R&D preparedness should be properly targeted and sustained over time. To better target funding for R&D preparedness and avoid unnecessary R&D funding overlaps, the status of funded roadmaps for specific diseases and Disease X should be made publicly available. Monitoring of funding for different pathogens can be carried out by organizations at the national and regional levels. If needed, the activities of these organizations can be assisted by the WHO’s Global Observatory on Health R&D. Other organizations like Policy Research Cures through its G-Finder survey can also monitor financial flows for R&D, the source of funding, the identity of intermediaries, and the firms that will eventually develop

vaccines. WHO's Global Observatory on Health R&D and Policy Research Cures can facilitate information sharing to help identify R&D gaps and priorities and opportunities for vaccines and drugs.

❖ R&D preparedness requires concomitantly funding a range of vaccine candidates and platforms. Although traditional vaccine platforms are set up in several Asia-Pacific countries, including developing countries, the newer RNA- and DNA-based technologies can accelerate vaccine development. Efforts to implement these technologies are currently underway in several Asia-Pacific countries and should be strengthened. In addition, efforts should be made to develop regional capacities in new technologies—e.g., sequencing, bioinformatics, and data, artificial intelligence, and machine learning analysis—for rapid identification of new pathogens and new variants of known pathogens, and identifying what are the best targets in pathogens for rapid vaccine design and development. These platforms do not need to be available in each country and can be shared at a regional location.

❖ Ensuring a rapid and effective vaccine R&D response. Only a strong R&D preparedness can then support a rapid and effective vaccine R&D response once an outbreak emerges. R&D responsiveness demands the rapid sharing of data and developing technology systems for rapidly identifying antigens and assessing the efficacy and safety of vaccine candidates. The sharing of specimens should be facilitated through informal and formal research networks. For already known pathogens for which adequate R&D preparedness has already brought vaccine candidates to Phase II, R&D response will allow Phase III to commence as soon as an outbreak begins. For previously unknown Disease X pathogens, the R&D response will have to begin from the fundamental and preclinical research but, as shown with COVID-19, a strong R&D preparedness will accelerate the stages of vaccine development.

❖ Mobilizing financial resources for a rapid and effective vaccine R&D response. Even countries with strong R&D preparedness will have to mobilize a significant amount of additional financial resources to respond to a major health outbreak. The search for financial resources to fund a rapid and effective R&D response cannot start at the time of the outbreak as this will delay the development of vaccines. Funding for an R&D response should be readily available at short notice. Financial mechanisms can include the creation of a permanent special pandemic fund that can be mobilized and disbursed immediately to the WHO, CEPI, and other R&D funding intermediaries to finance a rapid R&D response. The GloPID-R network can coordinate funding flows into such a permanent fund that can be modeled upon the Pandemic Emergency Financing Facility that was created and managed by the World Bank to help the low-income countries to finance their healthcare response to epidemics.

❖ Role of regional and subregional intergovernmental organizations in R&D preparedness and response. Regional and subregional intergovernmental organizations can assist member states to identify which infectious diseases to prioritize for vaccine R&D preparedness. Regional and subregional intergovernmental organizations in Asia-Pacific, as well as cross-regional intergovernmental forums like the G7 and the G20, can coordinate the pooling of financial and scientific resources for building R&D preparedness and response plans for emerging infectious diseases within their own membership and beyond.

List of references

Al-Jighefee HT, Najjar H, Ahmed MN, Qush A, Awwad S, Kamareddine L. (2021) COVID-19 Vaccine Platforms: Challenges and Safety Contemplations. *Vaccines*. 9:1196.

Aars OK, Clark M, Schwalbe N. (2021) Increasing Efficiency in Vaccine Production: a primer for change. *Vaccine X*, 8:100104

Africa Centres for Disease Control and Prevention (Africa CDC) (2021) Policy Paper: Research and Development Priorities for COVID-19 in Africa. Addis Ababa, Ethiopia: Africa CDC. Available at: https://africacdc.org/download/policy-paper-research-and-development-priorities-for-covid-19-in-africa/ (last accessed on 30 April 2022).

Ahmed SS, Ellis RW, Rappuoli R. (2018) Technologies for making new vaccines. In S.A. Plotkin, W. Orenstein, P. Offit and K. M. Edwards (eds.) *Vaccines*. (pp. 1283-1304). Amsterdam: Elsevier.

Ahuja A, Athey S, Baker A, Budish E, Castillo JC, Glennerster R, Kominers SD, Kremer M, Lee J, Prendergast C, Snyder CM, Tabarrock A, Tan BJ, Więcek W. (2021). Preparing for a pandemic: Accelerating vaccine availability. *National Bureau of Economic Research (NBER) Working Paper Series* No. 28492. Washington DC: NBER.

Alemayehu C, Mitchell G, Nikles J. (2018) Barriers for conducting clinical trials in developing countries-a systematic review. *International Journal for Equity in Health*. 17:37

Amaya AB, De Lombaerde P. (2021a) Regional cooperation is essential to combatting health emergencies in the Global South. *Globalization and Health*. 17:9

Amaya AB, Binagwaho A, De Lombaerde P. (2021b) Policy Brief: Regional collective action to address COVID-19 and prepare for future pandemics. G20 Summit. Think20 Task Force 1 on Global Health and Covid-19. Rome, Italy: G20 Summit. Available at: https://www.g20-insights.org/wp-content/uploads/2021/09/TF1_PB08_LM02.pdf (last accessed on 30 April 2022).

Andre FE. (2002) How the research-based industry approaches vaccine development and establishes priorities. Dev Biol. 110:25–29

Artaud C, Kara L, Launay O. (2019). Vaccine Development: From Preclinical Studies to Phase 1/2 Clinical Trials. In Ariey F, Gay F, Ménard R (eds.) *Malaria control and elimination* (pp. 165-176). New York, NY: Humana Press.

Association of Southeast Asian Nations (ASEAN) (2017). ASEAN Plan of Action on Science and Technology (APAST) 2007-2015 to APASTI 2016-2025. Available at: https://asean.org/wp-content/uploads/2017/10/01-APASTI-2016-2025-FINAL.pdf (last accessed on 30 April 2022).

Association of Southeast Asian Nations (ASEAN). (2021) COVID-19 Vaccines for all. The ASEAN. August-September issue. Jakarta, Indonesia: ASEAN.

Ayman Falak, A (2021) BioNTech to Build Vaccine Manufacturing Site in Singapore. ASEAN Briefing. 13 July 2021. Available at: https://www.aseanbriefing.com/news/biontech-to-build-vaccine-manufacturing-site-in-singapore/ (last accessed on 30 April 2022).

Balconi M, Lorenzi V. (2017) The increasing role of contract research organizations in the evolution of the biopharmaceutical industry. *African Journal of Business Management*. 11(18):478-90.

Bärnighausen T, Bloom DE, Cafiero-Fonseca ET, O'Brien JC. (2014) Valuing vaccination. *Proc Nat Acad Sci USA*. 111(34):12313-9.

Biotechnology Industry Research Assistance Council (BIRAC) (2019). Guidelines for Ind-CEPI Mission program on Epidemic preparedness through rapid vaccine development. Available at: https://birac.nic.in/webcontent/1578561123_Guidelines_IndCEPI.pdf (last accessed on 30 April 2022).

Biotechnology Industry Research Assistance Council (BIRAC) (2020). Ind-CEPI Mission. Available at: https://dbtindia.gov.in/sites/default/files/uploadfiles/IndCEPI%20WEB%20.pdf (last accessed on 30 April 2022).

Boulet P, 't Hoen E, Perehudoff K, Mara K and Tan E. Advanced purchase agreements for COVID-19 Vaccines: Analysis and Comments. Brussels, Belgium: Study for The Left in the European Parliament. Available at: https://left.eu/issues/publications/eu-vaccine-deals-with-big-pharma-failed-to-protect-the-public-interest-study/ (last accessed 30 April 2022).

Brende B, Farrar J, Gashumba D, Moedas C, Mundel T, Shiozaki Y, Vardhan H, Wanka J, Røttingen JA. (2017) CEPI—a new global R&D organisation for epidemic preparedness and response. *The Lancet*. 389(10066):233-5.

Bulc B, Ramchandani R (2021). *Accelerating global health R&D: the role of product development partnership*s. Global Development and Antara Global Health Advisors. Geneva, Switzerland: Global Development.

Chakma J, Masum H, Perampaladas K, Heys J, Singer PA (2011) Indian vaccine innovation: the case of Shantha Biotechnics. *Globalization and Health*. 7:9

Chakraborty C, Sharma AR, Bhattacharya M, Agoramoorthy G, Lee SS. (2021) Asian-Origin Approved COVID-19 Vaccines and Current Status of COVID-19 Vaccination Program in Asia: A Critical Analysis. *Vaccines*. 9(6):600.

Coalition for Epidemic Preparedness Innovations (CEPI) (2019) Business Plan 2019-2022. Oslo, Norway: CEPI. Available at: https://cepi.net/wp-content/uploads/2019/10/CEPI-Business-Plan-2019-2022.pdf (last accessed on 30 April 2022).

Crommelin DJ, Anchordoquy TJ, Volkin DB, Jiskoot W, Mastrobattista E. (2021) Addressing the cold reality of mRNA vaccine stability. *J Pharm Sci*. 110(3):997-1001.

Department of Science and Technology of India (2021a). List of Licensed Human Vaccine Manufacturing Facilities in India. Available at: https://www.indiascienceandtechnology.gov.in/covid-19-vaccine/list-licensed-human-vaccine-manufacturing-facilities-india (last accessed on 30 April 2022)

Department of Science and Technology of India (2021b). Research-based Institute/organization/labs involved in vaccine development programme in India. Available at: https://www.indiascienceandtechnology.gov.in/covid-19-vaccine/institutes-labs-involved-vaccine-development (last accessed on 30 April 2022)

David PA, Hall DH, Toole AA (2000) Is public R&D a complement or substitute for private R&D? A review of the econometric evidence. *Research Policy*. 3:497-529.

Danzon PM, Sousa-Pereira N (2011) Vaccine Supply: Effects of Regulation and Competition, *International Journal of the Economics of Business*. 18(2):239-271.

Department of Science and Technology (DOST) of Philippines (2021). *Collaborative Research and Development to Leverage Philippine Economy (CRADLE) Programme.* Available at: https://s4cp.dost.gov.ph/programs/cradle/ (last accessed on 30 April 2022).

Dimachkie-Masri M, Ramirez B, Popescu C, Reggie EM (2012). Contract research organizations: an industry analysis. *International Journal of Pharmaceutical and Healthcare Marketing*, 6(4):336-350.

DiMasi JA, Grabowski HG, Hansen RW (2016) Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of Health economics*. 47:20-33.

Douglas, R. G. and V. B. Samant (2018). The Vaccine Industry. In S.A. Plotkin, W. Orenstein, P. Offit and K. M. Edwards (eds.) *Vaccines*. Amsterdam: Elsevier.

Duke Global Health Innovation Center (DGHIC) (2021a) Launch and Scale Speedometer. Tracking COVID-19 vaccine purchases across the globe. Available at: https://launchandscalefaster.org/covid-19/vaccinepurchases. (last accessed on 30 April 2022)

Duke Global Health Innovation Center (DGHIC) (2021b) Launch and Scale Speedometer. Tracking COVID-19 vaccine manufacturing. Available at: https://launchandscalefaster.org/covid-19/vaccinemanufacturing (last accessed on 30 April 2022).

Endarti D, Riewpaiboon A (2016). Vaccination externalities: The concept and application in pharmacoeconomic studies. *Asian J Pharm Clin Res*. 9(1):204-8.

Evaluate (2020). EvaluatePharma® World Preview 2020, Outlook to 2026. Available at: https://info.evaluate.com/EvaluatePharma-World-Preview-2020.html (last accessed on 30 April 2022).

Evenett SJ, Hoekman B, Rocha N, Ruta M. (2021) The Covid-19 Vaccine Production Club: Will Value Chains Temper Nationalism? *World Bank Policy Research Working Papers,* No. 9565. Washington, DC: World Bank.

Gad SC, Spainhour CB, Serota DG (2020) CROs in China, India, and Elsewhere in the Broader World: Outsourcing Science Gone Global. In SC Gad, CB Spainhour and DG Serota (eds). *Contract Research and Development Organizations-Their History, Selection, and Utilization*. Cham, Denmark: Springer.

Gersovitz M, Hammer JS (2003) Infectious Diseases, Public Policy, and the Marriage of Economics and Epidemiology. *The World Bank Research Observer*. 18(2):129-157

Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM, Schulman KA. (2009) Ethical and scientific implications of the globalization of clinical research. *N Engl J Med*. 360(8):816-23.

Global Burden of Disease Collaborative Network (GBD-CN) (2020) Global Burden of Disease Study 2019, Results. Seattle, United States: Institute for Health Metrics and Evaluation. Available from http://ghdx.healthdata.org/gbd-results-tool (last accessed on 30 April 2022).

Global Burden of Diseases and Injuries 2019 Collaborators (GBDI-2019C) (2020) Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet.* 396(10258):1204-22.

GlobalData (2021) Coronavirus Disease 2019 (COVID-19) *Vaccines. Opportunity Assessment and Major Market Forecast to 2026*. Report GDHCOA006. Available at: https://store.globaldata.com/report/gdhcoa006—coronavirus-disease-2019-covid-19-vaccines-opportunity-assessment-and-forecast-to-2026/

Global Preparedness Monitoring Board (GPMB). (2019) *A world at risk. Annual report on global preparedness for health emergencies.* Geneva, Switzerland: World Health Organization and the World Bank.

Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R). GLOPID-R Charter. Available at: https://www.glopid-r.org/wp-content/uploads/2018/03/glopid-r-charter-12032018.pdf (last accessed on 30 April 2022).

Ghosh PK. (2020) Human vaccines industry in China, 2019: Part—I. *MGM Journal of Medical Sciences*. 7(1):7:35-45.

Ghosh PK. (2020) Human vaccines industry in China, 2019: Part II. *MGM Journal of Medical Sciences*. 7(2):86-96.

Ghosh PK. (2020) Human vaccines industry in China, 2019: Part III. *MGM Journal of Medical Sciences*. 7(3):148-54.

Gouglas D, Le TT, Henderson K, Kaloudis A, Danielsen T, Hammersland NC, Robinson JM, Heaton PM, Røttingen JA. (2018) Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. *The Lancet Global Health*. 6(12):e1386-1396.

Gouglas D, Marsh K. (2019) Prioritizing investments in new vaccines against epidemic infectious diseases: A multi-criteria decision analysis. *Journal of Multi-Criteria Decision Analysis*. 26(3-4):153-163.

Hall W, Jamieson A, Wardle G (2019). *Advancing epidemics R&D to keep up with a changing world: Progress, challenges and opportunities*. London, UK: Welcome Trust.

Hasan I, Tucci CL. (2010) The innovation–economic growth nexus: Global evidence. *Research Policy*. 39(10):1264-1276.

Hayman B, Pagliusi S. (2020) Emerging vaccine manufacturers are innovating for the next decade. *Vaccine X.* 5:100066.

Hayman B, Suri R, Prasad SD. (2021) COVID-19 vaccine capacity: Challenges and mitigation–The DCVMN perspective. *Vaccine*. 39(35):4932-7.

Hayter CS and Nisar MA (2018). Spurring vaccine development for the developing world: a collaborative governance perspective on product development partnerships. *International Journal of Public Administration*. 41(1):46-58.

Higher Education Development (HEC) of Pakistan (2021). Technology Transfer Support Fund. Available at:
https://www.hec.gov.pk/english/services/faculty/TTSF/Pages/default.aspx
(last accessed on 30 April 2022).

Hotez PJ. (2020) The rise or fall of neglected tropical diseases in East Asia Pacific. *Acta Tropica*. 202:105182.

Hu Y, Chen S. (2021) What can we learn from COVID-19 vaccine R&D in China? A discussion from a public policy perspective. *Journal of Travel Medicine*. 28(4):taab026.

Huzair F, Borda-Rodriguez A, Upton M. (2011) Twenty-first century vaccinomics innovation systems: capacity building in the global South and the role of Product

Development Partnerships (PDPs). *Omics: a Journal of Integrative biology*. 15(9):539-43.

Iwasaki A, Omer SB. (2020) Why and how vaccines work. *Cell*. 183(2):290-5.

Jackson NA, Kester KE, Casimiro D, Gurunathan S, DeRosa F. (2020) The promise of mRNA vaccines: a biotech and industrial perspective. *npj Vaccines*. 5:11

Japan International Cooperation Agency (JICA) (2018) Project completion report on technical cooperation for strengthening capacity for measles-rubella combined vaccine production in the Socialist Republic of Vietnam. Available at: https://openjicareport.jica.go.jp/pdf/12308250.pdf (last accessed on 30 April 2022).

Jonkmans N, D'Acremont V, Flahault A. (2021) Scoping future outbreaks: a scoping review on the outbreak prediction of the WHO Blueprint list of priority diseases. *BMJ Global Health.* 6(9):e006623.

Kamat VR. (2014) Fast, cheap, and out of control? Speculations and ethical concerns in the conduct of outsourced clinical trials in India. *Social Science & Medicine*.104:48-55.

Kent SJ, Cooper DA, Chhi Vun M, Shao Y, Zhang L, Ganguly N, et al. (2010) AIDS Vaccine for Asia Network (AVAN): Expanding the Regional Role in Developing HIV Vaccines. PLoS Med 7(9): e1000331

Keusch G, Lurie N (2020). The R&D Preparedness Ecosystem: Preparedness for Health Emergencies. Report to the Global Preparedness Monitoring Board. 9 August 2020. Global Health Centre, Graduate Institute of International and Development Studies, Geneva, Available at: https://www.gpmb.org/annual-reports/overview/item/the-r-d-preparedness-ecosystem-preparedness-for-health-emergencies (last accessed on 30 April 2022).

Khan NJM, Zulkipli ZN (2018) Compulsory vaccination for children in Malaysia: legislation and realisation. *Yuridika*. 33(3):402-416.

Kim JH, McCann C. (2021) The emergence of a South-South and Triangular Cooperation approach to vaccine development. *Journal of Global Health Science. 3(1):e6*

Knezevic I, Liu MA, Peden K, Zhou T, Kang H-N. (2021) Development of mRNA Vaccines: Scientific and Regulatory Issues. *Vaccines*. 9(2):81.

Kojom LP, Singh V. (2021) A Review on Emerging Infectious Diseases Prioritized Under the 2018 WHO Research and Development Blueprint: Lessons from the Indian Context. *Vector-Borne and Zoonotic Diseases*. 21(3):149-59.

Kremer, M (2000), Creating Markets for New Vaccines Part I: Rationale, NBER Working Paper No 7716. Cambridge, MA: National Bureau of Economics Research.

Kremer, M and C M Snyder (2015), Preventives versus treatments, *The Quarterly Journal of Economics*.130(3):1167-1239.

Kruesi, L., Burstein, F. and Tanner, K. (2020). A knowledge management system framework for an open biomedical repository: communities, collaboration, and corroboration. *Journal of Knowledge Management*, 24(10):2553-2572.

Leroux-Roels G, Bonanni P, Tantawichien T, Zepp F. (2011) Vaccine development. *Perspectives in Vaccinology*. 1(1):115-150.

Lobo, F (2021). Restructuring the vaccine industry. *Global South Research Paper 134*. Geneva, Switzerland: Global South.

London Schol of Economics and Political Sience, Department of International Relations (LSE-IR) (2020). COVID-19 and the Global South responses of regional organisations to this transnational challenge. Available at: https://www.lse.ac.uk/international-relations/centres-and-units/global-south-unit/COVID-19-regional-responses/COVID-19-and-the-Global-South (last accessed on 30 April 2022).

Madhavi Y (2008) Human vaccine science and technology status in India. In: P Banerjee (ed.) *India Science & Technology 2008*. New Delhi, India: NISTADS CSIR 2009

Market Study Report (2021) *Global Covid-19 Vaccine Market. Analysis By Product Type, Patient Type, End User, By Region, By Country (2021 Edition): Market Insights, Competition and Forecast (2020-2030).* Available at: https://www.marketstudyreport.com/reports/global-covid-19-vaccine-market-analysis-by-product-type-patient-type-end-user-by-region-by-country-2021-edition-market-insights-competition-and-forecast-2020-2030 (last accessed on xxxx).

Medicines Patent Pool (2021). The mRNA vaccine Technology Transfer Hub. Available at: https://medicinespatentpool.org/covid-19/technology-transfer-hub (last accessed on 30 April 2022).

Mehand MS, Al-Shorbaji F, Millett P, Murgue B. (2018a) The WHO R&D Blueprint: 2018 review of emerging infectious diseases requiring urgent research and development efforts. *Antiviral Research*. 159:63-67.

Mehand MS, Millett P, Al-Shorbaji F, Roth C, Kieny MP, Murgue B. (2018b) World health organization methodology to prioritize emerging infectious diseases in need of research and development. *Emerging Infectious Diseases*. 24(9): e17142

Mollentze N, Babayan SA, Streicker DG (2021) Identifying and prioritizing potential human-infecting viruses from their genome sequences. *PLoS Biol* 19(9): e3001390.

Monrad JT, Sandbrink JB, Cherian NG. (2021) Promoting versatile vaccine development for emerging pandemics. *npj Vaccines*. 6:26

Moran M, Guzman J, Ropars AL, Illmer A. (2010) The role of Product Development Partnerships in research and development for neglected diseases. *International Health*. 2(2):114-22.

Mossialos E, Ge Y, Hu J, Wang L, (2016) *Pharmaceutical policy in China: challenges and opportunities for reform.* Copenhagen, Denmark: World Health Organization Regional Office for Europe

Mueller-Langer F. (2013) Neglected infectious diseases: are push and pull incentive mechanisms suitable for promoting drug development research?. *Health Economics, Policy and Law*. 8(2):185-208.

National Science and Technology Development Agency (NSTDA) (2012). Thai-made vaccines. Available at: https://www.nstda.or.th/en/news/news-year-2012/356-thai-made-vaccines.html (last accessed on 30 April 2022).

National People's Congress of the People's Republic of China (NPC-PRC) (2019) Vaccine Administration Law of the People's Republic of China. Available at: http://www.npc.gov.cn/englishnpc/c23934/202012/0b1fd779c29e49bd99eb0e65b66aa783.shtml (last accessed on 30 April 2022).

Ni J, Zhao J, Ung CO, Hu Y, Hu H, Wang Y. (2017) Obstacles and opportunities in Chinese pharmaceutical innovation. *Globalization and Health*.13:21

Nuzzo JB, Mullen L, Snyder M, Cicero A, Inglesby TV (2019) Preparedness for a High-Impact Respiratory Pathogen Pandemic. Washington DC: Johns Hopkins Center for Health Security.

Nolen, S (2021) *Here's Why Developing Countries Can Make mRNA Covid Vaccines*. New York Times. Oct 22, 2021.

Odevall L, Hong D, Digilio L, Sahastrabuddhe S, Mogasale V, Baik Y, Choi S, Kim JH, Lynch J. (2018) The Euvichol story–Development and licensure of a safe, effective and affordable oral cholera vaccine through global public private partnerships. *Vaccine*. 36(45):6606-14.

Organisation for Economic Cooperation and Development (OECD) (2015) *The Measurement of Scientific, Technological and Innovation Activities. Frascati Manual 2015. Guidelines for Collecting and Reporting Data on Research and Experimental Development.* Paris, France: OECD.

Organisation for Economic Co-operation and Development (OECD) (2021a), Effective policies to foster high-risk/high-reward research, OECD Science, Technology and Industry Policy Papers, No. 112. Paris, France: OECD. Available at: https://doi.org/10.1787/06913b3b-en (last accessed on 30 April 2022).

Organisation for Economic Co-operation and Development (OECD) (2021b). OECD Science, Technology and Innovation Outlook 2021: Times of Crisis and Opportunity.

Paris, France: OECD. Available at: https://www.oecd.org/sti/oecd-science-technology-and-innovation-outlook-25186167.htm (last accessed on 30 April 2022).

Ozawa S, Clark S, Portnoy A, Grewal S, Brenzel L, Walker DG. (2016) Return on investment from childhood immunization in low-and middle-income countries, 2011–20. *Health Affairs*. 35(2):199-207.

Pardi N, Hogan MJ, Porter FW, Weissman D. (2018) mRNA vaccines: a new era in vaccinology. *Nat Rev Drug Discov*. 17(4):261-79.

Pharmaceutical Technology (2021). COVID19 vaccines advanced purchase agreements tracker: insights on pre-orders and prices. Available at: https://www.pharmaceutical-technology.com/pricing-and-market-access/covid19-vaccines-apa-tracker-preorders-price-html (last accessed on 30 April 2022).

Phelan AL, Eccleston-Turner M, Rourke M, Maleche A, Wang C. Legal agreements: barriers and enablers to global equitable COVID-19 vaccine access. *The Lancet*. 2020 Sep 19;396(10254):800-2.

Piwowar H, Priem J, Larivière V, Alperin JP, Matthias L, Norlander B, Farley A, West J, Haustein S. (2018) The state of OA: a large-scale analysis of the prevalence and impact of Open Access articles. *PeerJ*. 6:e4375.

Plotkin SA. (2010) Correlates of protection induced by vaccination. *Clinical and Vaccine Immunology*. 17(7):1055-1065.

Pollard AJ, Bijker EM. (2021) A guide to vaccinology: from basic principles to new developments. *Nat Rev Immunol*. 21(2):83-100.

Policy Cures Research (PCR) (2021a). G-Finder 2020. Landscape of emerging infectious disease research and development: preventing the next pandemic. Sydney, Australia: PCR.

Policy Cures Research (PCR) (2021b). G-Finder 2020. Neglected Disease Research and Development. Where to now? Sydney, Australia: PCR.

PricewaterhouseCoopers (2008) The changing dynamics of pharma outsourcing in Asia: Are you readjusting your sights? Available at: https://www.pwc.com/gx/en/pharma-life-sciences/pdf/change_asia_10_08_08.pdf (last accessed on 30 April 2022).

Pronker ES, Weenen TC, Commandeur H, Claassen EHJHM, Osterhaus ADME (2013) Risk in Vaccine Research and Development Quantified. *PLoS One* 8(3): e57755.

Qiu L, Chen ZY, Lu DY, Hu H, Wang YT. (2014) Public funding and private investment for R&D: a survey in China's pharmaceutical industry. *Health Research Policy and Systems.* 12:27

Ramachandran S, Satapathy SR, Dutta T. (2022) Delivery Strategies for mRNA Vaccines. *Pharm Med*. 36:11-20.

Reuters (2021) China's mRNA vaccine technology firm Abogen raises over $700 mln. August 19, 2021. Available at: https://www.reuters.com/business/healthcare-pharmaceuticals/chinas-mrna-vaccine-technology-firm-abogen-raises-over-700-mln-2021-08-19/ (last accessed on 30 April 2022).

Riordan P, Langley W (2021) China's Sinopharm seeks to develop its own mRNA Covid vaccine. *Financial Times*, 6 September 2021

R&D Blue Print - World Health Organization (2021). COVID-19 vaccine tracker and landscape. Updated regularly at: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (last accessed on 30 April 2022).

Saluja T, Giri BR, Chaudhary S, Tamrakar D, Kanodia P, Palkar S, Vemula S, Chinaworapong S, Kim B, Gupta BP, Kyoung Jo S, Aspinall S, Rai GK, Steele D, Kim JH, Wartel TA, Sahastrabuddhe S (2021) Challenges and opportunities in setting up a phase III vaccine clinical trial in resource limited settings: Experience from Nepal. *Human Vaccines & Immunotherapeutics*. 17(7):2149-57

Sanofi Pasteur China (2020). Corporate Social Responsibility Report 2019. Available at: https://www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/common/docs/our-responsibility/documents-center/2019-Sanofi-China-Corporate-Social-Responsibility-Report.pdf?la=en (last accessed on 30 April 2022).

Shahid Shah, Ghulam Abbas, Nabeel Riaz, Anees ur Rehman, Muhammad Hanif & Muhammad Fawad Rasool (2020) Burden of communicable diseases and cost of illness: Asia pacific region*, Expert Review of Pharmacoeconomics & Outcomes Research*, 20(4): 343-354.

Sharma, Y (2021). New and strengthened research priorities post-pandemic. University World News, 6 March 2021. Available at: https://www.universityworldnews.com/post.php?story=20210304105937958 (last accessed at 30 April 2022).

Shretta R, Silal SP, Celhay OJ, Mercado CE, Kyaw SS, Avancena A, Fox K, Zelman B, Baral R, White LJ, Maude RJ. (2019) Malaria elimination transmission and costing in the Asia-Pacific: Developing an investment case. *Wellcome Open Research*. 4:60.

Siripitayakunkit, U (2017) Procurement Policies – an example for ensuring vaccine security: the ASEAN vaccine security and self-reliance initiative. National Vaccine Institute, Thailand. Available at: https://www.who.int/influenza_vaccines_plan/objectives/SLPIVPP_Session5.6_Siripitayakunkit.pdf (last accessed on 30 April 2022).

Sripa B, Leonardo L, Hong SJ, Ito A, Brattig NW. (2021) Status and Perspective of Asian Neglected Tropical Diseases. *Acta tropica*. 21:106212.

Sloan FA (2012) The Economics of Vaccines. In PM Danzon, S Nicholson (eds). The Oxford Handbook of the Economics of the Biopharmaceutical Industry. New York, NY: Oxford University Press.

State Department of the United States of America (USDoS). (2021) Fact sheet-U.S. Support to ASEAN in Fighting COVID-19, August 4, 2021. Available at: https://www.state.gov/u-s-support-to-asean-in-fighting-covid-19/ (last accessed on 30 April 2022).

Southeast Asian Ministers of Education Organization (SEAMEO) (2015) Thailand Country Study: R&D on Health. Available at: https://bit.ly/3CuB0bq (last accessed on 30 April 2022).

Shrotri M, Swinnen T, Kampmann B, Parker EPK (2021). An interactive website tracking COVID-19 vaccine development. *Lancet Glob Health*; 9(5):e590-e592.

Taylor EM, Smith J. (2020) Product development partnerships: Delivering innovation for the elimination of African trypanosomiasis?. *Tropical Medicine & Infectious Disease*s. 5(1):11.

The Hindu (2021) *IISc-incubated Mynvax to get funding to bring "warm" Covid vaccine to market*. July 19, 2021. Available at: https://www.thehindu.com/business/Industry/iisc-incubated-mynvax-to-get-funding-to-bring-warm-covid-vaccine-to-market/article35408618.ece (last accessed on 30 April 2022).

Thiem VD, Anh DD, Ha VH, Hien ND, Huong NT, Nga NT, Thang TC, McNeal MM, Meyer N, Pham HL, Huong NM. (2021) Safety and immunogenicity of two formulations of rotavirus vaccine in Vietnamese infants. *Vaccine*. 39:4463-4470.

Tsai TF, Rao RD, Xu ZY (2018) Immunization in the Asia-Pacific region. Plotkin's Vaccines. In S.A. Plotkin, W. Orenstein, P. Offit and K. M. Edwards (eds.) *Vaccines.* (pp. 1466-1485). Amsterdam, The Netherlands: Elsevier.

Tull, K. (2021). Economic impact of local vaccine manufacturing. K4D Helpdesk Report 974. Brighton, UK: Institute of Development Studies. Available at: https://opendocs.ids.ac.uk/opendocs/handle/20.500.12413/16470

(last accessed on 30 April 2022).

Turner, M (2016) Vaccine procurement during an influenza pandemic and the role of Advance Purchase Agreements: Lessons from 2009-H1N1, *Global Public Health*, 11(3):322-335.

United Nations, Department of Economic and Social Affairs (UN-DESA) (2018) SDG Indicators. Global indicator framework for the Sustainable Development Goals and targets of the 2030 Agenda for Sustainable DevelopmentAvailable at: https://unstats.un.org/sdgs/indicators/indicators-list/ (last accessed on 30 April 2022).

United Nations Economic and Social Commission for Asia-Pacific (UN-ESCAP) (2020). The Impact and Policy Responses for COVID-19 in Asia and the Pacific. Bangkok, Thailand: UNESCAP. Available at: https://www.unescap.org/sites/default/files/COVID%20_Report_ESCAP.pdf (last accessed on 30 April 2022).

United Nations Educational, Scientific and Cultural Organization (UNESCO) (2015). *UNESCO Science Report. Toward 2030*. Paris, France: UNESCO

United States Mission to ASEAN (US-ASEAN) (2020). Fact sheet US-ASEAN Health Features. Available at: https://asean.usmission.gov/u-s-asean-health-futures/ (Last accessed on 30 April 2022)

Vanderslott S, Marks T. (2021) Charting mandatory childhood vaccination policies worldwide. *Vaccine*. 39(30):4054-4062.

Viergever RF, Hendriks TC. (2016) The 10 largest public and philanthropic funders of health research in the world: what they fund and how they distribute their funds. *Health Research Policy and Systems*, 14:12.

Vu JT, Kaplan BK, Chaudhuri S, Mansoura MK, Lo AW (2020). Financing Vaccines for Global Health Security. medRxiv 2020.03.20.20039966; doi: 10.1101/2020.03.20.20039966

Widdus R. (2001) Public-private partnerships for health: their main targets, their diversity, and their future directions. *Bulletin of the World Health Organization*. 79:713-20.

World Bank (2019). Pandemic Emergency Financing Facility (PEF)

Operational Brief for Eligible Countries. Available at: https://thedocs.worldbank.org/en/doc/478271550071105640-0090022019/original/PEFOperationalBriefFeb2019.pdf (last accessed on 30 April 2022).

World Health Organization (WHO) (2010) Global Vaccine Action Plan 2011-2020. Geneva, Switzerland: World Health Organization. Available at: https://apps.who.int/iris/rest/bitstreams/110564/retrieve (last accessed on 30 April 2022).

World Health Organization. (2011). Strengthening response to pandemics and other public-health emergencies : report of the Review Committee on the Functioning of the International Health Regulations (2005) and on Pandemic Influenza (H1N1) 2009. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/75235 (last accessed on 30 April 2022).

World Health Organization (WHO) (2012).Consultative Expert Working Group on Research and Development: Financing and Coordination. 65th World Health Assembly. Geneva, Switzerland: WHO. A65/24.

World Health Organization (WHO) (2016) *WHO R&D Blueprint for action to prevent epidemics. Being ready for the next epidemic: How to improve R&D funding for preparedness and response to emerging pathogens*. Geneva, Switzerland: WHO. WHO/EMP/PHI/2016.02

World Health Organization (WHO) (2017) *WHO R&D Blueprint for action to prevent epidemics*. Update 2017. Geneva, Switzerland: WHO. WHO/HIS/HIA/17.5

World Health Organization (WHO) (2019) Global Vaccine Market Report 2018. Geneva, Switzerland: WHO. WHO/IVB/19.03. Available at: https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/MI4A_Global_Vaccine_Market_Report.pdf

(last accessed on 30 April 2022)

World Health Organization (WHO) (2021) Global Vaccine Market Report 2020. Working Draft. Geneva, Switzerland: WHO. Available at: https://bit.ly/2YL37V5 (last accessed on 30 April 2022).

World Health Organization R&D Blueprint (2020). A coordinated global research roadmap. 2019 novel coronavirus. Geneva, Switzerland: WHO R&D Blueprint. Available: https://www.who.int/blueprint/priority-diseases/key-action/Coronavirus_Roadmap_V9.pdf (last accessed on 30 April 2022).

World Health Organization, Regional Office for Southeast Asia (WHO-SEARO) (2003). South-East Asia Regional Vaccine Policy. 28th Session of WHO SEARO Advisory Committee on Health Research. 12-13 August 2003, Maldives. SEA/ACHR/28/9

World Health Organization-Regional Office for South-East Asia (WHO-SEARO) (2017). South-East Asia regional vaccine action plan 2016-2020. New Delhi, India: WHO-SEARO. Available at: https://apps.who.int/iris/handle/10665/272397

(last accessed on 30 April 2022).

World Health Organization (WHO) Secretariat-Strategic Advisory Group of Experts Working Group on Oral Cholera Vaccines, the and the Centers for Disease Control and Prevention (2017) Background Paper on Whole-Cell, Killed, Oral Cholera Vaccines. Available at: https://www.who.int/immunization/sage/meetings/2017/april/OCV_Background_Document_SageWG_FinalVersion_EditedPS_.pdf (last accessed on 30 April 2022).

Xue QC, Ouellette LL. (2020) Innovation policy and the market for vaccines. *Journal of Law and the Biosciences*. 7(1):lsaa026

Yi W, Long CX. (2021) Does the Chinese version of Bayh-Dole Act promote university innovation?. *China Economic Quarterly International*. 1(3):244-57.

Younes GA, Ayoubi C, Ballester O, Cristelli G, de Rassenfosse G, Foray D, Gaulé P, Pellegrino G, van den Heuvel M, Webster E, Zhou L (2020) COVID-19: Insights from innovation economists. *Science and Public Policy*. 47(5):733-45.

da Veiga CR, da Veiga CP, Del Corso JM, da Silva WV. (2016) Vaccine R&D in Brazil: The effectiveness of push and pull regulations. *World Patent Information*. 46:11-18.

Vu JT, Kaplan BK, Chaudhuri S, Mansoura MK, Lo AW (2020) Financing Vaccines for Global Health Security. medRxiv 2020.03.20.20039966; doi: 10.1101/2020.03.20.20039. Available at: https://www.medrxiv.org/content/10.1101/2020.03.20.20039966v1

(last accessed on 30 April 2022).

Zainzinger V (2021). Big ambitions for India's contract research firms

The country's CROs want a seat at the global drug discovery table. Chemical & Engineering News. 8 August 2021. Available at: https://cen.acs.org/business/outsourcing/Pharmaceuticals-india-contract-research-ambitions/99/i29 (last accessed on 30 April 2022).

Zheng Y, Rodewald L, Yang J, Qin Y, Pang M, Feng L, Yu H. (2018) The landscape of vaccines in China: history, classification, supply, and price. *BMC Infectious Diseases*.18(1):1-8.

Websites

ASEAN Network for Drugs, Diagnostics, Vaccines and Traditional Medicines Innovation (ASEAN-NDI). Website: http://www.asean-ndi.net/

Association of Academies and Societies of Sciences in Asia (AASSA). Website: http://aassa.asia/

Coalition for Epidemic Preparedness Innovations (CEPI). Website: https://cepi.net/

ClinicalTrials.gov. Database of privately and publicly funded clinical studies conducted around the world. Website: https://clinicaltrials.gov/ct2/search/advanced?cond=&term=&cntry=&state=&city=&dist=

COVID-19 Vaccine Market Dashboard. UNICEF. Website: https://www.unicef.org/supply/covid-19-vaccine-market-dash

COVID-19 Vaccine Tracker. London School of Hygiene & Tropical Medicine Vaccine Centre (Vaccine Tracker-LSHTM). Website: https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/#

COVID-19 Vaccine Tracker. McGill University COVID19 Vaccine Tracker. Website: https://covid19.trackvaccines.org/

Developing Countries Vaccine Manufacturers Network (DCVMN). Website: https://www.dcvmn.org/

G-FINDER: tracking funding for global health R&D. Policy Research Cures. Website: https://gfinderdata.policycuresresearch.org/

Global Alliance for Vaccines and Immunization (GAVI), The Vaccine Alliance. Website: https://www.gavi.org/

Global Burden of Disease Results tool. Global Health Data Exchange. Institute for Health Metrics and Evaluation. Website: http://ghdx.healthdata.org/gbd-results-tool

Global Health Innovative Technology Fund (GHIT) (Japan). Website: https://www.ghitfund.org/

Global Health Observatory. World Health Organization (WHO-GHO). Website: https://www.who.int/data/gho

Global Observatory on Health Research and Development. World Health Organization (WHO-GOHR&D). Website: https://www.who.int/observatories/global-observatory-on-health-research-and-development

Global Research Collaboration for Infectious Disease Preparedness (GOLPID-R). Website: https://www.glopid-r.org/

Global Vaccine Action Plan. World Health Organization (WHO). Website: https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/global-vaccine-action-plan

List of Contract Research Organizations. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Network (ICH-GCP). Website: https://ichgcp.net/cro-list

Patentscope. WIPO IP Portal. World Intellectual Property Organization (WIPO). Website: https://patentscope.wipo.int/search/en/search.jsf

PDP Funders Group. Website: https://www.pdpfundersgroup.org/

Prequalification of Vaccines. World Health Organization (WHO). Website: https://extranet.who.int/pqweb/vaccines

PubMed. United States National Library of Medicine at the National Institutes of Health. Website: https://pubmed.ncbi.nlm.nih.gov/

R&D Pipeline Tracker. Policy Research Cures. Website: https://www.pipeline.policycuresresearch.org/

Southeast Asia Infectious Disease Clinical Research Network (SEAICRN). Website: http://www.seaicrn.org/infobox.aspx?pageID=1

Strategic Partnership for Health Security and Emergency Preparedness (SPH) Portal. World Health Organization (WHO). Website: https://extranet.who.int/sph/hom

Sustainable Development Goals Database. United Nations. Department of Economic and Social Affairs. Website: https://unstats.un.org/sdgs/unsdg

United Nations Comtrade. International Trade Statistics Database: https://comtrade.un.org

UNESCO Institute for Statistics (UIS). Website: http://data.uis.unesco.org/

UNESCO Science Report 2021. Statistics and Resources (UNESCO-SR) Website: https://www.unesco.org/reports/science/2021/en/dataviz

R&D Blueprint. World Health Organization (WHO). Website: https://www.who.int/teams/blueprint/about

World Bank. Open Data (WB-OD). Website: https://data.worldbank.org/.

The Asia-Pacific Research and Training Network on Trade - ARTNeT - is an open network of research and academic institutions and think-tanks in the Asia-Pacific region. Since its inception, ARTNeT aims to increase the amount of high quality, topical and applied research in the region by harnessing existent research capacity and developing new capacities. ARTNeT also focuses on communicating these research outputs for policymaking in the region including through the ARTNeT Working Paper Series which provide new and policy–relevant research on topics related to trade, investment and development. The views expressed in this publication are those of the authors and do not necessarily reflect the views of the United Nations and ARTNeT secretariat or ARTNeT members.

This and other ARTNeT publications are available from **artnet.unescap.org**

ARTNeTontrade

@ARTNeTontrade

ARTNeT Group

artnetontrade@un.org

ARTNeT Secretariat, United Nations ESCAP

Rajadamnern Nok Avenue

Bangkok 10200, Thailand

Tel: +66(0) 22881425

Fax: +66(0) 22881027