GLOBAL HEALTH CENTRE, GENEVA GRADUATE INSTITUTE | 2023

RISING PHARMACEUTICAL INNOVATION IN THE GLOBAL SOUTH:

PAINTING WITH NEW COLORS

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COVER LETTER

This report is part of the broader "Research Collaboration on Technology, Equity, and the Right to Health", between the Global Health Centre (GHC) at the Geneva Graduate Institute in Switzerland, the James P. Grant School of Public Health at BRAC University in Bangladesh, and the Universidad de los Andes (ANDES) in Colombia, supported by the Open Society University Network (OSUN). The larger research collaboration consists of two research projects – one on digital health and human rights, and the other on pharmaceutical research and development (R&D) in the Global South.

As part of the latter research project, three individual research reports present the findings on pharmaceutical R&D in the Global South: one report led by BRAC about pharmaceutical R&D in Bangladesh, another report led by ANDES about pharmaceutical R&D in Colombia, and finally, one report led by the GHC about pharmaceutical R&D in low- and middle-income countries (LMICs).

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Supported by:

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AUTHOR NOTE

We would like to express our deepest gratitude to our research collaborators at BRAC University in Bangladesh, and Universidad de los Andes in Colombia, without whom this research project would not have been possible. We are grateful for the fruitful collaboration we have experienced over the past 1.5 years, and the opportunity we have had to learn in-depth about the role of both Bangladesh and Colombia in the pharmaceutical innovation system. We would also like to extend our sincere thanks to Dr. Sara LM Davis, for coordinating the research collaboration between the universities, and acting as liaison with the digital health part of the project. Lastly, we would like to acknowledge and thank Bétina Zago, who provided tremendous support with the design and layout of this report.

Financial support for this research project came from the Open Society Foundations (OSF)/ Open Society University Network (OSUN) (grant numbers: OR2021-82568 and OR2022-87393) and the Swiss National Science Foundation (SNSF) (Project PR00P1_179842).

Suggested citation: Marcela Vieira, Yiqi Liu, Azizah Siddiqui, Adrián Alonso Ruiz, Kaitlin Large, and Suerie Moon (2023). Rising Pharmaceutical Innovation in the Global South: Painting with New Colors. Global Health Centre, Geneva Graduate Institute. License: CC BY-NC 4.0.

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EXECUTIVE SUMMARY

INTRODUCTION

Information on existing activities, capacities, and outcomes of pharmaceutical innovation in low- and middle-income countries (LMICs) is scarce. To fill this knowledge gap, this report aims to: 1) provide a baseline picture of pharmaceutical innovation in LMICs, and 2) identify possible alternative R&D models being implemented in LMICs.

METHODOLOGY

We conducted a literature review of pharmaceutical R&D in LMICs, complemented by semi-structured scoping interviews. We then mapped, synthesized, and analyzed information from open databases regarding R&D funding, activities, and capacities. Finally, we explored the proposals submitted to the World Health Organization (WHO) in 2013 in response to a global call for projects with innovative approaches to R&D.

FINDINGS

Literature review and scoping interviews: The literature described growing activity in pharmaceutical innovation in developing countries but referred mostly to only a few LMICs (China, India, Brazil, South Africa, and Cuba). "Imitation to innovation" was highlighted as a particularly important pathway to build innovation systems in LMICs. Financing for R&D within firms usually came from cash flow from the sales of generics and/or providing research services. Private capital to support R&D in most LMICs was limited, and companies obtained significant government support. Philanthropic funding and development assistance were also mentioned as important funding sources, especially in Southern Africa.

Nevertheless, government policies and funding were reportedly insufficient, and R&D was a low political priority, especially beyond upper-middle-income countries (UMICs). The importance of academic institutions and small and medium enterprises (SMEs), especially in the earlier stages of R&D, was raised frequently. However, there was a key gap in translational research since knowledge produced at universities was usually not translated into product development, as most LMICs lack intermediaries to take development further.

A few LMICs, particularly Brazil, Cuba, India, and Indonesia, were mentioned among the countries that have implemented policies linking R&D capacity, technological and industrial development, and public health needs. China and Russia were mentioned as having mandatory local manufacturing policies, aimed at national security of supply and strengthening cumulative capacity for innovation. Many countries required clinical trials to be conducted domestically for regulatory approval, which strengthened local capacity to conduct such trials.

Several studies and interviewees noted that pharmaceutical R&D in LMICs focused more on addressing local needs and improving ease of use in local contexts. However, market returns still seemed to shape the R&D priorities of the private sector in LMICs, such that companies were unlikely to address diseases mostly affecting “poor market segments”. A few studies and interviewees gave examples of innovative products developed in LMICs (Table 1), indicating growing concrete outcomes from policies and investments over the past years.

Frequently mentioned challenges to conducting pharmaceutical R&D in LMICs included a lack of financial and human resources, research infrastructure, targeted policies, regulatory issues, and limited pharmacovigilance. International intellectual property agreements also restricted access to information, knowledge, and technology.

Database analysis: To complement the findings from the literature and interviews, we also analyzed information from publicly available databases. For R&D funding, we synthesized data on gross domestic R&D expenditure on health and medical sciences (health GERD) from the WHO Global Observatory on Health Research and Development. We found that South Africa had the highest percentage of GDP invested in health GERD among UMICs, Kenya among LoMICs, and Mozambique among LICs (Figure 1). Bulgaria had the highest number of health researchers among UMICs and Egypt among LoMICs, but there were no LICs among the top 10 LMICs (Figure 2).

We also examined grants for biomedical research from public and philanthropic funders in the World RePORT. Among LMICs, South Africa had the highest number of grants, followed by China and Kenya (Table 3). In terms of the number of research organizations receiving grants, of the UMICs, China, South Africa, and Brazil had the highest number; of the LoMICs, it was India and Kenya, while among LICs, it was Uganda and Malawi (Table 4).

We then analyzed R&D funding for diseases "that disproportionately affect people in low- and middle-income countries", from G-FINDER. From 2010 to 2020, there was an increase of more than 450% in the total amount funded by MICs, while funding from LICs remained roughly the same. India was the most significant public funder among LMICs (Table 5). India and South Africa were the top receiving countries (Table 6). Funding received by LMICs also increased over time, indicating growing capacity for conducting R&D.

Thirdly, we analyzed clinical trial activities, looking at the number of trials, phases, type of diseases, and sponsors/funders involved. During the period covered (1990-2020), most clinical trials were conducted in HICs (80%), but growth in LMICs was rapid. The number of trials increased by 375% in LMICs from 2010 to 2020, particularly in China, India, and Iran (Figure 5). Most trials were in phase 3, both in HICs and LMICs. However, there was a growing number in phase 0. Notably, China and India had a large proportion of trials in phases 0 and 1, and Egypt and Thailand showed significant growth in earlier phases from 2010 to 2020 (Figures 7 and 8). These trends suggested increasing capacity in the riskier, more innovative, earlier stages of R&D.

Both in HICs and LMICs, the disease category with the largest number of trials was malignant neoplasms, while infectious and parasitic diseases represented only about 5% of trials in HICs, and 9% in LMICs. Over time, there was a significant increase in trials for respiratory diseases in all countries. In LMICs, other categories also increased significantly, particularly non-communicable diseases and congenital anomalies (Figure 13).

The analysis of trial sponsors and funders showed a higher number of non-commercial than commercial sponsors both in HICs and LMICs, and of non-commercial funders in LMICs (Figure 9). Moreover, we observed an increasing involvement of non-commercial sponsors and funders over the past years, particularly in the early R&D phases (Figures 11 and 12). In some areas, such as maternal conditions, sexual health, perinatal conditions, and nutritional deficiency, non-commercial actors played a markedly dominant role (Figure 14).

Innovative proposals of R&D: We found information regarding 52 of the 106 project proposals for innovative approaches to pharmaceutical R&D submitted to the WHO in 2013. Out of the 52 proposals, most were submitted by governments, public research institutes, and universities, and included 34 proposals from LMICs (Appendix 5.3). This reflected both some willingness to take alternative approaches to R&D in LMICs, and the important role of non-commercial actors in doing so, but further research is needed in this area.

Discussion and conclusions: Despite data limitations, by triangulating between the literature, interviews, and publicly-available databases, it was possible to paint a broad picture of who was involved in pharmaceutical R&D in LMICs, in which particular countries, for which diseases, in which R&D phases, and with what results – as well as how these trends have changed over time. A group of 16 countries leads on various indicators: Brazil, Bulgaria, China, Colombia, Cuba, Egypt, Georgia, India, Iran, Kenya, Malaysia, Mozambique, Russia, Serbia, South Africa, and Uganda (table 8). Investment has increased, particularly from MICs, in the past decade. Capacity also seems to be growing, with an increase over time in the number of research organizations and the amount of funding received by LMICs from external sources. Not only has the total number of trials and the proportion of all trials in LMICs increased, but there is also growing activity in the earlier, more innovative and riskier phases. Non-commercial funders and sponsors play a very significant – and growing – role in clinical trials in LMICs. The high number of non-commercial actors in LMIC R&D suggests there is fertile soil to experiment with alternative R&D models that are not driven primarily by market incentives.

Finally, investments in building R&D capacities have already begun to bear fruit, as indicated by several drugs, biologics and vaccines, plant-based medicines, diagnostics platforms, monoclonal antibodies, and gene therapies developed in LMICs. The list of products developed in the Global South can be expected to grow in the coming years (table 1).

While this report has provided a baseline snapshot, ongoing systematic data collection and analysis of R&D activities in LMICs is still needed. Country-level studies analyzing strengths, weaknesses, and trajectories are also needed to deepen understanding of effective policies for building R&D capacity (see also the companion reports on Bangladesh and Colombia). Finally, there is a need for further research on potential alternative R&D models in LMICs that may better meet domestic needs, as well as the needs of global public health. Pharmaceutical innovation in the Global South is a rich, promising, and rapidly-evolving area with strategic importance for global health, which merits far more research and attention than it has received to date.

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Supplementary data

Two files with supplementary data used for the analysis of clinical trials are available at: https://zenodo.org/record/7801929 and https://zenodo.org/record/7802113.

List of Abbreviations

Abbreviation	Definition
AMR	Antimicrobial resistance
ANDI	African Network for Drugs and Diagnostics Innovation
AUDA-NEPAD	African Union Development Agency - New Partnership for Africa's Development
BIRAC	Biotechnology Industry Research Advisory Council (India)
BRICS	Brazil, Russia, India, China, and South Africa
BSL-3	Biosafety level 3 labs
CDC	Centers for Disease Control and Prevention (USA)
CDRI	Central Drug Research Institute for drug R&D (India)
CEWG	Expert Working Group on Financing and Coordination (WHO)
CITMA	the Science and Technological Innovation System (Cuba)
COVID-19	Coronavirus disease 2019
CSIR	Council for Scientific and Industrial Research (South Africa)
C-TAP	COVID-19 Technology Access Pool (WHO)
DNDi	Drugs for Neglected Diseases initiative
DSI	Department of Science and Innovation (South Africa)
EID	Emerging infectious diseases
EMA	European Medicines Agency
FDA	Food and Drug Administration (USA)
Fiocruz	Oswaldo Cruz Foundation (Brazil)
GDP	Gross domestic product
GERD	Gross domestic expenditure on R&D
GHC	Global Health Centre (Geneva Graduate Institute)
HIC	High-income country
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
HRISA	Health Research and Innovation Strategy for Africa
HSRI	Health System Research Institute (Thailand)
H3D	The Drug Discovery and Development Centre (University of Cape Town research centre)
ICMR	Indian Council for Medical Research
ICTRP	International Clinical Trial Registry Platform

Abbreviation	Definition
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IIL	Indian Immunological Limited
IP	Intellectual property
IPASA	Innovative Pharmaceutical Association South Africa
KEI	Knowledge Ecology International
LIC	Low-income country
LMICs	Low- and middle-income countries
LOLA	Lead Optimization Latin America project
LoMIC	Lower-middle-income countries
MMV	Medicines for Malaria Venture
MPP	Medicines Patent Pool
mRNA	Messenger RNA
NBM	New business model
NCDs	Non-communicable diseases
NCE	New chemical entity
NTDs	Neglected tropical diseases
OSDD	Open Source Drug Discovery programme of the Council of Scientific & Industrial Research (India)
PDP	Product Development Partnership
R&D	Research and development
SADC	Southern African Development Community
SciELO	Scientific Electronic Library Online
SMEs	Small and Medium Enterprises
SUMA	Ultramicroanalytical System developed by the Cuban Immunoassay Center
TB	Tuberculosis
TCM	Traditional Chinese Medicine
TDR	The Special Programme for Research and Training in Tropical Diseases, co-sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank, and the World Health Organization (WHO)
THSTI	Translational Health Science and Technology Institute (India)
TIDREC	Tropical Infectious Diseases Research and Education Centre (Malaysia)

Abbreviation	Definition
TRIPS	Trade Related Aspects of Intellectual Property Agreement (WTO)
UMICs	Upper middle-income countries
UNICAMP	The University of Campinas in São Paulo, Brazil
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

1. INTRODUCTION

Ensuring globally equitable innovation and access to medicines is a major challenge across high-, middle-, and low-income countries. Addressing this challenge requires an improved understanding of the global pharmaceutical innovation system. Over the past several decades, this system has evolved considerably and has expanded beyond the traditional strongholds of biomedical innovation in a few high-income countries (HICs). In the wake of the Covid-19 pandemic, there is also increased interest in strengthening research & development (R&D) capacity in the Global South. However, information on existing activities, capacities, and outcomes of pharmaceutical innovation in low- and middle-income countries (LMICs) is scarce. The literature largely focuses on the United States and a few Western European countries.

To help fill this information gap, we began a research collaboration with the BRAC University in Bangladesh and the Universidad de los Andes in Colombia, to further our collective understanding of pharmaceutical R&D activities in the Global South. Three research reports were developed as part of this collaboration, one focused on pharmaceutical R&D in Bangladesh, led by BRAC University; one focused on pharmaceutical R&D in Colombia, led by Universidad de los Andes; and this report, which is focused on R&D activities in LMICs in general, led by the Global Health Centre (GHC).

This research collaboration is part of the broader research project "New Business Models for Governing Innovation and Global Access to Medicines" (NBM)[1], which aims to deepen understanding of the factors required to implement new business models of medicines R&D that can deliver both innovation and globally accessible medicines. While the term “business model” can be used in different ways, we use it to refer to the specific combination of resources, actors, and rules and norms that shape R&D processes and outcomes (Moon et al., 2022). Therefore, this report has two objectives:

a. To gather, map, and analyze publicly available data to provide a baseline picture of pharmaceutical innovation in LMICs, including changes over time and outputs (Sections 3.1-3.5).

b. To identify possible alternative R&D models being implemented in the Global South (Section 3.6)

1 More information about the NBM project is available at: https://www.graduateinstitute.ch/NBM

2. METHODOLOGY

During the first stage of the research, we examined available evidence on capabilities and activities of LMICs in R&D in the pharmaceutical sector. First, we conducted a literature review of pharmaceutical R&D focusing on countries from the Global South. The literature review was complemented by semi-structured scoping interviews with key experts on the topic. We then mapped, synthesized, and analyzed information from databases regarding funding for pharmaceutical R&D, and R&D activities. A more detailed methodology is presented at the beginning of each section of the report.

There is no single definition of "Global South". The term has been used to refer to economically developing countries on one side of the imagined global North–South divide, which are often, but not always, geographically located in the southern part of the world. It has also been used to refer to countries classified by the World Bank as low or middle-income, oftentimes with a geographic limitation to those located in Africa, Asia, Oceania, Latin America, and the Caribbean (excluding Europe and North America). For this report, we used the World Bank classification of income level regardless of geographical location, and used low and middle-income countries (LMICs) as a proxy for Global South. For the literature review, scoping interviews, and clinical trials analysis, countries were separated into two groups: high-income countries (HICs) and low and middle-income countries (LMICs). For the analysis of funding flows and health researchers, countries were classified into four income levels: high-income countries (HIC), low-income countries (LIC), lower-middle-income countries (LoMIC), and upper-middle-income countries (UMIC). The acronym "LoMIC" was used to refer to lower-middle-income countries, while the acronym "LMIC" was used to refer to low- and middle-income countries collectively.

There were a few available centralized databases providing information on different aspects of pharmaceutical R&D, but they were limited in scope in terms of diseases, stages of R&D covered, and countries and funders providing data. Nevertheless, they were able to provide insight into pharmaceutical innovation capacities and activities in LMICs. We present information on 1) R&D funding, 2) R&D scientific capacity, and 3) clinical trial activities acquired from these databases below.

We looked at funding flows for pharmaceutical R&D, and synthesized data from three databases: 1) gross domestic R&D expenditure on health and medical sciences (referred to as health GERD) provided by the WHO Global Observatory on Health Research and Development, 2) data from grants for biomedical research from 14 major public and philanthropic funders of health research in the World RePORT, and 3) data on funding for health R&D for diseases "that disproportionately affect people in low- and middle-income countries, such as neglected diseases, emerging infectious diseases, and sexual and reproductive health issues" from G-FINDER. We then analyzed another indicator of scientific capacity from the WHO Global Observatory, related to the number of researchers in health and medical sciences, referred to as health researchers. Thirdly, we conducted a more detailed analysis of clinical trial activities, and looked at which countries were more active in conducting clinical trials, the phases of development performed, the types of diseases researched, and the sponsors and funders involved.

Finally, we began to explore the existence of alternative R&D models in LMICs. To do so, we mapped the proposals initially submitted to the WHO in 2013 in response to a global call for projects with innovative approaches to R&D, to address unmet medical needs of developing countries – the so-called "demonstration projects" which followed the process of the Consultative Expert Working Group on Financing and Coordination (CEWG). We sought information about the proposals from the WHO and the regional offices' websites, and requested information via email from the respective regional offices. Information on the current status of the projects was obtained from the respective organizations' websites.

3. RESEARCH FINDINGS

3.1. LITERATURE REVIEW

The literature on pharmaceutical research and development (R&D) provided information mostly about activities in the Global North, especially in the United States and Western Europe, the two most significant contributors to innovative products (which in particular include Germany, France, the United Kingdom, and Switzerland) (IDEA Pharma, 2022; Akkari et al., 2016; Rezaie et al., 2012a). There is limited information on pharmaceutical R&D in the Global South, including where R&D activities are conducted, by whom, what products have been developed or are under development, and what policies or regulations are in place. To help fill this knowledge gap, a scoping literature review which focused on countries in the Global South was conducted.

Searches were conducted in English in major databases, including PubMed, SciELO, and Global Index Medicus, from the earliest available literature until April 2022. Keywords and search terms included “pharmaceutical”, “drug”, “medicine”, “vaccine”, "health", “innovation”, “research and development”, “product development”, “global south”, “developing countr*”, “emerging countr*”, and “low middle-income countr*”. To complement the search, we manually snowballed references in the selected articles and used the tool Litmaps to trace citations of key articles (in October 2022). Grey literature, including reports from national governments, international and regional organizations, and consulting firms was also included through targeted research on Google, primarily to complement information not available in the identified academic literature. Due to resource constraints, we did not conduct literature searches on each developing country or region, and this is a significant limitation of the review, as is the limitation of the search to only English language sources. Nevertheless, we believe this is the most comprehensive recent literature review on pharmaceutical innovation in the Global South publicly available in English. We present a summary of the identified literature below, organized by theme.

- **Most active LMICs in pharmaceutical R&D**

Research in the pharmaceutical sector is highly concentrated in high-income countries, encompassing nearly 72% of all research conducted (IFPMA, 2017). In recent years, there have been growing activities in the pharmaceutical sector in developing countries, especially in the “BRICS” countries (Brazil, Russia, India, China, and South Africa) (IFPMA, 2021). The failure of the more established pharmaceutical industry (i.e., that of the US and Europe) to develop drugs for some significant, but less profitable markets has been highlighted as an opportunity for the sector's growth in developing countries (Chataway et al., 2007). The COVID-19 pandemic is also likely to change the dynamics of the pharmaceutical innovation sector at both domestic and global levels with the growing participation of "emerging economies", although the long-term impacts remain unclear at this point (OECD, 2019).

Most of the studies identified in the literature search referred to only a few LMICs, namely China, India, Brazil, South Africa, and Cuba. One study introduced the concept of "Innovative Developing Countries" to identify a group of countries in an “intermediary stage of social and economic development" with “impactful scientific programs”. Using international patent applications for medicines as one of the metrics, the study identified nine LMICs among the top 25 countries in the world (India - 1st, China - 3rd, Brazil - 12th, Turkey - 16th, Ukraine - 18th, Mexico - 20th, South

Africa - 22nd, Malaysia - 23rd, and Kenya - 25th) (Vasconcellos et al., 2018). Forecasts showed a positive trend in pharmaceutical innovation in emerging countries, especially China (Akkari et al., 2016).

A few studies focused on the African continent. A recent study mapping regional actors for health research in Africa identified 21 unique regional organizations and 26 specialized sub-organizations, concluding that the continent has a vast network of regional bodies related to health research issues. The study did not identify one particular organization that acts as a hub, but did identify poles of influence emerging in the Eastern and Western African regions (Hedquist et al., 2022). Another study mapped capacities for health sciences research across 54 countries in Africa, analyzing indicators such as research institutions, research funding, clinical trial infrastructures, and regulatory capacities (the complete data for all indicators is available online). South Africa, Egypt, and Tunisia scored highly across most metrics (Wenham et al., 2021).

- **Innovation pathways**

Historically, developing countries like Brazil, China, India, and South Africa have mainly focused on the development of generic drugs and manufacturing, with little attention and resources allocated to R&D for innovative drugs (Vidotti et al., 2008; Ding et al., 2011; Edwin, 2012; Rezaie et al., 2012a). Reverse engineering of existing drugs has been highlighted as an important factor leading to the learning effect in domestic pharmaceutical industries, thus facilitating the transition into innovative activities, considered an "imitation to innovation" trajectory (Chataway et al., 2007, Rezaie et al., 2012a). For example, South Africa, as a major manufacturing site for the African continent, is venturing into an independent, innovative pharmaceutical industry (Chibale, 2021). The growth of South Africa's pharmaceutical industry began primarily by producing generics and branded antiretroviral drugs during the HIV/AIDS crisis in the country (Kudlinski, 2013).

Another prominent example is India. First, companies began by copying and innovating around patents, then moved to the improvement of processes to reduce costs, then to "more creative imitation" in product development, and finally started with incremental innovation and the beginning of innovative R&D in the early 2000s (Chataway et al., 2007). A study about the development of the pharmaceutical industry in India argued that Indian firms did not follow the innovation pathway usually followed by multinational pharmaceutical companies (intellectual property protection, venture capital, health reimbursement schemes, etc.), but had a different strategic trajectory: "first, make generics to sell in India; second, obtain approval for and market generics in the USA and Europe; and then develop in-house capability in discovery—inventing and developing new patented drugs," with the discovery capabilities being financed by the cash flow generated by the sales of generics (Bower and Sulej, 2007).

In India, the national patent law adopted in 1971 (which allowed for patents on manufacturing processes but not on final products) was prompted by public health concerns; it encouraged local imitation of expensive and often unavailable imported drugs, shaping the innovation path in the country - a "public-policy trigger" (Chataway et al., 2007). The second main driver of the Indian pharmaceutical industry was the exportation of generic drugs to the US with the enactment of the 1984 Hatch–Waxman Act to lower drug costs and change regulation to allow for the importation of generics produced abroad - a "market-led trigger", that originated from a policy change abroad (Chataway et al., 2007). Therefore, India's pharmaceutical industry experienced significant growth stimulated by the development of an industry-led pharmaceutical sector, as opposed to a health service-driven one as, for example, in Cuba (Chataway et al., 2007). Additionally, India's policies emphasized export markets for generics, as opposed to Brazilian and South African policies that focused primarily on import substitution and lowering the cost of health products for local populations (Rezaie et al., 2012b).

Other strategies used by Indian companies to build up their innovation capabilities were to act as R&D service providers to multinational pharmaceutical companies, out-licensing early-stage discoveries for later-phase clinical trials, or in-licensing molecules for further development (Chataway et al., 2007). For example, the case of the Indian company Dr. Reddy's suggests that out-licensing helped it strengthen its knowledge of discovery, development, and commercialization, while the company Nicholas Piramel has strengthened its innovation capabilities by in-licensing molecules (Chataway et al., 2007). Another more recent study about the pharmaceutical industry in India also highlighted the role of providing contract research services in co-development projects and building up capacity for conducting proprietary R&D, in addition to generating revenues for investing in their own R&D projects (Differding, 2017).

China, for many years, depended on foreign pharmaceutical companies to produce "me-too" or biosimilar and generic drugs needed for its national population (Ding et al., 2011). Today, it has one of the most robust pharmaceutical industries in the world. One study found that it contributed to 7.8% of global drug innovation and 11.6% of new drug launches in 2018 (Tsai, 2019). There are a variety of actors involved in pharmaceutical R&D activities in the country, including large state-owned pharmaceutical companies and small and medium enterprises (SMEs). State-owned R&D companies were highlighted as being relatively quicker in their innovation performance than privately-owned companies, due to the funding and policy support from the government (Xu et al., 2021).

Chinese companies often leverage traditional Chinese medicine (TCM) knowledge and resources, and have been credited with having a considerable focus on developing novel therapeutics in frontier areas, such as the development of innovative gene therapies by Shenzhen SiBiono for the treatment of head and neck cancer, marketed as Gendicine® (Rezaie et al., 2012a). Another prominent example of pharmaceutical innovation from China is the H1N1 influenza vaccine by the company Sinovac, which was the first worldwide to receive approval during the H1N1 pandemic in 2009 and 2010 (Sinovac, 2021).

Studies about Brazil showed that the pharmaceutical industry has expanded significantly and made much progress from the manufacturing of generics toward R&D activities, as a collective result of regulatory standards, improvements in scientific and technological capacity-building, consolidation of university-based research and development groups, and better interaction between research groups and pharmaceutical companies (Vidotti et al., 2008; de Medeiros Rocha et al., 2012; Tigre et al., 2016; Alves et al., 2019). In 2004, the first drug developed entirely in Brazil was registered. The herbal medicine, Acheflan®, is an anti-inflammatory derived from the plant species Cordia verbenaceae, whose active principle is alpha-humulene (Vidotti et al., 2008). The product was developed by the private company Aché Laboratórios in partnership with four universities, three public and one private: Universidade Federal de Santa Catarina, Unifesp, Unicamp, and PUC-Campinas (Abifina, 2015). Brazil is also actively involved in the R&D of other plant-based therapies. NuBBE, a Brazilian open science database, was created to increase knowledge sharing for compound development and drug discovery, documenting Brazil's biodiversity and sharing other data on how to use chemical compounds for drug development (Ferreira et al., 2018).

Cuba's pharmaceutical innovation system was built to improve local public health capacities "under the pressure first, of US sanctions, and later, the collapse of the Soviet system" (Chataway et al., 2007). There was a huge public investment to build a national health system with strong biomedical innovation capacity, including investments in human capacity (health workers and scientists) and institutional capacity to conduct R&D and clinical trials (Chataway et al., 2007). The main driver of health innovation is to attend to local health needs, with research priorities defined by the national scientific policy based on the health status of the population (Rojo Pérez et al., 2018). The State's commitment to developing and funding scientific research,

including identifying priorities and providing systematic training of human resources, has been the driving force of the Cuban pharmaceutical innovation system (Rojo Pérez et al., 2018). One of Cuba's significant steps in organizing the domestic pharmaceutical industry is the formation of BioCubaFarma, a national effort to improve the biopharma sector (Escobar, 2018). BioCubaFarma comprises 34 companies and institutes involved in R&D and manufacturing in the pharmaceutical and biotechnological sectors (Escobar, 2018).

A 2012 study showed that after decades of copying products developed elsewhere, a growing number of innovative products were being developed in China, India, and Brazil, identifying 165 innovative products or candidates within 41 indigenous firms in those three countries (Rezaie et. al. 2012b). Chemistry-based pharmaceuticals represented the majority (53%) of products and were predominant in India, followed by biotech products (38%) predominant in China, and plant-based medicines (9%) predominant in Brazil (Rezaie et. al., 2012b). The authors attributed this variation to India's expertise in chemistry-based products, and considerable government support, as well as a more flexible regulatory framework for "leading edge technologies (such as genetic and stem cell therapies)" in China (Rezaie et. al., 2012b).

- **R&D policies**

National regulations, policies, and laws shape the development of the pharmaceutical innovation system in many countries. For example, Cuba has a robust healthcare and innovation system embedded in the national policy system (Mytelka, 2006). In 2016, the Science and Technological Innovation System (CITMA) of Cuba had 37 research institutes dedicated to health research and innovation (about 26% of all Cuban scientific institutions are dedicated to health-related research) (Rojo Pérez et al., 2018). To hasten the regulatory process of new drugs and technologies, the Cuban regulatory agency established an Office of Innovation to boost R&D initiatives and efficiently improve the productivity of national research institutes (Romeu & Perez Cristiá, 2021).

In the early 2000s, the Brazilian government introduced a 'health-industrial complex' policy, which linked health issues to national development and industrial policy, and invested in technology transfer, financial assistance, and price control of the end products (da Fonseca, 2018). In 2008, the Ministry of Industry and Trade in Russia introduced the program "Pharma 2020" to promote Russia's pharmaceutical R&D by fostering collaborations among various sectors to contribute to drug development, such as innovative drug developers, manufacturers, universities, research institutes, and logistics services, with USD 4 billion in funding pledged by the government for its implementation (Peach, 2011; Bryzgalova et al., 2018, 2021; Peskova et al., 2019).

In 2008, the Department of Science and Innovation (DSI) of South Africa (formerly the Department of Science and Technology) introduced a ten-year innovation plan to strengthen pharmaceutical innovation capacities (Gabru, 2008). The DSI also has platforms to tackle consistent health issues in the country, such as HIV/AIDS, malaria, and TB, by coordinating R&D, funding, and project management (Department of Science and Technology, 2018). In 2018, the South African government aimed to target 1.5% of the gross domestic expenditure on research and development (GERD) for the national innovation system to provide a platform for innovation, research, and financial support for researchers (Department of Science and Technology, 2018).

The African Union Development Agency has developed the "Health Research and Innovation Strategy for Africa (HRISA): 2018-2030," which advocates for intensive research and innovation by engaging academic institutions and organizations, as well as fostering partnerships with public and private sectors to improve health security and meet universal health coverage targets (African Union Development Agency-NEPAD, 2019). It focuses on innovation policy for the Africa Health Strategy initiative. HRISA aims to amplify African research, promote South-South

collaboration and sustainable mechanisms for investment and financing innovation for health, strengthen data-sharing platforms, and integrate regulatory and IP mechanisms (African Union Development Agency-NEPAD, 2019).

Soon after gaining independence in 1947, India established the Council of Scientific and Industrial Research's Centre - Central Drug Research Institute (CDRI) for drug R&D (CSIR-CDRI | Home, accessed October 26, 2021). As India has a robust traditional medicine system, the initial research was based on Ayurveda[2] and Unani[3], but soon followed suit with synthetic molecule discovery (Differding, 2017). In the early 1990s, the discovery of ormeloxifene, the world's first nonsteroidal oral contraceptive, was a significant success of the CDRI (ibid).

The first Indian new chemical entity (NCE), saroglitazar, used for the treatment of diabetes, was developed by the Indian company Zydus Cadila Healthcare in 2013 (Ritesh, 2014). Another example is India's indigenous research on rabies vaccines, which has played a critical role globally in reducing morbidity and mortality caused by rabies. Before the Indian vaccine came out, the vaccine developed by Novartis was widely used, but expensive (Masum et al., 2011). To be suitable for low-resource settings, one of Indian Immunological Limited (IIL)'s divisions, called the "Human Biologicals Institute", developed a low-cost vaccine, Abhayrab® (Deshpande et al., 2020). The vaccine development cost about USD 2.5 million in a public-private partnership between the Human Biologicals Institute and the government-owned National Dairy Development Board of India (Masum et al., 2011). To further improve the accessibility of rabies vaccines in rural parts of India, an affordable innovation mechanism called the Abhay Clinic Model was developed, which realized distribution and cold-chain supply to hard-to-reach areas via local clinics (Frew et al., 2009).

- **R&D funding**

In general, there was scarce information in the identified literature about pharmaceutical R&D funding. One study mapped global investments in health R&D in 2009, and found a total of USD 240 billion spent, of which 89% (USD 214 billion) was invested in HICs (Røttingen et al., 2013). Another study investigated global public and philanthropic funders of health research that together spent USD 93 billion, demonstrating that the ten largest funders (accounting for 40% of the total) are from North America, Europe, or Oceania (Viergever and Hendriks, 2016). Of the 55 total major funders identified by the study, 20 are based in eight LMICs (Argentina, Brazil, China, India, Mexico, Russia, South Africa, and Turkey) (Viergever and Hendriks, 2016).

A study analyzing the emergence of pharmaceutical innovators in Brazil, China, India, and South Africa pointed out that, historically, multinational companies have concentrated their R&D activities in high-margin segments, leaving domestic companies to address less profitable segments (Rezaie et al., 2012a). As a result, there has been a dearth of private capital to support R&D, and innovative domestic companies have obtained significant support from governmental sources, especially in China, Brazil, and South Africa, while Indian companies have had less direct support (Rezaie et al., 2012a). For example, pharmaceutical R&D financing in China comes from multiple channels, including public, private, and subsidies. Budget allocation is usually done by state-owned banks, government purchases, and beneficiary companies (Delgado, 2016). The most preferred funding source of pharmaceutical companies is a governmental R&D subsidy because it increases corporate R&D investments, reduces debt, and facilitates risk reduction (Xu et al., 2021). In Cuba, pharmaceutical innovation programs are funded mostly by the state, which in 2016, allocated 35% of its national science and technology budget to the health sector (Rojo Pérez et al., 2018).

2 Ayurveda is the "ancient Indian medical system based on ancient writings that rely on a "natural" and holistic approach to physical and mental health" (nccih.nih.gov, n.d.).

3 Unani medicine is a "traditional system of healing and health maintenance observed in South Asia", and practitioners rely on "natural healing based on principles of harmony and balance, uniting the physical, mental, and spiritual realms" (britannica.com, n.d.).

A common approach for generating revenues for investment in R&D activities in Brazil, China, India, and South Africa remains the manufacturing and marketing of generic products, in contrast with industrialized economies where "it is well established that financing new product development with current revenues is more expensive and constraining compared to investment-driven financing" (Rezaie et al., 2012b). A 2007 study about the Indian pharmaceutical industry mentioned that R&D spending in the top firms was increasing over the years, from around 2–3% of sales in 1999–2000 to around 7–8% in 2004–2005 (Chataway et al., 2007). A 2017 study mentioned that major Indian pharmaceutical companies with significant R&D activities reported R&D expenditures in the range of 5-10% of revenues (Differding, 2017). Revenues from the sales of generics were pointed out as the main source of funds for investing in R&D (Bower and Sulej, 2007), while revenues from research contract services were also mentioned as a source of funding for proprietary R&D (Differding, 2017).

- **Actors involved in pharmaceutical R&D**

The literature identified a variety of actors involved in the R&D process, including academic institutions, public research institutions, large pharmaceutical companies, SMEs, and others. Health service providers such as clinicians were also identified as important actors in the knowledge flow between companies and academic institutions (Gadelha et al., 2020). One study about Brazil argued that university and research institutions' collaboration with pharmaceutical companies has recently been increasing to complete the early research phase of drug development (Delgado, 2016). Collaboration with domestic academic and research institutions has been highlighted as an important factor contributing to private companies' R&D activities, as firm-university linkages can fill gaps in internal R&D capabilities (Rezaie et al., 2012a). Nevertheless, Rezaie et al. concluded that "notwithstanding these benefits, domestic university-company links remain weak overall, largely for cultural and historical reasons" (2012a).

- **Type of products and therapeutic areas**

The literature mainly focused on R&D for drugs, followed by vaccines, and fewer studies about diagnostics. One study pointed out that diagnostics and medical devices were common starting points for innovative product development in Brazil and South Africa, respectively, while vaccines represented a significant entry point for many firms in India (Rezaie et al., 2012a). An example of a diagnostics platform developed in a LMIC is the Ultramicroanalytical System (SUMA) developed by the Cuban Immunoassay Center, which is used for mass screening of several infectious diseases such as HIV, hepatitis B and C, dengue, Chagas disease, and Hansen disease (leprosy) (Rojo Pérez et al., 2018).

Some of the identified literature provided information on the therapeutic areas being researched in the country of the study or LMICs generally. R&D is conducted for a range of diseases, including HIV/AIDS, tuberculosis, Malaria, neglected tropical diseases (NTDs), noncommunicable diseases (NCDs), respiratory diseases, and biosecurity-related diseases such as emerging infectious diseases (EID) and antimicrobial resistance (AMR) (Cole et al., 2018; Feldbaum et al., 2006). The aforementioned 2012 study analyzing innovative pharmaceutical products in Brazil, China, and India found that out of 165 products/candidates, about 18% were vaccines, and almost all targeted infectious diseases (Rezaie et. al., 2012b). Overall, the leading disease indications in the pipeline of products were infectious disease (27%), oncology (25%), and neurology (13%) (Rezaie et. al., 2012b). India, China, and Cuba were also mentioned for their involvement in cancer research and product development (Rojo Pérez et al., 2018; Jalali et al., 2022). With the onset of the COVID-19 pandemic, many LMICs have been involved in the R&D of COVID-19 vaccines, therapeutics, and diagnostics, including Russia, India, China, Brazil, and Cuba (Covid-19 R&D Tracker, Policy Cures Research, 2020).

Studies have suggested that, in general, pharmaceutical R&D conducted in developing countries focuses more on addressing diseases that mainly affect developing countries (Frew et al., 2009; Rezaie et al., 2012a; Vasconcellos et al., 2018). One study suggested that as a result of developed countries outsourcing steps of pharmaceutical development (such as manufacturing) to developing countries to reduce the cost of production, these countries have started investing profits generated from the sales of generics in innovating their own drugs to meet local health gaps (Casty & Wieman, 2013).

Responding to local health needs was mentioned as a key trigger and an opportunity for building up local R&D capacities (Chataway et al., 2007). Cuba was highlighted as a positive example, where attending to the needs of the local population is the main driver of the national innovation system (Thorsteinsdóttir, 2007). The field of neglected diseases, not well-researched by big pharmaceutical companies, was suggested as an opportunity for developing countries to enter the innovation field (Chataway et al., 2007). For example, in vaccine development, “Indian companies played a major role in developing a hepatitis B vaccine, and Cuba has become a major innovator and producer, including its meningitis B breakthrough” (Chataway et al., 2007).

However, it is also argued that diseases that almost exclusively affect "poor market segments'' are unlikely to be addressed by companies involved in pharmaceutical R&D in emerging markets, and they require specific policies to be addressed (Rezaie et al., 2012b). A 2007 study about the Indian pharmaceutical industry raised the concern that the change of the strategy toward international competitiveness was leading to R&D being conducted for “diseases of the wealthy", leaving unattended the needs of the local health system (Chataway et al., 2007). For example, in India, pharmaceutical R&D is mainly focused on rheumatological diseases, respiratory diseases, and neurological diseases, constituting a sharp contrast to the prevalent diseases within the country as a consequence of aiming to address "Western diseases" (Differding, 2017).

Recent studies analyzing clinical trial activities for cancer argued that most of the clinical trials conducted in LMICs are initiated by investigators in HICs, and do not adequately represent the global burden or priorities of cancer care most prevalent in LMICs (Jalali et al., 2022; Pramesh et al., 2022; Wells et al., 2021). Nevertheless, the authors concluded that, despite challenges (e.g., limited funding and research infrastructure), LMICs have enormous potential for the realization of clinical studies, and pharmaceutical companies in LMICs are emerging in the field of drug development, giving the anti-cancer drugs icotinib developed in China, and nanoxel developed in India, as examples of innovation (Jalali et al., 2022).

Wells and collaborators (2021) suggested that clinical trials from LMICs are more likely to identify new effective therapies based on the proportion of trials identifying treatments with substantial clinical benefit (48% in LMICs vs. 31% in HICs) (Wells et al., 2021). In opposition to the "megatrials'' that dominate cancer research in HICs that are associated with marginal therapeutic benefits (e.g., extending survival by a few weeks), the study found that clinical trials led by researchers in LMICs are smaller in size, more likely to have positive results, and are associated with a "larger magnitude of benefit", attributed to the pragmatism in the trial design, probably due to limitation of resources (Wells et al., 2021). The same study also observed a funding and publication bias against clinical trials led by LMICs, and concluded that there is a "historical colonial approach (prioritizing HICs over LMICs) to global health" which "perpetuates substantial structural barriers to conducting clinical research in low-resource settings" (Wells et al., 2021).

- **International collaboration**

In many cases, R&D activities happening in the Global South are closely related to collaboration with countries outside the country or region (Thomas et al., 2016; Weng et al., 2018; IPASA, n.d.). For example, the Innovative Pharmaceutical Association South Africa (IPASA) was established in

April 2013, and comprised numerous research-based international pharmaceutical companies, in an effort to foster innovative R&D in the country (IPASA, n.d.). The Drug Discovery and Development Centre (H3D), the first integrated drug discovery and development center in the African continent, was founded by the University of Cape Town in South Africa and partnered with multiple international organizations to strengthen its research capacities, such as the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and Medicines for Malaria Venture (MMV) (H3D-Foundation, 2021). It was responsible for developing a novel antimalarial compound (MMV048), reportedly the first clinical candidate to come out of Africa (H3D-Foundation, 2021). Indian companies have also developed many drugs in collaboration with multinational corporations recently. For example, Alembic Pharmaceutical (India), which holds 50% of shares of Rhizen (Swiss), jointly developed the drug umbralisib with TG Therapeutics (USA), which is a novel drug for blood cancer that received approval from the US FDA by priority review in 2021 (Globe Newswire, 2021).

There have also been efforts in data and information sharing to further promote pharmaceutical R&D. For example, open source platforms are proficiently used in China to accelerate the elimination of NTDs via the Chinese National Compound Library, which is a public-private partnership of the National Center for Drug Screening, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, WHO, and Novo Nordisk, containing over 2.2 million chemical entities useful for conducting screening campaigns for research and innovation against molecular targets of NTDs (Weng et al., 2018). In addition, Cuba was also mentioned as a country with strong international collaboration with other developing countries, including technology transfer (Chataway et al., 2007).

In general, there is less pharmaceutical R&D happening in the Global South compared with the Global North, usually attributed to a lack of funding, R&D facilities and infrastructure, and human resources (Rezaie et al., 2012a). However, the literature showed growing pharmaceutical R&D activities in LMICs, with growing outputs (see Table 1 below). The development of the pharmaceutical industry is, however, uneven among countries in the Global South, with a few in the lead and growing at considerable speed. These findings from the literature are largely consistent with this study's analysis of data from interviews and databases, as described further in the following sections.

3.2. SCOPING INTERVIEWS

To complement the literature, scoping interviews were conducted early in the project with experts in the field of pharmaceutical R&D in the Global South. Interviewees were selected based on the authors' knowledge and aimed for geographical representation. In total, 12 people/organizations were contacted for interviews, and seven interviews were conducted with eight individuals (58% response rate). Appendix 5.1 and 5.2 contains a list of interviewees and sample interview questions. The interviews aimed to gather more information about pharmaceutical R&D activities in LMICs in general, or to understand further the innovation system in countries identified as particularly relevant in the field, especially BRICS. Information from the scoping interviews has been anonymized and summarized below, organized into eight distinct topics. Interview quotes have been edited for length and clarity.

- **Mapping R&D capacities**

It was raised that thousands of institutions are involved in some pharmaceutical R&D activity in LMICs, and mapping them is nearly impossible (SI_07). It was pointed out that each stage of the R&D process is conducted by different entities in both HICs and LMICs, and a stage-wise mapping could provide more detailed information about the organizations involved in each country (SI_01). Some countries might have more activities happening at one stage than others. For example, South Africa was mentioned to be more active at the end of the R&D process rather than at the earlier discovery stage (SI_01).

It was also suggested that instead of focusing on approved products, looking at candidates at different stages of development can provide a better picture of R&D activities taking place (SI_01). It is also essential to look not only at later-stage clinical trials but also at the early phases of the process, including the preclinical stage (SI_01). For example, it was suggested to look at early-stage clinical trials in countries from the Southern African Development Community (SADC), and Malawi and Zimbabwe were mentioned as countries where many research activities are taking place in the region (SI_01, SI_09).

Mapping manufacturers in LMICs was suggested as an entry point to identify actors involved in R&D activities, as manufacturing can lead to innovative capacities (SI_07, SI_08, SI_11). Several countries were cited as having an important pharmaceutical industry moving towards developing innovative products beyond manufacturing and formulations of biosimilars or generics, including India, China, South Africa, Kenya, Uganda, Brazil, Argentina, Mexico, Russia, Cuba, Indonesia, Malaysia, Thailand, Egypt, Philippines, Bangladesh, Costa Rica, and the Dominican Republic (SI_01, SI_03, SI_08). Senegal was mentioned as a country that is very active in diagnostics (SI_01, SI_03).

Finally, several databases were suggested for use, which provide information on different aspects of the R&D process, such as the WHO R&D Observatory, the Policy Cure's G-Finder report for funding of research on neglected diseases, the WIPO: Research for collaborations on early-stage R&D in the field of neglected tropical diseases, malaria, and tuberculosis, the TDR Grant and Resulting Publication Explorer, and the ICTRP - International Clinical Trial Registry Platform (SI_07). Interviewees also suggested mapping philanthropic funding supporting R&D activities, notably from the Bill and Melinda Gates Foundation and the Wellcome Trust (SI_03, SI_09).

- **Government role and R&D funding**

The importance of government involvement in promoting R&D in the Global South was mentioned in multiple interviews. Some governments sponsor institutions or invest in companies directly, while others have national-level policies to encourage investment and stimulate innovation, including through direct and indirect funding (SI_01, SI_08, SI_11).

> "There were efforts at the policy level to connect the national innovation system to the demands of the public health system. For example, within the context of the National Medicines Policy, the approval of the Generic Law was followed by incentives to strengthen national production of generic medicines. Later, to stimulate technology transfer of medicines to public manufacturers was guided by a list of products adopted by the public health system and based on the State purchasing power to guarantee demand". (SI_11)

It was noted that in many LMICs, organizations manufacturing pharmaceuticals and involved in R&D are state-owned (SI_03). China, Brazil, and Russia were mentioned as countries where most of the pharmaceutical R&D is funded by the government (SI_08, SI_11).

> "Typically, my understanding is that these are parastatal organizations, so medical research facilities that are funded primarily by the government, although their mandate is to be quite independent of government prioritization, in terms of the work that they do. And sometimes future access is not a priority." (SI_03)

India, and generally countries in the Southern African region, were highlighted as having less government funding for the pharmaceutical sector, which is driven mainly by the private sector, including by multinational firms (SI_06, SI_09). Philanthropic funds were also mentioned as an important source of funding for pharmaceutical R&D, especially in Africa, for example, through the Coalition of African Research and Innovation supported by the Bill and Melinda Gates Foundation and the Wellcome Trust (SI_09).

> "In terms of multinationals in Africa, there is Sanofi, Pfizer, all of those are still funding fill-and-finish instead of R&D. The Bill and Melinda Gates Foundation funds a lot of research in this region. They're funding the Coalition of African Research and Innovation, which is trying to consolidate research activities in the country. And it is working towards funding innovation and other areas as well. This works through a grant-making system that they have, because what we have seen is that there is no continental-level collaboration." (SI_09)

Governments also play a role in de-risking investments in R&D in multiple ways. For example, in Russia, most pharmaceutical R&D is government-funded, and there were many cases where Russian companies bought molecules initially developed by multinational companies for further development with the support of government funds (SI_08). The Indian Covid-19 vaccine "Covaxin" was developed by the private company Bharat Biotech with support from the government, particularly from the Indian Council for Medical Research (ICMR), a public body that developed some of the basic research. The state commitment to buy the vaccine was an important driver of private investment in its development as it guaranteed financial return (SI_06). The Brazilian innovation policy for the health sector includes government grants for projects involving technology internalization and technological risk, as well as guaranteed public purchases for use in the national public health system (SI_11).

> "The mechanism which allows the government to make a 'encomenda tecnologica (technological order)' is important for innovation projects, as the public administration can invest in something involving a technological risk (possibility of failure); it allows the government to take the risk of innovation." (SI_11)

Nevertheless, there were also mentions of insufficient government policies and guidance, as well as a lack of political prioritization of pharmaceutical R&D in most developing countries, especially beyond upper-middle-income countries (SI_03, SI_06, SI_09). Furthermore, there is a lack of prioritization of government funding for basic research and the early stages of product development, attributed to the fact that the results will come many years later (SI_03). Some interviewees raised the need to strengthen frameworks to measure success in innovation, not only in terms of financial return but also in terms of societal return, which could help to attract investments from governments in developing countries (SI_03, SI_07).

- **R&D policies**

It was mentioned that the policy space for "learning by doing" has been reduced in the past decades due to international agreements such as the 1994 World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which limits country's freedom to learn by imitation, except if further action is taken to remove IP-related barriers (e.g., compulsory licensing) (SI_01).

> "The other big issue is how the ability to learn from doing and to build up capacity has been crushed by the TRIPS agreement. For example, (...) if you're trying to produce in a country something which others have been making and it is patented, you can no longer just copy and then learn from that, which is what happened in the North." (SI_01)

Bangladesh was mentioned as an example of a country still exempted from fully implementing the TRIPS Agreement, since they are a "Least Developed Country". They have been building up their pharmaceutical manufacturing capacities, and therefore would be an interesting case study for understanding potential implications for more innovative activities (SI_01, SI_03).

Brazil, Cuba, India, and Indonesia were mentioned among the countries that have implemented policies linking R&D capacity, technological and industrial development, and health needs (SI_03, SI_11). Russia adopted policies (Pharma 2020, Pharma 2030) to incentivize the local production of generic medicines to promote self-sufficiency, and extended them to support the development of innovative drugs (SI_08). The Brazilian pharmaceutical innovation policy was designed to incentivize technology transfer and local production, to substitute the importation of priority high-cost products used by the public health system (SI_11). The mRNA hub in South Africa was mentioned as a recent example of reverse engineering and learning by doing, since it focuses on a platform technology with several uses, including new uses developed by, and for, LMICs (SI_01, SI_03).

China and Russia were mentioned as having a policy of mandatory local manufacturing, which aims to promote national security of supply and potential cumulative capacity for innovation (SI_08).

> "Another thing I think is worth mentioning is this practice of localization of manufacturing. So they demand Western companies to localize the production and manufacturing of their drugs in the country; this is a part of the overall strategy for this drug security, pharmaceutical security. So the idea is that once they have the production facilities on the territory, it makes them more sustainable." (SI_08)

It was also mentioned that many countries have a policy that requires clinical trials to be conducted domestically to be able to obtain market approval, which has led to the development of countries' capacity to conduct clinical trials (SI_08).

> "There are a number of facilities where they run clinical trials, and it is a pretty developed market because one of the requirements to register drugs in the country is to have local clinical trials. And there are pros and cons to this policy, probably more cons than pros. But this strategy, the idea behind this strategy, is to develop the market for clinical trials." (SI_08)

- **R&D priorities**

It was pointed out that as HICs prioritize funding for their own needs, and given the resource constraints of LMICs, there is limited funding for research (including basic research) into diseases that primarily affect developing countries (SI_03). Overall, it was suggested that local needs

frequently drive R&D activities in LMICs, and they tend to innovate more in aspects such as ease of use (SI_06, SI_09). For example, during the COVID pandemic, a few developing countries were actively involved in developing vaccines, partly because vaccines developed by HICs were not sufficiently available to fulfill urgent needs. Projects are looking at developing nasal spray vaccines, particularly in India and Cuba (SI_06).

> "For some of the people in the South, they see this as a way both to serve their populations, but also it's a potentially very large market." (SI_01)

> "It is interesting that when you think of innovation, of course, we look at efficacy, ability to adapt to new variants, etc. But, I think that it is a particular developing country thing to also think about ease of use. A manner of creating a vaccine that requires the least infrastructure to put it out." (SI_06)

Necessity was also pointed out as an important factor driving the development of pharmaceutical R&D capacities, particularly in countries excluded or sanctioned by the international market, such as Cuba and Iran (SI_06). India and South Africa were also mentioned as countries that built up their pharmaceutical capacities in response to economic sanctions in the recent past (SI_06).

Finally, it was mentioned that some R&D is directed at employing technologies for additional areas or diseases (SI_03).

> "Once a country has the capacity to produce, they can produce any kind of important therapeutic based on that platform technology that they're using, which is no longer new, but it will be innovative because it's being applied to disease x. Similarly, with monoclonal antibody technologies, once you have that technology, whether you are applying it to dengue or cholera or anything else, it is sort of secondary." (SI_03)

- **Pharmaceutical products developed by LMICs**

Some interviewees mentioned examples of pharmaceutical products developed by LMICs. For example, bulevirtide was initially developed by a Russian company and approved by the EMA for use in hepatitis D treatment in Europe (SI_08). Russian companies also developed a drug used to treat HIV/Aids (elsulfavirine) and multidrug-resistant tuberculosis (perchlozone) (SI_08). Other examples were the Cuban vaccine for lung cancer, the meningitis and rotavirus vaccines developed in India, the collaboration between Egypt, Malaysia, and the Drugs for Neglected Diseases initiative (DNDi) to develop a novel molecule to treat hepatitis C, and the development of a pediatric formulation of benznidazole for the treatment of Chagas disease by DNDi and a state-owned laboratory in Brazil (SI_01, SI_06, SI_11).

> "The hepatitis C example is a good one in pushing back against this concept that new chemical entities can only be developed and registered by big pharmaceutical companies or companies based in the North." (SI_01)

There was also mention of the vaccines for COVID-19 developed in China, India, Russia, and Cuba, and of a mRNA vaccine being developed in Thailand, as well as an open license vaccine project in Mexico, and a vaccine candidate under development by the state-owned laboratory Instituto Butantan in Brazil (SI_06, SI_07, SI_08, SI_11). It was noted that in China, there was one vaccine developed by a state-owned company (Sinopharm) and another by a private company (Sinovac), and that in India, the government supported early research for the development of the vaccine by the private company Bharat Biotech (SI_06). In particular, the COVID-19 vaccine developed in Russia was mentioned as a good licensing model that merits further study, despite some production problems it ran into (SI_06).

> "The Russian vaccine created a really excellent network of licensing. It included 34 companies around the world - more even than the AstraZeneca vaccine was licensed to. This was a really impressive set of manufacturers and a model which I think was not given as much attention as it should be, despite the fact the second dose of the vaccine could not be produced with the process they developed, which rendered the vaccine unfeasible from a manufacturing point of view." (SI_06).

- **Role of academia and SMEs**

Interviewees also highlighted the role of academic institutions and SMEs, especially in the earlier stages of product development (SI_03, SI_09, SI_11). Changes in the innovation system, moving beyond a vertically integrated model and reducing the costs of earlier discovery stages, have allowed more actors to be involved, including outside HICs. However, most of those activities happen "below the radar" and are difficult to map, only getting noticed once bigger companies pick up a promising candidate to take it forward through the development pipeline (SI_03, SI_09).

> "The University of Cape Town does a lot of R&D. That could be the case in many universities in other African countries, as it must start somewhere. Many universities receive externally funded R&D within Southern Africa. There are 16 countries of SADC, yet there is respectable R&D taking place in universities and institutes in countries such as Malawi, Botswana, and Zimbabwe." (SI_09)

However, it was noted that there is an important gap in translational research from academia to other actors that might carry out the later stages of development (SI_01, SI_03, SI_09).

> "That is what you call the 'valley of death,' which is the translation from the bench to either an intermediary, which in the North tends to be an SME spun out of universities." (SI_01)

India, Brazil, South Africa, and Thailand were mentioned as having more capacity to involve SMEs in the R&D process (SI_01, SI_03, SI_09). However, it was suggested that this model in the Global South might be replicating problems faced in the Global North in terms of prioritization of market needs (SI_01).

> "In India, there is a lot of work being done on creating an environment for SMEs. The concern that I think that we have, if you're working in public health, is that, to what extent are these approaches importing some of the problems we see from the North? Which is that, if they are solely market-based, it will replicate the neglect of certain populations." (SI_01)

- **Knowledge management**

A few interviewees tackled knowledge management practices. It was suggested that, in general, companies and institutions based in the South are conservative regarding their IP policies, and they seek IP protection and restrictive licensing agreements (SI_01, SI_07). Even some innovative patent-free projects, regardless of location, are considering some type of data or market exclusivity to recoup R&D investments (SI_01).

Nevertheless, a few cases were mentioned where more open policies were in place (SI_06, SI_07, SI_08). For example, Biomanguinhos, a state-owned laboratory in Brazil, has a knowledge management policy based on open innovation (SI_11). Another example is an open discovery project for developing new medicines (the Lead Optimization Latin America project - LOLA) led by DNDi in Latin America in partnership with Unicamp, a public university in Brazil (SI_01, SI_11). Other examples are the COVID-19 vaccines with more open licensing arrangements, such as

the aforementioned Sputnik vaccine developed in Russia and those developed in Cuba (SI_06, SI_08). Cuba was an example of an innovative model that produces therapeutics, vaccines, and diagnostics, and engages in technology transfer and licensing practices with small profit margins, but is rarely discussed and could provide valuable information on how to build a successful pharmaceutical R&D system in a resource-poor setting (SI_01, SI_03, SI_06).

One interviewee suggested that whenever there is public funding, the product should be made available as a public good, and not be owned by a private entity (SI_09).

> "If it is government funding, then we need to make sure that these are public goods and are widely accessible. This way, companies can not claim ownership over them. (...) These are ideas that we bring to the table, that if it's going to be publicly financed, then we should actually put parameters or ring fences or guardrails in place within the IP agreement, so that whatever is produced becomes a public good." (SI_09)

- **Challenges and barriers**

Several interviewees mentioned barriers and challenges for conducting pharmaceutical R&D in LMICs, including the lack of financial resources, human resources, research infrastructure, and policies directed at the pharmaceutical innovation ecosystem (SI_01, SI_03, SI_09). It was mentioned that while a few LMICs have national innovation systems for pharmaceutical R&D, most lack policies and incentives directed to the field. One interviewee highlighted the lack of political prioritization of R&D as the most relevant challenge in developing countries (SI_03).

> "What is mostly needed is the public policy coherence and political prioritization of this issue. So if I come to rank the challenges, I think number one ranking is policy, lack of policy coherence, and lack of political prioritization, and then everything else that we race with, for me, some of them are technical, they're all important, but they're kind of secondary to the lack of policy coherence, and the lack of political vision and leadership." (SI_03)

Even in countries with innovation policies, there is an important gap in translational research since knowledge produced at universities or research institutions is frequently not translated into product development, the so-called "valley of death" (SI_01, SI_03, SI_09).

> "So there's a lot of capacity in developing countries, but sometimes it is not really linked to the university research capacity, industrial manufacturing capacity, and policy-making, including in public health priorities. So the lack of links between academia, manufacturers, and policymakers is a gap." (SI_03)

Countries in the Global South are also, in general, less equipped with some of the essential equipment to conduct R&D (SI_09). For example, high-quality biosafety level 3 labs (BSL-3) are needed to develop some new vaccines, but these hardly exist in most countries in the Global South (SI_09). Another challenge mentioned is that brain drain is rampant in LMICs, which deepens the innovation gap (SI_03, SI_09).

> "A lot of environments are under-resourced and have a weak laboratory infrastructure. And for R&D, you need state-of-the-art equipment. In Africa, we don't have those lab facilities outside of countries like South Africa, Egypt, Nigeria, Kenya, and Senegal, to name a few. A lot of other countries really struggle to have good institutions for R&D, which is why a lot of researchers move overseas." (SI_09)

There is also a legal barrier beyond financial resources and capacities, resulting in a lack of access to information, knowledge, and technology. Scientific knowledge and technologies are often proprietary and held by institutions based in HICs, restricting access needed to develop R&D capacities (SI_01, SI_03). For many LMICs, the ability and space to learn from doing have been

limited by TRIPS, and IP creates another barrier and sometimes discourages companies from the Global South from conducting R&D, as does the lack of technology transfer and limitations in voluntary licensing agreements, including through international initiatives (SI_01, SI_03, SI_07, SI_09).

> "If you take what Aspen is doing, it does not seem to move very far beyond generic manufacturing through voluntary licenses with companies. It seems very clear that the agreement with Big Pharma is that it won't go beyond certain bounds. So they'll do fill and finish, or they will do generic manufacturing of a particular molecule, but you don't see them trying to break out and do their own thing; where you see that happening more is with smaller companies." (SI_03)

It was also suggested that there is less focus on what is happening in the Global South (SI_01, SI_03, SI_06). In general, products developed in the Global South received less attention from other countries and a lack of recognition from developed countries' regulatory agencies, especially the FDA and EMA, as well as difficulties in meeting WHO regulations for pre-qualification (SI_06, SI_08). For example, vaccines or drugs that were only for diseases that were prevalent in poor countries, like the meningitis vaccine, the rotavirus vaccine that originated in India, or any other vaccines that came out of places other than the United States and Europe, typically did not receive global recognition as valuable pharmaceuticals (SI_06). In addition, the existing market hierarchy creates barriers for companies based in the Global South to enter the same market (SI_06, SI_08). The COVID-19 pandemic brought more attention to what was happening in some LMICs. However, even so, there was less attention to what was happening in pharmaceutical innovation outside of the US and Europe, for example in China, India, and Russia, and even less regarding the Cuban vaccines and projects in development in Brazil, Mexico, Vietnam, and Thailand, which include an mRNA vaccine (SI_01, SI_06).

> "Firstly, public information on R&D is mostly controlled and collated by institutions in the North; they are not well-embedded in the South. Some innovative work is not noted or followed, or for political reasons, it is excluded. If you look at Cuba, for example, which is one of the most innovative models producing therapeutics, vaccines, and diagnostics in a very open way, and providing it to the region, that's never talked about. We've seen the same in COVID-19 in relation to vaccines when the focus is on Northern pharmaceutical companies. There is little focus on what's happening in China, Russia, and India." (SI_01)

> "There must be better ways to accept the help and recognize the innovation in poor countries because it would better serve the entire world. But at the moment, the entire infrastructure...we have to recognize innovation is geared in an unfair way only to recognize innovation if it comes from Pfizer or Moderna, and not recognize it if it comes from Cuba. And there are real problems that are associated with that in terms of what people think of these vaccines, and how much they want to make these vaccines." (SI_06)

Regulatory issues for clinical trials and manufacturing practices were also raised as barriers, as well as limited pharmacovigilance systems (SI_07, SI_08, SI_09, SI_11). Finally, also mentioned was the language constraint of disseminating knowledge in globally recognized peer-reviewed journals for non-English speaking countries (SI_06).

3.3. PHARMACEUTICAL PRODUCTS DEVELOPED IN LMICS

The literature and the interviewees mentioned a number of pharmaceutical products developed in LMICs, indicating the outputs of pharmaceutical R&D from those countries. Among them, there are several drugs, biologics and vaccines, plant-based medicines, diagnostics platforms, monoclonal antibodies, and gene therapies. Products are used to treat several diseases, including NTDs, infectious diseases, HIV, tuberculosis, meningitis, viral hepatitis, diabetes, antibiotics, and cancer. They were developed by private companies, public and private universities, public research centers, and state-owned institutions, as well as in collaboration with global initiatives, such as product development partnerships (PDPs). The table below summarizes information about these products.

Table 1. Examples of pharmaceutical products developed in LMICs, in order of year developed (from oldest to most recent)

Product	Type of product	Main indication	Main developer	Type of developer	Country	Year
Ultra Micro Analytical System (SUMA)	diagnostics platform	screening of several infectious diseases	Cuban Immunoassay Center	Public institute	Cuba	1986
VA-MENGOC-BC®	vaccine	meningitis B and C	National Center for Meningococcal Vaccine Development	Public institute	Cuba	1989
Ormeloxifene	drug	nonsteroidal oral contraceptive	Central Drug Research Institute	Public institute	India	1991
Shanvac-B	vaccine	hepatitis B	Shantha Biotechnics	Private company	India	1998
Abhayrab®	vaccine	rabies	Human Biologicals Institute National Dairy Development Board	Private company Public institute	India	2001
Gendicine® (recombinant human p53 adenovirus)	gene therapy	head and neck cancer	Shenzhen SiBiono	Private company	China	2003

Product	Type of product	Main indication	Main developer	Type of developer	Country	Year
Acheflan®	herbal medicine	anti-inflammatory	Aché Laboratórios Universidade Federal de Santa Catarina Unifesp Unicamp PUC-Campinas	Private company University (public) University (public) University (public) University (private)	Brazil	2004
Nepidermin	biologic drug	diabetic foot ulcer	Cuban Center for Genetic Engineering and Biotechnology (CIBG)	Public institute	Cuba	2006
Nimotuzumab	monoclonal antibody	cancer	Centre of Molecular Immunology	Public institute	Cuba	2006
Lodenafil carbonate	drug	erectile dysfunction	Cristalia	Private company	Brazil	2007
CIMAvax EGF	therapeutic vaccine	lung cancer	Center of Molecular Immunology	Public institute	Cuba	2008
Panflu.1®	vaccine	H1N1 influenza A	Sinovac Biotech	Private company	China	2009
MenAfriVac	vaccine	meningitis A	Serum Institute of India	Private company	India	2009
Risorine	drug	tuberculosis	Cadila Pharmaceutical Indian Institute of Integrative Medicine	Private company Public institute	India	2009
Icotinib	drug	lung cancer	Betta Pharmaceuticals	Private company	China	2011
Perchlozone	drug	multidrug-resistant tuberculosis (MDR-TB)	JSC Pharmasyntez	Private company	Russia	2012

Product	Type of product	Main indication	Main developer	Type of developer	Country	Year
Saroglitazar	drug	type 2 diabetes mellitus and dyslipidemia	Zydus Cadila Healthcare	Private company	India	2013
Nanoxel	drug	cancer	Dabur Pharma Ltd	Private company	India	2013
ROTAVAC	vaccine	diarrheal disease (rotavirus)	Bharat Biotech	Private company	India	2014
Bulevirtide	drug	hepatitis D	Hepatera	Private company	Russia	2017
Elsulfavirine	drug	HIV	Viriom	Private company	Russia	2017
Levonadifloxacin / alalevonadiflox-acin	drug	antibiotic	Wockhardt Ltd.	Private company	India	2019
Ravidasvir	drug	hepatitis C	Pharco Pharmaceuticals Ministry of Health Pharmaniaga Berhad DNDi	Private company Government Private company PDP	Egypt Malaysia Malaysia Switzerland *(headquar-ters)*	2021

3.4. INDICATORS OF PHARMACEUTICAL R&D CAPACITIES AND ACTIVITIES

The WHO Global Observatory on Health Research and Development provides some data from global data sources that allows health R&D activities to be monitored. It builds on existing data and reports from a range of sources and gathers new information, including reports by WHO's member states. Data is organized under three categories: inputs to R&D, processes for R&D, and outputs for R&D. Inputs to R&D include information on funding flows for health R&D, grants for health research, and capacity for undertaking health R&D. Processes for R&D include pipeline and clinical trials analysis. Outputs for R&D include publication of research. The available data is not comprehensive and is often related to only a few diseases (in particular, neglected diseases), but it is representative of the data sources available on the topic and can provide valuable insights regarding where pharmaceutical R&D activities are taking place and by whom. Below, we draw on the information and data sources listed by the WHO Global Observatory to provide information on pharmaceutical R&D capacities in LMICs.

3.4.1. FUNDING FLOWS

One indicator of funding flows for health R&D is the gross domestic R&D expenditure on health and medical sciences, referred to as health GERD, as a percentage of the gross domestic product (GDP)[4]. The latest available data at the time of our analysis was published by the WHO Global Observatory on Health R&D in December 2021, with information available for 86 countries. It should be noted that the year of the data differs from country to country, and the figures shown are from the most recent year available for each respective country. Countries are classified by four income levels: high-income countries (HICs), upper-middle-income countries (UMICs), lower-middle-income countries (LoMIC), and low-income countries (LICs). As a group, HICs invest the highest percentage of their GDP in health GERD, more than 10x higher than other income groups (WHO Global Observatory on Health R&D, 2021). A comparison with the earliest available data for this indicator, published in January 2017 with data reported by 62 countries, shows that the average percentage invested in health GERD in HICs dropped significantly in recent years, as well as the average for LICs, while the figure for UMICs and LoMICs remained the same (WHO Global Observatory on Health R&D, 2017).

Table 2. Percentage of GDP invested in health GERD by income group, 2017 and 2021

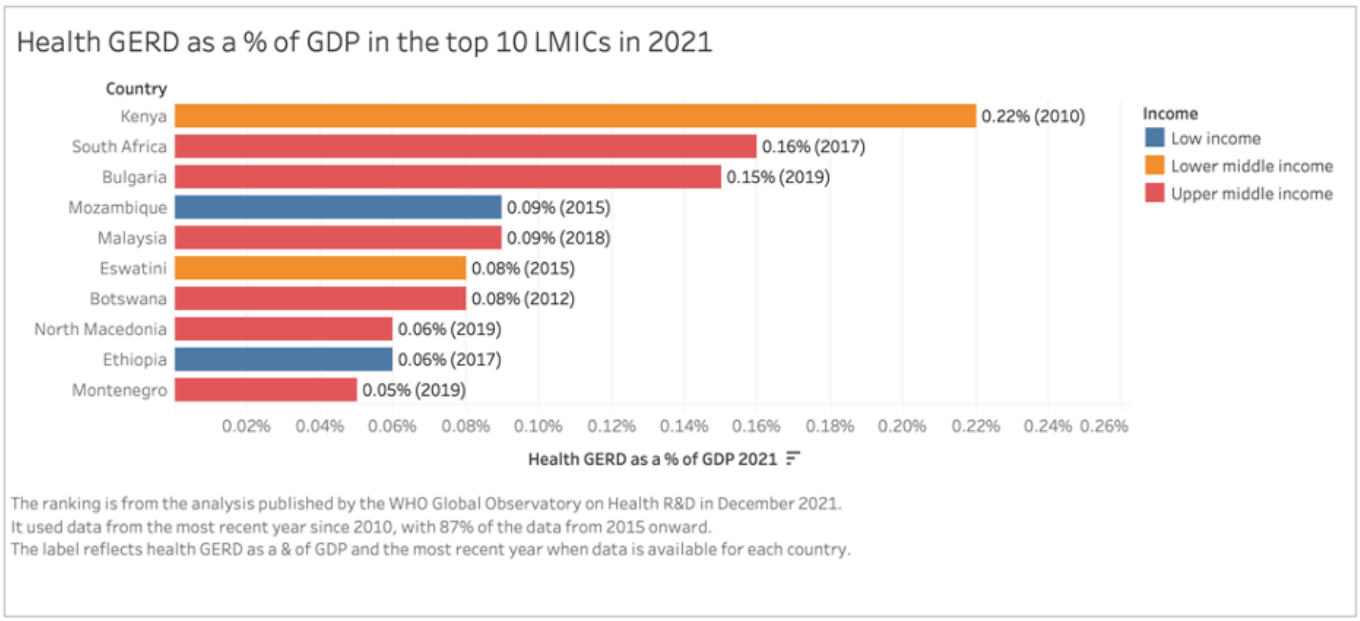
Income group	2017	2021
HICs	0.46%	0.21%
UMICs	0.02%	0.02%
LoMICs	0.02%	0.02%
LICs	0.06%	0.01%

Source: Data from WHO Global Observatory on Health R&D, 2017 and 2021a.

4 Available at: https://www.who.int/observatories/global-observatory-on-health-research-and-development/indicators/gross-domestic-r-d-expenditure-on-health-as-a-percent-of-gross-domestic-product. The data is collected from UNESCO's (United Nations Educational, Scientific and Cultural Organization) Institute for Statistics (UIS), the statistical office of the European Union (Eurostat), the Ibero-American and Inter-American Network of Science and Technology Indicators (RICYT), and the Organisation for Economic Co-operation and Development (OECD). The gross domestic product (GDP) data are collected from the World Bank. Note: not all countries have reported data on this indicator.

The graph below shows the top 10 LMICs with the highest percentage of their GDP invested in health GERD in 2021. South Africa had the greatest investment among UMICs, Kenya among LoMICs, and Mozambique among LICs, respectively. The data available was not suitable for a calculation of the variation over time, as most countries did not report information for more than one year in the period covered by the Observatory.

Figure 1. Top 10 LMICs by % of GDP invested in health GERD



Source: Data from the WHO Global Observatory on Health R&D, 2017 and 2021a.

Another source of information on funding for health R&D is the World RePORT[5], which since 2012 has collected data from grants for biomedical research from 14 major public and philanthropic funders of health research[6], all of which are from HICs. It contains over 700,000 grants, with information on the funding organization, the year, funding amount, the recipient research organization, the recipient country, collaborators, and the title and abstract of the program. Despite the limitation of the number of funders contributing to the database, it can be a helpful resource to identify actors funding and conducting biomedical R&D in different countries. A detailed analysis of the information contained in this database is beyond the scope of this report. Below, we present a few analyses indicative of R&D activities and capacities in LMICs, particularly research grants received and recipient research organizations, based on data downloaded in October 2022. More detailed information about each grant and research organization is available in the World RePORT database.

The database contained information on 650,875 grants awarded to 23,005 recipient research organizations in 188 countries. Among all income groups, the United States received the highest number of grants by far (53% of the total). Among LMICs, South Africa received the highest number of grants, followed by China and Kenya.

5 Available at: https://worldreport.nih.gov

6 The funding organizations that have contributed data are: Bill & Melinda Gates Foundation (BMGF), Canadian Institutes of Health Research (CIHR), European Commission (EC), European & Developing Countries Clinical Trials Partnership (EDCTP), German Federal Ministry of Education and Research (BMBF), Global Alliance for Chronic Diseases (GACD), Japan Agency for Medical Research and Development (AMED), Medical Research Council (MRC), National Institutes of Health (NIH), Institut Pasteur, Swedish International Development Cooperation Agency (Sida) Swedish Research Council (SRC), United States Agency for International Development (USAID), Wellcome Trust. Not all funders have submitted information for every year. More detailed information is available at: https://worldreport.nih.gov, About World RePORT.

Table 3. Top LMICs by number of research grants received, World RePORT, 2022

Country/Income group	Number of grants received
South Africa (UMIC)	7,044
China (UMIC)	4,851
Kenya (LoMIC)	3,553
Uganda (LIC)	3,458
India (LoMIC)	3,133
Brazil (UMIC)	3,026
Thailand (UMIC)	1,413
Peru (UMIC)	1,313
Tanzania (LoMIC)	1,296
Nigeria (LoMIC)	1,253
Malawi (LIC)	1,166
Mexico (UMIC)	1,112

Source: Data from World RePORT, 2022.

In terms of the number of research organizations receiving grants, 74% were based in HICs, while 12% were based in UMICs, 10% in LoMICs, and 4% in LICs, respectively. In the UMIC group, China, South Africa, and Brazil had the highest number of recipient research organizations. In the LoMIC group, it was India and Kenya, while in the LIC group, it was Uganda and Malawi.

Table 4. Number of grant recipient research organizations by income group, World RePORT, 2022

Income group/Country	Number of Research Organizations
Low income	**935**
Uganda	247
Malawi	110
Ethiopia	85
Zambia	79
Mozambique	74
Lower middle income	**2,277**
India	476
Kenya	304

Income group/Country	Number of Research Organizations
Zimbabwe	123
Nigeria	115
Vietnam	113
Upper middle income	**2,749**
China	571
South Africa	500
Brazil	346
Mexico	175
Argentina	175
High income	**17,044**
Grand Total	**23,005**

Source: Data from World RePORT, 2022.

Another database with information on funding for health R&D is the G-FINDER[7], which tracks investment into R&D for basic research and for the development of new health tools for a group of diseases "that disproportionately affect people in low- and middle-income countries, such as neglected diseases, emerging infectious diseases, and sexual and reproductive health issues" (G-FINDER, 2022). Data has been collected through an annual survey since 2007, with the latest available information from 2020[8]. The database contains several types of information, including disease or health area, product, funder and country, recipient and country, funder and recipient type, stage of R&D, funding amount, and year. Again, a detailed analysis of the information available in this database is beyond the scope of this study, and as with other databases, the information available is limited. Nevertheless, it contains useful information about funders and research organizations involved in pharmaceutical R&D worldwide. Below, we present a few analyses indicative of R&D activities and capacities in LMICs, based on data downloaded in October 2022.

The total funding tracked in the period from 2007 to 2020 amounted to approximately USD 61.5 billion. Of this funding, 81% came from HICs, 2% from LMICs, 1% from UMICs, and less than 1% from LICs, with the remaining funding unclassified. The table below shows the top LMIC funders during this period based on the amount of funding contributed, with India as the most significant funder among them. The complete list of countries and names of funders is available through the G-FINDER database.

7 Available at: https://gfinderdata.policycuresresearch.org/

8 More information on G-FINDER's methodology is available at: https://gfinderdata.policycuresresearch.org/pages/static/methodology

Table 5. Amount funded for health R&D by income group and country, G-FINDER, 2007-2020

Income group/Country	Amount (USD)
High income	**49,514,838,988**
Low income	**520,803**
Rwanda	250,124
Gambia	112,869
Ethiopia	97, 273
Lower middle income	**931,455,043**
India	921,038,235
Egypt	4,642,225
Indonesia	2,178,064
Philippines	1,481,493
Upper middle income	**527,299,949**
Brazil	228,032,716
South Africa	111,831,640
Russia	41,567,705
Colombia	36,100,113
Mexico	34,660,082
China	27,030,281
Unclassified	**10,523,440,761**
Grand Total	**61,497,555,545**

Source: Data from G-FINDER, 2022.

For the year 2010, the G-FINDER database included USD 91 million funded by MICs, and less than USD 0.1 million funded by LICs. In 2020, while LICs continued to fund USD 0.1 million, MICs funded a total of USD 416 million, an increase of more than 450% in 10 years (G-FINDER, 2022).

HICs accounted for over 66% of the funding received, while UMICs and LMICs accounted for about 2% each, and LICs accounted for only 0.3%, with the remaining received funding unclassified. The table below presents the top funding recipient LMICs, with India and South Africa being the largest recipients among them. The complete list and names of the recipient organizations are available through the G-FINDER database.

Table 6. Amount received for health R&D by income group and country, G-FINDER, 2007-2020

Income group/Country	Amount (USD)
High income	**40,849,557,815**
Low income	**194,517,036**
Malawi	66,878,265
Gambia	40,386,664
Uganda	40,228,555
Lower middle income	**1,236,080,823**
India	960,557,650
Ghana	80,936,027
Bangladesh	51,355,381
Kenya	48,922,220
Upper middle income	**1,150,535,609**
South Africa	486,540,102
Brazil	253,008,026
China	87,306,008
Thailand	85,497,187
Colombia	55,066,738
Unclassified	**18,066,864,262**
Grand Total	**61,497,555,545**

Source: Data from G-FINDER, 2022.

Funding received for health R&D by LMICs also increased over time, indicating growing capacity for conducting R&D activities. In 2010, LICs received USD 13 million, and MICs received USD 162 million. In 2020, LICs received USD 16 million, and MICs received USD 250 million (G-FINDER, 2022).

It is worth mentioning that Policy Cures Research, the organization responsible for G-FINDER, has a tool monitoring the R&D pipeline for neglected diseases – the R&D pipeline tracker[9]. It was last updated in August 2019 and contains information on 585 candidate products for 35 neglected diseases in various stages of the R&D process. It also contains the name of the organizations working on the development of each candidate. However, it does not have information about the location of each organization, making it unsuitable for country analysis for this study. Nevertheless, the information about the research organizations can provide valuable insight into who is conducting research for product development for neglected diseases.

9 Available at: https://www.pipeline.policycuresresearch.org/

3.4.2. HEALTH RESEARCH CAPACITY

Another indicator of scientific capacity in the WHO Observatory is the number of researchers in the fields of health and medical sciences, referred to as "health researchers"[10]. The latest available data was published in January 2022, with information on 82 countries. However, it should be noted that the actual date of the information varies from country to country as it reflects the latest year reported by each country. The number of health researchers per million inhabitants was higher in HICs than in other income groups. When comparing the first available data for this indicator (published in January 2017) with the most recent data from 56 countries, there was an increase in the number of health researchers per million inhabitants over the years, for all income groups besides LICs.

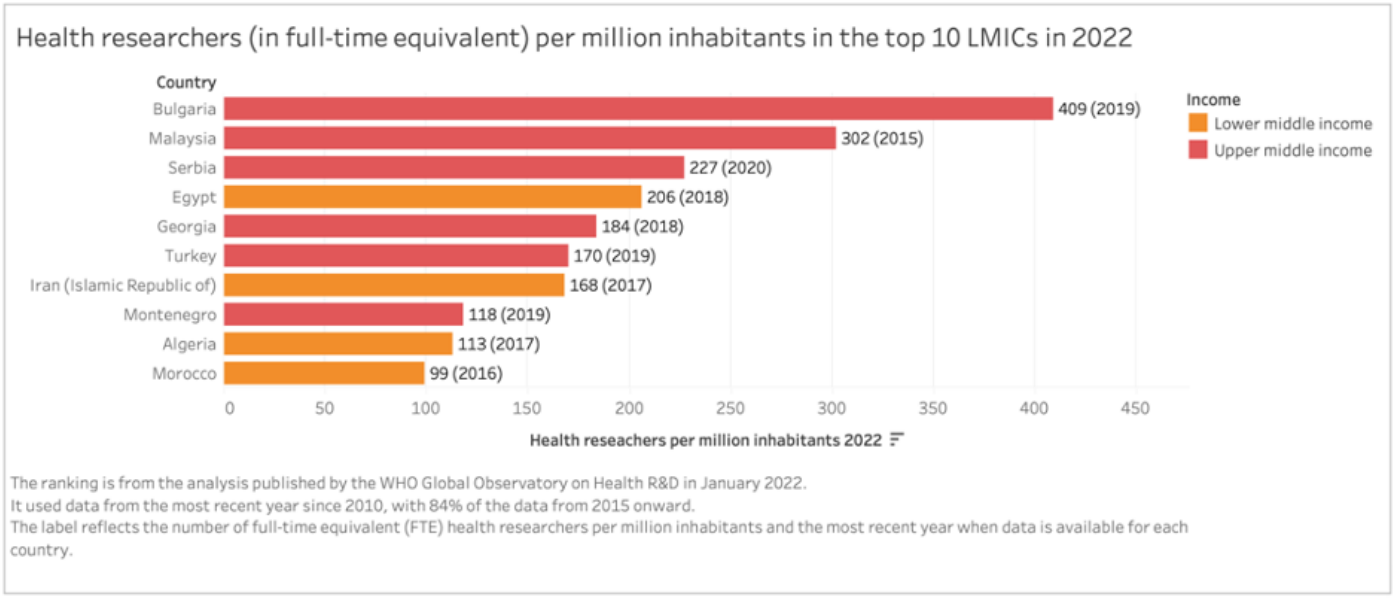
Table 7. Health researchers per million inhabitants by income group, 2017 and 2022

Income group	2017	2022
HICs	320	391
UMICs	87	100
LoMICs	49	64
LICs	9	7

Source: Data from WHO Global Observatory on Health R&D, 2022.

The figure below shows the list of the top 10 LMICs with the highest number of health researchers per million inhabitants, as of January 2022. Bulgaria had the highest number among UMICs, and Egypt among LoMICs. There were no LICs among the top 10. The data was not suitable for a comparison over time as most countries did not report data for more than one year in the period covered by the Observatory.

Figure 2. Health researchers per million inhabitants by country, 2022



Source: Data from WHO Global Observatory on Health R&D, 2022.

10 Available at: https://www.who.int/observatories/global-observatory-on-health-research-and-development/indicators/health-researchers-in-full-time-equivalent-per-million-inhabitants-by-income-group-second-set-of-charts. The information is collected from the UNESCO's (United Nations Educational, Scientific and Cultural Organization) Institute for Statistics (UIS), the statistical office of the European Union (Eurostat), the Ibero-American and Inter-American Network of Science and Technology Indicators (RICYT) and the Organisation for Economic Co-operation and Development (OECD). Information is calculated in FTE – full time equivalent. Note: not all countries have reported data on this indicator.

3.4.3. CLINICAL TRIALS ANALYSIS

As part of the R&D process for developing pharmaceuticals, clinical trials are a type of research that study new tests and treatments and evaluate their effects on human outcomes (WHO, health topics, clinical trials, n.d.). Analyzing clinical trial activities can provide valuable information about the type of research being conducted, where, and by whom. Clinical trials must often be registered with a regulatory body to be conducted in a given country, and there are many clinical trial registries at the national level (GHC, Knowledge Portal on Innovation and Access to Medicines, Data Sources, Clinical trials registries, n.d.). In 2005, the WHO International Clinical Trials Registry Platform (ICTRP) was created as a central database with the mission "to ensure that a complete view of research is accessible to all those involved in health care decision making" (WHO ICTRP, n.d.).

The ICTRP groups together information provided by several data sources, which includes 18 national and/or regional registries from around the world[11]. The database is updated weekly and includes information dating from 1990. There is an internationally-agreed upon set of information that has to be provided about the design, conduct, and administration of clinical trials, and the WHO has a Trial Registration Data Set with 24 items considered to be the minimum amount of information required for a trial to be fully registered (WHO ICTRP, n.d). The information provided by the data providers is grouped under these 24 categories, and includes other fields required by each registry according to their individual policies and guidance on registration. Analyzing the full dataset can be challenging, given the massive amount of data and that the data is grouped under categories but is displayed in different formats as a text field. Several filters can be used to identify more targeted information, such as countries of recruitment, phases, primary sponsors, date of registration, and an open field for advanced search using keywords.

For this report, we used a previously cleaned dataset by Merson et al. (2022) made available as part of their study analyzing data sharing in clinical trials (2022a, 2022b). The dataset contained information until 15 December 2020. The information was divided into three excel files, one with raw data from 17 registries except for clinicaltrials.gov, one with raw data only from the registry clinicaltrials.gov, and one with curated data for their analysis (Merson et al., 2022a), which was cleaned for duplications. The original ICTRP dataset included 643,414 clinical study registrations, and 593,595 registrations after removing duplicate records, for a total of 216 countries (Merson et al., 2022b). The curated dataset also included information about the income level, categorized as "high-income countries" and "low and middle-income countries" as per the World Bank classification in June 2020, and the type of sponsor, categorized as "commercial" for “organisations where evidence of profit-driven corporate mission or company structure was identified", or "non-commercial" for “organisations where evidence of non-profit status was identified, including governments, foundations, academic and research institutions, health care provision facilities, and public health agencies" (Merson et al., 2022a, 2022b). For this study, we used the curated dataset and added the information about clinical trials phases from the other two datasets, as this information was unavailable in the curated dataset. The total number of trials by country/region might be higher than the total number of trials included in the dataset, as trials conducted in multiple countries/regions were counted for each country/region in which they were listed.

Furthermore, we analyzed the trials by health category. The categorization of health categories was obtained from the WHO Global Observatory on Health Research and Development. While this information is used for an analysis made available by the Observatory (WHO, 2022b), the

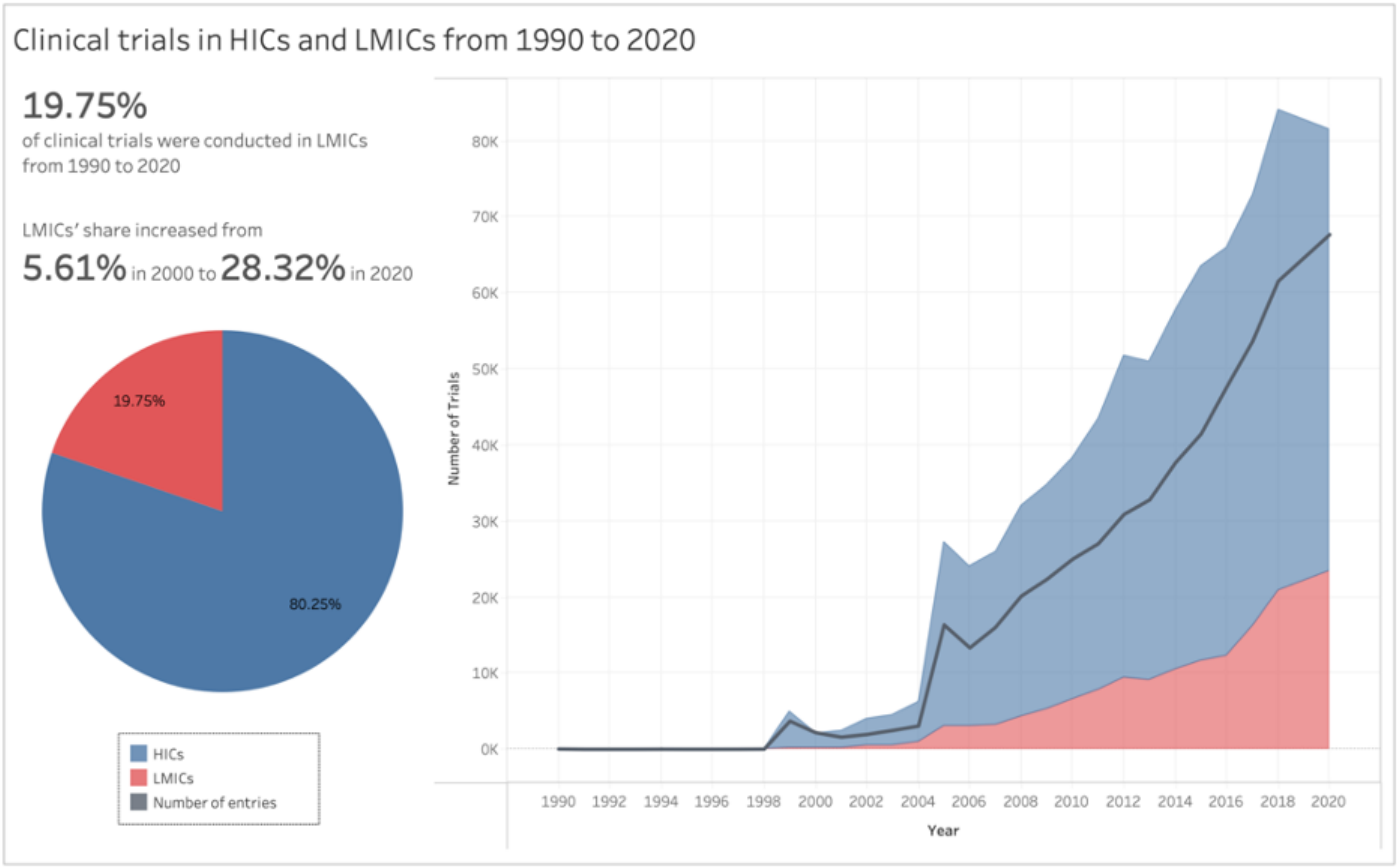
11 Australian New Zealand Clinical Trials Registry, Chinese Clinical Trial Registry, ClinicalTrials.gov, EU Clinical Trials Register (EU-CTR), ISRCTN, The Netherlands National Trial Register, Brazilian Clinical Trials Registry (ReBec), Clinical Trials Registry - India, Clinical Research Information Service - Republic of Korea, Cuban Public Registry of Clinical Trials, German Clinical Trials Register, Iranian Registry of Clinical Trials, Japan Registry of Clinical Trials (jRCT), Pan African Clinical Trial Registry, Sri Lanka Clinical Trials Registry, Thai Clinical Trials Registry (TCTR), Peruvian Clinical Trials Registry (REPEC), and Lebanese Clinical Trials Registry (LBCTR).

full dataset is not available for download online and was sent to the research team by email. We then used the trial IDs to add the information on health categories to our previous dataset, resulting in 98.5% (584,951) of the trials with information on health categories. The information was categorized into five health categories, 27 health sub-categories, and 462 disease categories. We used the variable "health sub-categories" for our analysis. Our unique dataset used for this study, with the added information about phases and health categories, is available as supplementary data. The principal aim of this analysis was to identify which LMICs are most active in conducting and/or hosting clinical trials, as an indicator of innovative activity in the pharmaceutical sector.

- **Number of clinical trials**

We began by analyzing the number of clinical trials according to the income level of the country of registration (93% of the trials had country information available)[12]. From 1990 to 2020, 80.25% (1,381,926) of the trials were conducted in HICs, and 19.75% (340,148) of the trials were conducted in LMICs. An analysis of the variation over time showed that the total number of trials increased significantly from the late 1990s to 2020. The share of LMICs in global clinical trials also increased. In 2000, 5.61% of the trials were conducted in LMICs. In 2010, 16.98% of the trials were conducted in LMICs, while in 2020, 28.32% of the trials were conducted in LMICs.

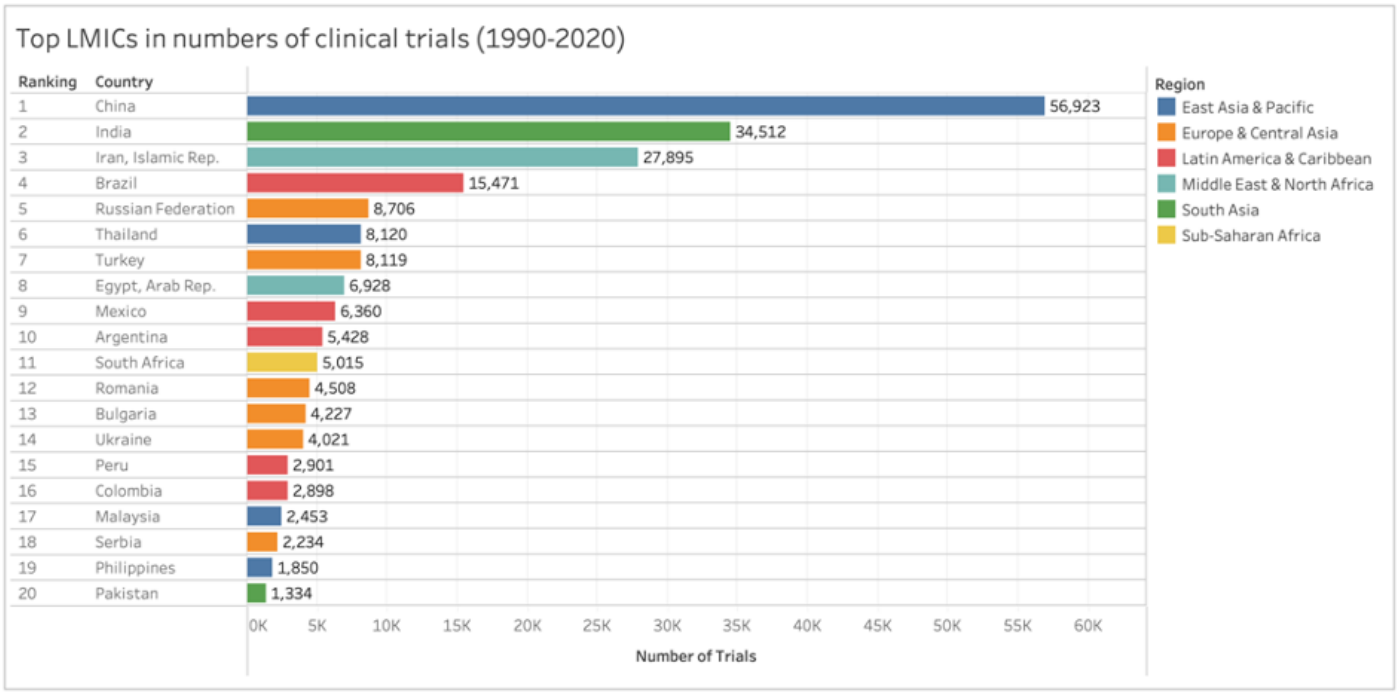
Figure 3. Number of clinical trials by income level (1990-2020)



Overall, the top 20 LMICs conducting clinical trials during this time period were, respectively, China; India; Iran, Islamic Rep.; Brazil; Russia; Thailand; Turkey; Egypt, Arab Rep.; Mexico; Argentina; South Africa; Romania; Bulgaria; Ukraine; Peru; Colombia; Malaysia; Serbia; Philippines; and Pakistan.

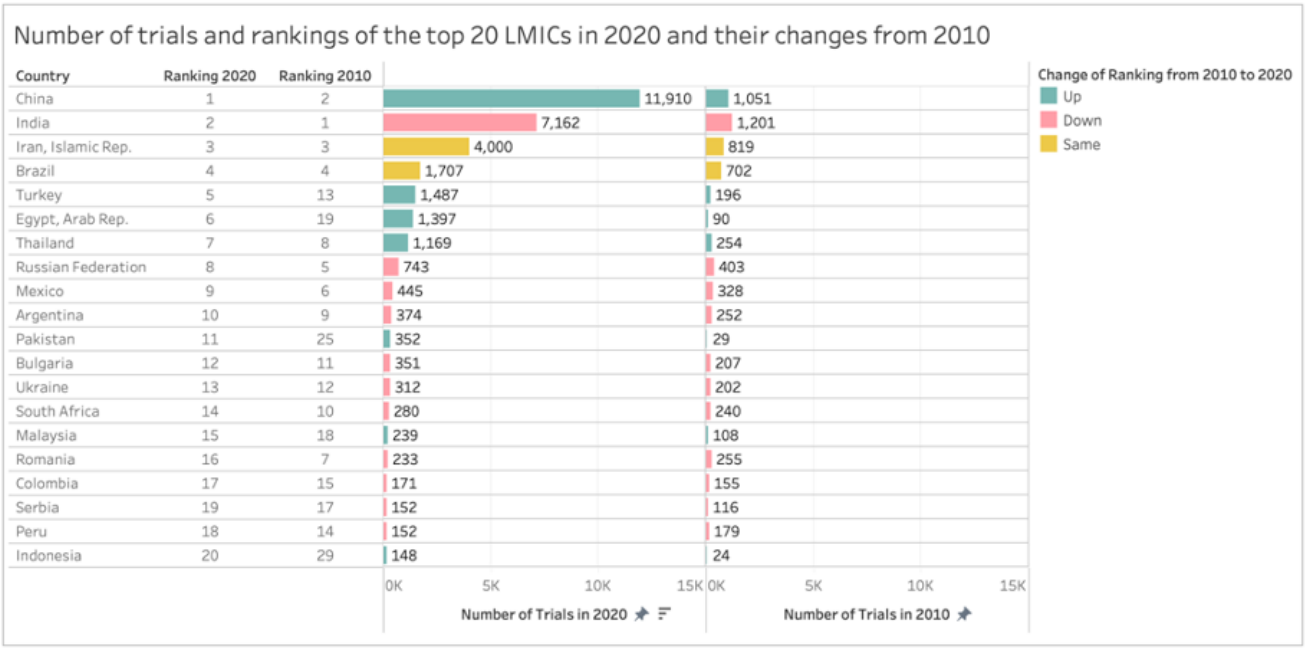
12 There were 40,458 entries without country information out of a total of 593,595 trials.

Figure 4. Top LMICs in number of clinical trials (1990-2020)



A comparison of the number of clinical trials conducted in LMICs in 2010 and 2020 showed almost no variation in the list of the top 20 LMICs with the highest number of clinical trials. All of the countries generally remained the same, with some variation in their ranking position. However, Cuba was the exception, as they were ranked in the top 20 countries in 2010, but not in 2020.

Figure 5. Top LMICs in number of clinical trials in 2020 and 2010



- **Phases**

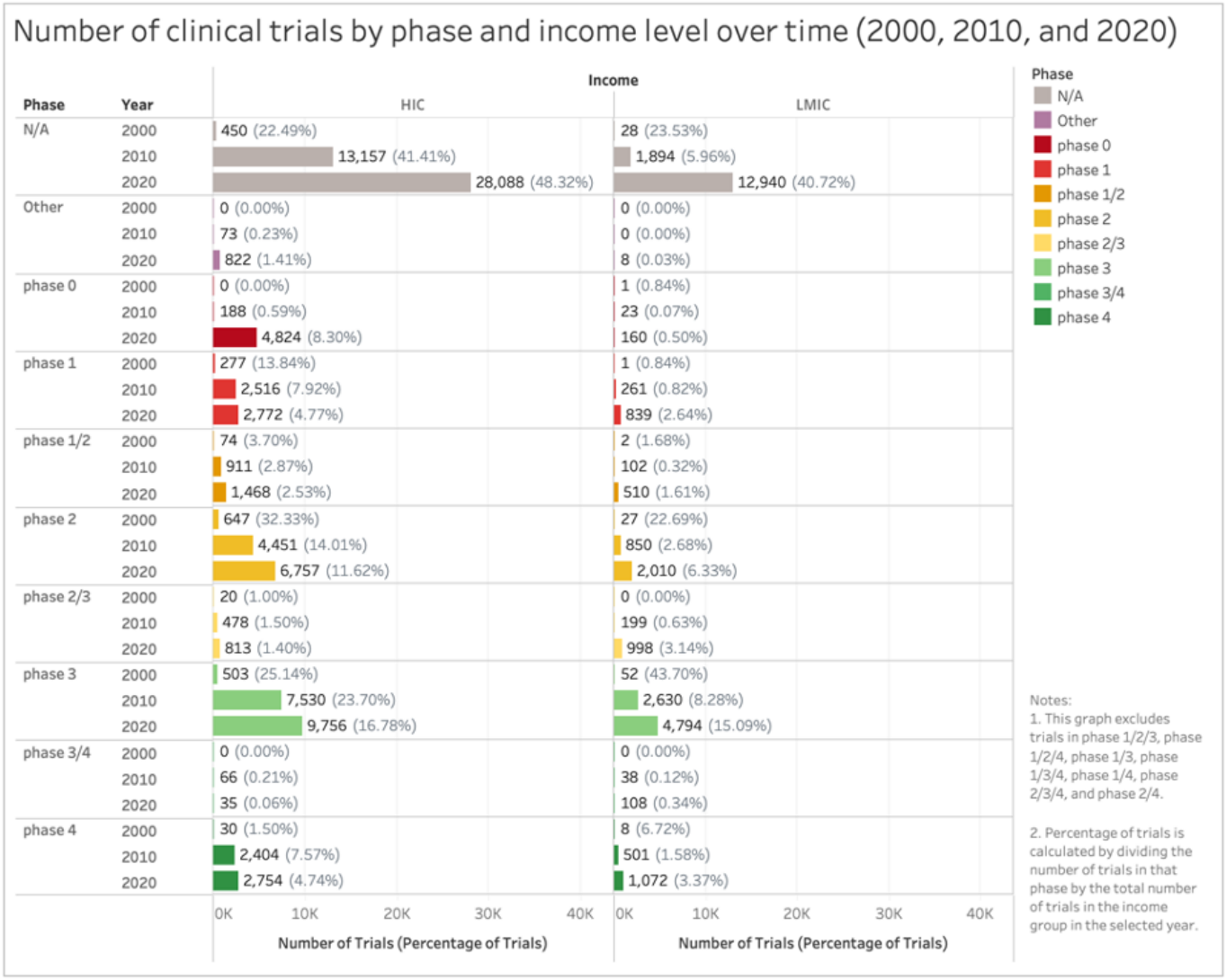
Furthering the analysis, we sought to identify which phases of clinical trials were most frequent in LMICs. Clinical trials are usually categorized under four phases[13]. However, one trial can be a

13 "Phase I studies usually test new drugs for the first time in a small group of people to evaluate a safe dosage range and identify side effects. Phase II studies test treatments that have been found to be safe in phase I but now need a larger group of human subjects to monitor for any adverse effects. Phase III studies are conducted on larger populations and in different regions and countries, and are often the step right before a new treatment is approved. Phase IV studies take place after country approval and when there is a need for further testing in a wide population over a longer timeframe" (WHO, Health topics, Clinical trials).

mix of two phases (e.g., phase 1/2, phase 3/4), can be conducted before phase 1 often as proof of concept (phase 0), or might have other purposes not categorized into these phases. For our analysis, we used the curated dataset from Merson et al. (2022a), which included information about 593,595 trials but did not include information about their phases. The information about their phases was extracted from the two other datasets available from the study (Merson et al., 2022a). The "clinicaltrials.gov" dataset had the information standardized, and was extracted and included in the dataset. The "all but CT" dataset displayed information about phases in multiple ways, which were standardized for our analysis[14]. In total, 56% of the entries (334,918) did not have information on phases. There were more trials in phase 3, both in HICs (23%) and in LMICs (30%). Combined, phase 0, phase 1, and phase 1/2 represented 11% of the trials in HICs and 5% in LMICs; phases 2, 2/3, and 2/4 represented 16% in HICs and 15% in LMICs; and phase 4 trials represented roughly 7% both in HICs and LMICs.

Analysis over time showed an increase from 2010 to 2020 in the total number of trials in phase 0, both in HICs and LMICs. Particularly in LMICs, the most significant increase occurred in the earlier stages of clinical trials (phase 0 increased by 596% from 2010 to 2020; phase 1 by 221%, and phase 1/2 by 400%, while phase 2 increased by 136%, phase 3 by 82%, and phase 4 by 114%).

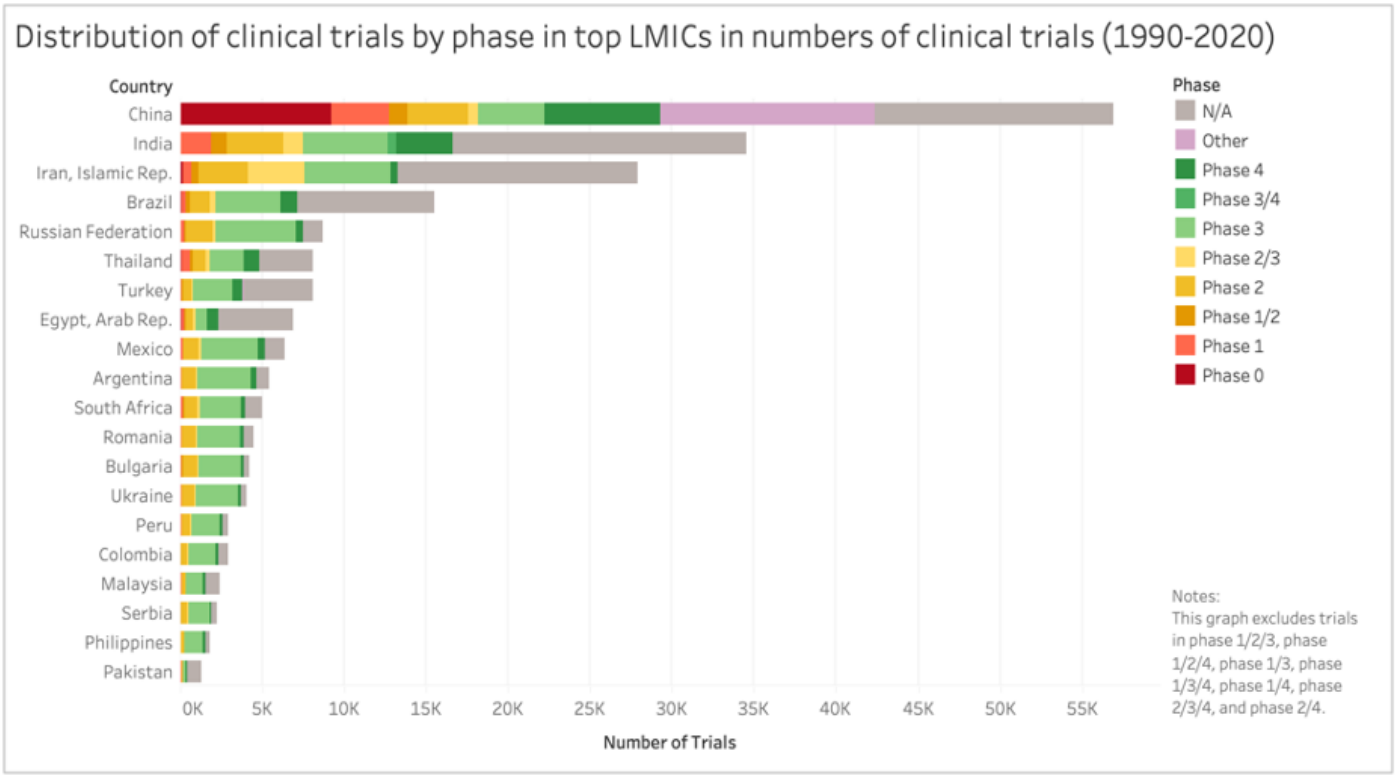
Figure 6. Number of clinical trials by phase and income level over time (2000, 2010, and 2020)



14 There were 164 different ways of classifying the "phase" field in the "all but CT" dataset. We standardized phases displayed with different text formats (e.g., "phase I", "phase 1"), and grouped some categories under phase 0 (e.g., "basic science", "clinical pre-test", "pilot study") and phase 4 (e.g., "post-market", "post-market surveillance"). When it was not obvious to include it under one given phase or when the study was not categorized by phase, it was included in the group "other" (e.g., "Diagnostic New Technique Clinical Study", "Health Services Research", "New Treatment Measure Clinical Study").

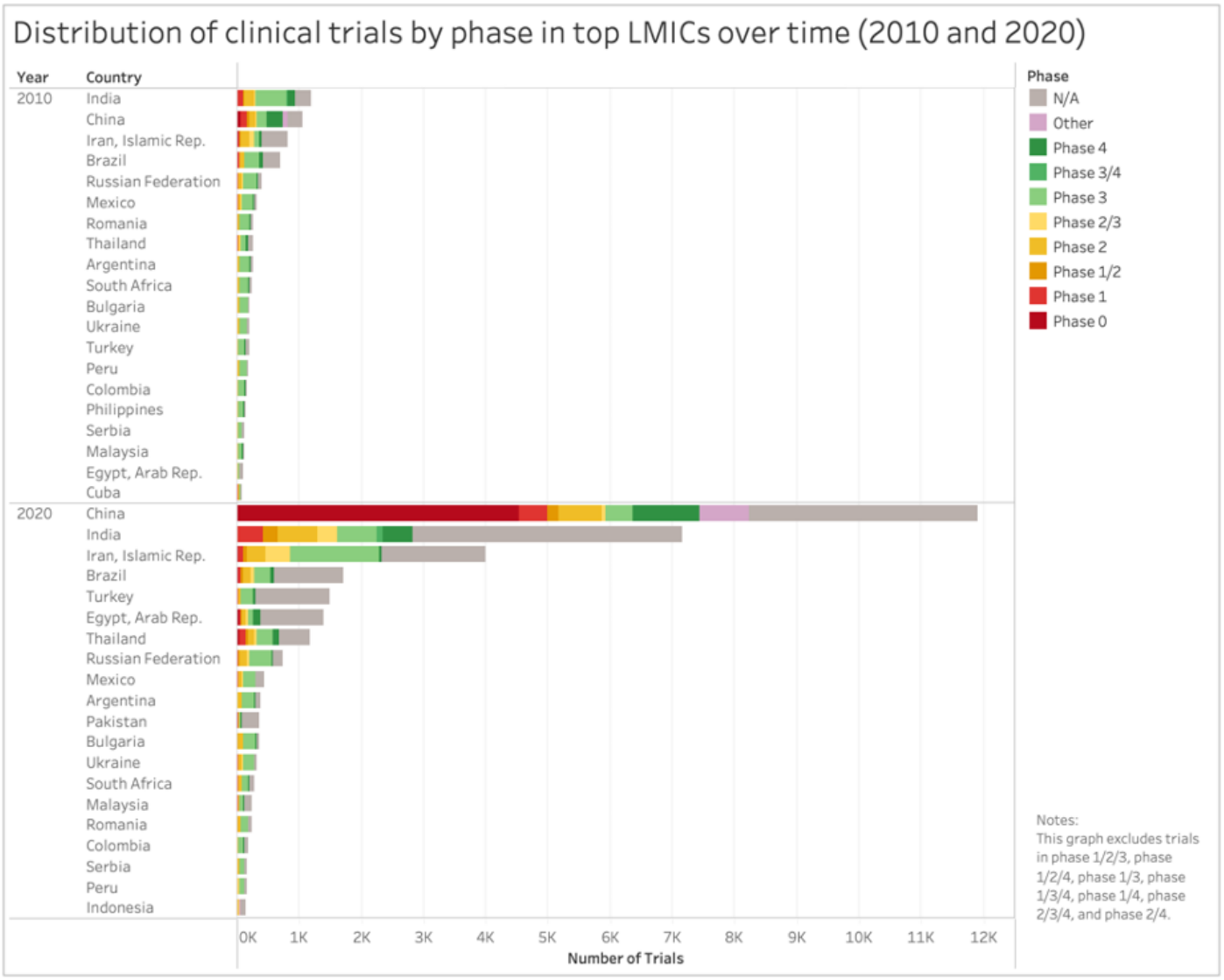
Looking at the list of the top 20 LMICs with the highest overall number of clinical trials, most had a relatively larger number of phase 2 and phase 3 trials. Notably, China had a significant share of trials in phases 0 and 1, and India in phase 1 (which included some basic research and earlier involvement in the R&D process).

Figure 7. Distribution of clinical trials by phase in top LMICs in number of clinical trials (1990-2020)



Looking at the comparison between trials in 2010 and 2020, we saw a significant increase (above 500%) in phase 0 trials in China (7,570%), Egypt (2,900%), and Thailand (1,100%), and in phase 1 trials in Egypt (2,600%), Thailand (1,275%), and Ukraine (1,100%). Phase 2 trials increased the most in China (600%), phase 3 in Iran (1,600%), and phase 4 in Egypt (980%) and Ukraine (500%).

Figure 8. Distribution of clinical trials by phase in top LMICs over time (2010 and 2020)



- **Commercial vs. non-commercial sponsors and funders**

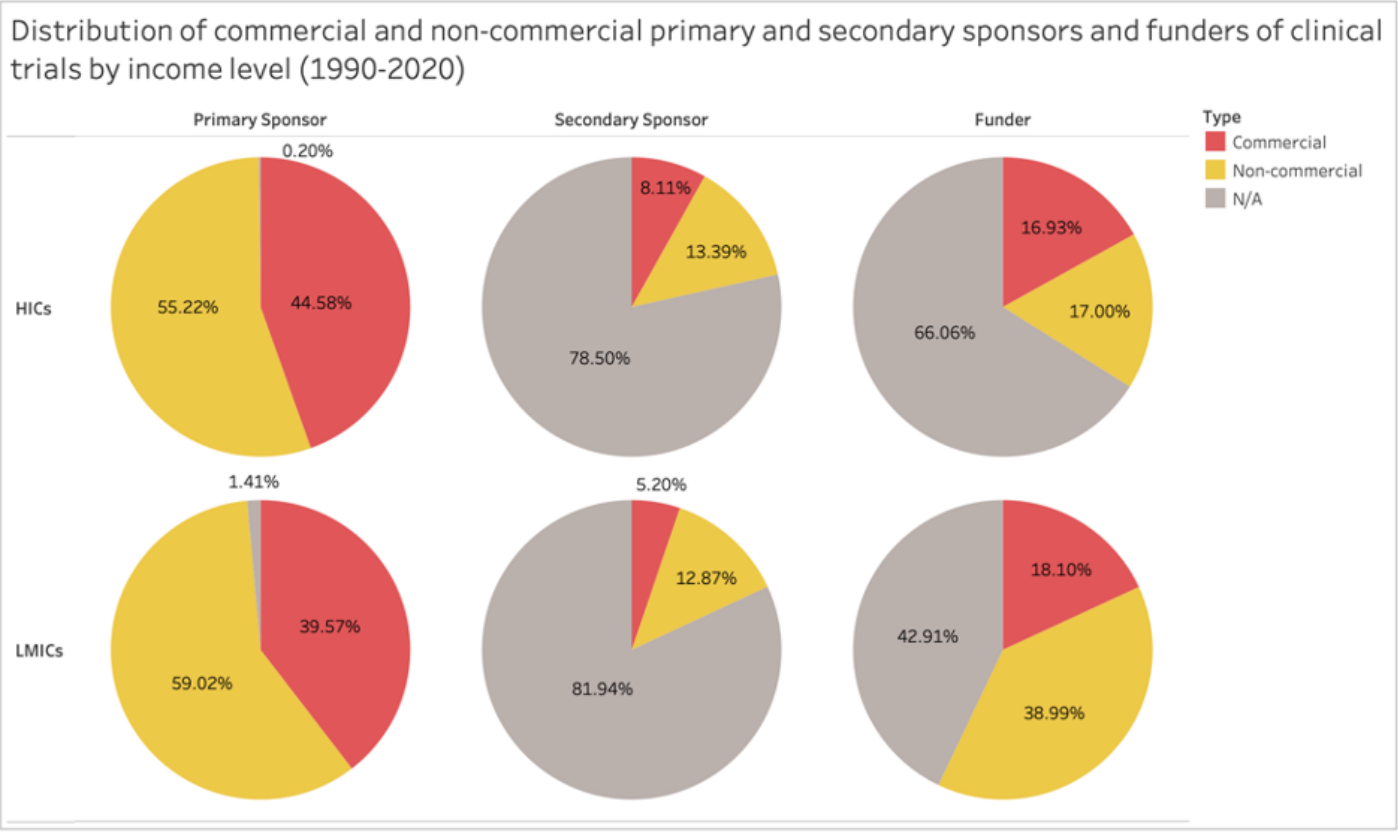
In addition, we analyzed the number of trials according to the sponsor/funder type[15], as categorized in the curated dataset by Merson et al. (2022a). Primary sponsors are the main sponsors responsible for the trial, while secondary sponsors assume responsibilities agreed upon with the primary sponsors. Funders are major sources of financial support for the trial. The primary and secondary sponsors, as well as funders, were classified as either commercial or non-commercial[16]. Almost all trials (99%, 589,373) had information on the primary sponsor, and only 24% (142,379) of the trials had information on the secondary sponsor. The categorization of the funders was available for about 35% of the trials (210,547).

15 ICTRP definitions: Funder: "Source(s) of Monetary or Material Support: Major source(s) of monetary or material support for the trial (e.g. funding agency, foundation, company, institution)". "Primary sponsor: The individual, organization or company responsible for initiating, managing and/or financing a trial. The Primary Sponsor may or may not be the main funder". "Secondary sponsor(s): Additional individuals, organizations or other legal persons, if any, that have agreed with the primary sponsor to take on responsibilities of sponsorship" (WHO, ICTRP, WHO data set).

16 "Commercial: For organisations where evidence of profit-driven corporate mission or company structure was identified". "Non-commercial: For organisations where evidence of non-profit status was identified, including governments, foundations, academic and research institutions, health care provision facilities, and public health agencies". The categorization was done by individually searching each sponsor and funder "on the internet to determine the status, registration, type, mission, structure, remit and/or links of the organisation/institution" (Merson et al., 2022b).

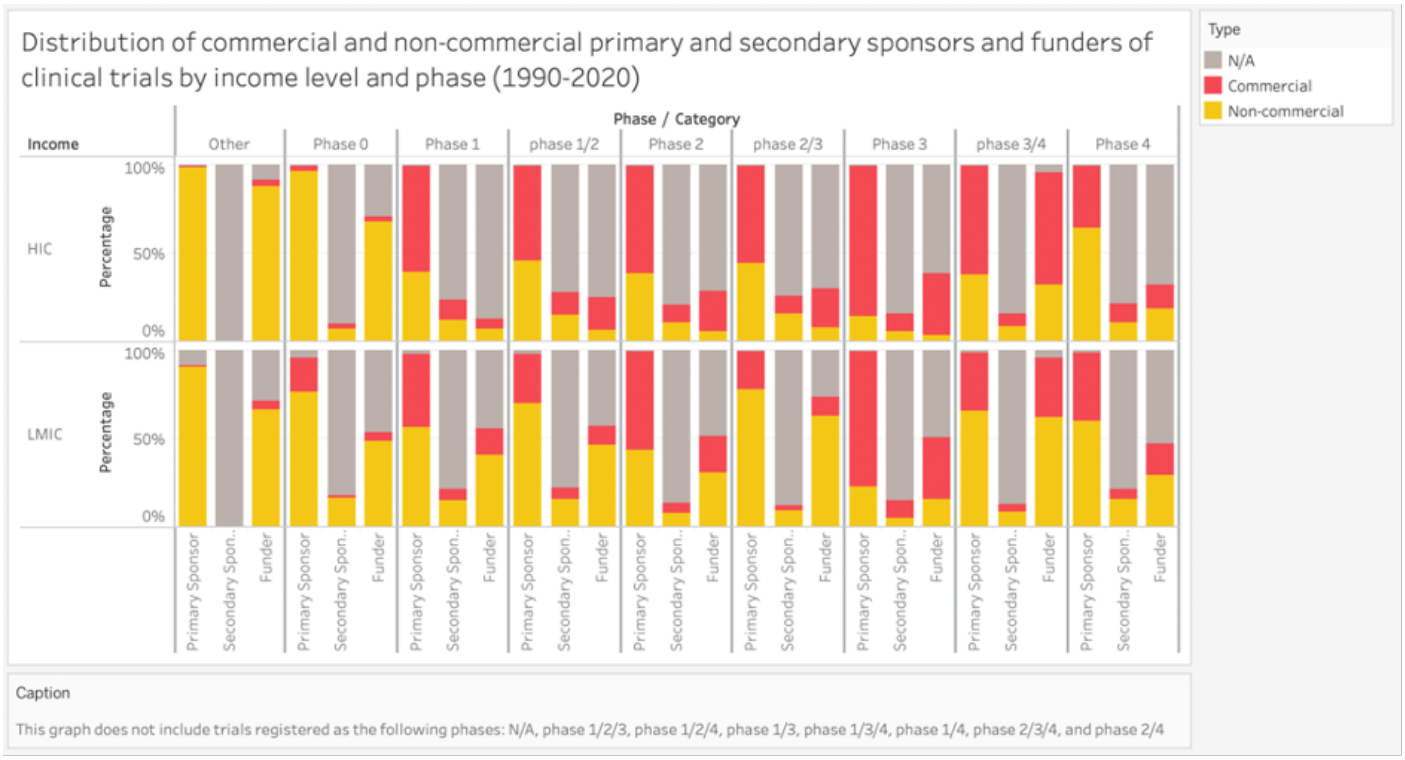
For those with information available, the analysis showed that non-commercial primary and secondary sponsors were the majority both in HICs and in LMICs. Concerning funders, in HICs, non-commercial funders were slightly more frequent than commercial funders, while in LMICs, non-commercial funders accounted for a significant majority.

Figure 9. Distribution of commercial and non-commercial primary and secondary sponsors and funders of clinical trials by income level (1990-2020)



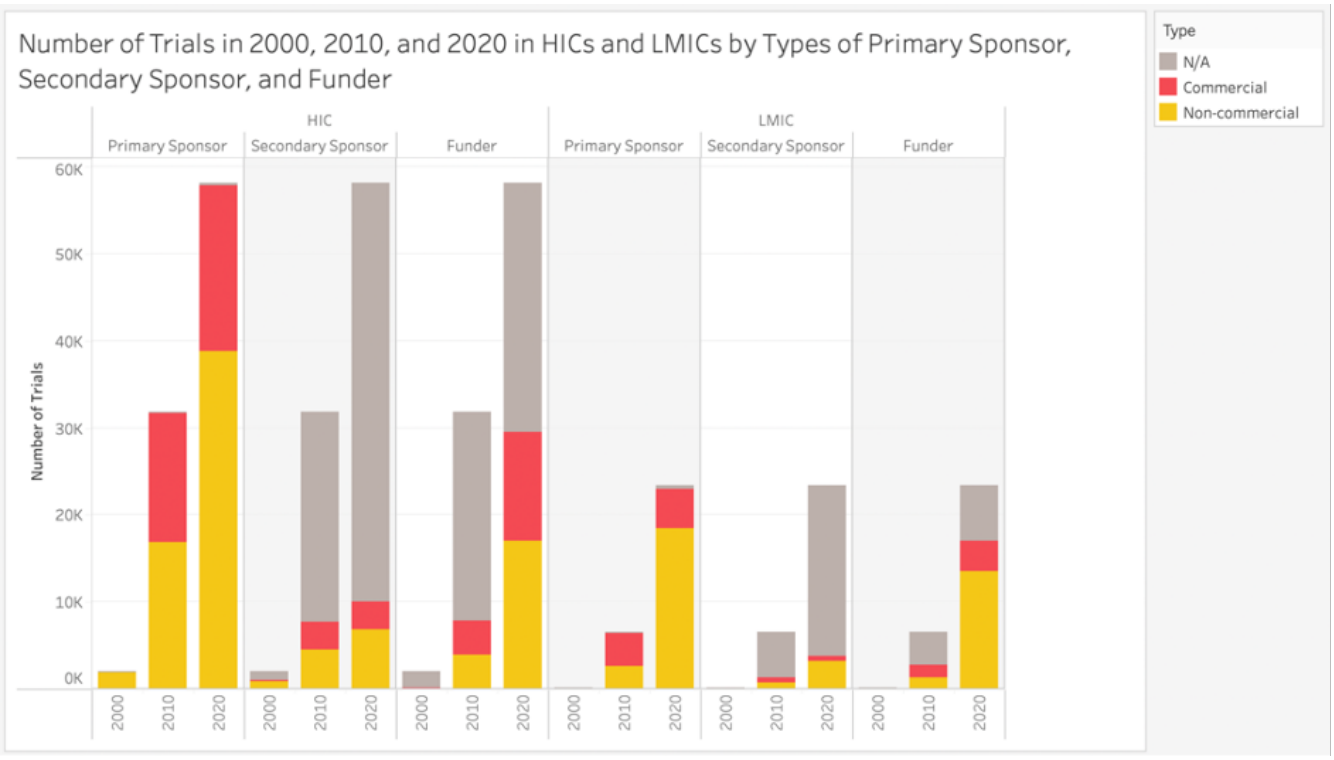
Furthering the analysis, and looking at the prevalence of each type of actor by phase of clinical trials, overall, non-commercial primary and secondary sponsors were the majority in all phases, except in phase 1, in which commercial primary sponsors represented 53% of the total. Non-commercial funders were also more prevalent than commercial in all phases of clinical trials, with the greatest difference in phase 0 trials. Looking at the distribution by income level, in HICs, commercial sponsors were more prevalent than non-commercial in almost all phases, except in phase 0, phase 4, and "other". In LMICs, commercial sponsors were prevalent in phases 2 and 3. Regarding funders, in HICs, commercial funders were prevalent in phases 1/2, 2, 2/3, 3, and 3/4, while in LMICs, they were prevalent only in phase 3.

Figure 10. Distribution of commercial and non-commercial primary and secondary sponsors and funders of clinical trials by income level and phase (1990-2020)



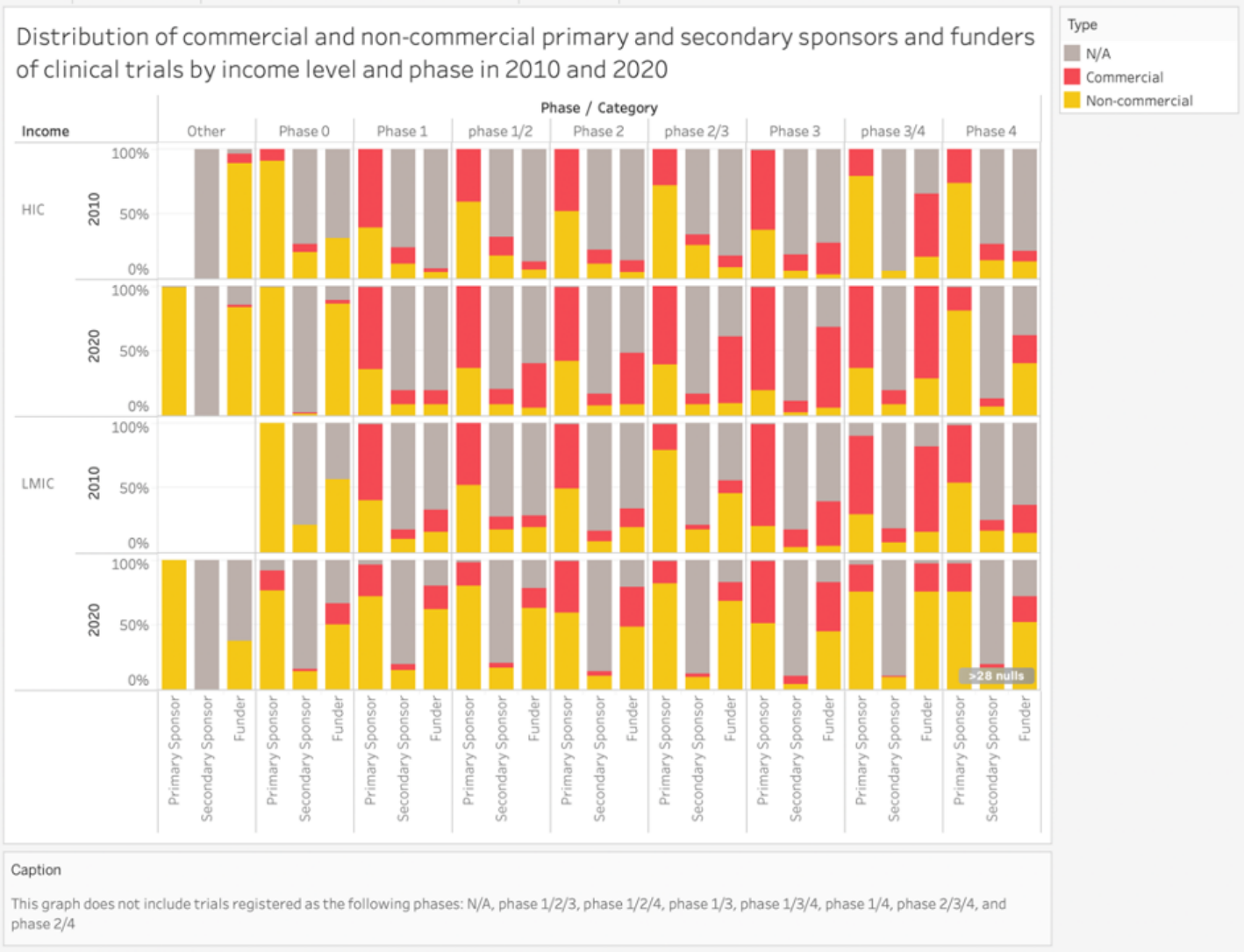
From 2010 to 2020, there was a growing involvement of non-commercial funders and sponsors in both HICs and LMICs. The total number of trials with non-commercial primary and secondary sponsors increased by 130% and 48% in HICs, respectively, and by 603% and 310% in LMICs, respectively. Meanwhile, the number of trials with commercial primary and secondary sponsors increased by 29% and 4% in HICs, and by 17% and 4% in LMICs. Regarding the funders, the total number of trials with non-commercial funders increased by 326% in HICs, and by 940% in LMICs, while commercial funders increased by 220% in HICs, and by 141% in LMICs.

Figure 11. Distribution of commercial and non-commercial primary and secondary sponsors and funders of clinical trials by income level over time (2000, 2010, and 2020)



Looking at the distribution by phase, in HICs, the most significant variation from 2010 to 2020 occurred in phase 0 trials, with the growing involvement of non-commercial primary sponsors and the increase of both commercial and non-commercial funders. In LMICs, the largest variation was in the involvement of non-commercial primary sponsors in phase 3/4, and additional trials funded by non-commercial funders in phases 1, 1/2, 3, and 3/4.

Figure 12. Distribution of commercial and non-commercial primary and secondary sponsors and funders of clinical trials by income level and phase over time (2010 and 2020)



The important role of non-commercial funders and sponsors, and the disproportionate increase in the proportion of trials they supported over the past decade, suggests they play a much more significant role in R&D than is widely-understood. Furthermore, consistent with the literature review and interviews, non-commercial funders and sponsors seem to play an even more important role in LMICs vs in HICs. Further research is needed to explain what accounts for these findings.

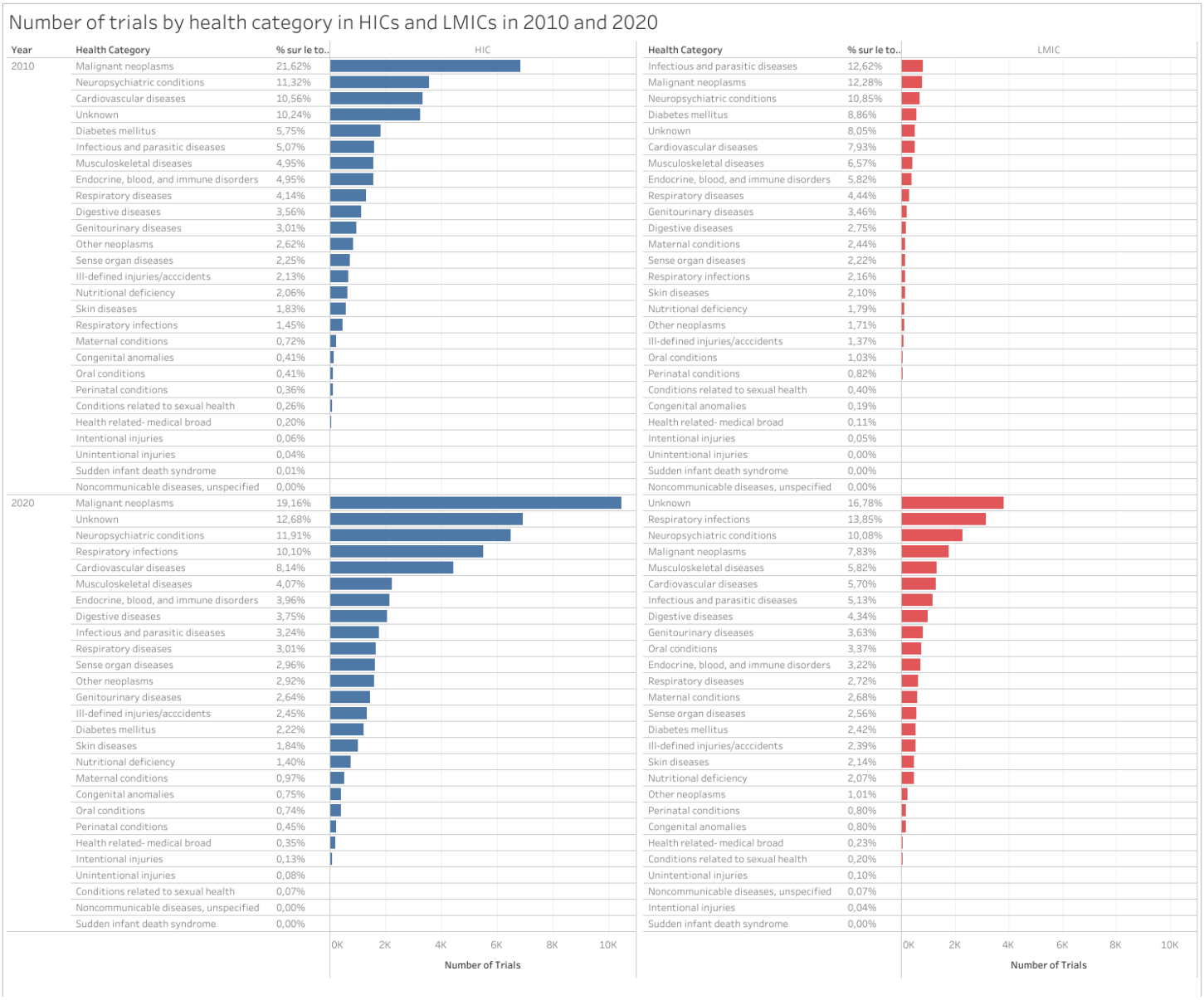
- **Health (or disease) category**

We also analyzed the disease category of the trials, using the categorization obtained from the WHO Global Observatory on Health Research and Development. For the analysis, we used the information categorized into 27 different health sub-categories, including "unknown" (hereafter referred to as "health category" or "category").

The first analysis was the number of trials by health category in HICs and LMICs for the entire period of our dataset. It shows that both in HICs and in LMICs, the most prevalent category in

the clinical trials was malignant neoplasms (not considering "unknown"). Infectious and parasitic diseases represented almost 5% of the trials in HICs, and 9% in LMICs. The figure below shows the variation of health categories over time, comparing the clinical trials in 2010 and 2020. In HICs, the most significant increase in clinical trials was in respiratory infections, while in LMICs, six different categories had a very significant increase (above 500%): respiratory infections, non-communicable diseases, unspecified, congenital anomalies, oral conditions, health-related-medical broad, and ill-defined injuries/accidents. For further analysis, the file available as supplementary data includes detailed information on the number of trials by health category and phase in HICs and LMICs, and the changes from 2010 to 2020.

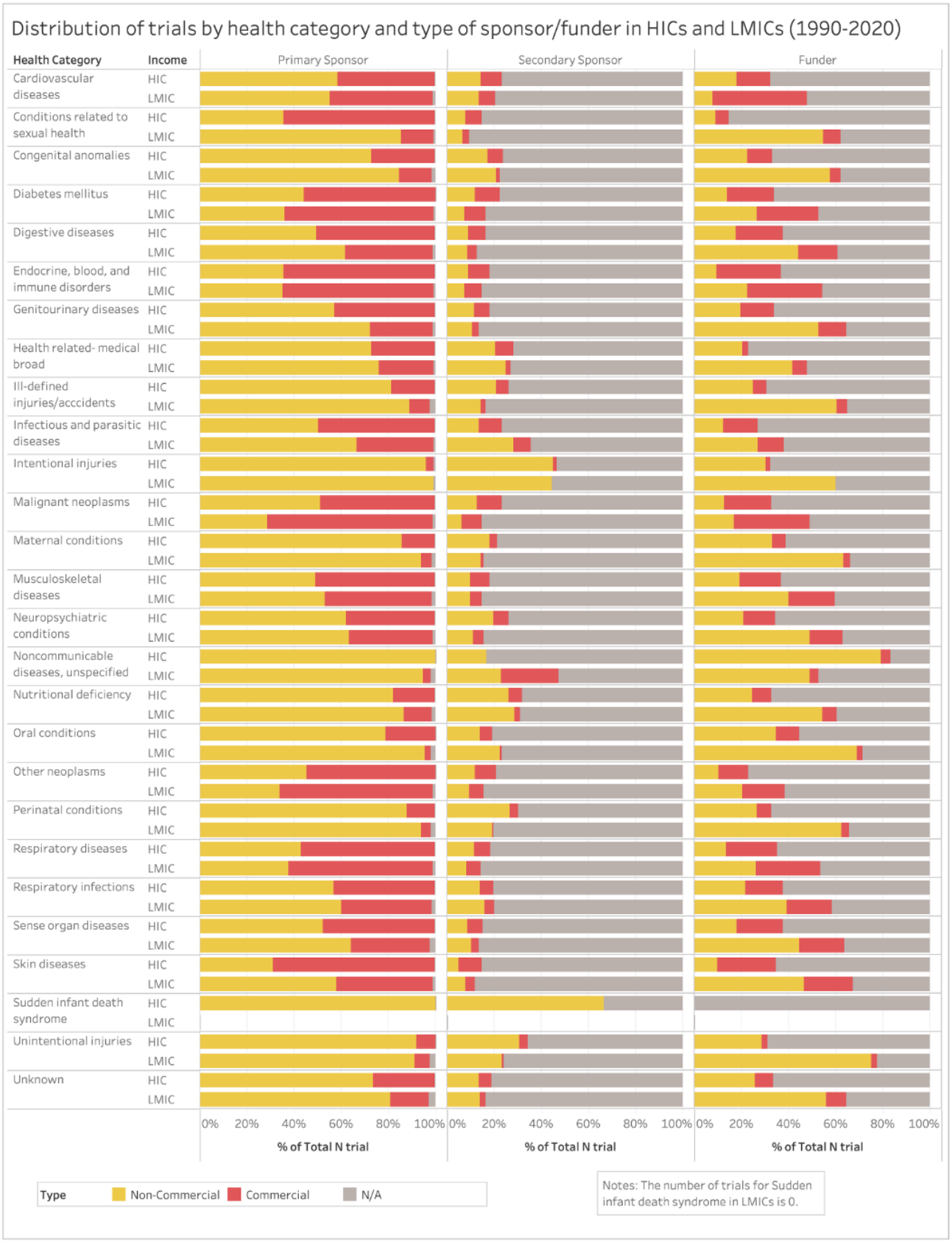
Figure 13. Number of trials by health category in HICs and LMICs over time (2010-2020)



We also analyzed the health category for the clinical trials taking place in the top 20 LMICs (ranked by the number of trials). For the entire period (1990-2020), “malignant neoplasms” was the highest area of research in almost all countries, except for Iran, Serbia, and Pakistan, in which it was “neuropsychiatric conditions”, and South Africa, with “infectious and parasitic diseases”. Comparing the figures for 2010 and 2020, the health category with the most significant increase in most countries was “respiratory infections”, except in China, where it was “perinatal conditions”; in India, “congenital anomalies”; in Thailand, “maternal conditions”; and in Turkey, “oral conditions” (see supplementary data).

Finally, we analyzed the health category by type of sponsor/funder. In HICs, malignant neoplasms was the most researched category by all actors involved. In LMICs, commercial sponsors and funders were more involved in research for malignant neoplasms as well, while non-commercial sponsors were mostly involved with infectious and parasitic diseases, and non-commercial funders with neuropsychiatric conditions (Figure 14). The supplementary data contains additional information showing the changes from 2010 to 2020.

Figure 14. Distribution of health category by type of sponsor/funder in HICs and LMICs (1990-2020)



3.5. SUMMARY OF RESEARCH FINDINGS

A number of LMICs were highlighted in the literature as having important pharmaceutical R&D activities. The analyzed data showcased countries with the highest investments and capacities in R&D, based on the following indicators: percentage of GDP invested in health GERD, number of health researchers per million inhabitants, number of recipient research organizations and research grants received (World RePORT), amount funded and received for health R&D (G-FINDER), and number of clinical trials. The table below provides a list (in alphabetical order) of the top countries most often mentioned in pharmaceutical R&D, combining information from each of the sources analysed throughout the report[17].

Table 8. List of top 16 LMICs in pharmaceutical R&D combining the indicators from the different sources (in alphabetical order)

Top 16 LMICs involved in pharmaceutical R&D			
Brazil	Cuba	Iran	Russia
Bulgaria	Egypt	Kenya	Serbia
China	Georgia	Malaysia	South Africa
Colombia	India	Mozambique	Uganda

3.6. WHO DEMONSTRATION PROJECTS OF INNOVATIVE HEALTH R&D

Finally, to begin to identify potential "new business models" of pharmaceutical R&D in LMICs, we mapped organizations that submitted proposals to a global call for projects with innovative approaches to pharmaceutical R&D, led by the WHO. The so-called “demonstration projects” followed the process of the WHO Consultative Expert Working Group on Financing and Coordination (CEWG), which published a comprehensive report in 2012 analyzing proposals submitted by many stakeholders through an open call, and made recommendations on innovative mechanisms to fund and coordinate health R&D at the global level (World Health Organization, 2012). Following the presentation of the CEWG report at the World Health Assembly in 2012, Member States adopted a resolution (WHA 66.22) requesting the WHO Director-General to create demonstration projects to support the recommendations of the report, and in particular, to foster collaborative approaches, including open knowledge approaches for R&D coordination; promote the delinkage of the cost of R&D from product price; and propose and foster financing mechanisms including innovative, sustainable, and pooled funding (WHO, 2013).

Any organization or individual could submit demonstration projects through consultations held by WHO regional offices. In total, 106 proposals for demonstration projects were received by the six WHO regional offices. Information about each of the proposals submitted at each WHO regional office was not easily available. After searching the WHO’s and regional offices’ websites, and requesting information by email to the respective regional offices, we found information regarding 52 of the 106 proposals. Out of the 52 proposals, most were presented by member states, public research institutes, and universities, and included 34 proposals from LMICs listed in the table below. Appendix 5.3 provides more information on the 34 proposals submitted by organizations located in LMICs.

17 Information from the scoping interviews was not used for the list of the top LMICs, as there were few interviews conducted and several focused in a specific country or region.

Table 9. List of LMICs with organizations that submitted proposals of projects of innovative R&D to the WHO (in alphabetical order by region), 2013

African Region	Asian Region	Latin American Region
Ethiopia	Bangladesh	Bolivia
Kenya	India	Brazil
South Africa	Indonesia	Colombia
Sudan	Malaysia	Costa Rica
Tanzania	Sri Lanka	Cuba
Zimbabwe	Thailand	El Salvador
		Ecuador
		Guatemala
		Peru
		Venezuela

Of the 106 proposals submitted, 22 were selected by the regional offices to be assessed by the WHO Executive Board and a group of experts, to form a final shortlist of demonstration projects to be presented to the Member States. In the end, six demonstration projects were selected to receive support from the WHO. Of the six projects selected, two were led by global Geneva-based PDPs (DNDi and MMV); three by public research institutes in India (Translational Health Science and Technology Institute - THSTI), Brazil (Oswaldo Cruz Foundation - Fiocruz), and South Africa (Council for Scientific and Industrial Research - CSIR); and one by two consortiums founded with the support of the WHO/TDR comprising public institutions, universities, and private companies - the African Network for Drugs and Diagnostics Innovation (ANDI) and the Chinese Network for Drugs and Diagnostics Innovation.

Funding for the implementation of the demonstration projects was very limited. The total budget for the six selected projects was proposed at USD 76.8 million. To meet this amount, the WHO created a voluntary pooled fund, to which about USD 11 million was contributed by Brazil, Germany, India, Norway, South Africa, and Switzerland, including direct contributions and donations received through an incentive mechanism established by Norway and Switzerland to provide an additional US$ 1 for every US$ 2 received from LMICs (TDR, 2019). The lack of funding was heavily criticized and led to limited implementation or the discontinuation of some projects.

After 2019, we could not find updates on the demonstration projects by the WHO. Several projects continued to be carried out by the respective organizations involved. The DNDi leishmaniasis project (drug candidate CpG-D35), in partnership with Ajinomoto Bio-Pharma Services (GeneDesign, Inc.) and the University of Tokyo both in Japan, is undergoing clinical trials with funding received from the Global Health Innovative Technology Fund, Japan, UK aid, Swiss Agency for Development and Cooperation, and WHO/TDR (DNDi, 2021). The pathogen box by MMV, an open-source tool to accelerate drug development, was fully developed and widely used until 2020, being unavailable since then (MMV, 2021). As of 2021, the development of a point-of-care test for acute febrile illness was still under development by THSTI in India (THSTI, 2021). The development of a schistosomiasis vaccine by Fiocruz in Brazil is under clinical development, having successfully completed phase 1 trials (Santini-Oliveira et. al, 2022). As of 2021, the CSIR in South Africa was still developing an antimalarial nanoformulation product, which was being prepared for testing in human clinical trials (CSIR, 2021). ANDI has been suspended and decommissioned due to a lack of funding (personal communication by e-mail in 2021). The Chinese Network for Drug and Diagnostics Innovation held its 8th meeting on September 2018, after which we could not find any updated information.

The mapping of the proposals submitted to the WHO showed several actors that are conducting or willing to conduct pharmaceutical R&D in alternative ways. The high number of non-commercial actors in LMICs, such as public research institutes, universities, and PDPs, suggests fertile soil exists to experiment with alternative R&D models that are not driven primarily by market incentives.

4. DISCUSSION OF THE RESULTS, LIMITATIONS, AND CONCLUSIONS

There is quite limited information and understanding about pharmaceutical R&D capacities and activities in countries in the Global South, despite the growing importance and interest in this topic. The WHO Global Observatory on Health Research and Development is a centralized database of information on the topic. Nevertheless, the information available is not always up to date and is limited to a few indicators and disease areas. For instance, indicators of health R&D are limited to the number of health researchers and gross domestic R&D expenditures on health (health GERD). For both indicators, data is not available for all countries and is not frequently updated, making it difficult for analysis across countries and time.

The section on "monitoring R&D activities" of the WHO Global Observatory brings additional information regarding funding flows for health R&D, drawing on two outside sources: G-FINDER and World RePORT. As seen in the findings, both sources provide valuable but limited information. G-FINDER is limited to a set of diseases identified as "global health priorities that disproportionately affect people in low- and middle-income countries, such as neglected diseases, emerging infectious diseases, and sexual and reproductive health issues". Furthermore, the data has to be interpreted with caution because of the scope, restrictions, and limitations of the G-FINDER survey [18], which leads to an underestimate of the total R&D funding. In turn, the World RePORT is limited to only 14 funders of health R&D, none of which are from a LMIC.

Information for funding health R&D beyond those two sources is very difficult to find, especially for LMICs. Some interviewees mentioned the availability of such information at the national level for a few countries, but that it would require local expertise to find, and for most countries it was suggested that this type of information would not be available at all, at least not in the public domain. As seen in the literature review section, there were very few studies that we could identify with information about funding. A study worth highlighting is the one by Viergever and Hendriks conducted in 2016, which maps global public and philanthropic funders, including those from LMICs. A database was created from that study, "Health Research Funders" (https://www.healthresearchfunders.org/), developed to address the paucity of data about R&D funders in the world. However, the database is still limited, with information about only 30 countries, and does not seem to have been updated since its creation. A more comprehensive and frequently updated database on funding for health R&D would be a valuable addition to the field.

Despite its limitations, the information that we were able to identify provides valuable knowledge about pharmaceutical R&D capabilities and activities in countries in the Global South. The literature review and scoping interviews highlighted a number of LMICs where pharmaceutical R&D is taking place more intensively. The indicators on R&D funding, health researchers, and clinical trial activities spotlighted countries with the highest performance in those metrics. The mapping of proposals submitted to the call by WHO indicates organizations that are taking, or willing to take, alternative approaches to pharmaceutical R&D that might lead to improved global health outcomes.

18 For more information about the limitations of G-FINDER, refer to: G-FINDER, Data limitations, at https://www.policycuresresearch.org/g-finder/, and WHO Global Obervatory on Health R&D, R&D funding flows for neglected diseases by disease, year and funding category - https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/r-d-funding-flows-for-neglected-diseases-by-disease-year-and-funding-category.

A detailed analysis of each source and indicator is beyond the scope of this report. Further research is necessary to analyse the availability, affordability, and public health impact of the products developed in LMICs, and to assess how well they are addressing local and global public health needs. Furthering the analysis of the actors involved in clinical trials in each country could provide valuable information about the development of indigenous technologies vs. contract research for products developed abroad. A deeper analysis of the actors across all the databases could also reveal local, regional, and global networks of collaboration in the development of health technologies.

Nevertheless, it is worth highlighting a few key findings from the analysis done throughout the report. The analysis of R&D funding from G-FINDER showed an increase of more than 450% in the total amount funded by MICs in the past decade, indicating growing investment in R&D for "global health priorities that disproportionately affect people in low- and middle-income countries". Funding received by LMICs also increased over time, indicating growing capacity for conducting R&D activities. The World RePORT showed a significant number of organizations receiving grants to conduct health R&D in LMICs, indicating where and by whom pharmaceutical R&D is being conducted with funding from major global health funders.

The number of clinical trials increased by 375% in LMICs in the period between 2010 and 2020 (from 6,498 to 23,440). Particularly, in the top three countries, China had an 11x increase in the number of trials in the period, India had an increase of about 6x, and Iran about 5x. A detailed analysis of the "ownership" of the product being researched is beyond the scope of this report. However, even if clinical trials are being conducted as "services" (that is, testing products originally developed abroad), the literature suggests that it can have an important cumulative impact on innovation capacities of local actors.

The analysis of phases of clinical trials showed increasing activity in the earlier phases in LMICs as a group, which can be indicative of strengthened upstream research capacities in those countries in the earlier, more innovative and risky phases[19]. Considering the entire period of analysis (1990-2020), China and India had significant shares of trials in phases 0 and 1. Egypt and Thailand had a significant increase in phases 0 and 1 between 2010 and 2020.

The analysis of the health categories of the clinical trials showed that in LMICs as a group, as well as in HICs, the most prevalent category was "malignant neoplasms". That was also the case for 17 out of the top 20 LMICs in number of clinical trials. It is worth noting that the share of trials in "infectious and parasitic diseases" was greater in LMICs than in HICs, but still represents less than 10% of the total number of trials. South Africa was the only country among the top 20 LMICs that had the greatest number of trials in the "infectious and parasitic diseases".

The analysis of actors showed that non-commercial sponsors and funders are very active in clinical trial activities, particularly in LMICs. Non-commercial primary and secondary sponsors, as well as funders, were more involved in clinical trials than commercial actors, particularly in the earlier phases (phases 0 and 1). The analysis of the variation over time showed that the participation of non-commercial actors in clinical trials in LMICs has increased significantly from 2010 to 2020. That is indicative of organizations involved in pharmaceutical R&D with purposes beyond making profit, which is an important element of alternative business models of R&D.

The mapping of the proposals submitted to the WHO global call for innovative projects of pharmaceutical R&D showed that a number of governments and research organizations in several LMICs are at least willing to take, if not already taking, different approaches to developing health technologies that can result in better global public health outcomes.

19 For an overview of success rates in clinical trials, see: Kimmitt, Ryan, Marcela Vieira, Suerie Moon, and Anna Bezruki. 2020. "Research Synthesis: Time and Success Rate of Pharmaceutical R&D." Knowledge Portal on Innovation and Access to Medicines, Global Health Centre, Graduate Institute of International and Development Studies, Geneva. https://www.knowledgeportalia.org/r-d-time-success.

Finally, beyond clinical trial activities, the literature review and scoping interviews also indicate growing activity of LMICs in pharmaceutical R&D. Investments in building R&D capacities have already borne fruit, as indicated by several pharmaceutical products developed in LMICs as seen above (Table 1).

This report has provided a baseline snapshot, but ongoing systematic data collection and analysis of R&D in LMICs is still needed. Country-level studies analyzing strengths, weaknesses, and trajectories are also needed to deepen understanding of effective policies for building R&D capacity (see also the companion reports on Bangladesh and Colombia). Finally, there is a need for further research on potential alternative R&D models in LMICs that may better meet domestic needs, as well as the needs of global public health. Pharmaceutical innovation in the Global South is a rich, promising, dynamic, and rapidly-evolving area with strategic importance for global health, which merits far more research and attention than it has received to date.

5. APPENDIX

5.1. SCOPING INTERVIEWS - LIST OF INTERVIEWEES (IN ALPHABETICAL ORDER OF LAST NAMES)

- Michelle Childs, Drugs for Neglected Diseases Initiative (DNDi)
- Gabriela Costa Chaves, Independent researcher (licensed from Fiocruz)
- Spring Gombe, former consultant at United Nations Development Programme (UNDP)
- Lynette Mabote, Sustainable Access to Pharmaceuticals & Affordability Models (SAPAM)
- Achal Prabhala, Access IBSA
- Judit Rius Sanjuan, United Nations Development Programme (UNDP)
- Robert Terry, TDR - Special Programme for Research and Training in Tropical Diseases
- Anonymous, civil society organization, Russia

5.2. SCOPING INTERVIEWS - SAMPLE INTERVIEW QUESTIONS

1. Who are the main organizations involved in pharmaceutical R&D activities in low and middle-income countries (LMICs), whether implementing, financing or facilitating R&D? Please feel free to focus on a specific country or group of countries (not all LMICs need be covered in your response), and include both organizations with which you are involved directly or that you are familiar with. What roles do they play (e.g. implement R&D, finance or facilitate)?

2. What do you consider to be the most significant differences, if any, between pharmaceutical R&D projects conducted in high-income countries (HICs) and those conducted in LMICs?

3. In your view, what are the main obstacles/challenges for carrying out pharmaceutical R&D projects in LMICs? What are the main facilitating factors?

4. Based on your knowledge of the pharmaceutical research and development (R&D) system, what are the initiatives that you believe can represent alternatives to the current mainstream business model of conducting pharmaceutical R&D? To what extent do R&D initiatives in LMICs represent alternatives to the traditional business model?

5. Who are the organizations in LMICs engaged in “alternative” models of pharmaceutical R&D? What roles do they play (e.g. implement, finance or facilitate R&D)?

6. Who else would you recommend we should try to speak with about this topic?

5.3. LIST OF PROPOSALS WITH INNOVATIVE APPROACHES TO PHARMACEUTICAL R&D SUBMITTED TO THE WHO/CEWG IN 2013 BY ORGANIZATIONS BASED IN LMICS

Proposals	Disease	Type of proposal	Submitted by	Country
Development of easy to use and affordable biomarkers as diagnostics for types II and III diseases	Helminths and protozoan infection	product development: diagnostics	African Network for Drugs and Diagnostics Innovation (ANDI); Chinese Network for Drugs and Diagnostics Innovation	Ethiopia (headquarters); China
Dengue vaccine development	Dengue	product development: vaccines	Health System Research Institute (HSRI)	Thailand
Multiplexed Point-of-Care test for acute febrile illness (mPOCT) (Originally named: New point-of-care diagnostics for fever of unknown origin in field settings)	Fever	product development: diagnostics	Translational Health Science and Technology Institute (THSTI)	India
Demonstration of the potential of a single dose malaria cure of artemether-lumefantrine through reformulation in a nano-based drug delivery system	Malaria	product development: therapeutics	Nanomedicine malaria project group (CSIR - Council for Scientific and Industrial Research) and collaborators (UCT, KEMRI, CREATES, MUHAS, AiBST)	South Africa, Kenya, Tanzania, Zimbabwe
Development of a vaccine against schistosomiasis based on the recombinant Sm14, a member of the fatty acid-binding protein family: controlling transmission of a disease of poverty	Schistosomiasis	product development: vaccines	Oswaldo Cruz Foundation (Fiocruz)	Brazil
A Platform for Pioneering Proper Treatment of the Forgotten HIV-Infected Paediatric Patient	Paediatric HIV/AIDS	product development: therapeutics	University of the Witwatersrand	South Africa
ANDI as the regional coordination mechanism for demonstration projects and product R&D in Africa	Not disease specific	coordination and funding mechanism	African Network for Drugs and Diagnostics Innovation (ANDI)	Ethiopia (headquarters)

Proposals	Disease	Type of proposal	Submitted by	Country
Combating Tuberculosis in the Region by development of Diagnostics and Drugs	Tuberculosis	product development: diagnostics and therapeutics	A. Diagnostics: Translational Health Science and Technology Institute (THSTI); Biotechnology Industry Research Advisory Council (BIRAC), India. B. Drug: Open Source Drug Discovery (OSDD) programme of the Council of Scientific & Industrial Research (CSIR), India	India
Improving health quality and wellbeing of the economically marginalized populations in Southeast Asia: An initiative towards the introduction of a human hookworm vaccine (IIHHVac)	Hookworm disease	product development: vaccines	Tropical Infectious Diseases Research and Education Centre (TIDREC), University of Malaya, Kuala Lumpur, Malaysia in partnership with National School of Tropical Medicine, Baylor College of Medicine, Houston, USA and the Ministry of Health, Malaysia	Malaysia, USA
Project on medicines and devices for diabetes mellitus	Diabetes mellitus, Diabetic foot ulcer	product development: therapeutics and medical devices	University of Colombo	Sri Lanka
Cholera caused by vibrios of the O1 serogroup	Cholera	product development: diagnostics; healthcare	Ministry of Health, Brazil	Brazil
Pan serotype pneumococcal vaccine for use in low and middle income countries	Pneumonia	product development: vaccines	N/A	India
The Development of Novel Treatment Diagnostic Test for mycetoma	Mycetoma	product development: diagnostics	University of Khartoum	Sudan
Affordable Diagnostic Tests for Cancer	Cancer	product development: diagnostics	Ministry of Health and Social Protection, Colombia; Knowledge Ecology International (KEI)	Colombia, USA
R&D in new drugs and diagnostics for cancer (type of cancer to be identified referring to disease burden)	Cancer	product development: diagnostics and drugs	N/A	Indonesia

Proposals	Disease	Type of proposal	Submitted by	Country
Development of active pharmaceutical ingredients for medicines	Not disease specific	product development: therapeutics	Bangladesh	Bangladesh
Determination of the effect biological of compounds phenolics of the tropical blackberry height (rubus adenotrichos) in models cell phones, tissue and animals	Cancer	product development: therapeutics	Costa Rica	Costa Rica
Ceiba consortium for population pharmacogenetics to improve drug safety and efficacy in Latin America	Drug metabolism	product development: therapeutics	CEIBA consortium	Multicountry (Latin America)
Medical device development for early diagnosis of neoplasias by means of tissue characterization using electrical impedance techniques	cancer	product development: diagnostics	Venezuela	Venezuela
Use of slow freezing in the storage of foods in the kitchen area of the hospital system in order to implement the process of transformation of plant and animal foods to therapeutic forms in the treatment of diseases. (new technology)	degenerative disease	product development: therapeutics	Dr. Javier Urrutia García (El Salvador)	El Salvador
Development of strategies for the reduction of maternal mortality from the analysis of governance and social participation in maternal health programmes in Guatemala	Reproductive health, Maternal mortality	other	Ministry of Health and Social Assistance	Guatemala
Mobile e-doctor	Obstetric haemorrhage and obstetric hypertension	other	Guatemala	Guatemala
Production of liposomal amphotericin b for the treatment of visceral leishmaniasis	Visceral leishmaniasis	product development: therapeutics	Ministry of Health, Brazil	Brazil

Proposals	Disease	Type of proposal	Submitted by	Country
Development and regional production of L-asparaginase for the treatment of childhood acute lymphoblastic leukaemia (all)	Acute Lymphoblastic Leukaemia	product development: therapeutics	Ministry of Health, Brazil	Brazil
Point of care platform for diagnostics of chagas disease, applicable to others tropical diseases and potentially on oncology	Chagas and infectious diseases	product development: diagnostics	Fiocruz	Brazil
Integrated research and education project on intestinal parasitosis, malaria and traditional knowledge in rural schools in Bolivia-Ecuador-Peru	Intestinal parasites, malaria	knowledge sharing	Bolivia, Peru, Ecuador	Bolivia, Peru, Ecuador
Development and evaluation of an integrated project to treat patients with advanced, unresectable lung cancer in the Villa Clara province	Lung cancer	product development: therapeutics	Cuba	Cuba
Human papillomavirus and the immune response in the control of laryngeal cancer	Laryngeal cancer	product development: diagnostics	Cuba	Cuba
21, 129-5p, 155 and 200c microarrays as prognostic and predictive markers in diffuse large b-cell lymphoma	Cancer, Non-Hodgkin's lymphoma	drugs?	Cuba	Cuba
Evaluation and preparation for deployment of a new single dose live attenuated oral cholera vaccine	Cholera	product development: vaccines	Cuba	Cuba
Urogenital mycoplasmas and cancer in Cuba: a comprehensive approach to public health prevention and control	Infection by microplasma	product development: diagnostics	Cuba	Cuba
Development of herceptin's biosimilar/ biobetter antibody, for use in breast cancer	Breast cancer	product development: therapeutics	Cuba	Cuba

Proposals	Disease	Type of proposal	Submitted by	Country
Clinical evaluation of a Cuban heptavalent pneumococcal conjugate vaccine in children aged 1-5 years in developing countries, as a novel strategy to reduce pneumococcal circulation and avoid serotype replacement	Pneumonia	product development: vaccines	Cuba	Cuba
Development of a therapeutic vaccine for the treatment of rheumatoid arthritis and other autoimmune diseases	Rheumatoid arthritis	product development: vaccines	Cuba	Cuba

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