

## Access to vaccines in Brazil and the global dynamics of the Health Economic-Industrial Complex

Acesso a vacinas no Brasil no contexto da dinâmica global do Complexo Econômico-Industrial da Saúde

Acceso a vacunas en Brasil en el contexto de la dinámica global del Complejo Económico-Industrial de la Salud

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### Abstract

*This study analyzed the main economic trends, market structure, production, and innovation in vaccines against infectious diseases at the global and national levels, observing the effects on access to vaccination in Brazil and on the sustainability of the Brazilian Unified National Health System. In order to update a global overview of R&D and the market, the authors conducted a literature search and drew on a competitive intelligence database. In order to understand Brazil's role in this context, with the Health Economic-Industrial Complex as the structural focus, the authors accessed information from the Brazilian Health Regulatory Agency, the National Immunization Program, and the Questel Orbit Intelligence database on patent protection in Brazil; identified the technologies transferred to public institutions in Brazil; and analyzed the trend in the trade balance deficit in health. The analysis revealed a global trend of concentration of vaccine production in a few leading pharmaceutical companies and the exacerbation of economic and technological asymmetries in the vaccine sector. In Brazil, the study identified technological weaknesses, risks, and manufacturing bottlenecks that impact the guarantee of immunizations in the country and showed that despite the installed industrial base, public policies and actions by domestic manufacturers have not been sufficient to confront and overcome the global context of structural dependence. In conclusion, the study indicates the need for progress in the Brazilian national strategy to link domestic production, technological capacity-building, and innovation in the vaccine sector to help guarantee universal access to health in Brazil.*

*National Science, Technology and Innovation Policy; Vaccines; Immunization Programs; Innovation; Access to Essential Medicines and Health Technologies*

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## Introduction

Vaccine development and the establishment of global immunization strategies against highly infectious diseases have been decisive in the radical change in the pattern of diseases that affect humankind. Evidence shows that in the last 50 years, vaccination has saved more lives in the world than any other medical product or procedure, which makes vaccines “*the miracle of modern medicine*”, in the words of Roy Anderson <sup>1</sup>. Acknowledged as one of the most effective public health interventions in the world <sup>2</sup>, despite recent antivaccine movements in certain segments of society, vaccination is acknowledged as both an essential component of the right to health and an individual, community, social, and government responsibility <sup>3</sup>.

However, access to vaccination is conditioned by economic factors, since the vaccine industry is part of the chemical and biotechnological subsystem of the Health Economic-Industrial Complex (HEIC) <sup>4,5</sup> and mirror the sector’s competitive standard. As part of an industrial system with high complexity and technological dynamism, the vaccine market is a differentiated science-based oligopoly whose industry has experienced heavy concentration in recent decades. The growing predominance of major global pharmaceutical companies in the sector <sup>6,7</sup> has increased the cost of vaccine purchases, especially new generation products, and creating limits that can hinder or even completely prevent access by more vulnerable populations, countries, and regions, thus further aggravating inequities.

Whereas inherent aspects of innovation and globalization are central to conceiving national strategies in the vaccine sector, the current study analyzed the main economic trends in the global vaccine market and vaccine production and Brazil’s position in this context. The study takes a systemic focus and aims to analyze the recent dynamics in the development, production, and supply of vaccines in the world, identifying their effects and the challenges for universal access to health in Brazil.

## Methodology

The inevitable focus of innovation from a seminal Schumpeterian <sup>8,9</sup> and neo-Schumpeterian perspective <sup>10,11</sup>, namely that technological change in its broadest sense is the main endogenous factor in corporate competitive strategies (i.e., that innovation does not result from random facts or casual external knowledge), is essential for conceiving the economic dynamics, understanding global asymmetries to identify risks and opportunities for less developed countries and their institutions, and detecting threats to health systems’ sustainability.

To update the global scenario of vaccine research and development (R&D), we conducted a literature search and used secondary data from the Cortellis database, of Clarivate Analytics (<https://clarivate.com/cortellis/>, accessed on 15/Apr/2019). In this database, due to the inherent challenges of this sector’s technological complexity, alongside the lengthy development timeframes and high failure rate, our methodological cross-section limited the search fields to clinical trials underway on vaccines against infectious diseases. The search did not consider products already registered or launched on the market, since the interest was to identify a short and middle-term scenario for introducing innovations on the market. Taking this search as the point of departure, we analyzed the main target diseases, the leading countries, and the main patents-holders associated with these technologies.

Shifting from the global to the Brazilian domestic market, we consulted secondary data sources from the Chamber for Pharmaceutical Market Regulation (CMED), a regulatory body affiliated with the Brazilian Health Regulatory Agency (Anvisa) <sup>12,13,14</sup> that compiles all data on purchases made for the private market and part of those for the public market, and primary data from the Brazilian National Immunization Program (PNI) (which gathers information on the public vaccine market), having raised data on all the vaccine purchases by the Brazilian Ministry of Health in the last ten years. The CMED and PNI data are complementary and indispensable for understanding Brazil’s human vaccines market.

In addition, whereas patents are acknowledged (notwithstanding the limitations and criticisms) as an indicator of innovation <sup>15</sup>, capable of associating investors’ commercial strategies in R&D, a study was conducted on the panorama of patent protection in this sector in Brazil. This was based on data for patent families indexed in the Questel Orbit Intelligence patent database (<https://www.>

questel.com/business-intelligence-software/orbit-intelligence/#, accessed on 23/Jun/2019). Successive searches were performed, using the advanced search mode, without a time restriction, with the keywords “vaccin” or “antigen”, combined with Boolean operators and truncation; associated with the International Patent Classification (IPC) A61K39/00 (“Medicinal preparations containing antigens or antibodies”) applied to the title, claims, and summary of the patent documents. An initial sample was obtained with 2,776 prevailing patent families in Brazil (among patents filed and granted). For greater precision of the sample, an individualized data classification was performed, which considered both prophylactic and therapeutic vaccines, excluding documents related to vaccines targeted exclusively to the veterinary field or vaccination methods, materials, and vaccine-related devices, thus reducing the sample to 1,475 documents. This study revealed the leading organizations in patent ranking in Brazil, showing the kinds of filings in which the main patent filers are concentrating their investments, research efforts, and commercial strategies.

In order to understand the technology transfer strategies adopted by Brazil’s public laboratories, we consulted official documents and press releases by these institutions in order to identify which technologies are being absorbed and who the main partners are.

Finally, based on the structuralist tradition<sup>16</sup> and the modern theory of complexity<sup>17</sup>, which recommends trade balance as the principal indicator of productive specialization and global asymmetries between countries, companies, and regions, including a tradition in the study of the HEIC and its spinoffs for public policy<sup>18</sup>, this study focused on aspects of Brazil’s trade balance deficit in the vaccine sector. This used information available in the Comex Stat database of the Brazilian Ministry of Industry, Foreign Trade, and Services (<http://comexstat.mdic.gov.br/pt/geral>, accessed on Feb/2019), with the data collection and systematization based on a methodology developed by the Coordinating Division for Prospecting Activities and the Research Group on Development, Health Economic-Industrial Complex, and Innovation in Health (GIS) of the Sergio Arouca National School of Public Health and the Office of the President of the Oswaldo Cruz Foundation (Fiocruz). This process identified the vaccines’ share and fluctuations in the trade deficit of the HEIC, pointing to persistent weaknesses and risks in guaranteeing access to immunization in Brazil and the configuration of the country’s universal health system.

The study included a survey and analysis of data and information on the global and Brazilian vaccine markets, corporate and innovation dynamics, and aspects that revealed asymmetries and dependence. The methodology did not require studies involving human subjects or submission to an institutional review board, and no conflict of interest was identified.

## Results and discussion

### Global vaccine market: research, development, and innovation

The modern origin of vaccine development dates to the work of Edward Jenner in the late 18th century. Since then the world has witnessed enormous progress in terms of technological complexity. From simple vaccines produced with attenuated viruses, we have evolved to multivalent vaccines that use antigen strains from the circulating pathogen, such as pneumonia and human papilloma virus (HPV)<sup>1</sup>. In the Fourth Industrial Revolution, vaccines are starting to be developed from genetic mosaics, built according to conceptual models using a wide variety of sequenced genes accumulated in global databases<sup>19</sup>.

Initially, universities, research institutes, and public laboratories (singly or in partnership with private companies) spearheaded the development of vaccines, but private initiative’s importance increased over time<sup>20</sup>. Today, R&D activity in the vaccine industry is permeated by strong linkage between the public and private sectors. Government bears the risk in the more basic and uncertain phases of innovation, and industry carries the more advanced stages of development and the subsequent introduction of new products and processes on the market<sup>21</sup>. Capital’s financial logic prevails in this scenario, with the leading companies’ clear hegemony in the innovation standard in terms of the search for new products and in orienting R&D activities, generating asymmetries between

regions, countries, and populations<sup>18,22,23</sup>. Investors that connect public and private funds in various forms of risk capital, public banks, and international funding agencies also participate in this process.

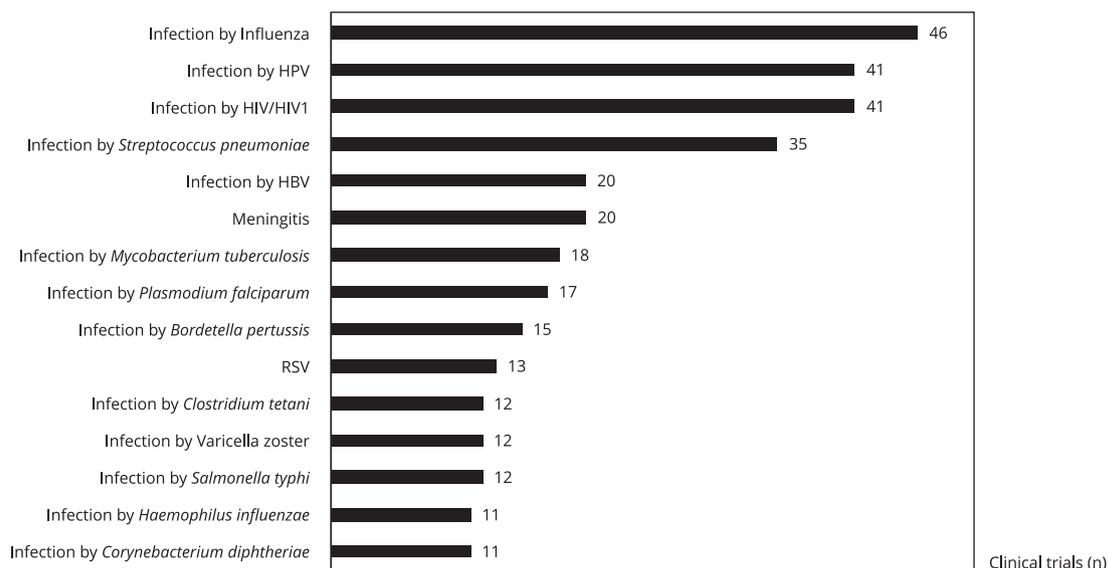
Change in the dynamics of vaccine development can be associated with various factors. Besides the pharmaceutical industry's consolidation and growth, the high added value of more technologically advanced vaccines (some with sales of over a billion dollars), this market's expansion – especially due to universal immunization policies promoted by the World Health Organization (WHO) since the late 1970s – and the drop in productivity of new drugs in the 2000s have helped expand the industry's interest in investing in this sector<sup>3,24,25</sup>.

Today, the vaccine sector's dynamics are permeated by the market logic of the major pharmaceutical conglomerates (whose competitive strategy restricts access to new technologies), thereby increasing the prices of more technologically advanced products<sup>7</sup>. A handful of corporate conglomerates, almost exclusively with headquarters in the United States and Europe, account for nearly all of the currently developed vaccines, thus revealing the global asymmetries manifested in the health innovation process<sup>26,27</sup>. A search in the Cortellis database (<https://clarivate.com/cortellis/>, accessed on 15/Apr/2019) on clinical trials under way against infectious diseases in the world shows that the development of vaccines against diseases that disproportionately affect underprivileged populations is still not a priority. The database search yielded 374 studies, and considering prophylaxis, only vaccines against tuberculosis (*Mycobacterium tuberculosis*) and malaria (*Plasmodium falciparum*) are featured on the list of 15 vaccines with the most trials under way (Figure 1), revealing the logic of concentration of technological efforts on meeting the demands of higher-income populations.

These trials, conducted mainly in the USA, followed by China and Europe (especially the UK, Spain, Germany, Finland, and Belgium), are associated with patents held by a diversity of companies, universities, scientific institutions, and government agencies, featuring GlaxoSmithKline (GSK), the U.S. Government, Merck, Janssen, Sanofi Pasteur, and Novartis. The last five years have seen a slowdown in the growth of large industry's vaccine pipeline<sup>26,28</sup> and an increase in the share of emerging market players and small biotech companies<sup>26</sup>.

**Figure 1**

Vaccines against infectious diseases. Clinical trials under way in the world.



HBV: hepatitis B virus; HIV: human immunodeficiency virus; HPV: human papilloma virus; RSV: respiratory syncytial virus.

Source: prepared by the authors based on data from Cortellis (<https://clarivate.com/cortellis/>, accessed on 15/Apr/2019).

This analysis requires caution, since investment on startups and other venture projects, without losing control over the pace and direction of innovations, is a typical strategy of industrial concentration in the pharmaceutical market, where power asymmetries are reproduced in the vaccine sector's innovation dynamics, shaping a pattern of center-periphery dependence and a process of modernization with marginalization, translated as limitations in access to health, not only due to the prohibitive cost of new generation products, but likewise associated with a standard of technologies that does not necessarily serve the priorities of underprivileged populations <sup>16,29</sup>.

### **Global vaccine market: recent dynamics of production and supply**

In 2018, the global pharmaceutical market reported a turnover of USD 864 billion, USD 30.5 billion of which from vaccine sales, or 3.5% of the industry's revenue. The vaccine sector ranked fifth in the market, after cancer drugs (14.3%), antirheumatics (6.7%), antidiabetics (5.6%), and antivirals (4.5%) <sup>30</sup>. Market data show that in recent decades the vaccine sector's growth rate was twice that of the rest of the pharmaceutical industry <sup>26</sup>. This pace has slowed in more recent years, but expectations are that the upward trend will be maintained, with forecasts pointing to a turnover of nearly USD 37 billion in 2027, which should result in this sector's expansion in the global pharmaceutical market <sup>31,32</sup>.

These forecasts consider such aspects as the persistently high rate of diseases that are avoidable with vaccines already available on the market and vaccines that are in the pipeline <sup>33</sup>, besides the development of therapeutic vaccines, which unlike traditional vaccines (targeted to the prevention of diseases) aim to control chronic infections or existing degenerative diseases. Vaccines indicated to improve the immune response to the human immunodeficiency virus (HIV) and the effects of hepatitis B will thus have an even greater impact on the future market <sup>26</sup>.

In 2017, just four pharmaceutical companies, GSK (24%), Merck (23%), Pfizer (22%), and Sanofi (21%), accounted for approximately 90% of global vaccine sales revenues <sup>31</sup>.

In this market, high-income countries, more prone and in better conditions to implement innovative and more expensive vaccines, account for 82% of global sales revenues but only 20% of the annual volume of vaccine doses supplied <sup>34</sup>. In low and middle-income countries, the supply is partially operated by international agencies like the United Nations Children's Fund (UNICEF) and the Pan-American Health Organization (PAHO), which acquire large volumes of vaccines and thus carry considerable influence and obtain lower prices than many countries individually. In these regions, emerging countries' manufacturers, established mainly since the 1980s and whose portfolios consist particularly of underutilized basic vaccines and some combined vaccines, play a critical role in supply. Participation by these manufacturers has been identified as a factor in increasing competition and thus a reduction in prices in these markets, leading large corporations to outsource production, participate in joint development activities, and conduct technology transfers, as occurred in Brazil in the last 20 years as a strategy for competitiveness <sup>35</sup>.

Despite the growth in the number of vaccine manufacturers, there are still few that are capable of meeting international quality standards set by WHO, leading to a delicate balance between supply and demand in many markets and compromising the world population's immunization <sup>20,36</sup>.

### **Brazilian vaccine market**

According to CMED data, the Brazilian pharmaceutical market's turnover in 2017 was approximately BRL 69.5 billion (approximately USD 22 billion), or 9.4% nominal growth over the year 2016 <sup>12</sup>, setting the sector apart from Brazil's heavy economic crisis. The vaccine sector accounted for BRL 3.8 billion (USD 1.2 billion), or 5.4% of the total. Two vaccines ranked among the sector's five highest turnovers in Brazil: 10-valent pneumococcal conjugate, in 3rd place, and trivalent influenza (fragmented, inactivated) in 5th place, each with revenues of more than BRL 500 million (USD 156 million) <sup>12</sup>.

However, these figures do not include all the vaccine purchases by the PNI, more than BRL 3.6 billion (USD 1.1 billion) that same year, possibly due to underreporting by public manufacturers, considering the specificity of budget administration at the state and federal levels (including revenues such as budget resources, for example) and because they do not include data such as those related to

vaccines supplied via PAHO. This means that vaccines' share of the domestic pharmaceutical market is even greater than suggested by the CMED data.

These combined data reveal the economic importance of human vaccines in Brazil, with a market consisting of two segments: one public, where the population has access to the products defined as essential by the State, with the Ministry of Health responsible for the purchase and distribution of the vaccines supplied through the public network of the Brazilian Unified National Health System (SUS), and the other, private, organized around private clinics, medical offices, and other services<sup>37</sup>.

The public market, whose reach and specificity result from strategies determined by the PNI, now accounts for approximately 90% of the demand for doses of human vaccines in Brazil<sup>38</sup>. The program has steadily increased its presence in a scenario of the future through the continuous inclusion of new technologies and new generation products<sup>39</sup>. Brazil's capacity to organize and conduct national vaccination campaigns, tied to an annual schedule that currently covers at least 18 diseases, reaching all age brackets and involving large population segments, is known as an international example<sup>40,41</sup>. The breadth of the PNI and the size of the Brazilian population make Brazil one of the world's largest markets in terms of amounts of vaccine doses.

Meanwhile, the private market emerged, focused on providing differential access to modern vaccines still not supplied by the public health system and fueled by the technological mismatch between the supply of products by the PNI and the pace of development of new vaccines in the early 1980s, which produced an area of inequality that had not previously existed in Brazil<sup>7,37</sup>, but which ended up functioning as a portal of entry for more technologically advanced vaccines in Brazil's public market.

On the supply side, according to data from PNI and CMED for the year 2017, the Brazilian market was served by a limited number of suppliers: four public institutions, namely Bio-Manguinhos/Fiocruz, Ataulpho de Paiva Foundation (FAP), Butantan Institute (Butantan), and Ezequiel Dias Foundation (Funed); five large companies belonging to the main pharmaceutical conglomerates, Abbott, GSK, Merck, Pfizer, and Sanofi<sup>13,14</sup>; and two international agencies, PAHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO), whose supplies include vaccines produced by companies that are not part of the above-mentioned conglomerates, like the Serum Institute of India<sup>13,14</sup>.

Despite the size of the Brazilian demand and action by the large pharmaceutical conglomerates in the supply of vaccines in the country, the last private Brazilian manufacturer terminated its activities in the 1980s<sup>37</sup>. Currently, the entire domestic production is done by public manufacturers, incentivized by the National Program for Self-Sufficiency in Immunobiological Products (PASNI) and using technology transfer strategies to expand their portfolios and capacity-building in the production of vaccines required by the National Immunization Program, especially vaccines on the technological frontier. GSK, Merck, and Sanofi Pasteur were the main suppliers of technologies transferred to the public Brazilian laboratories in recent years, as shown in Box 1.

The large pharmaceutical companies are the main world manufacturers of human vaccines against infectious diseases and the global leaders in R&D in this sector, besides holding the largest volume of patent assets both in the world and in Brazil, as shown by the search in the Questel Orbit Intelligence database (<https://www.questel.com/business-intelligence-software/orbit-intelligence/#>, accessed on 23/Jun/2019).

The search identified a universe of 1,475 patent families in human vaccines (both prophylactic and therapeutic) in force in Brazil. Combining all the companies belonging to the same financial group, the British conglomerate GSK ranks first in patent filings in Brazil, followed by Oncotherapy Science (Japan), Immatics Biotechnologies (Germany), Merck (USA), Sanofi (France), and Pfizer (USA). The share of Brazilian companies in this ranking is negligible. GSK's large share in Brazil (Figure 2) mirrors the company's global leadership in patent filings in this market segment.

In the public area, the main holder of patent families in Brazil is the U.S. Department of Health and Human Services (HHS), in ninth place, as shown in Figure 2. Fiocruz is the leading domestic Brazilian manufacturer, ranking 35th, with six patent families.

A detailed analysis of the portfolios of patent families in Brazil reveals different scenarios. The main patent applicant in the country, GSK, has a diversified list of inventions in vaccines. The largest concentration is families of vaccines against meningitides (meningococcal and pneumococcal), with 16, followed by cancer (14), diphtheria, tetanus, and pertussis (DTP) (12), pneumonia (11), allergies

**Box 1**

Technology transfers to public laboratories in Brazil.

PUBLIC MANUFACTURER	VACCINE	TECHNOLOGY SUPPLIER
<b>Fiocruz</b>	HIB ( <i>Haemophilus influenzae</i> do sorotipo B)	SmithKline/GSK *
	10-valent Pneumococcal (conjugate)	GSK
	Rotavirus (attenuated)	GSK
	MMR (measles, mumps, rubella)	GSK
	MMRV (measles, mumps, rubella, varicella)	GSK
	IPV (inactivated polio)	Sanofi Pasteur
<b>Funed</b>	Meningococcal C	Novartis/GSK
<b>Butantan Institute</b>	HPV (human papilloma virus)	Merck
	Hepatitis A	Merck
	Pertussis, acellular	GSK
	Influenza	Sanofi Pasteur

Fiocruz: Oswaldo Cruz Foundation; Funed: Ezequiel Dias Foundation.

\* The technology transfer contract for HIB vaccine was originally signed in 1998 with SmithKline Beecham (SmithKline). In the 2000s, with the merger of Glaxo Wellcome and SmithKline Beecham, the technology transfer under way was taken over by the GlaxoSmithKline (GSK) group.

Source: prepared by the authors based on the Activities Report of Bio-Manguinhos/Fiocruz/2017, the Management Report by the Butantan Foundation/2018, and Funed/2019.

(10), and malaria and HIV (nine families each). With fewer families, but with a significant presence, there are patent filings for influenza (8) and respiratory syncytial virus (RSV) and immune-enhancing vaccines (6 families each). The other families are scattered across *Clostridium difficile*, *Chlamydia*, rotavirus, poxvirus vectors, arteriosclerosis, and Alzheimer, among others.

The above-mentioned portfolio partly corresponds to the company's history as a supplier of vaccines and technology to public laboratories in Brazil. Many patent filings are part of a new generation of vaccines that are already supplied, while others are new developments. Among the patents filed for unique or scarcely explored targets, such as arboviruses and parasitic diseases, GSK has only filed for vaccines against dengue and malaria. The company has also invested heavily in therapeutic vaccines in oncology, with 14 families in the portfolio covering various cancers.

The study showed a strong trend towards investments in oncology. In addition to GSK's relevant presence in the patent families, the next two leading companies in Brazil had portfolios that were extremely concentrated in this segment. Oncotherapy Science has 39 patent families in various types of cancer and only two patent families in ophthalmology (maculopathy). One hundred percent of the Immatics Biotechnologies' portfolio is targeted to various types of cancer.

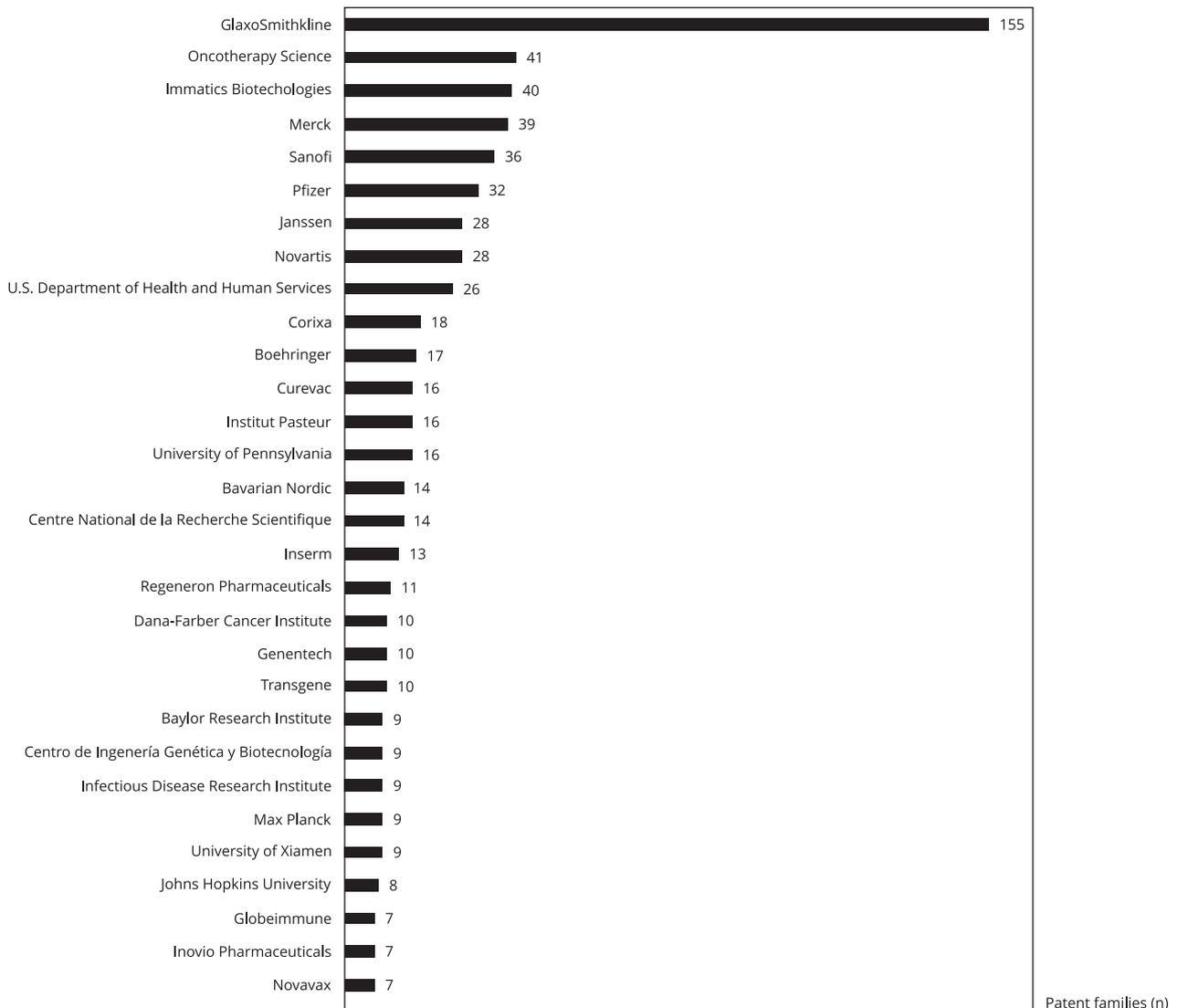
Merck's portfolio is more diversified, with nine patent families in cancer therapies. The company's other wagers are as follows, in decreasing order: dengue, meningococcal meningitis, allergies, HIV, flavivirus diseases, Alzheimer, rotavirus, and other areas with just one family each (RSV, pneumonia, varicella, cytomegalovirus, and *C. difficile*).

Sanofi's portfolio is similar to that of GSK in terms of choice of targets. It includes nine families related to meningitides (meningococcal and pneumococcal), two against hepatitis B, two against pneumococcal diseases, and two DTP vaccines. The most striking characteristic is the investment in flavivirus diseases: five families against dengue, one against Nile fever, and three others with a specific target disease.

A comparison of the HHS (the leading public institution in the ranking) and Fiocruz (the leading Brazilian public institute) shows great similarity in relation to arboviruses: Fiocruz holds patent families against diseases caused by flavivirus, mostly against yellow fever, while HHS holds families against Zika and dengue. However, the two differ as to the other types of vaccines: Fiocruz holds pat-

**Figure 2**

Leaders in filing families of active patents for human vaccines in Brazil (1999-2017 \*).



\* 2017 is the last year in which patent filings are reported publicly. Most of the patent filings in 2018 and 2019 have still not been disclosed, due to the 18-month rule between filing an application and its publication in Industrial Property journals.

Source: information generated in Questel IP Business Intelligence (<https://www.questel.com/business-intelligence-software/orbit-intelligence/#>), based on a search by the authors, accessed in June-July 2019.

ent families against malaria and helminths, while the other HHS families are in the areas of cancer, RSV, filovirus, influenza, pneumonia, HPV, tuberculosis, leishmania, and rotavirus, among others.

Considering the market of human vaccines against infectious diseases in Brazil, GSK, Merck, and Sanofi are the leading holders of patent families, which guarantees their public market reserve, despite not investing in vaccines R&D or manufacturing in Brazil.

## The Brazilian vaccine market: analysis of data from the PNI and trade balance

The search of primary data from the PNI for the last 10 years (2009-2018) showed that Fiocruz and Butantan are the main suppliers to the program, both in the variety of vaccines and the volume of doses, and that private manufacturers also serve the residual demand not supplied by public laboratories. Box 2 shows the supplies to the PNI in 2018 by public laboratories and types of vaccines. Figure 3 provides the overall history of supplies to the PNI by volume of doses during the same period.

Public spending by the PNI in vaccine purchases also increased significantly during the same period (Figure 4). However, this increase was not due to the increase in the number of vaccine doses purchased per year, but to the mean cost per dose, even considering the amount in dollars (USD 1.43 per dose in 2009 and USD 4.07 in 2018), coinciding with the increase in the international cost of new generation vaccines, alongside the industry's growing technological complexity and the market's concentration. Considering only the year 2018, more than 304 million doses were supplied to the PNI at a total cost of more than BRL 4.5 billion (USD 1.2 billion), as shown in Figure 4.

Purchases by the PNI in 2018 show wide variation in the price of vaccine doses: the least expensive was DTP, produced by the Serum Institute of India and supplied at BRL 0.69 per dose, while the most expensive was varicella, produced by Merck Sharp & Dohme and supplied at BRL 75.20.

Comparing the number of doses and price per dose of various vaccines, influenza is the most critical vaccine, not because of the cost per dose, but because of the large volume purchased, as shown in Figure 5.

### Box 2

Brazilian laboratories – supplies to the Brazilian National Immunization Program (PNI). Human vaccines (2018).

LABORATORY *	VACCINE
<b>Fiocruz **</b>	Yellow fever
	HIB ( <i>Haemophilus influenzae</i> do sorotipo B)
	IPV (inactivated polio)
	OPV (oral polio)
	10-valent Pneumococcal
	MMR (measles, mumps, rubella) ***
	MMRV (measles, mumps, rubella, varicela)
	Rotavirus
<b>Butantan Institute</b>	Influenza
	Hepatitis A #
	Hepatitis B
	HPV (human papilloma virus)
	Human rabies
	DTaP (diphtheria, tetanus, acellular pertussis)
<b>FAP</b>	BCG (tuberculosis)
<b>Funed</b>	Meningococcal C conjugate

FAP: Ataulpho de Paiva Foundation; Fiocruz: Oswaldo Cruz Foundation; Funed: Ezequiel Dias Foundation.

\* Did not include the Paraná State Technology Institute (Tecpar), since it only supplied veterinary vaccines to the PNI;

\*\* According to the Fiocruz Management Report for 2018, in addition to the vaccines listed above, Fiocruz also supplied the varicella vaccine;

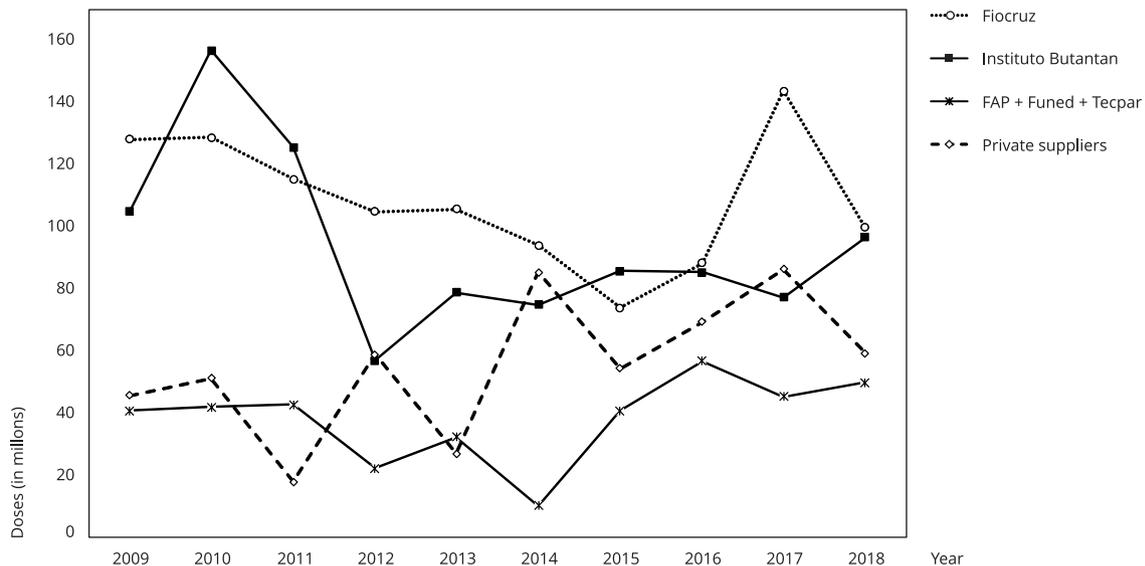
\*\*\* MMR vaccine was also supplied to the PNI by the Serum Institute of India and Merck Sharp & Dohme;

# Hepatitis A vaccine was also partly supplied to the PNI by Merck Sharp & Dohme.

Source: prepared by the authors based on information from the PNI/Department of Communicable Disease Surveillance/Health Surveillance Secretariat/Ministry of Health.

**Figure 3**

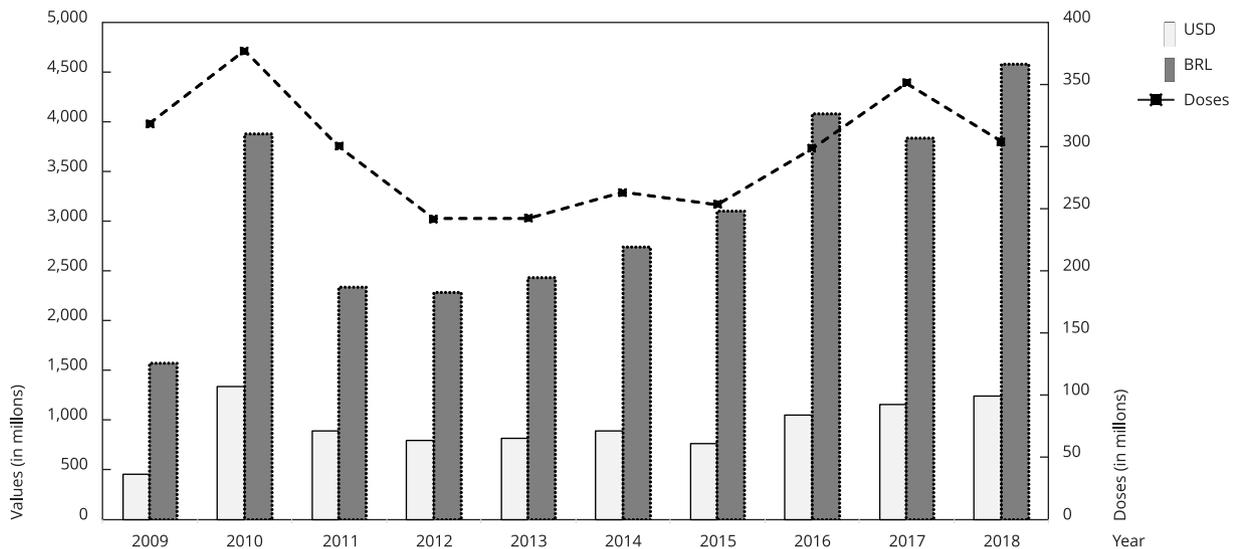
Vaccine purchases by the Brazilian Ministry of Health: number of doses, 2009-2018.



FAP: Ataulpho de Paiva Foundation; Fiocruz: Oswaldo Cruz Foundation; Funed: Ezequiel Dias Foundation; Tecpar: Paraná State Technology Institute. Source: prepared by the authors based on information from the PNI/Department of Communicable Disease Surveillance/Health Surveillance Secretariat/Ministry of Health.

**Figure 4**

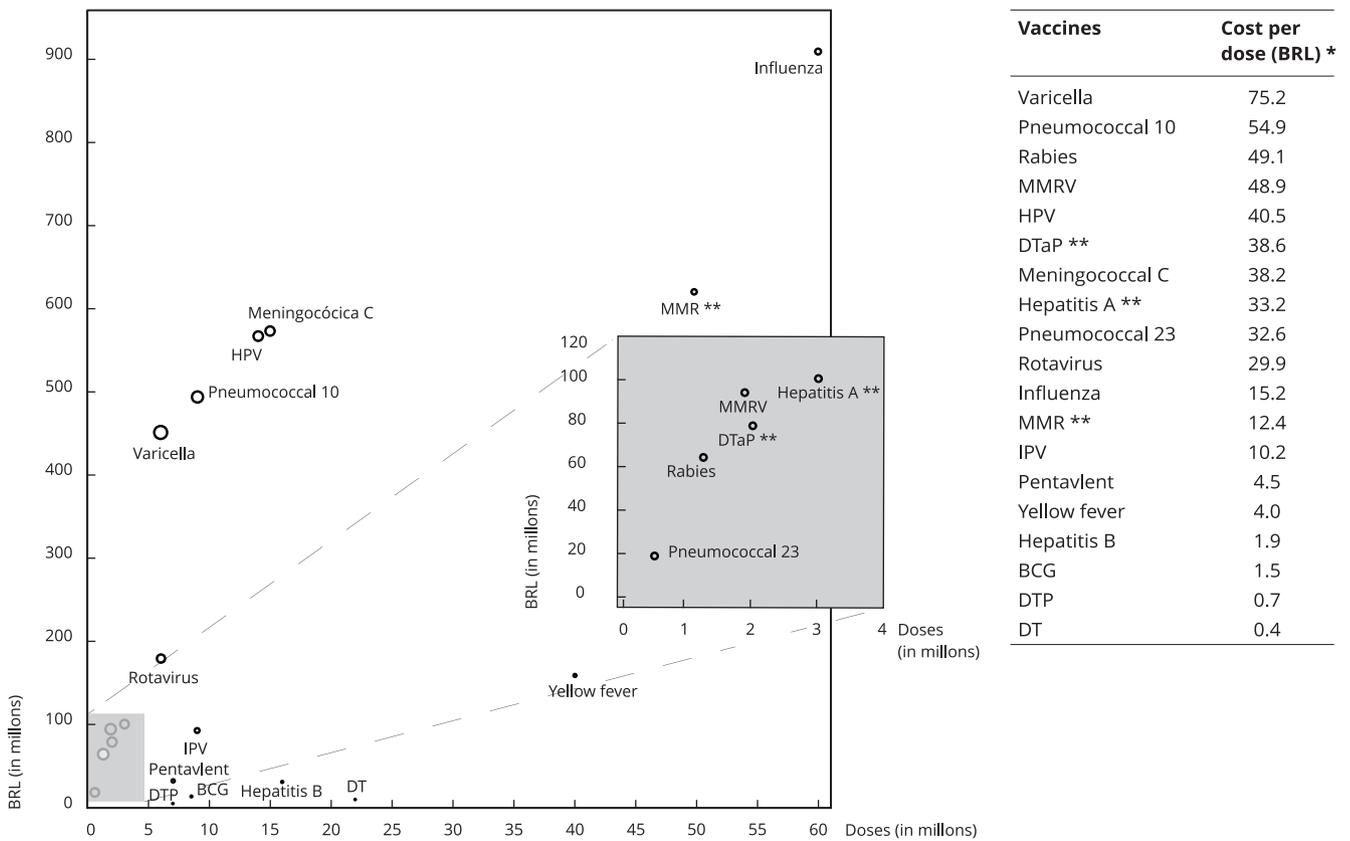
Brazilian National Immunization Program (PNI). Vaccine purchases – main Suppliers (millions of doses) (2009-2018).



Source: prepared by the authors based on information from the PNI/Department of Communicable Disease Surveillance/Health Surveillance Secretariat/Ministry of Health.

**Figure 5**

Purchases by the Brazilian National Immunization Program (PNI) (2018) – doses purchased x total expenditure x mean price per dose \*.



Abbreviations and indication: BCG (Bacillus Calmette-Guérin, against tuberculosis); DT (diphtheria and tetanus); DTP (diphtheria, tetanus, pertussis); DTaP (diphtheria, tetanus, acellular pertussis); HPV (human papilloma virus); MMR (measles, mumps, rubella); MMRV (measles, mumps, rubella, varicella); Pentavalent (diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type B); IPV (inactivated polio vaccine).

\* When there was more than one supplier of the same vaccine, we calculated the mean final price per dose;

\*\* The price of the MMR vaccine showed the widest variation. From four different suppliers, it ranged from BRL 6.40 to BRL 24.55 (mean value, BRL 12.40). There was also significant variation in the price per dose of hepatitis A vaccine (from BRL 33.00 to BRL 50.68) and DTaP (from BRL 38.14 to BRL 59.60). Purchases of the more expensive hepatitis A and DTaP vaccines were small and did not significantly impact the mean final price.

Note: The circle's size indicates the prices per dose (BRL 0.40 to BRL 75.20). The marks are labeled with the abbreviated names. The Figure on the left expands the view of the figure's area with sales less than BRL 120 million and fewer than 3.5 million doses administered.

Source: prepared by the authors based on information from the PNI/Department of Communicable Disease Surveillance/Health Surveillance Secretariat/Ministry of Health.

Figure 5 also shows that the vaccines against HPV, meningococcal C conjugate, pneumococcal 10, and varicella are also critical in terms of price. The figure also shows that the global tension between market values, social demands, and prices, inherent to the HEIC dynamics<sup>42</sup>, can be reproduced in the field of vaccines. This tension creates the need for a public strategy that allows linking the innovation-access dyad, reproducing a dichotomy which, at the limit, can compromise vaccines' characteristics as a public good, as an essential industrial sector for guaranteeing universal access to health.

With the expansion of the portfolio in the vaccination schedule and the incorporation of products supplied by the SUS whose technology was not available or was not totally available, there was a steady increase in the sector's trade balance deficit, which started to grow in 1999. The deficit grew by

308% in 2010, due to the purchase of a single product, the H1N1 vaccine. The deficit increased from just over USD 300 million in 2009 to more than USD 1.2 billion in 2010. Despite a subsequent drop, this deficit has not returned to the previous level. There was a new upturn in 2014, when the deficit exceeded 930 million, returning afterwards to the previous level, with a mean of USD 664 million a year from 2015 to 2018.

There has been a gradual increase in the vaccine sector's share of the trade balance deficit in the HEIC. Vaccines now account for 6% of the total deficit in the HEIC, and 9% of the deficit when considering only the chemical and biotech segments of the industry (Figure 6).

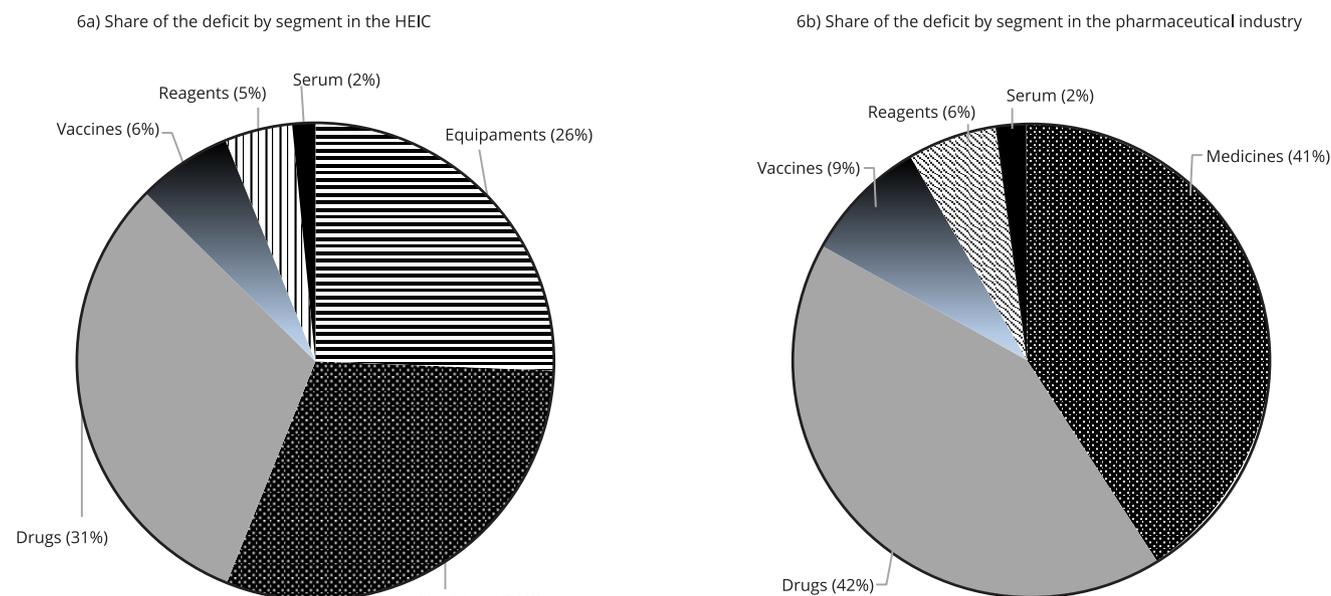
These data reveal Brazil's technological vulnerability and the country's position in the global asymmetries associated with the unequal dissemination of technical progress and innovations in health. In terms of public policies and the public laboratories' role, the situation emphasizes the urgent need to combine technology transfer processes with endogenous capacity-building strategies in order to avoid permanent and structural reproduction of dependence, even in the sector of the HEIC in which the most progress has been made in Brazil.

## Conclusions

The pace of innovation in the vaccine sector has diminished in the last five years<sup>26,28</sup> but has not affected the sector's economic importance in the HEIC<sup>30,31,32,43</sup>. A static analysis might lead to the conclusion that vaccines are losing ground compared to other groups of products. In fact, vaccines' promise as the portal of entry in modern biotechnologies has been fulfilled. However, the vaccine sector's subordination to the leading pharmaceutical companies' strategies has increased, reinforcing global asymmetries and barriers to access<sup>27,28</sup>, which may further widen the gap between innovations and the health demands of neglected populations and regions.

**Figure 6**

Share of the deficit by segment in the Health Economic-Industrial Complex (HEIC) and the pharmaceutical industry.



Source: prepared by the authors based on a methodology developed by the Coordinating Division for Prospecting Activities and the Research Group on Development, Health Economic-Industrial Complex, and Innovation in Health/Fiocruz, with data from Comex Stat/MDIC (<http://comexstat.mdic.gov.br/pt/geral>, accessed on Feb/2019).

This global scenario is replicated in Brazil. Cross-analysis of market data through searches in official documents of public Brazilian laboratories and data on patent protection in Brazil shows that the industry's main global leaders orient the dominant technological standard in the Brazilian market. Domestic production is exclusively public and essentially subordinated to technology transfer strategies. However, these initiatives have not been sufficient to reverse the conditions of structural and long-term dependence, as shown by the economic, R&D, and trade balance data. The incipient (nearly non-existent) share of domestic institutions and companies in patent filings in the Brazilian Patent and Trademark Office (INPI) for inherent technologies in the development and production of vaccines suggests a tendency to maintain or even increase the dominance of the large global leaders' technological standard in the country.

Brazil successfully installed an industrial base that has been important for guaranteeing universal access to vaccination in the country, but efforts at innovation have still proven insufficient. The main challenge is to go beyond strategies that link the domestic production base and domestic public demand and achieve the capacity to innovate. This perspective contributes to resolving the global dilemma of orienting efforts in science, technology, and innovation in health to social needs with a sustainable and less asymmetric basis, allowing for a greater variety of players, countries, and technological alternatives.

## Contributors

C. A. G. Gadelha was responsible for coordinating the study, conception, definition of the methodological focus, discussion, writing, critical analysis of the content, revision, and approval of the final version for publication. P. S. C. Braga was responsible for structuring the writing of the article, participated in the coordination, critical analysis of the content, and revision of the article, and collaborated in the literature review and data search and systematization. K. B. M. Montenegro was responsible for the data search and systematization and participated in the writing, critical analysis of the content, and revision of the article. B. B. Cesário participated in the data search and systematization and writing and critical analysis of the content.

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## Additional informations

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## Resumo

*Este estudo investigou as principais tendências econômicas, da estrutura de mercado, e da produção e inovação em vacinas contra doenças infecciosas, em âmbito global e nacional, observando os reflexos no acesso à vacinação no Brasil e sustentabilidade do Sistema Único de Saúde. Para atualização do panorama mundial de P&D e de mercado, foi realizada uma pesquisa bibliográfica, e, utilizada a base de dados de inteligência competitiva. Para a compreensão da inserção do Brasil nesse contexto, segundo enfoque estrutural do Complexo Econômico-Industrial da Saúde, foram levantadas informações da Agência Nacional de Vigilância Sanitária, do Programa Nacional de Imunização e da base Questel Orbit Intelligence, referentes à proteção patentária no país; identificadas as tecnologias transferidas para as instituições públicas nacionais; e investigada a evolução do déficit da balança comercial em saúde. A análise efetuada evidenciou a tendência global de concentração da produção em poucas empresas farmacêuticas líderes e de acirramento de assimetrias econômicas e tecnológicas também no segmento de vacinas. No Brasil, a pesquisa identificou fragilidades tecnológicas, riscos e gargalos produtivos que recaem sobre a garantia à imunização no país e revelou que, a despeito da base industrial instalada, as políticas públicas e ações dos produtores nacionais não têm sido suficientes para enfrentar e superar o contexto global de dependência estrutural. Em conclusão, o estudo indica a necessidade de se avançar na estratégia nacional de vincular produção local, capacitação tecnológica e de inovação no segmento de vacinas para contribuir na garantia do acesso universal à saúde no país.*

*Política Nacional de Ciência, Tecnologia e Inovação; Vacinas; Programas de Imunização; Inovação; Acesso a Medicamentos Essenciais e Tecnologias em Saúde*

## Resumen

*Este estudio investigó las principales tendencias económicas, de estructura de mercado, y de producción e innovación en vacunas contra enfermedades infecciosas, en el ámbito global y nacional, observando sus reflejos en el acceso a la vacunación en Brasil y sostenibilidad del Sistema Único de Salud. Para la actualización del panorama mundial de P&D y de mercado, se realizó una investigación bibliográfica y se utilizó una base de datos de inteligencia competitiva. Para la comprensión de la inserción de Brasil en ese contexto, según el enfoque estructural del Complejo Económico-Industrial de Salud, se recogió información de la Agencia Nacional de Vigilancia Sanitaria, del Programa Nacional de Inmunización y de la base Questel Orbit Intelligence, referente a la protección de patentes en el país; identificadas las tecnologías transferidas para las instituciones públicas nacionales; e investigada la evolución del déficit de la balanza comercial en salud. El análisis efectuado evidenció la tendencia global de concentración de la producción en pocas empresas farmacéuticas líderes y de exacerbación de asimetrías económicas y tecnológicas, también en el segmento de vacunas. En Brasil, la investigación identificó fragilidades tecnológicas, riesgos y cuellos de botella productivos que recaen sobre la garantía de inmunización en el país y reveló que, a pesar de la base industrial instalada, las políticas públicas y acciones de los productores nacionales no han sido suficientes para enfrentar y superar el contexto global de dependencia estructural. En conclusión, el estudio indica la necesidad de avanzar en la estrategia nacional de vincular la producción local, capacitación tecnológica y de innovación en el segmento de vacunas, para contribuir en la garantía del acceso universal a la salud en el país.*

*Política Nacional de Ciencia, Tecnología e Innovación; Vacunas; Programas de Inmunización; Innovación; Acceso a Medicamentos Esenciales y Tecnologías Sanitarias*

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