DOI: 10.1590/1413-812320212611.13932021

Vaccines in Brazil: historical analysis of the Sanitary registration and vaccine availability in the Brazilian Unified Health System

Kaite Cristiane Peres (https://orcid.org/0000-0001-6811-925X) [1]
Fabíola Bagatini Buendgens (https://orcid.org/0000-0002-0229-0852) [2]
Ediana Adriano Prates (https://orcid.org/0000-0001-5632-1071) [3]
Norberto Rech Bonetti (https://orcid.org/0000-0003-4808-4277) [1]
Luciano Soares (https://orcid.org/0000-0001-7633-5681) [4]
Claudia Marcela Vargas-Peláez (https://orcid.org/0000-0001-5011-8718) [5]
Mareni Rocha Farias (https://orcid.org/0000-0002-4319-9318) [1]

Abstract *Given the COVID-19 pandemic and the importance of public social protection policies, health issues, including immunizations, have gained prominence. This paper aims to analyze the dynamics of vaccine registration in Brazil and the vaccines made available through the National Immunization Program (PNI in Portuguese), with emphasis on the 2004-2018 vaccination schedule. This descriptive, exploratory, documentary research analyzed vaccine registration procedureswith the Brazilian Health Regulatory Agency (ANVISA, in Portuguese) and the incorporation of vaccine products into the PNI. The study drew on information from the national sanitary registration database, made available by ANVISA; a document analysis of official/normative publications; and data from published literature. The data shows the incorporation of vaccines into the PNI, evidencing that Brazil is a country with industrial potential for vaccine production but that is still focused on the transfer of technologies and in need of public attention and investments for developing new technologies as a way to ensure the sector's independence.*

Key words *Vaccines, Brazilian Health RegulatoryAgency, Biological products, Public Health*

[1] Centro de Ciências da Saúde, Universidade Federal de Santa Catarina. R. Delfino Conti S/N Trindade, 88040-370. Florianópolis SC Brasil. kaitecris@gmail.com
[2] Farmácia Escola, Universidade Federal de Santa Catarina. Florianópolis SC Brasil.
[3] Escola de Saúde Pública de Florianópolis. Florianópolis SC Brasil.
[4] Universidade da Região de Joinville. Joinville SC Brasil.
[5] Fundación IFARMA. Bogotá Colômbia.

Introduction

The COVID-19 pandemic has emphasized the importance of public policies for social protection, especially sanitary and economic policies. Vaccines have become protagonist in terms of controlling the pandemic and have revealedthe core role of the Government in this sector. Research, development, and production institutions, both state-owned or private, as well as the Brazilian Health Regulatory Agency (ANVISA, in Portuguese) and the National Immunization Program (PNI, in Portuguese) have become frequent subjects in the media. Considering this context, the analysis of the dynamics of vaccine registration in Brazil and itsincorporation in the PNI overthe past 15 years may contribute to improving the debate and the public policies related to it.

The PNI, established in 1973, is part of the mission to control and/or eradicate vaccine-preventable diseases in Brazil[1]. As a program, it seeks to articulate immunization actions in the country, which were previouslyorganized as disease control campaigns[2,3]. PNI's scope includes strategies to expand the vaccination network, reaching rural populations, epidemiological surveillance, health education, and the establishment of national laboratories equipped and enabled to produce diagnostic tests and to carry outvaccine quality control[4].

In the context of the establishment of the PNI, vaccines used to be mostly supplied through importation, which resulted in low autonomy and high vulnerability in the accessibility tothose resources[5]. In 1985, the creation of the National Immunobiological Self-Sufficiency Program, aimed at fulfilling the country's needs in terms of vaccines and serums, was one of the strategies to boost the national development of the sector. Gradually, the investments in structure and organization of the health services - for example, the investments in cold chain facilities - made it possible to conductnationwide vaccination actions[6]. Since 2004, the country has stood out in the eradication of vaccine-preventable diseases, such as poliomyelitis, urban yellow fever, and even measles. In time, besides distributing vaccines to its population through the PNI, Brazil has also become a vaccine exporter to more than 70 countries, especially countries from the African continent[7].

In terms of addressing the national sanitary regulation requirements, the pharmaceutical manufacturers are expected to obtain marketing authorization and to provide documentation evidencing clinical data and production capability, as well asprovide evidence of quality control. The medicines regulatory agency must evaluate safety data, efficacy, and quality of the products, including *in loco* verification of compliance of Good Manufacturing Practices by the manufacturers[8], since the adequate regulation of this sector tends to boost the population's confidence in the health system and contributes to commercializing those technologies in more adequate conditions[9,10]. In Brazil, this is the purpose of ANVISA, a regulatory agency created in 1999, inspired by the Food and Drug Administration (FDA) from the United States[11,12].

As part of the Brazilian Unified Health System (SUS in Portuguese), health surveillance constitutes a privileged space of government intervention aimed at improving the quality of products and services, and to adjust the productive segments of the health sector to the social demands and needs of the health system[13]. As the country's national regulatory authority, ANVISA keeps the records of pharmaceutical products approved in the country.

Therefore, this article aims toanalyze the dynamics of vaccine registration in Brazil and the vaccines made available through the PNI, especially in the period between 2004 and 2018.

Methodology

This is a descriptive, exploratory study based on document analysis, concerning the marketing authorization of vaccines in Brazil until 2018, and the distribution of those products for the PNI, especially duringthe vaccination period between 2004 and 2018. We used the first vaccination year (2004) after the creation of ANVISA (1999) as the starting point for the analyses of vaccine incorporation into the PNI.

To obtain data, on December 31, 2018, a consultation was conducted on the ANVISA website[14]under "Consultation of medication and hemoderivatives", including the filter "biological" in the regulatory category. For the analysis, only vaccines destined to humans were considered. The details of the marketing authorizations (authorization date, holder company, and situation) were consulted considering the active ingredient. To complement the information on marketing authorization expiration date, cancelation date and reason (if available), a search was done on the ANVISA website, named as "Documentation

Status - type of technical document"[15], using as keyword the vaccine registration numbers. For this study, we considered the situation of the marketing authorization as active/current or cancelled/expired at the moment of consultation (December 2018). Only the products with "active/current" marketing authorization are allowed to be commercialized in the country. It is worth to mention that since 2019, ANVISA's information system has been significantly improved, making the search tools much more agile.

The comparison between vaccines registered in the country and vaccines incorporated into the PNI was carried out by the documental analysis of official and normative publications from the Ministry of Health, referring to vaccination schedules during the period of 2004-2018, as well as in published data.

Data was collected and analyzed using *Microsoft Office Excel*®, 2016 version, and the variables were presented in absolute values.

This study was conductedusing public access data, and therefore there was no need for evaluation and approval by aResearch Ethics Committee[16].

Results

Marketing authorization of vaccines in Brazil

Marketing authorization of products commercialized before 1999, when ANVISA was created, can be found in the agency's website since the registration process by the pharmaceutical companies became mandatory, according to Ordinance no. 801, from October 7th, 1998[17].

The first marketing authorizations of vaccines are from 1993 (hepatitis B vaccine and meningococcal BC). From that year on, data show a trend of an annual increase in the number of approved vaccines, peaking in 2010. In December 2018, 186 approvals were counted in the country in the category of "vaccine", with 45.1% (n=84) in active (current) status (Figure 1).

Until 2010, there was a predominance of new registrations of vaccines, in comparison to those cancelled/expired, with the highest frequencies of new approvals in 1999, 2009, and 2010. In the last two years, there was an increase in the marketing authorization processes, especially forthe Influenza vaccine, accounting for 40.0% (n=35) of the total number of vaccines registered in the period.

Among the marketing authorization of vaccines with drawn from the market in the period of 1993-2018 (102 registrations), It is worth to highlight that: in 47.0% (n=48) of those cases, the company requested the cancellation of the marketing authorization; however, for such cases, the reason was not available for public consultation. In 26.5% of the cases (n=27), the holder requested the cancellation of the sanitary registration for reasons of change in ownership, in other words, the holder transferred the rights to produce and commercialize the product to another company. In 20.6% of the cases (n=21), the holder had no interest in renewing the marketing authorization after five years of license (considering the applicable legislation in the period studied); in 5.0% of the cases (n=5) the registration was cancelled by ANVISA, usually by actions of pharmacovigilance; and for the remaining 0.9% of the cases, there was no information about causes.

Among the vaccines whose marketing authorization were cancelled/expired, peaks were observed in 2011, 2012, 2016, and 2017. Change of holder was the main reason for cancellations in 2011, 2012, and 2017. The number of cancellations due to change in holder in those three years represents 48.2% (n=13) of the 27 products cancelled for that reason during the 15 years of study. In 2016, there was predominance of the cancellation of influenza vaccine marketing authorization processes.

Table 1 shows that four state-owned and 21 private companies were at some point holders of vaccines registered during the period. Among the private companies, some went through a process of mergers, while others did not maintain the marketing authorization of the vaccines, corroborating data on cancellations due to change of holder (in cases of companies mergers) and cases of un renewed marketing authorizations. In December 2018, only eight private companies had active registrations. Private companies held 80.6% of the registrations duringthe period, of which 69.0% of the active registrations were concentrated in three companies: Sanofi-Aventis (25.0% of active registrations), GlaxoSmithKline Brasil (22.6%), and Merck Sharp & Dohme (11.9%); the other five private companies own 9.5% of the active registrations. The four public companies: FundaçãoAtaulpho de Paiva, Fundação Ezequiel Dias – Funed, Fundação Oswaldo Cruz, and Instituto Butantanheld19.4% of the vaccine registration in the period of 2004 to 2018, and in December 2018, owned 31.0% of the active registrations.

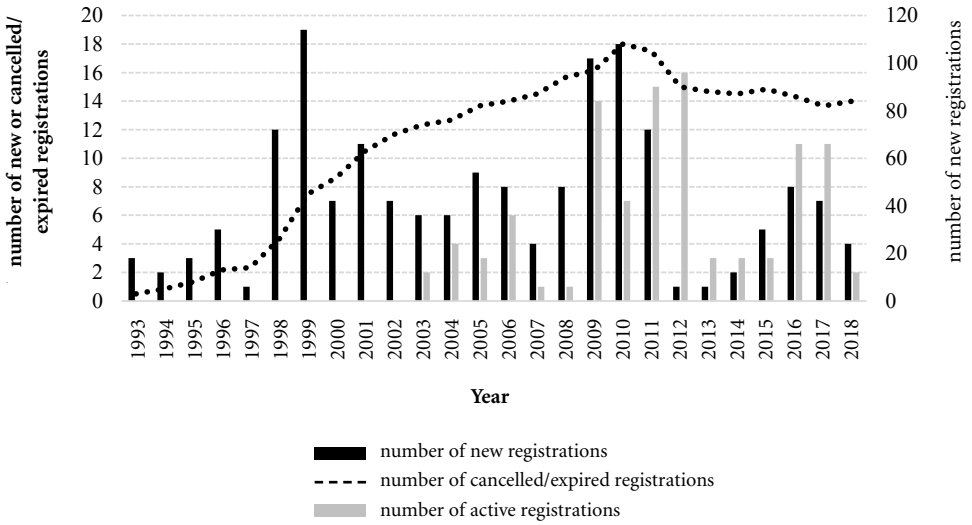


Figure 1. Number of sanitary registrations, active (current) and cancelled/expired, and new sanitary registrations, annually, at ANVISA, consulted on December 31, 2018.

Sources: Created by authors using data from ANVISA.

National vaccination program and vaccination schedule

The National Vaccination Program (PNI in Portuguese) describes the vaccines which make up the vaccination schedule. Until 2013, the new ordinances revoked the previous ones, creating new schedules. With the Ministerial Ordinance no. 1,498/2013[18], the vaccination schedule was established, with updates, should they occur, by means of yearly notices/technical notes, which publish the expansion of population to be covered by a vaccine or the availability of new vaccines as a complement of the vaccination schedule, depending on the country's needs, for example, the rabies vaccine or the COVID-19 vaccine. In those cases, situations of emergency or states of exception determine which vaccines should be made available, or the changes in targeted population.

Updating the vaccination schedule by notices and technical notes is the responsibility of the general coordination of the PNI. Expansion of age groups or inclusion of new vaccines are the most common alterations, as occurred in the inclusion of the HPV, the hepatitis A, the tetra viral, and the COVID-19 vaccines (according to data shown in Figure 2).

One aspect related to Figure 2 concerns the target population, which describes the dimension of the coverage offered to age groups or categories, but it does not specify exactly what age it refers to. For instance, the HPV vaccine was offered in 2014 only to girls aged 11 to 13 years, whilein the following year, the coverage was expanded to children aged 9 to 13 years. In 2017, this was changed to girls aged 9 to 14 years and boys and girls aged 9 to 26 years living with HIV/AIDS, or whohad an organ transplant or bone marrow transplant, as well as cancer patients.For the indigenous population, that vaccine has been provided since 2014 to individuals aged 9 to 13 years. A wider coverage was observed for some vaccines, such as that for yellow fever and others aimed at specific populations (as in the case of the varicella vaccine and the dTpa). The vaccines present in vaccination campaigns take into consideration the necessity at the time, in order to define the population to be covered. Therefore, over time, the expansion of access considers the epidemiological profile and the sanitary risk as principles for the incorporation of new vaccines into the PNI.

Ciência & Saúde Coletiva, 26(11):5509-5522, 2021

Table 1. Number of vaccine registrations at ANVISA up to Dec. 31, 2018; and status of the registrations by December 31, 2018, according to the companies which own the registration.

Companies owning sanitary registrations	Total number of registrations in the period	Number of active registrations in December 2018
Private Companies		
Abbott Laboratórios do Brasil LTDA	2	2
Abbott Produtos para Saúde LTDA	1	0
Astrazeneca do Brasil LTDA	1	0
Baxter Hospitalar LTDA	3	0
Biotest Farmacêutica LTDA	1	0
Blau Farmacêutica S.A.	3	0
Brasvit Indústria e Comércio LTDA	2	0
Cristália Produtos Químicos Farmacêuticos LTDA	4	0
Cubanacan Comércio Internacional LTDA	2	0
GlaxoSmithKline Brasil LTDA	31	19
Laboratórios Pfizer LTDA	2	2
Medstar Importação e Exportação Eireli	2	2
Merck Sharp & Dohme Farmacêutica LTDA	11	10
Novartis Biociências S.A	12	1
Novo Nordisk Produção Farmacêutica do Brasil LTDA	1	0
Nutoth - Pharma Indústria e Comércio LTDA	2	0
Prophylaxis Clínica de Vacinação LTDA	2	0
Sanofi Pasteur LTDA	30	0
Sanofi-Aventis Farmacêutica LTDA	34	21
UCB Biopharma LTDA	1	1
Wyeth Indústria Farmacêutica LTDA	3	0
State-owned companies		
Fundação Ataulpho de Paiva	2	2
Fundação Ezequiel Dias - Funed	1	1
Fundação Oswaldo Cruz	15	11
Instituto Butantan	18	12
Totais	186	83

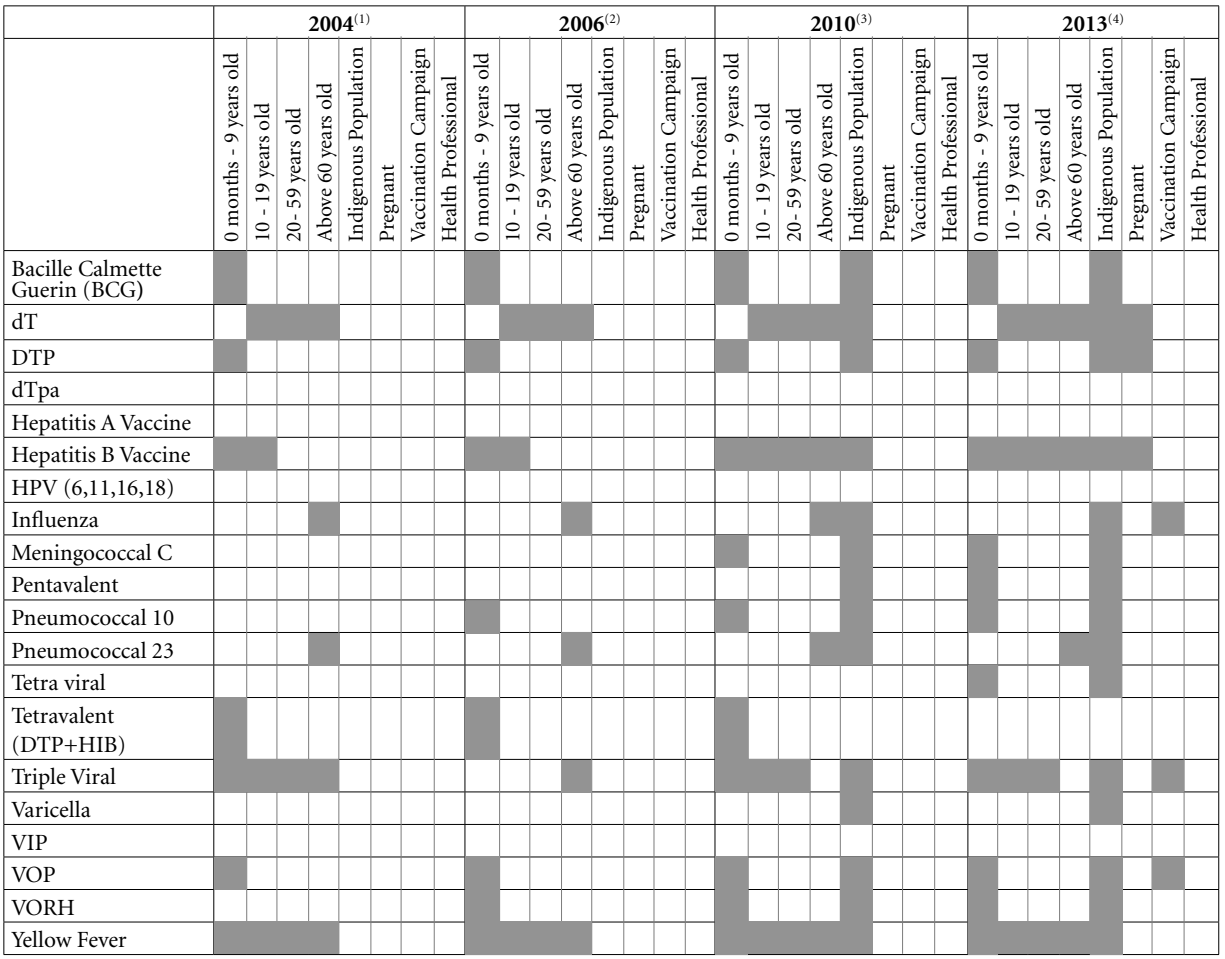
Source: Table created by authors from data provided by ANVISA.

Marketing authorization of vaccines and PNI, 2004 -2018

Table 2 shows the approvals of vaccines, and whether or not they are incorporated into the PNI from 2004 on, and the date of incorporation. It also shows the number of active registrations, cancelled/expired registrations, and the companies which hold these registrations, including the registrations active in December 2018; as well as the year of the first registration by state-owned laboratories and by private companies, for each vaccine.

The data in Table 2 indicate 181 registrations of 45 different vaccines in the period of 2004 to 2018. Considering the total number of ANVISA registrations (n=186), there were 5 separate registrations of measles vaccines, made available from 1977 on. However, on the vaccination schedule, immunization against measles has been incorporated in the triple vaccine since 2004.

Considering the vaccines incorporated inthe PNI since 2004, 142 registrations were identified, for 25 different vaccines, until 2018. Except for the BCG and the yellow fever vaccines, the first marketing authorizations was got by a private company, and afterwards, a state-owned company. Among the registrations of the PNI vaccines,107 (75.4%) are held byprivate companies and 35 (24.6%) by state-owned companies. In December 2018, 67 registrations (47.2%) were active, of which 41 (61.2%) were held by private



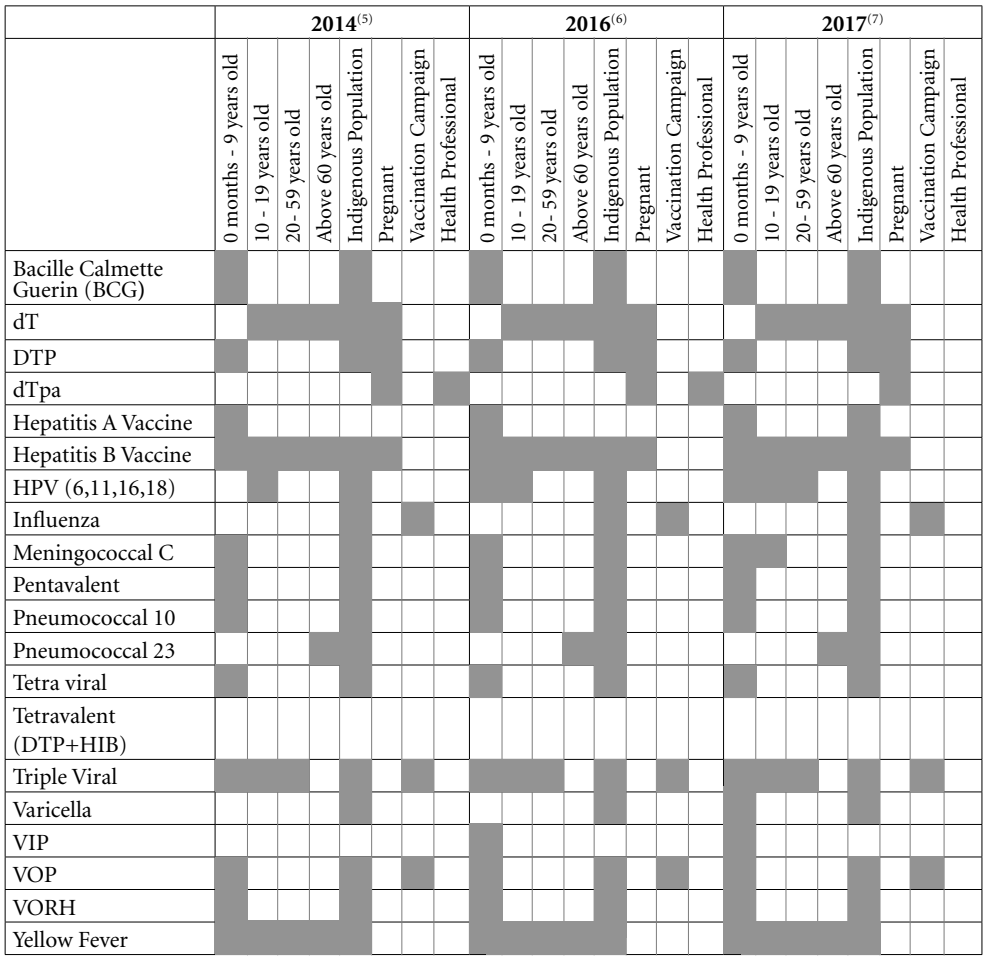
it continues

Figure 2. Vaccines available by category/age group and legally defined for the vaccination schedules from the National Immunization Program (PNI in Portuguese), in the 2004 to 2018 period in Brazil.

companies and 38.8% (n=26) by state-owned companies. Considering cancelled registrations of PNI vaccines, 61.7% (n=66) were held by private companies and 25.7% (n=9) by state-owned companies (Table 1).

In terms of vaccines not incorporated in the PNI (20 different vaccines), 39 marketing authorizations were identifiedduringthe period of 2004 to 2018, all of which werefrom private companies. Out of those, 17 (43.6%) were active in December 2018, corresponding to 11 vaccines which partially vary in terms of association. The registration cancellations of non-incorporated vaccines represent 56.4% (n=22), often because of incorporation of the isolated vaccines into an association, or because of the expansion of the strains of infectious agents.

Among the 25 vaccines present in the PNI in the analyzed period, there were two which do not have active registration in the country (pentavalent and double viral). The pneumococcal 23, varicella, and typhoid fever vaccines have registrations only by private companies, while the dT vaccine (double adult against diphtheria and tetanus) had only a registration by a state-owned company. The majority of the vaccines had active registrations hold by state-owned companies as well as by private companies (Table 2).



Key:
Vaccines incorporated into the National Immunization Program (PNI)
DTP= triple bacterial (against Diphtheria, Tetanus, Pertussis; HIB= Haemophilus Influenzae B; HPV= Human Papillomavirus; VIP (in Portuguese) = Inactive Polio vaccine;
dT= double adult (diphtheria and tetanus);
dTap= diphtheria, tetanus and acellular pertussis;
VOP (in Portuguese)= oral human rotavirus vaccine;
Triple viral= measles, mumps, and rubella;
Tetraviral= mumps, measles, rubella and attenuated varicella;
VORH (in Portuguese)= oral poliomelitis vaccine (adult)

(1) Ordinance 597 - Creation of basic vaccination schedules for children, adolescents, adults and the elderly. (2) Ordinance 1,602 - Updating of the basic vaccination schedules for children, adolescents, adults and the elderly. (3) Ordinance 1,946 - Institution, in the entire territory of Brazil, of the vaccination schedule for indigenous peoples and Ordinance 3,318 - updating the vaccination schedules for children, adolescents, adults, and the elderly. (4) Ordinance 1,498 - Updating and redefinition of the national vaccination schedule, the vaccination schedule for indigenous peoples and of the national vaccination campaigns, and Technical Announcement of the introduction of the tetra viral vaccine (mumps, measles, rubella, and attenuated varicella). (5) Technical Announcement of the introduction of the HPV vaccine, technical announcement of the introduction of the hepatitis A vaccine, and technical announcement of implementation of the dTap vaccine (Diphtheria, Tetanus and acellular Pertussis). (6) Information note 149 - Changes in the national vaccination schedule for 2016. (7) Information note 384 - Changes in the national vaccination schedule for 2017; Information note 154: expansion of the age groups covered by the human papillomavirus vaccine; Technical information on expansion of the offer of human papillomavirus vaccines 6, 11, 16, and 18 (recombinant) – HPV tetravalent vaccine and meningococcal C (conjugate)

* Even after the publication of Information note 135-SEi2017/CGPNI/DEVIT/SVS/MS, referring to the 2018 schedule, according to availability for the age groups shown in Figure 2, the presentation was the same as in 2017, therefore, it was not shown here.

Figure 2. Vaccines available by category/age group and legally defined for the vaccination schedules from the National Immunization Program (PNI in Portuguese), in the 2004 to 2018 period in Brazil.

Source: Created by authors based on official/normative publications by the Ministry of Health about the official vaccination schedule in the period of 2004 - 2018.

Regarding the companies which produce vaccines, with the exception of Pfizer, the other seven companies thathad active registrations in December 2018 produced vaccines which are included in the PNI. Abbott, Medstar, Novartis and UBC had only active registrations for the Influenza vaccine. Sanofi-Aventis, GlaxoSmithKline, and Merck Sharp & Dohme had active registrations

of vaccines which, individually, are included in the PNI, as well as registrations of associations which are commercialized privately.

Table 2. Display of the number of registration processes (active or cancelled/expired) of vaccines registered at the ANVISA by December 31, 2018, considering vaccines which were incorporated into the PNI and those that were not, from 2004 on. The independent variables are: company which hold the registration, kind of company (private or state-owned), and year of vaccine's incorporation into the vaccination schedule, from 2004 to 2018.

	First registration by private company	First registration by state-owned company	Year of incorporation into the PNI	Total number of registration processes cancelled/ expired (state owned company)	Total number of active registrations (state-owned company)	Companies which own the sanitary registration (number of active registrations in December 2018)
Bacillus Calmette Guerin (BCG)	-	1998	2004*	1 (1)	2 (2)	J(2); N(0)
Cholera	2004	-	NI	2 (0)	0 (0)	V(0); X(0)
DT	1996	2003	2004	2 (0)	2 (2)	N(2); R(0); V(0)
DTP	1995	2003	2004*	1 (0)	3 (1)	M(1); N(1); V(0); X(1)
DTP + Hepatitis B	2000	-	NI	1 (0)	0 (0)	M(0)
DTP + VIP	1994	-	NI	3 (0)	3 (0)	M(1); V(0); X(2)
DTP + VIP + HIB	1999	-	NI	3 (0)	2 (0)	M(1); V(0); X(1)
DTP + VIP + HIB + Hepatitis B	2001	-	NI	0 (0)	3 (0)	M(2); X(1)
DTP + VIP + HIB + Tetanus		-	NI	2 (0)	0 (0)	V(0)
DTpa	1998	2016	2014	1 (0)	3 (1)	M(1); N(1); V(0); X(1)
Double viral ***	2000	-	-	3 (0)	0 (0)	M(0); V(0); X(0)
Yellow fever	2006	1999	2004	1 (0)	2 (1)	L(1); V(0); X(1)
Yellow fever + dengue	2015	-	NI	0 (0)	1 (0)	X(1)
Hepatitis A	1996	2016	2014	3 (0)	4 (1)	H(0); M(1); N(1); Q(1); V(0); X(1)
Hepatitis A and B	1998	-	NI	0 (0)	1 (0)	M(1)
Hepatitis B	1993	1999	2004	2 (0)	5 (2)	I(0); M(1); N(2); Q(1); V(0); X(1)
HIB + Tetanus	1998	-	NI	1 (0)	1 (0)	M(0); X(1)
HPV (16,18)	2008	-	NI	0 (0)	1 (0)	M(1)
HPV (6,11,16,18)	2006	2015	2014	0 (0)	2 (1)	N(1); Q(1)
HPV (6,18,16,11,58,52,45,33,31)	2017	-	NI	0 (0)	1 (0)	Q(1)
Influenza	1997	2000	2004	26 (4)	13 (2)	A(2); B(0); C(0); D(0); F(0); H(0); L(1); M(1); N(1); P(2); Q(0); R(1); T(0); U(0); V(0); X(4); Y(1)
Leishmaniasis	2001	-	NI	1 (0)	0 (0)	S(0)
Meningitis C + HIB	2007	-	NI	1 (0)	0 (0)	M(0)

it continues

Table 2. Display of the number of registration processes (active or cancelled/expired) of vaccines registered at the ANVISA by December 31, 2018, considering vaccines which were incorporated into the PNI and those that were not, from 2004 on. The independent variables are: company which hold the registration, kind of company (private or state-owned), and year of vaccine's incorporation into the vaccination schedule, from 2004 to 2018.

	First registration by private company	First registration by state-owned company	Year of incorporation into the PNI	Total number of registration processes cancelled/ expired (state owned company)	Total number of active registrations (state-owned company)	Companies which own the sanitary registration (number of active registrations in December 2018)
Meningococcal,C,Y,W-135	2014	-	NI	1 (0)	2 (0)	M(1); O(1)
Meningococcal AC ***	1995	2005	-	3 (0)	2 (1)	L(1); R(0); V(0); X(1)
Meningococcal BC	1993	-	NI	1 (0)	0 (0)	I(0)
Meningococcal B	2015	-	NI	1 (0)	1 (0)	M(1); R(0)
Meningococcal C	2001	2009	2010	3 (0)	2 (1)	F(0); K(1); M(1); R(0); Z(0)
Meningococcal C + Tetanus	2002	-	NI	1 (0)	0 (0)	D(0)
Pentavalent	2007	-	2010	1 (0)	0 (0)	M(0)
Pneumococcal 10	2009	2012	2010	0 (0)	2 (1)	L(1); M(1)
Pneumococcal 13	2010	-	NI	1 (0)	1 (0)	O(1); Z(0)
Pneumococcal 23	1995	-	2004	2 (0)	1 (0)	Q(1); V(0); X(0)
Pneumococcal 7	2001	-	NI	1 (0)	0 (0)	Z(0)
Rabies**	1998	2004	-	5 (2)	3 (2)	N(2); R(0); T(0); V(0); X(1)
Rubella	1994	-	NI	2 (0)	0 (0)	G(0); V(0)
Tetanus**	1996	2003	-	1 (0)	2 (1)	N(1); V(0); X(1)
Tetraviral	2008	2015	2013	0 (0)	3 (1)	L(1);M(1); Q(1);
Tetravalent (DTP + HIB)	1996	2002	2004	2 (1)	2 (1)	L(1); V(0); X(1)
Typhoid ***	2006	-	-	1 (0)	1 (0)	V(0); X(1)
Triple Viral	1996	2004	2004	4 (0)	3 (1)	L(1); M(1); Q(1); R(0); U(0); V(0); X(0)
Varicella	1998	-	2010	4 (0)	3 (0)	E(0);G(0); M(1); Q(2); V(0); X(0)
VIP	1998	1999	2013	4 (1)	2 (1)	F(0); L(1); M(0); V(0); X(1)
VOP	1998	2007	2004*	5 (0)	2 (2)	L(2); M(0); R(0); V(0); X(0)
VORH	2005	2010	2006	0 (0)	3 (1)	L(1); M(1); Q(1)
Total				97 (9)	84 (26)	

Source: Created by the authors using data collected from ANVISA.

Haemophilus Influenzae B; HPV= Human Papillomavirus; VIP (in Portuguese)= Inactive Polio Vaccine; dT= double adult (Diphtheria and Tetanus); dTap= Diphtheria, Tetanus, and acellular pertussis; VOR (in Portuguese)= Oral Human Rotavirus vaccine; triple viral= measles, mumps, and rubella; Tetraviral= mumps, measles, rubella, and attenuated varicella; VORH= oral poliomyelitis vaccine (adult); A= Abbott Laboratórios do Brasil LTDA; B= Abbott Produtos para Saúde LTDA; C= Astrazeneca do Brasil LTDA; D= Baxter Hospitalar LTDA; E= Biotest Farmacêutica LTDA; F= Blau Farmacêutica S.A.; G= Brasvit Indústria e Comércio LTDA; H= Cristália Produtos Químicos Farmacêuticos LTDA; I= Cubanacan Comércio Internacional LTDA; J= Fundação Ataulpho de Paiva; K= Fundação Ezequiel Dias; L= Fundação Oswaldo Cruz; M= GlaxoSmithKline Brasil LTDA; N= Instituto Butantan; O= Laboratórios Pfizer LTDA; P= Medstar Importação e Exportação Eireli; Q= Merck Sharp & Dohme Farmacêutica LTDA; R= Novartis Biociências S.A; S= Novo Nordisk Produção Farmacêutica do Brasil LTDA; T= Nutoth - Pharma Indústria e Comércio LTDA; U= Prophylaxis Clinica de Vacinação LTDA; V= Sanofi Pasteur LTDA; X= Sanofi-Aventis Farmacêutica LTDA; Y= UCB Biopharma LTDA; Z= Wyeth Indústria Farmacêutica LTDA.

Note: *Vaccines present in the vaccination schedule in 2004, which were, however, present since the first basic vaccination schedule (1977); ** vaccines incorporated into the PNI but made available in case of need; *** vaccines produced exceptionally, in case of outbreaks or for exporting, which are present in the PNI.

Discussion

Although Brazil has adopted vaccination programs since 1925, and the country has had a vaccination schedule since 1977, the first approvals of this kind of product, found in ANVISA's data bank, are from 1993. The creation of the data bank with the registration of products occurredwhen Ordinance no. 801, from October 7th, 1998[17] was published. Therefore, any information about registrations prior to 1998, which have not been renewed due to alack of interest by the holder company or cancellation of the registration, has not been kept and is not included in that data bank.

Historically, in order to understand the success of the vaccine sector in Brazil, it is worth to consider the first developments, which occurred in the 19th century, when several state-owned institutions began the development of this sector, such as: Instituto de Tecnologia em Imunobiológicos / Bio-Manguinhos which produced the yellow fever vaccine using the 17DDstrain; Instituto Butantan, which consolidated the production of the triple bacterial vaccine (DTP); the Fundação Ataulpho de Paiva, which began to produce vaccines against tuberculosis; and Instituto do Paraná (Tecpar), which developed the production of the rabies vaccine[5,8,19].

Looking at the registrations in the ANVISA data bank, a significant increase in registration of new products in 1998 and 1999 was observed, especially by private companies, probably because of the institutionalization of ANVISA, making a sanitary reorganization in the countrypossible. Between 2000 and 2008, the scenario of new registrations and cancellations of registrations was quite dynamic, with a growth curve in the number of active registration processes. In that period, an important biotechnological development was observed, bringing in new perspectives of vaccine production and boosting the interest of large companies in this area, also due to the expansion of the PNI[8].

In 2009 and 2010, there was a significant increase in the number of approvals, related to the Influenza pandemic which hit Brazil in May 2009. Among the measures to control that situation, a partnership was formed between Instituto Butantan and Sanofi Pasteur to enable the technology transfer. This strategy allows the transferring company to expand its market and its production. Concerning the national legislation, this strategy involved a differentiated regulatory path, for products with a priority for registration, in addition to a temporary exclusivity in the public health system, by means of the medicines purchases. In turn, the institutions which receive the technology are able to develop products faster and guarantee their access to technology, with better chances of financial sustainability[20].

The 2009 partnership for the production of the Influenza vaccine made it possible to provide vaccines for the Brazilian population and allowed Instituto Butantan to prepare itself to increase its production capability[1]. In 2018, Instituto Butantan expanded its facilities and in 2020 it became the main producer of Influenza vaccine in the Southern hemisphere, exporting to Asian countries[22,23].

Data shows that the PNI can be considered the booster of national production, by means of technology transfer, which expands the possibilities of development and production of vaccines in Brazil. This process also took place for other vaccines from the vaccination schedule, as in the case of the contract between GlaxoSmithKline and Bio-Manguinhos / Fundação Oswaldo Cruz, for the technology transfer for the triple viral, tetravalent, pneumococcal 10, and rotavirus vaccines[20]. It is worth to note that there is also a partnership for technology transfer between Sanofi Pasteur and Bio-Manguinhos / Fundação Oswaldo Cruz for the inactivated polio vaccine[20].

In 2011, 2012, and 2017 there was a considerable number of cancellations due to change of holder, possibly related to Resolution 55/2010[24], which deals with registration of biological products, and Resolutions 22/2010[25] and 102/2016[26], which made it easier to change holding. In 2010, besides the new regulations concerning commercializing biological products, defined in RDC 55/2010[24], there was also a simplification in the transfer process, minimizing bureaucracy[25], and in 2016, the transfer of holding was expanded beyond corporate operations, alsoreaching commercial operations, allowing cases which involved only the purchase and sale of assets[26].

The expressive number of registration cancellations in 2016 referred to the influenza vaccines, demonstrating the market's turnover. In 2009 and 2010, with the influenza pandemic, several companies registered their products in the market; however,over time, the self-sufficiency of Instituto Butantan, providing the product for the PNI, reduced the market for private companies, and many did not renew their registration. Sanitary, regulatory, and economic contexts facilitate the inclusion of products in the market (pandemics, epidemics, expansion of/incorpo-

Ciência & Saúde Coletiva, 26(11):5509-5522, 2021

ration to the PNI) and in other cases facilitate withdrawing products from the market (self-sufficiency of state-owned institutions, end of a pandemic or epidemic).

Concerning the production of vaccines by private companies, the increase in number of vaccine registrations by ANVISA from 1993 on does not mean a dissemination of manufacturers, considering that four companies hold 63.0% of the marketing autorizations. In Brazil, as well as in the international market[27], there is a situation of oligopoly, with a predominance of few companies in the market, with the occurrence of mergers or company transfers for the development of technologies, especially concerning biotechnological products[20,28-30]. That is coherent with the expressive number of registrationcancellations verified in this study.

Among the vaccines included in the vaccination schedule, from 2004 on, as an attempt to guarantee access to new technologies, all had an active marketing authorization before becoming available for the health system. The marketing authorization in the country prior to incorporation to the schedule, increases the possibility of access, by guaranteeing safety, efficiency and quality of the product, and favors price negotiation and formalization of commercial contracts.

However, even with the strategy of maintaining vaccines with an active registration, after the cancellation of the pentavalent vaccine, we had a situation of shortage in the country and had to rely on importation[31]. In 2017, the process of incorporation of technology by Instituto Butantan was initiated; nevertheless, it has yet to be finalized[32]. Another kind of vaccine provided by the PNI in cases of outbreaks, but with no active registration at ANVISA, is the double viral vaccine, which is going through the process of technology transfer at Bio-Manguinhos. However, there is no additional information on that case[33,34].

The number of cancellations of registrations by private companies is higher than that by state-owned companies, since state-owned companies aim toproduce the vaccines thatare essential for the country, taking into consideration the PNI. Therefore, state-owned companies maintain the registrations active, guaranteeing access to the technology whenever necessary, making the fight against immune preventable diseases feasible. The private sector does incremental innovation, registers patents, and introduces products intothe market, and isthus a complementary supplier for PNI, which is the main buyer of vaccines in the country. The government sector, notably by means of technology transfer, acquires representativeness, or even self-sufficiency in terms of providing vaccines to the PNI, and that often results in the cancellation of some sanitary registrations of products belonging to the private sector, which in turn resorts to introducing "new technologies" to regain space in the market.

In the case of the vaccines provided by the private sector thathave not been incorporated inthe PNI, until 2018 (Table 2), the analisys showed that 50% of them are products which provide immunization comparable to those available in the public sector, but offered in associations. The association of vaccines is more practical for the patients; however, it may bring an additional risk in terms of safety, with the possibility of allergic reactions. Moreover, associations, in most cases, may have an additional cost, since they require technological development, and consequently, investments inresearch. On the other hand, the vaccines available in the private sector and incorporated inthe PNI may be defined as complementary, allowing for the expansion of the coverage, which may be restricted to some groups, as shown in Figure 2. For example, the influenza vaccine in the vaccination schedule is directed towardsgroups with higher risks, while in private health care providers it is accessible to everyone. On the other hand, the production of PNI vaccines by the private sector may complement the demands in case of large scale immunization campaigns.

In general terms, the data in this study allowedus to verify that the marketing authorization in Brazil is very dynamic, with the presence of both private and state-owned companies, and the registrations are concentrated in the hands of only a few companies. Data presented by the Brazilian Pharmo chemicals Manufacturers Association(ABIQUIFI, in Portuguese) indicates that Brazil produces only 5% of the active pharmaceutical ingredients that the country needs[35]; therefore, the national production of vaccines is essentially a transformation industry.

The need to stimulate the economic and industrial development in the sector is corroborated by the findings of Gadelha and collaborators[20], who also showed that the national production of vaccines is done by state-owned laboratories, often through the process of technology transfer. Although the strategy of bringing in technologies is important for the national sector, it is necessary to adopt public policies aimed at the development of the economic, industrial health complex in order to overcome the asymmetry in

relation to the global context by stimulating research, development, and innovation in the field of vaccines. This need has become even more evident with the pandemic that has been ongoing since 2020.

Since that year, the country has been facing a situation similar to that caused by the influenza outbreak in 2009. To face the COVID-19 pandemic, promising partnerships were established in unparalleled time between *Oxford University/ AstraZeneca* and Fiocruz and between *Sinovac Life Science* and Instituto Butantan, made possible by the experience accumulated from previous vaccines[36], enablingthe production of the new vaccines for the Brazilian population. All the raw materials and vaccines come from China or India; therefore, the country depends on diplomatic relations thatare unstable at the moment. Unfortunately, denial and poor decision making by the Brazilian government whenfaced with the COVID-19 pandemic have compromised the Brazilian reputation and expertise in terms of mass vaccination programs.

Finally, it is wort to mention that, since this is an exploratory study, such details as the type of technologies to be made available for the PNI (attenuated virus, inactive, or sub-units) as well as population coverage (specific age for the useof each technology and vaccination procedure) are some of the gaps in this study and shouldbe complemented in further studies.

Conclusions

ANVISA certifies the efficiency, safety, and quality of the products in the market through the sanitary regulation of commerce. However, this study has demonstrated that there is missing information in the data bank which compiles information on vaccine registrations (at the time that we collected information - December 31st, 2018), both in terms of temporal limitations (the data available is only from 1993 on) and in terms of the lack of information about companies involved in transfers of ownership. Considering that the database has had information on biological medicines since the 1970's, it seems viable and essential that improvements bemade in the information system in order to make data on the registration of all products - including vaccines - more available, thereby building a historical identity for this sector.

Brazil has an important immunization policy, having developed suchstrategies as the PNI and vaccination schedules, and having the ability to produce vaccines thatare essential to the population, and the country is searchingfor the sustainability of the sector. All this has made the country become a reference in the control of immune preventable diseases, until the most recentpandemic.

However, even with the success of the immunization program overthe years, national production is still focused on technology transfer or the import of active ingredients. There is a need for more investments and government attention in order to develop new technologies and achieve independence in this field. The vaccines market, especially in terms of technological development, of the process of incorporation, as well as in terms of accessibility to the population, is a crucial field of research for the strengthening of the country's policies for the sector. Recent news on research and development of the COVID-19 vaccine and the discussion concerning its incorporation, although not an object of this study, seems to lead to the same conclusion. The data identified in this study, especially regarding the predominance of registrations by private companies, indicates the need for investments so that the national strategy of immunization, through the establishment of partnerships or transfer contracts, may be complemented by research initiatives, development, and innovation in the field of vaccines, otherwise the country will not become independent in this sector.

The results show that Brazil has the industrial potential for the production of vaccines, and this potential could be mobilized through well-coordinated public policies, making it possible for the country to fulfill its needs and contribute at the global level. In this context, the state-owned production structure stands out, especially the Instituto de Tecnologia em Imunobiológicos (Bio-Manguinhos / Fiocruz) and Instituto Butantan.

Collaborations

KC Peres, NR Bonetti, L Soares, CM Vargas-Peláez and MR Farias participated in the conception, planning, discussion, and final revision of the article. EA Prates, FB Buendgens, and KC Peres contributed in the analysis of the results, discussion and revision of the manuscript.

Funding

This article was financed by a Ph.D. grant from the Brazilian funding agency, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES - Brasil).

References

1. Brasil. Decreto nº 78.231, de 12 de agosto de 1976. Regulamenta a Lei nº 6.259, de 30 de outubro de 1975, que dispõe sobre a organização das ações de Vigilância Epidemiológica, sobre o Programa Nacional de Imunizações, estabelece normas relativas à notificação compulsória de doenças, e dá outras providências. *Diário Oficial da União* 1976; 12 ago.
2. Manguinhos vol III. A Produção e o Desenvolvimento de Vacinas no Brasil. *Debate*. Março-junho, 1996 [acessado 2021 abr 20]. Disponível em: https://www.scielo.br/pdf/hcsm/v3n1/v3n1a08.pdf.
3. Gadelha C, Azevedo N. Inovação em vacinas no Brasil: experiência recente e constrangimentos estruturais. *Hist Cienc Saude Manguinhos* 2003; 10(2):697-724.
4. Benchimol JL, coordenador. O Programa Nacional de Imunizações. *In: Febre amarela:* a doença e a vacina, uma história inacabada [online]. Editora Fiocruz 2001; p.320-322. [acessado 2021 mar 15]. Disponível em: https://static.scielo.org/scielobooks/4nktq/pdf/benchimol-9788575413951.pdf.
5. Brasil. Ministério da Saúde (MS). *Sistema de Informação do Programa Nacional de Imunizações* – Apresentação [online] [acessado 2020 dez 29]. Disponível em: http://pni.datasus.gov.br/apresentacao.asp.
6. Brasil. Ministério da Saúde (MS). *Programa Nacional de Imunizações – 30 anos*. [online] [acessado 2020 dez 29]. Disponível em: https://bvsms.saude.gov.br/bvs/publicacoes/livro_30_anos_pni.pdf.
7. Brasil. Ministério da Saúde. *Brasil é referência mundial em produção de vacinas.* [online] [acessado 2020 dez 29]. Disponível em: http://www.blog.saude.gov.br/index.php/52930-brasil-e-referencia-mundial-em-producao-de-vacinas.
8. Gava CM, Bermudez JAZ, Pepe VLE, Reis ALAD. Novos medicamentos registrados no Brasil: podem ser considerados como avanço terapêutico? *Cien Saude Colet* 2010; 15(3):3403-3412.
9. Aith FMA, Cunha ACNMF, Castellaro FAB, Soares DFL, Dallari SG. Regulação de medicamentos no Brasil: desafios no contexto do mundo globalizado. In: Regulação de medicamentos no mundo globalizado. São Paulo, *Centro de Estudos e Pesquisas de Direito Sanitário* 2014:31-46.
10. Aith FMA, Dallari SG. São Paulo; *Centro de Estudos e Pesquisas de Direito Sanitário* 2014: 636 p.
11. Costa EA, Fernandes TM, Pimenta TS. A vigilância sanitária nas políticas de saúde no Brasil e a construção da identidade de seus trabalhadores (1976-1999). *Cien Saude Colet* 2008; 13(3):995-1004.
12. Brasil. Lei n. 9.782, de 26 de janeiro de 1999. Define o Sistema Nacional de Vigilância Sanitária, cria a Agência Nacional de Vigilância Sanitária, e dá outras providências. *Diário Oficial da União* 1999; 26 jan.
13. Silva JAA, Costa EA, Lucchese, G. SUS 30 anos: Vigilância Sanitária. *Cien Saude Colet* 2018; 23(6):1953-1962.
14. Brasil. Agência Nacional de Vigilância Sanitária. *Consulta Anvisa – Medicamentos e hemoderivados* [online] [acessado 2020 dez 29]. Disponível em: https://consultas.anvisa.gov.br/#/medicamentos/.
15. Brasil. Agência Nacional de Vigilância Sanitária. Consulta Anvisa. *Situação de documentos – tipo de documento técnico* [online] [acessado 2020 dez 29]. Disponível em: https://consultas.anvisa.gov.br/#/documentos.
16. Brasil. Conselho Nacional da Saúde. Resolução n. 510, de 07 de abril de 2016. *Dispõe sobre as normas aplicáveis a pesquisas em Ciências Humanas e Sociais cujos procedimentos metodológicos envolvam a utilização de dados diretamente obtidos como participantes ou de informações identificáveis ou que possam acarretar riscos maiores do que os existentes na vida cotidiana, na forma definida nesta Resolução*. Publicado em: 2016, maio 24, 2016, 98(1), p. 44.
17. SAID DMP. *Registro Sanitário de medicamentos: uma experiência de revisão* [dissertação]. Rio de Janeiro: Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz; 2004.
18. Brasil. Portaria nº 1.498, de 19 de julho de 2013 Brasil. *Redefine o Calendário Nacional de Vacinação, o Calendário Nacional de Vacinação dos Povos Indígenas e as Campanhas Nacionais de Vacinação, no âmbito do Programa Nacional de Imunizações (PNI), em todo o território nacional*. [acessado 2021 mar 14]. Disponível em: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2013/prt1498_19_07_2013.html.

19. Chaves CG, Moraes EL, Osorio-de-Castro CGS. Estratégias de produção e aquisição de produtos farmacêuticos em contexto de dependência. *Cad Saude Publica* 2021; 37(3):e00036821.
20. Gadelha CAG, Braga PSC, Montenegro KBM, Cesário BB. Acesso a vacinas no Brasil no contexto da dinâmica global do Complexo Econômico-Industrial da Saúde. *Cad Saude Publica* 2020; 36(2):e00154519.
21. São Paulo. Secretaria de Estado da Saúde de São Paulo. *Instituto Butantan - A serviço da vida.* São Paulo: SES; 2019. [acessado 2021 mar 01]. Disponível em: https://butantan.gov.br/noticias/butantan-comemora-20-anos-de-parceria-com-farmaceutica-francesa-para-combate-a-gripe-no-brasil.
22. São Paulo. Secretaria de Estado da Saúde de São Paulo. *Instituto Butantan - A serviço da vida.* São Paulo: SES; 2020. [acessado 2021 mar 01]. Disponível em: https://butantan.gov.br/noticias/em-feito-historico-butantan-vai-exportar-550-mil-doses-da-vacina-contra-a-gripe-.
23. Agência Brasil. *Butantan vai exportar vacinas contra a gripe para países asiáticos.* São Paulo: SES; 2020. [acessado 2021 mar 01]. Disponível em: https://agenciabrasil.ebc.com.br/saude/noticia/2020-08/butantan-vai-exportar-vacinas-contra-gripe-para-paises-asiaticos.
24. Brasil. Agência Nacional de Vigilância Sanitária (Anvisa). Resolução - RDC nº 55, de 16 de dezembro de 2010. *Dispõe sobre o registro de produtos biológicos novos e produtos biológicos e dá outras providências*. [online] [acessado 2021 jun 28]. Disponível em: https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/res0055_16_12_2010.html.
25. Brasil. Agência Nacional de Vigilância Sanitária. Resolução - RDC nº 22, de 17 de junho de 2010. *Dispõe sobre a regulamentação da transferência de titularidade de registro de produtos sujeitos à vigilância sanitária em razão de operações societárias.* Brasília: Anvisa; 2010. [acessado 2021 abr 12]. Disponível em: http://www.sbpc.org.br/upload/noticias_setor/320100625154151.pdf.
26. Brasil. Ministério da Saúde (MS). Agência Nacional de Vigilância Sanitária (Anvisa). Resolução - RDC nº 102, de 24 de agosto de 2016. Dispõe sobre os procedimentos para a transferência de titularidade de registro de produtos sujeitos à vigilância sanitária, transferência global de responsabilidade sobre ensaio clínico e atualização de dados cadastrais relativos ao funcionamento e certificação de empresas, em decorrência de operações societárias ou operações comerciais. *Diário Oficial da União*, 2016; ago 25.
27. Evaluate Pharma. *World Preview 2018, outlook to 2024*. [online] [acessado em 2020 dez 29]. Disponível em: http://info.evaluategroup.com/rs/607-YGS-364/images/WP2018.pdf.
28. Homma A, Martins RM, Leal MLF, Freire MS, Couto AR. Atualização em vacinas, imunizações e inovação tecnológica. *Cien Saude Colet* 2011; 16(2):445-458.
29. Gadelha CAG, Nascimento MAC, Braga PSC, Cesário BB. Transformações e assimetrias tecnológicas globais: estratégia de desenvolvimento e desafios estruturais para o Sistema Único de Saúde. *Cien Saude Colet* 2018; 23:2119-2132.
30. Bahia L, Scheffer M, Tavares LR, Braga IF. From health plan companies to international insurance companies: changes in the accumulation regime and repercussions on the healthcare system in Brazil. *Cad Saude Publica* 2016; 32 (2):e00154015.
31. Souza L. Em falta, vacina pentavalente começa a ser distribuída aos estados. *Veja Saúde* [acessado 2020 dez 29]. Disponível em: https://saude.abril.com.br/medicina/vacina-pentavalente-distribuida-aos-estados.
32. Brasil. Ministério da Saúde (MS). Vacina Pentavalente passa a ser produzida e adquirida no Brasil. *Blog da Saúde*. Brasília: MS; 2017. [acessado em 2020 dez 29]. Disponível em: http://www.blog.saude.gov.br/index.php/entenda-o-sus/52359-vacina-pentavalente-passa-a-ser-produzida-e-adquirida-no-brasil.
33. Labnetwork. 100% nacional: vacinas contra sarampo e rubéola do Brasil para o mundo. *BD*. [*online*][acessado em 2020 dez 29. Disponível em: https://www.labnetwork.com.br/noticias/100-nacional-vacinas-contra-sarampo-e-rubeola-do-brasil-para-o-mundo/. Publicado em 2013; oct 31.
34. Fundação Oswaldo Cruz (Fiocruz). *Brasil vai exportar vacina contra sarampo e rubéola a partir de 2017*. [online] [acessado em 2020 dez 29]. Disponível em: https://portal.fiocruz.br/noticia/brasil-vai-exportar-vacina-contra-sarampo=-e-rubeola-partir-de2017-#:~:text-Biomanguinhos%2FFiocruz,-O%20laborat%-C3%B3rio%20Biomanguinhos&text=O%20Brasil%20produz%20atualmente%2096,para%2075%20pa%C3%ADses% 20no%20mundo. Publicada 2013; oct 29.
35. Santos S. Em quatro décadas, Brasil reduz de 55% para 5% capacidade de produção de insumos farmacêuticos. *Folha de São Paulo* 2021; 20 fev. [online] [acessado em 27/04/2021]. Disponível em: https://www1.folha.uol.com.br/autores/sheyla-santos.shtml.
36. Instituto de Ciência, Tecnologia e Qualidade (ICTQ). *Por que a vacina contra covid-19 foi desenvolvida em tempo recorde.* [online] [acessado 2021 mar 01]. Disponível em: https://www.ictq.com.br/farmacia-clinica/2636-por-que-a-vacina-contra-covid-19-foi-desenvolvida-em-tempo-recorde.

Article presented 12/12/2020
Approved 07/07/2021
Final version presented 09/07/2021

Chief editors: Romeu Gomes, Antônio Augusto Moura da Silva