Pharmaceutical Innovation in Latin America and the Caribbean

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Abstract: This study assesses Latin America and Caribbean countries' capacity to innovate new pharmaceuticals, defined as developing new drugs and vaccines, repurposing existing drugs, and inventing around patents to produce new drug variations. Vaccine innovation includes reengineering existing vaccines, developing new manufacturing methods, and the clinical development of unapproved vaccine candidates initiated elsewhere.

Introduction

Innovation is the creation of new products or processes that improve well-being and is crucial for economic growth and social progress.[1] Innovation in the pharmaceutical sector depends greatly on scientific advances. The process of drug discovery involves the identification of drug targets, the design and synthesis of potential drug molecules to affect these targets, the development of appropriate drug formulations, and the testing of these formulations in preclinical and clinical trials. This process requires a profound understanding of the biology and chemistry underlying a disease or condition and the ability to apply this knowledge to develop effective and safe treatments.

Traditionally, most innovations have occurred in developed countries, but middle-income countries are increasingly playing an important role. This shift can be attributed to increased investment in research and development (R&D) activities by the governments of these countries or by their universities and businesses.[2] The implementation of treaty provisions, particularly those addressing patent or other intellectual property rights, has generated new challenges for state and non-state actors.[3] The increased R&D activity has also been driven by the rising prevalence of chronic conditions and the emergence of new infectious diseases or their variants.

Innovation

The traditional innovation model assumes a direct relationship between R&D spending and innovation. Proponents of this model tend to advocate for increased public funding, tax incentives, and intellectual property rights to incentivize R&D. However, the literature on innovation in developing countries suggests that R&D spending is only one of the many factors that influence innovation. Other factors may also be important, such as scientific infrastructure, regulatory institutions, treaty provisions, firm capabilities, and business networks. According to this perspective, the presence of complementary factors working in synergy is required to facilitate knowledge generation, adaptation, and utilization.[4] A similar idea applies to the biotechnology industry, where many highly innovative firms have emerged because of a critical mass of complementary competencies and skills, including spatial proximity to academic organizations.[5]

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This viewpoint that values complementary competencies may have particular relevance to developing countries such as those in the Latin American and Caribbean (LAC) region. To evaluate the LAC region's innovative capacity, we considered a broad set of inputs: R&D spending, human resources, and outputs such as patents, publications, and innovative products in the R&D pipeline and the market. Innovative products include not only new medicines but also the adaptation of foreign products to domestic environments, the repurposing of drugs for new therapeutic uses, products derived from "inventing around" existing patented drugs, new formulations or delivery methods, and the adoption of pending drug development projects of both universities and companies.

Intellectual Property and Treaty Provisions

Intellectual property policies, especially patent policies, affect the ability of pharmaceutical companies to temporarily limit competition and keep prices high. The World Trade Organization's (WTO) 1995 Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement is intended to promote innovation and encourage technology transfer by harmonizing intellectual property across all WTO member countries and imposing minimum standards, such as a 20-year term of patent protection. The relevant provisions of the TRIPS Agreement thus generally apply throughout Latin America and the Caribbean except for Haiti.

After TRIPS became effective in 1995, many countries adopted bilateral preferential trade agreements that included supplementary provisions regulating intellectual property rights (IPRs). An analysis of 467 such agreements found that countries with industries dependent on continuous innovation, such as the pharmaceutical industry, tend to favor strong IP protection. In contrast, those with fewer such industries tend to oppose strong protection due to the increased costs of purchasing products that were invented or developed elsewhere.[6]

Consistent with TRIPS Article 27(3)(b), national intellectual property laws need not allow natural products (including plants, animals, or certain biological processes) to be patented, but novel and nonobvious human-made variations of natural products, such as chemical analogues, may be patentable. Similarly, new methods of extracting, synthesizing, or formulating naturally occurring substances may be patentable.[7] For example, between 2000 and 2013, 56 patents were filed in Brazil related to venoms or toxins of native animal species.[8]

The TRIPS Agreement does not require disclosing genetic resource information or traditional medicinal knowledge as part of the patent application process. This creates a misalignment with the 1992 Convention on Biological Diversity, as supplemented by the 2010 Nagoya Protocol, which recognizes the sovereignty of countries over their natural and genetic resources. Moreover, they require companies and researchers to agree on terms of access to genetic resources and benefit-sharing with countries and knowledge holders, such as indigenous communities.

As a result of this misalignment, when pharmaceuticals are developed in one country based on natural resources or traditional knowledge of another country, without obtaining prior informed consent or benefit sharing and sometimes in violation of the laws of the latter country, the result has sometimes been condemned as "biopiracy." The United States is not a party to the Convention on Biological Diversity, and appropriate benefit sharing remain an area of contention.

Latin American and Caribbean countries have widely adopted a model of innovation policy similar to the 1980 US Bayh-Dole Act, which allows universities and others receiving public research funds to patent the resulting inventions and license the technology to the private sector. Many universities in Latin America have established "technology transfer" offices to help faculty file for patent protection, license intellectual property, and launch faculty-initiated start-up companies. The model was first implemented in Argentina, Brazil, and Colombia in the 1990s, followed in

Latin America and the Caribbean have made progress in the R&D of innovative therapeutics, but few publications have been devoted to quantifying and characterizing these developments. This study seeks to fill this gap by assessing the capacity of Latin American countries to generate pharmaceutical innovations.

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the early 2000s by Chile, Costa Rica, Cuba, Panama, Peru, and Uruguay.[9] Even before the implementation of Bayh-Dole-style legislation, the University of São Paulo began patenting in the 1980s, and the Universidad Nacional Autónoma de Mexico and the University of Chile in the 1990s.[10]

The Burden of Disease and Drug Regulation

The aging population in Latin America faces significant health challenges from non-communicable diseases such as cardiovascular disease and cancer. Although COVID-19 deaths nearly equaled those caused by cancer in 2021, COVID-19 mortality decreased substantially by 2023.

Many biologics are used to treat cancer. Because biologics and biosimilars are more complex than small-molecule drugs, greater regulation of the manufacturing process is needed to ensure safety, quality, and efficacy. The World Health Organization updated its guidelines for evaluating biosimilars in 2022, which have been customized and adopted by Latin American countries. Six country regulators, in Argentina, Brazil, Chile, Colombia, Cuba, and Mexico, are recognized as references due to their high quality by the Pan American Health Organization (PAHO) and WHO. Regulations in these countries typically considered US Food and Drug Administration (USFDA) and European Medicines Agency (EMA) regulatory standards but with modifications.[11] For example, in Brazil the approval of biosimilars has two pathways with different levels of stringency: one requires phase 3 clinical studies and allows for expanding the indication to other diseases, and a second pathway with fewer requirements does not allow extending to other diseases.[12]

During the COVID-19 pandemic, national regulatory agencies worked closely with local scientists and companies like China's Sinovac to conduct clinical trials in-country and fast-track vaccine approval, including vaccines that had not been approved by either the USFDA or EMA.

Latin America and the Caribbean have made progress in the R&D of innovative therapeutics, but few publications have been devoted to quantifying and characterizing these developments.[13] This study seeks to fill this gap by assessing the capacity of Latin American countries to generate pharmaceutical innovations. This work advances the "Scientific capacity" section of Vargas, Rama, and Singh[14] and employs new indicators, definitions, and data.

Methods and Data Sources

R&D expenditure data, information on researchers, and the share of natural sciences researchers were extracted from the United Nations Educational, Scientific and Cultural Organization (UNESCO) Institute for Statistics from 2012-2021 or the latest available year. "Researchers" were defined as those with five or more years of university education in mathematics, computer and information sciences, physical sciences, chemical sciences, earth and related environmental sciences, and biological sciences.

The numbers of patents granted globally in biotechnology and pharmaceuticals by country of origin were extracted from the World Intellectual Property Organization statistics website based on patents registered between 2012 and 2021. In addition, the number of contributions in high-quality journals by country and institutions was determined using the Nature index based on publications between 2016 and 2021 in natural sciences journals.

New products were defined as drugs that had never been approved and were categorized as small molecules, biologicals, and natural-derived non-synthetic drugs. Innovation included repurposing existing approved drugs for new uses, creating new delivery methods or formulations, and inventing around existing patents. Vaccine innovation was defined to include the adaptation of approved vaccines for use against different diseases or strains, existing vaccines manufactured with novel technologies, or licensing a vaccine not yet approved by the FDA or EMA for further development and testing. The product also had to be in one of the following phases: 0, 1, 2, or 3 clinical trials or already on the market.

This study collected primary data on products from various sources: peer-reviewed articles, as well as websites from pharmaceutical and biotechnology companies, universities, research institutes, and project lead scientists. The data collection spanned from July 2018 to April 2023, resulting in three dataset versions. The first version was developed from mid-2018 to 2020 and had 130 products found by reviewing universities' and companies' websites. A second version, created in 2021, mainly added original products in the preclinical phase reported in the scientific literature and yielded 263 products. This second version was used by Vargas, Rama, and Sing 2022.[15] And the current version that has 309 products, which was expanded and revised with the help of an artificial intelligence tool called Microsoft Bing AI, which became available in 2023.

The search queries were: "drug in a clinical trial," "biological products in clinical trial," "biologics in clinical trial," "biosimilar," "monoclonal antibodies," "vaccines in a clinical trial or approved," and "natural-based new medicines." Also, the countries were used in the search terms: "Argentina," "Brazil," "Colombia,"

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Table 1
Cross-Country Comparison of Spending in R&D, Researchers, and Patents

	Expenditure in R&D as % GDP latest	Expenditure R&D annual growth 2012-2021	Researchers in natural sciences full-time equivalent (latest year)	Globally granted patents in biotech 2012-2021	Globally granted patents in pharmaceuticals 2012-2021	Biotech & pharma patents per million people 2012-2021
Argentina	0.46	-0.24 %	13,802	96	177	6.0
Brazil	1.21	0.15 %	56,201	491	786	6.0
Chile	0.34	2.22 %	3,328	118	141	13.3
Colombia	0.29	2.72 %	1,063	42	58	1.9
Costa Rica	0.37	0.38%	486	6	8	2.7
Cuba	0.52		2,086	237	456	61.6
Ecuador	0.44		1,258	1	9	0.6
Mexico	0.30	1.14 %	8,729	199	590	6.2
Panamá	0.15	3.22 %	187	16	30	10.6
Peru	0.17	2.78 %	1,600	0	15	0.4
Uruguay	0.48	2.00 %	864	11	26	10.8
LAC	0.67		165,407	1,205	2,274	5.4
USA	2.82	2.00	545,890	76,111	116,496	580.3
India	0.66	5.39 %	274,613	1,087	3,978	4.8

Source: UNESCO, WIPO

"Costa Rica," "Chile," "Cuba," "Ecuador," "Mexico," "Panama," and "Peru." In the case of original products, the names of the lead scientists working on the product, with their scientific publications on the product, were examined to triangulate the information.

Country of origin of the product was determined based on the addresses of the publishing authors or company owners. In cases where there were multiple authors from different countries, the addresses of the first and last authors were used to determine the country or countries of origin.

Results

Expenditures

In absolute terms, R&D expenditures grew an average of 1.60% yearly from 2012 to 2021 (Table 1). On average, countries in the region spent 0.67 percent of their GDP on R&D, with Brazil spending the largest share, at 1.21 percent. In contrast, Argentina, Colombia, Chile, Cuba, Mexico, Peru, and Uruguay spent less than the average.[16] The joint investment in R&D of Brazil, Mexico, and Argentina comprised more than 80 percent of the total for the listed countries.

Researchers

The number of natural sciences researchers in the region doubled over a decade.[17] Brazil accounted for about 63% of the natural sciences researchers in the region, followed by Argentina with about 15%. However, in per capita terms, Argentina came first.

Patents

There are two main categories of relevant patents: pharmaceutical and biotechnology. A patent application must disclose technical information about the invented product or process sufficient to enable skilled third parties to use the invention. In most Latin American countries such as Brazil, Chile, Cuba, and Mexico, patent application information is disclosed 12-18 months after application filing. The exclusive rights are applicable only in the country where the patent has been granted.

From 2012 to 2021, 2,274 pharmaceutical patents and 1,205 biotechnology patents with inventors based in Latin America were granted worldwide. Brazil, Mexico, Cuba, and Chile led the way, with 94% of all pharmaceutical patents and 86% of biotech patents. Cuba was the top performer in LAC on the number

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Table 2
Life Sciences and Biotechnology Publications in High-Quality Journals (2015-2021)

	2015	2016	2017	2018	2019	2020	2021	Per million people (2015-2021)
Brazil	179	201	192	222	236	259	301	1.05
Mexico	63	70	84	93	116	131	140	0.78
Argentina	97	77	88	90	98	130	116	2.15
Chile	61	51	51	65	83	90	104	3.68
Colombia	40	37	33	30	50	55	45	0.80
Panama	30	26	36	33	35	39	48	8.00
Peru	17	19	14	18	29	31	30	0.66
Ecuador	12	11	8	19	24	17	20	0.88
Uruguay	12	11	12	9	8	12	16	3.34
Costa Rica	10	13	1	6	16	10	18	2.04
Other*	27	31	25	30	61	64	37	
Total LAC	548	547	544	615	756	838	875	1.28
India	180	171	197	209	242	214	280	0.15
USA	11,530	11,106	11.397	12,192	12,176	12,952	12,809	36.07

*"Other" includes Venezuela, Bolivia, Jamaica, Nicaragua, Cuba, Guatemala, Honduras, Trinidad and Tobago, Barbados, Grenada, Guyana, Paraguay, Dominican Republic, Belize, Haiti, Suriname, Saint Kitts, El Salvador, Saint Lucia/Saint Vincent/Guadeloupe, and Netherland Antilles.
Source: Nature Index 2022

Table 3
Chemistry Publications in High-Quality Journals (2015-2021)

	2015	2016	2017	2018	2019	2020	2021	Per million people (2015-2021)
Brazil	107	85	108	124	115	103	96	0.49
Argentina	38	38	40	53	48	49	30	0.91
Mexico	40	35	41	48	45	45	34	0.32
Chile	10	10	18	22	33	31	32	1.14
Colombia	6	7	11	11	16	7	10	0.19
Ecuador	8	3	6	4	4	5	3	0.26
Uruguay	4	3	3	5	5	5	4	1.21
Cuba	2	2	2	4	6	4	7	0.34
Venezuela	1	4	3	3	2	5	4	0.11
Peru	2	3	3	1	2	2	3	0.07
Costa Rica	2	3	1	1	3	1	3	0.39
Panama	1	2	1	0	2	3	1	0.32
Other	1	0	1	1	5	0	1	
LAC Total	222	195	238	277	286	260	228	0.43
India	601	566	627	615	686	721	743	0.46
USA	5.534	6.571	7.017	7.248	7.162	7.209	6.612	20.30

Others include Bolivia, Guatemala, Jamaica, Nicaragua, Paraguay, Trinidad, Belize, and Grenada.
Source: Nature Index 2022

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of patents granted per million inhabitants worldwide, still having just one-tenth the rate of per capita grants of the US.

Publications

From 2015 to 2021, the number of Latin American publications in top life sciences journals such as Nature and Journal of Cell Biology increased by 60%, totaling 4,723 papers. The countries with the most publications were Brazil, Mexico, Argentina, and Chile, accounting for more than 70 percent of the total. Panama, Chile, Uruguay, and Argentina have the highest publication output per million people, but still considerably lower than the United States per million people rate. Mexico, Peru, and Costa Rica showed the most significant increase among the Latin American countries analyzed. In comparison, Argentina and Colombia exhibited some degree of stagnation.

There were 1,706 publications from Latin American authors in top-tier chemistry journals, such as Nature Chemistry and Analytical Chemistry, or roughly one-third as many as life sciences publications in 2015-2021.

Brazil, Argentina, Mexico, and Chile are the leading contributors, accounting for approximately 86 percent of the total publications. Uruguay, Chile, Argentina, and Costa Rica exhibited the highest output per million people but still far behind the US's rate. Finally, the publication trend in this field in the region has remained stagnant in the past six years, with an annual growth rate of only half a percent.

Novel Pharmaceutical Products

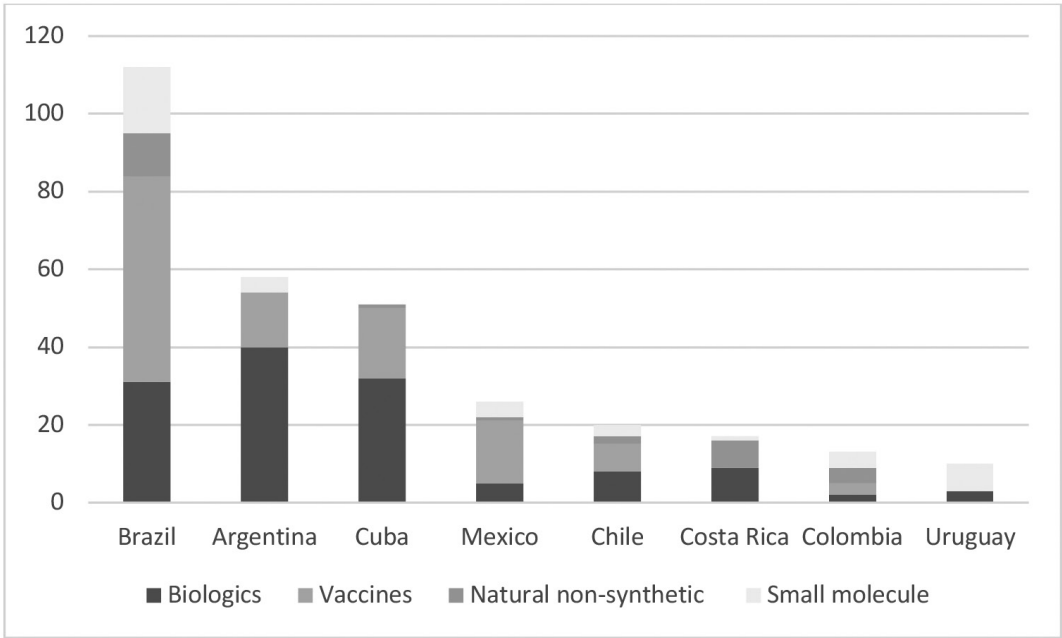
During the study period, Latin American countries had 309 innovative products either in development or already approved. These included vaccines (112), biologics (130), small molecules (40), and naturally non-synthesized products (27). Vaccine innovation was defined as reengineering existing vaccines for new purposes, manufacturing vaccines with new methods, or further developing and testing non-approved vaccines initiated elsewhere.

Biologics and vaccines were the primary focus of R&D, comprising 78% of total products. Fifty percent of drugs were originator products, 37% were biosimilars, and 18% were existing drugs repurposed for other diseases.

There were 130 biologics either in development or on the market, comprising 49% biosimilars and 51% originators. However, only Cuba, Costa Rica, and Brazil had successfully launched originator biologics by the study period cut-off. For instance, in 1997, the Center for Molecular Immunology in Cuba developed nimotuzumab, a monoclonal antibody used to treat cancer. It obtained approval in Cuba in 2002 and,

Figure 1

Innovative Drugs, in the Pipeline and Approved, by Country



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in subsequent years, was licensed to companies in Canada, Taiwan, and Europe and received approval in India, China, and several Latin American countries. Notably, nimotuzumab was granted orphan status in the EU in 2008 and the US in 2014.

Slightly more than half of biologics were still developing. Brazil led the way with about one-third of biologics in development, followed by Cuba, Argentina, and Chile. Second-generation biologics comprised one-third of all biologics in development.

Naturally Derived Non-synthesized Medicines

Latin America's vast biodiversity facilitates the development of naturally derived medicines. Brazil, Costa Rica, and Colombia are at the forefront of R&D using their natural biodiversity (Figure 1).

A total of 27 projects involving naturally-derived medicines were in development in Brazil, Costa Rica, Colombia, Mexico, and Peru. For example, Colombia's Pontificia Universidad Javeriana is investigating the use of co-adjuvants derived from natural sources that could augment the efficacy of cancer treatments. Of the 27 projects, three involved the repurposing of existing drugs. Around 51% were in preclinical development, one-third in Phase 1, 2, and 3, with the remaining five already approved. Most (39%) projects originated from universities, followed by industry-academic collaborations (23%), industry-only (19%), and "triple helix" partnerships (government, academic, and private sector collaborations; 8%).

Small Molecules

No novel small molecules were developed in LAC during the last decades. However, 12 novel small molecules were in preclinical development and Phases 1 or 2 clinical trials. These projects were based in Brazil and Uruguay and involved collaboration between private industry and universities. For example, Uruguay's Institute Pasteur of the University of la Republic was collaborating with a local company (EOLO Pharma) to address Type 2 diabetes and obesity. Regional collaboration was also occurring, including collaboration between universities and companies in Uruguay, Brazil, and Argentina to produce a new anti-inflammatory medication.

Incremental Innovative Drugs: Biosimilars

Sixty biosimilars were approved or in development, corresponding to about 29 reference biologics. Most of these biosimilars (84%) were first-generation, while 16% were second-generation, i.e., based on the fusion of antibody and receptor proteins. Argentina led the way in the development of first-generation biosimilars, having developed over half of the total number (32), followed by Brazil (14) and Cuba (8).

A significant proportion of biosimilars had been commercialized (65%), with approximately half of these products being used to treat different types of cancer. The remaining biosimilars were directed to chronic illnesses such as autoimmune diseases. Filgrastim, the reference product of which was approved in the US in 1991, is an example of a biosimilar that is widely manufactured by companies in Argentina, Brazil, and Cuba. The patent for filgrastim expired in Europe in 2006 and the US in 2013.

Seven additional biosimilars were in preclinical development for cancer and autoimmune diseases. Clinical trials for the biosimilar of trastuzumab, a treatment for HER2-positive breast cancer, were being conducted by Brazil's Bionovis/Ache and Cuba's Center for Molecular Immunology.

Companies can protect manufacturing details as trade secrets.[18] Consequently, biosimilar manufacturers must generally either license the know-how or attempt to reverse engineer products to arrive at suitable manufacturing methods. The Brazilian Product Development Partnership program is a strategic initiative that encourages the development of biosimilars, considering the confidential nature of manufacturing processes. This program involves the Brazilian public health system committing to purchase biosimilars for a fixed period in exchange for technology transfer and collaboration between foreign and local companies. Under this program, Janssen-Cilag Farmacêutica Ltda licensed a monoclonal antibody for treating autoimmune diseases to Bionovis S.A., a small Brazilian biotechnology company, and Bio-Manguinhos, a public manufacturer.[19]

Biosimilar development in North America and Western Europe is estimated to cost from $100-$250 million and take seven to eight years.[20] In Argentina, the cost of developing a biosimilar varies depending on where the active pharmaceutical ingredient is produced. It can range from $10 million to $100 million.[21] Most (85%) biosimilars have some involvement of local private pharmaceutical companies, and 53% involved international cooperation. Biosimilar manufacturers may also "invent around" patents to arrive at similar products, potentially leading to innovation and improvements in efficacy.[22]

Repurposed Drugs

Thirty-two existing drugs were undergoing clinical trials to assess their therapeutic potential in treating diseases for which they were not yet approved. Most (22) were off-patent small molecule drugs, 6 were biologics, and 3 were natural products.

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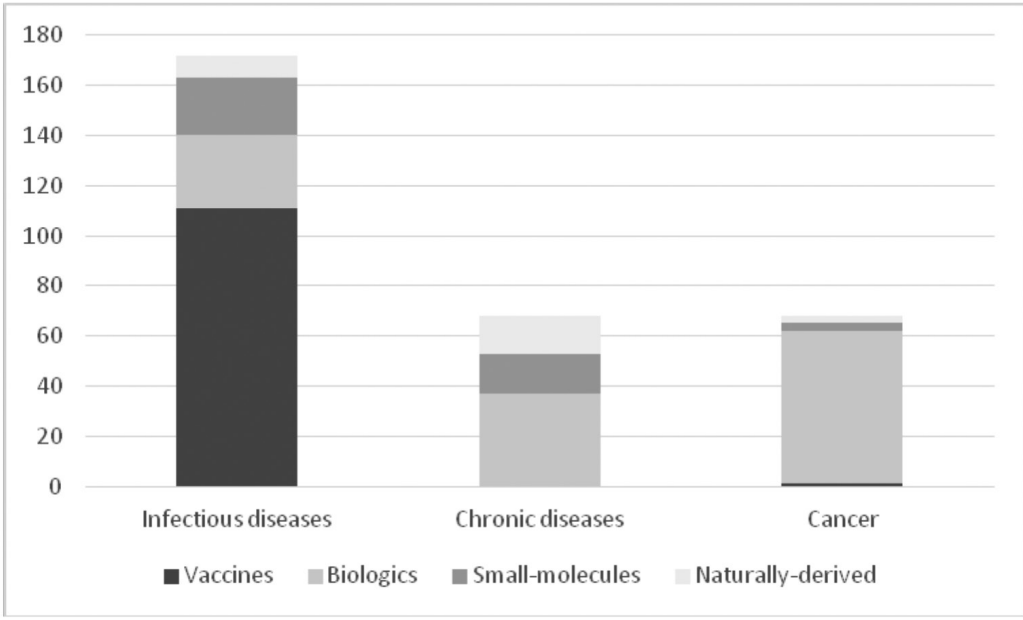
Figure 2
Pharmaceutical R&D Projects by Therapeutic Area



Mundo Sano, a non-governmental organization based in Argentina, successfully brought back the discontinued small molecule benznidazole to treat Chagas disease in children. This accomplishment was made possible in collaboration with Harvard Medical School and the World Health Organization. In 2017, the drug was granted orphan drug designation in the United States, further highlighting its potential as a viable treatment.[23]

There has been significant interest in repurposing previously approved drugs as a consequence of the global outbreak of COVID-19. Countries such as Cuba and Brazil have conducted clinical trials of monoclonal antibodies and small molecules to evaluate their efficacy in treating COVID-19 infections. Repurposing existing drugs for alternative diseases presents several advantages, including the potential for better-characterized safety profiles, expedited availability, and reduced capital investment.[24] However, to ensure the effectiveness and safety of repurposed drugs, well-designed clinical trials are needed, a consideration that became apparent with failed efforts to establish the effectiveness of ivermectin in treating COVID-19.

Therapeutic Areas

Around 56% of medicines approved by local regulatory agencies or in development in Latin America focused on infectious diseases, including COVID-19. Drugs for chronic diseases and cancer each accounted for 22%.

Of 172 infectious disease medicines, most were prophylactic vaccines (65%), followed by therapeutic biologics (17%), small molecules (13%), and naturally derived products (5%) (Figure 3). Among drugs directed to chronic diseases, biologics comprised 54%, while small molecules and naturally derived products comprised 24% and 22%, respectively. Nearly all cancer medicine development projects (90%) were biologics.

Innovative Pharmaceutical Products

Biologics comprised 41% of this portfolio, while vaccines accounted for 36%. The distribution of product portfolios varied across countries. In Cuba, biologics (including vaccines) made up 99% of the portfolio, compared to 95% in Argentina, 82% in both Chile and Mexico, and 70% in Brazil. By contrast, Costa Rica exhibited a mix of biological antivenoms and naturally derived therapies, such as the native plant *whitening solanacea* to treat diabetes, accounting for 53-41 percent of its portfolio. Peru's portfolio is split evenly between vaccines and natural products. Colom-

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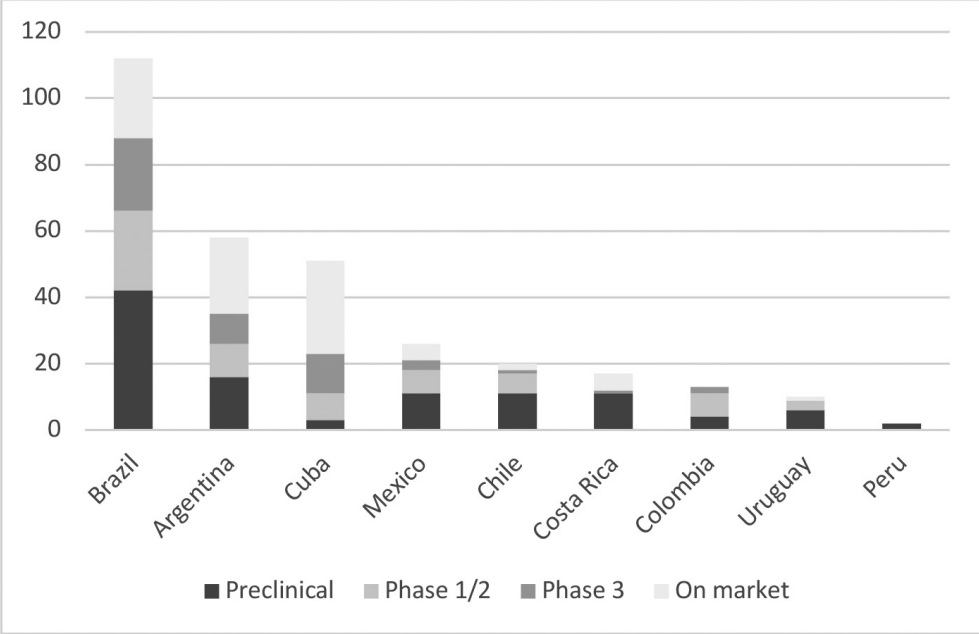
Figure 3
Pharmaceutical Innovative Products by Country and Development Stage



Note: Includes originals, biosimilars, and repurposed drugs in clinical trials and on the market

bia's portfolio consisted of a mix of vaccine and biologics and naturally derived products, 38-31 percent, respectively. Uruguay has pursued an alternative path focused primarily on small molecules, constituting 70 percent of its portfolio.

Approved and in Development

The 309 products identified in the present study spanned all stages of the R&D process, including 34% that were in preclinical development, 37% in clinical trials, and 28% already on the market. The countries with the highest number of products on the market were Cuba, Brazil and Argentina.

In 2022, there were approximately 221 drug products in various stages of pre-clinical development or phases 1, 2, or 3. Most of these products were vaccines or other biological products, such as biosimilars, with naturally derived products and small molecules following closely behind. Regarding country distribution, Brazil, Argentina, and Cuba had the highest number of therapeutics in clinical development.

Vaccines

In 2023, there were approximately 112 vaccines in various stages of development or on the market. The countries with the highest number of vaccines on the market or in development were Brazil, Cuba, and Mexico. Brazil and Cuba have successfully established a vaccine manufacturing base to guarantee their population vaccine access.

Only 21% of vaccines approved by the local regulatory agencies or in development were first-generation inactivated or attenuated forms of a pathogen. Second-generation "subunit" vaccines use an antigenic protein fragment associated with the pathogen to stimulate an immune response, constituting 46% of all vaccines on the market or in development. And the remainder, the newest generation vaccines, use a recombinant vector or DNA, protein-based virus-like particles, and DNA or RNA to stimulate an immune response and may be delivered using technology such as viral vectors or lipid nanoparticles.

Of the 112 vaccines, 20 were available for use. These vaccines are predominantly inactivated virus vaccines or protein-based, part of the first and second generation of vaccine technology, and were domestically manufactured and utilized within the national immunization program for children in Brazil and Cuba. Some were also exported to other countries.

In Brazil, the Fiocruz/Butantan public laboratory has been a prominent player in vaccine production for over a century, having developed vaccines for

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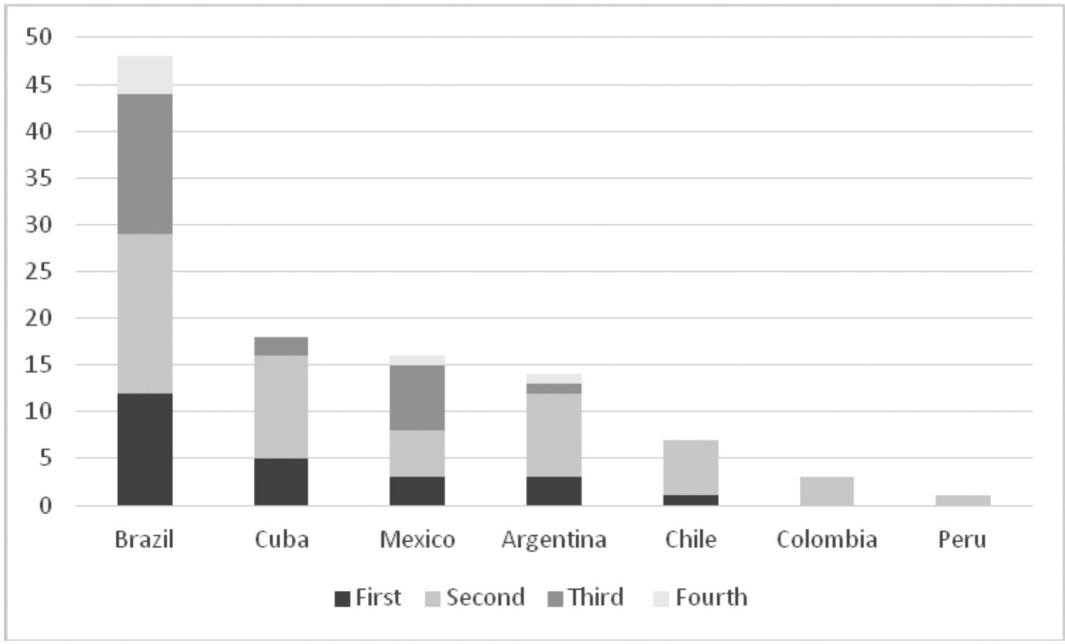
Figure 4
Vaccines on the Market and in Development by Country and Technology Generation



yellow fever, BCG, diphtheria, and smallpox, with clinical trials and regulatory approval in the country. Fiocruz has filed several patents related to the yellow fever vaccine over the years, covering various aspects of its production, formulation, and use. It has also transferred the technology to other countries, such as Senegal and Uganda.[25]

Other examples are the COVID-19 vaccines developed by Cuba's Vaccines Finlay Institute, including Soberana 1 and Soberana 2, and Abdala from the Center for Genetic Engineering and Biotechnology.[26] They involve the modification of already approved vaccines used for hepatitis B and meningococcal disease, respectively. The Cuban vaccines have also been exported to Mexico and Venezuela, with technology transfers to Vietnam and Iran.

Latin American countries had 92 vaccine projects spanning a range of technological approaches in various stages of development, with most (62%) in the preclinical stage, 29% in phases 1 and 2, and 9% in phase 3.

Brazil had nine preclinical research projects related to DNA and RNA-based vaccines. The Bio-Manguinhos Institute at the Oswaldo Cruz Foundation in Brazil and the company Sinergium in Argentina were developing mRNA vaccines under a technology-transfer agreement with the World Health Organization. Other vaccine research projects were acquired early, such as the dengue vaccine, which was licensed from the US National Institutes of Health to Brazil's Butantan in 2009 after phase 1 studies had been completed. The vaccine, based on an inactivated virus, is expected to complete phase 3 clinical trials in 2024.

Discussion and Conclusions

The pharmaceutical and biotechnology industries are research-intensive**.** However, beyond the spending on R&D, the presence of complementary factors that work in synergy is essential, scientific infrastructure, regulatory institutions, and intellectual proprietary framework. Among these factors, patents are especially important, as they play a critical role in ensuring that R&D investments are appropriately rewarded and incentivized.

In the past few decades, some countries in LAC have made progress in life sciences, pharmaceuticals, and biotechnology outputs. Although R&D expenditure as a share of GDP has remained stagnant for the past decade, total spending has increased by approximately 1.6% annually as GDP has risen. The number of qualified researchers has doubled (2008 to 2018), as has the number of biotech and pharmaceutical patents

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owned by Latin American entities granted globally in the last ten years. Moreover, life sciences publications in high-quality journals have seen a 60% increase from 2015 to 2021, with more modest increases in chemistry publications. Over the past few decades, the rise of these input indicators has been associated with more than 300 innovative products in the development pipeline and on the market.

According to the Nature Index, the top twenty life science universities in Latin American countries are responsible for more than half (56%) of the total life sciences publications in the region.[27] Most of the R&D projects in the pipeline involve partnerships with or are conducted solely by these universities. Furthermore, these universities also contribute to the total number of patents. In Latin America, the contribution of universities to patent filings is twice the global average of 5%. Brazilian universities account for 10% of patents filed in the country. Moreover, Colombia and Chile show an even more pronounced presence of universities as patent holders, surpassing 20% of patent filing.[28]

The top countries for life science research in South America were Brazil, Colombia, Uruguay, Argentina, and Chile, and in the Caribbean/Central America region, Cuba and Mexico. Among them, the São Paulo cluster in Brazil stands out for its combination of complementary competencies such as manufacturing capacity, public laboratories, and a solid scientific base, particularly in life science. It also benefits from the spatial proximity of top-ranked universities.

Cuba began working in the biotechnology field in the 1970s, roughly the same time as the US when the first biotech company, Genentech, was founded. Cuba developed its first vaccine in 1985 for meningitis B in response to a nationwide outbreak of a particular strain for which no commercially available vaccine was available. Its first biosimilar, interferon, was approved in 1986.[29] The first biosimilars in Brazil and Argentina were approved in 2004 (erythropoietin) and 2005 (somatropin), respectively.

In the case of Chile, although 259 patents have been granted to local institutions and scientists during the last decade, the dearth of domestic pharmaceutical companies hinders the effective transformation of the patented technology into commercial products.[30] To compensate and achieve a complete cycle of innovation, Chile actively pursues partnerships beyond its borders, such as the long-standing collaboration of *Ciencia y Vida* and the University of California.[31]

Most importantly, developing biologics and biosimilars requires robust, science-based regulatory institutions able to assess the benefits and risks of new products. Argentina, Brazil, and Cuba have built regulatory agencies that have been recognized for their high quality by WHO. Consistent with WHO protocols, Cuba, Brazil, and Argentina have maintained a Public Registry of Clinical Trials, which helps to ensure transparency and accountability in drug development.

Repurposing drugs for alternative diseases offers advantages such as well-characterized safety profiles, faster availability, and reduced financial investment. This approach suits upper-middle-income countries with limited financial resources but adequate scientific infrastructure. Brazil, Cuba, Argentina, Mexico, and Colombia are conducting clinical trials to repurpose drugs, including small molecules and biologics. Approximately 18% of all drugs in clinical trials were focused on repurposing, a particularly important approach during the COVID-19 pandemic. Another alternative is to reintroduce discontinued medicines; for example, the Argentinean NGO Mundo Sano has successfully reintroduced, based on clinical studies, the small molecule benznidazole for treating Chagas disease in children.

Vaccines

Vaccines are unique in that they have been promoted by universal immunization policies since the late 1970s and are considered public goods with positive effects beyond the individual. Governments provide financial support for vaccine development, making such development a significant scientific pillar associated with R&D, publications, patents, and researchers. Vaccines are also a portal to modern biotechnology.

Public subsidies can motivate companies to develop new products to address unmet public health needs.

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For example, the government of Argentina used the advance market commitment model to induce Sinergium to establish a new production facility for flu and pneumococcal vaccines, agreeing to a 10-year contract.

Universities and public laboratories lead most vaccine research in Brazil, Cuba, and Chile. Brazil's public Fiocruz laboratory has been a prominent player in vaccine production for over a century, developing vaccines for diseases such as yellow fever, BCG, diphtheria, and smallpox. However, it was after the TRIPS Agreement that international technology transfers began to play a significant role, and Brazil's public laboratories benefited from them. For example, in 2000, Fiocruz leveraged collaborations with the US NIH and Merck during a meningitis pandemic to produce a meningitis vaccine at a reduced cost.[32] Brazil has supplied UNICEF and PAHO their yellow fever and meningitis AC vaccines after pre-qualification by WHO in 2001 and 2007, respectively.[33]

Brazil has encountered obstacles in effectively completing the innovation cycle, resulting in relatively lower performance in patents per million individuals. These challenges can be attributed, in part, to regulatory vulnerabilities and a portfolio of publicly funded projects that stretches R&D too thinly.[34] During the COVID-19 pandemic, dozens of research groups in Brazil independently initiated vaccine development projects. By contrast, Cuba coordinated and selected only the most promising vaccine projects to pursue. Additionally, the COVID-19 treatment trials registered in the International Clinical Trials Registry Platform reveal some small, duplicate clinical trials that failed to yield meaningful conclusions.[35] These factors suggest a need for improved strategic focus in Brazil's innovation efforts.

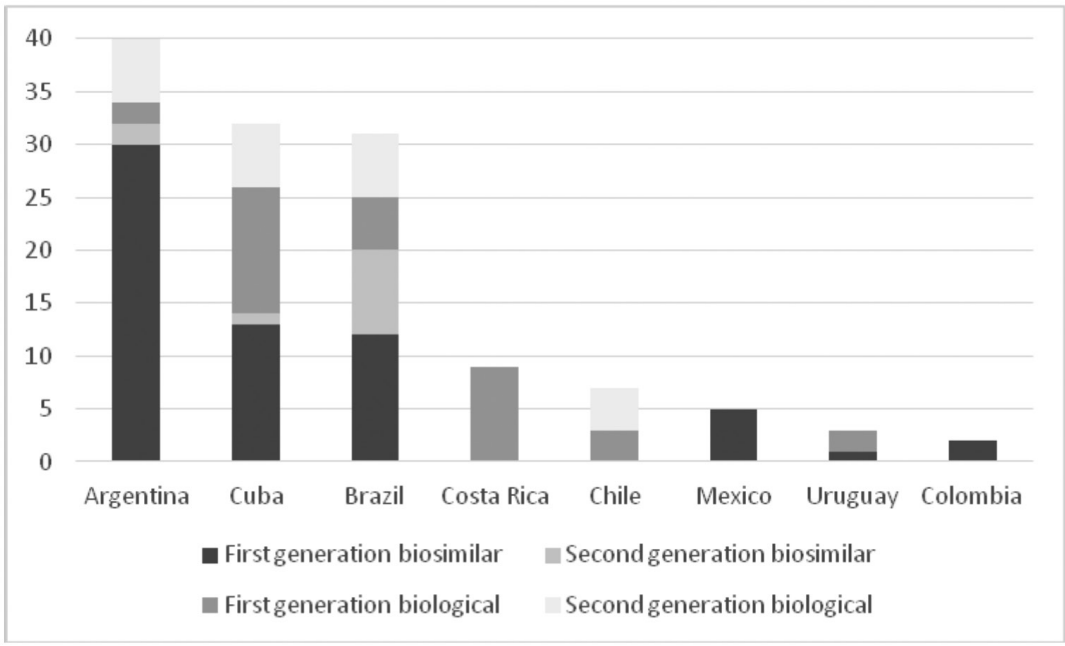
Biologics and Cancer

The high cost of cancer drugs, particularly those under patent protection, has created an access barrier for low- and middle-income countries. As a result, Argentina, Brazil, and Cuba have focused on developing affordable and effective cancer therapeutics. Argentina and Brazil focused more on biosimilar drugs, while Cuba led the way with original immunotherapies.

Most importantly, developing biologics and biosimilars requires robust, science-based regulatory institutions able to assess the benefits and risks of new products. Argentina, Brazil, and Cuba have built regulatory agencies that have been recognized for their high quality by WHO. Consistent with WHO protocols, Cuba, Brazil, and Argentina have maintained a Public Reg-

Figure 5

Biosimilars and Originator Biologics by Country and Technology Generation in the Pipeline and on the Market



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istry of Clinical Trials, which helps to ensure transparency and accountability in drug development. In oncology, regulatory agencies tend to be more flexible in approval requirements and faster to act due to the high unmet need among cancer patients.[36] Notably, certain biosimilars that have been approved in LAC do not have clinical trial results published in any peer-reviewed journals. Although not legally mandated to meet the scientific information demands of medical practitioners effectively, the publication of clinical trial results in reputable peer-reviewed journals is also important.[37]

Argentina's biosimilar industry has been developed through a critical mass of partnerships between industry, universities, foundations, and foreign corporations, as well as mergers, acquisitions, and licensing arrangements. These partnerships prioritize acquiring new knowledge and improving technological capabilities. The relatively low number of patents granted globally originating from Argentina may be due to its focus on biosimilar development and the incremental innovation typically associated with such biosimilars, which may be less likely to yield as many opportunities for intellectual property protection as originator biologics.

Cuba is one of the most innovative LAC countries in biotechnology, as measured by the number of pharmaceutical products on the market and patents granted globally. Although it underperforms R&D spending and publications in high-quality journals, Cuba's biotechnology sector benefits from the vertical integration of its R&D and manufacturing processes, which enhances efficiency and protects non-patented valuable information.[38]

Naturally Derived Products

Natural products have been the mainstay of pharmacopeia for centuries, and even today, modern drugs are often derived from natural products, especially for cancer treatment, where about half of the medicines mimic natural molecules or are natural molecules.[39] Latin America has abundant biodiversity, which also means chemical diversity. This has prompted thousands of academic publications on the medicinal benefits of some native plants in international peer-reviewed scientific journals. However, few patents or medicines have resulted from such studies.[40] A primary obstacle to the development of naturally derived drugs in the last decades is absence of consensus between two key international agreements, the Convention on Biological Diversity/Nagoya Protocol and the TRIPS Agreement, the latter governing patenting. The former seeks to allocate greater rights to the countries where biological materials and traditional knowledge originate and the latter to countries involved in the research and development of those final pharmaceutical products.[41] The discussion is ongoing, WIPO will convene a Diplomatic Conference in 2024 to consider amendments to the TRIPS Agreement related to intellectual property and genetic resources. Proposed changes could require member countries to disclose the country of origin of traditional knowledge and genetic resources that are related to inventions described in patent applications.

A primary obstacle to the development of naturally derived drugs in the last decades is absence of consensus between two key international agreements, the Convention on Biological Diversity/Nagoya Protocol and the TRIPS Agreement, the latter governing patenting. The former seeks to allocate greater rights to the countries where biological materials and traditional knowledge originate and the latter to countries involved in the research and development of those final pharmaceutical products.

While some countries like Costa Rica and the Andean group — Bolivia, Colombia, Ecuador, and Peru — have incorporated the requirement of certificate of origin and informed consent for any patent application involving genetic resources into their patent laws, it is crucial to include this requirement in bilateral trade agreements with advanced economies, where most patents are filed.[42] Additionally, Costa Rica and Peru, like India, are digitizing their traditional medicinal knowledge available in the public domain to eventually share it with developed country patent offices to prevent patents for non-novel inventions. It remains to be seen how these changes will affect the R&D of new natural-derived medicines. As of today, only a few

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local companies have patented new production processes for such medicines.

In summary, in the context of rising chronic disease prevalence and new infectious disease variants, only a handful of countries have successfully introduced innovative pharmaceutical products into the market, namely Argentina, Chile, Cuba, and Costa Rica, biologics, and Brazil, original natural products.

However, there are other countries that have a pipeline of projects that show promise because they benefit from the mix of complementary factors needed for innovation. For instance, Costa Rica, Panama, Peru, and Ecuador have a rich biodiversity. They have increased their contributions to high-quality chemistry publications, reflecting a growing cadre of talented scientists, and will start benefiting from productive discussions on genetic resources and intellectual property. Uruguay also a leader in high-quality chemistry publications and is forming multicountry collaborations with companies and universities to complete the innovation cycle.

Finally, this study has several limitations. Information about privately held projects or in the preclinical stage may not be publicly available and could lead to underestimating the number of projects in development. The Nature Index indicates scientific productivity but may differ from other rankings in natural sciences. Finally, the data extracted depends on the quality and completeness of available websites and the inclusivity of search terms, and country-level variations may exist.

Note

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