How vaccines has changed a country
THEME
How vaccines has changed a country

SUPERVISION
Antônio Britto | Executive president

GENERAL COORDINATION
Octávio Nunes | Director of Institutional Communication
Selma Hirai | Communication Coordinator
Bruno Folli | Press officer
Giselle Marques | Communication Analyst

WORDING AND EDITING
Fanny Zygband - Mtbg 13.464 | Duplo 2 Editorial

TECHNICAL REVIEW
Dirceu Barbano

GRAPHIC DESIGN AND DIAGRAMMING
Nebraska Composição Gráfica

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Presentation

More than two centuries have gone by since the first vaccination against smallpox in the country. Since then, we have accumulated victories in the control and eradication of several epidemics and immunopreventable diseases of great personal, social and economic impact. This is what happened with poliomyelitis, measles, diphtheria and neonatal tetanus, diseases that the new generations did not have to face.

If we were to count the number of lives spared in this period, we would surely reach surprising figures. There are plenty of examples for that. The relation between the increase in vaccination coverage and the reduction of infant mortality rates is direct, especially in the group of children under 1 year of age. Between 1997 and 2015, it fell from 31.9 per 1,000 live births to 13.8, according to the Brazilian Institute of Geography and Statistics (IBGE).

Vaccines, of course, were not the only cause of this decline, but played a key role in this outcome, according to the institute’s own analyzes. Few public healthcare actions have had such a large reach and made such a measurable contribution to improving the quality of life of the population, with such a favorable cost-benefit ratio. Its relevance also extrapolates the visible spectrum though.

Vaccines are both the result of and drivers of an extraordinary global scientific development, arising from centuries of research, studies and trials that have promoted - and continue to promote - innovation, advances in medicine and the technological level of the country.

In order for this reality to become possible, it has been necessary to create and maintain a solid network of interactions. It is made up of industries that, over 200 years, have mobilized resources and teams around the world in continuous research and development (R&D) activities; official laboratories with an extraordinary history of excellence, such as the Butantan Institute in São Paulo city and the Bio-Manguinhos Immunobiological Technology Institute in Rio Janeiro city; renowned and dedicated scientists; vaccination teams taking on the most adverse conditions to successfully carry out their mission, as well as managers committed to the continuity and improvement of Brazilian vaccination programs.

These partnerships, without which none of this would have been possible, now live a new and fundamental stage of this journey: the public-private agreements of technology transfer from the producing companies to the official laboratories. Initiatives such as these have enabled Brazil to produce much of its demand for immunobiologials, which currently revolve around 300 million annual doses of vaccines, according to the Ministry of Health.

As Brazil is a country with continental dimensions and deep geographical, economic and social contrasts, which is why vaccination coverage is not homogeneous, there is a long way to go, despite the achievements. We have been suffering with the return of Aedes Aegypti, which had been extinguished on two occasions, and with the transmission of devastating diseases such as dengue, zika, chikungunya and yellow fever.

In addition, we still have other issues to address, such as avoidable epidemics and problems stemming from the lack of sanitation and poverty. Also a great demographic challenge caused by population aging with chronic diseases more complex and expensive (cancer, diabetes, hypertension and Alzheimer) knocks at our door.
The results achieved by Brazil in immunization policies have a didactic character that cannot fade away without an instant of reflection, especially at this time of such difficulty for the health system.

The ultimate lesson is success itself, namely the proof that the country can organize and execute public healthcare projects that are consistent, planned and implemented with efficiency and competence. Vaccination in Brazil is ironically a powerful antidote to inferior complex.

This success, however, has some assumptions that are so necessary and unusual in our country regarding public healthcare. Among them, we could mention a public policy with a clear focus, objectives and methods, structured from the in-depth knowledge on the problem to be attacked, the goal to be achieved and the process that can lead to it; a rare example of cooperation between the Federal Union, States and City Councils, in which the responsibilities of each body seem clearer than in all other areas of public healthcare.

Another point is the absence of prejudice for common action between the public sector and the private sector, a covenant that, while beneficial, still faces obstacles in many areas of the healthcare system, as a result of outdated and anachronistic visions.

There is also the direct involvement of society, the protagonist of our vaccination campaigns - with a direct intervention by social organizations, the third sector and citizenship - and the target of the effort undertaken to increase access to vaccines throughout the year, either through its permanent availability in the Basic Health Units, or by the constant performance of the Primary health care program.

On the other hand, there are Brazilian contradictions: the liabilities we receive from past mistakes, such as the high prevalence of dengue and the gigantic challenge imposed by the new reality, from urbanization to the aging of the population, which require urgent action and the need for a new leap in our immunization efforts.

As a country, we will need to respond to these demands. And, it is with a view to these new needs, and to the old ones that have not yet been covered, that companies and laboratories in Brazil and in the world are dedicated to the research and development of vaccines that can prevent these diseases - as it has been for centuries in relation With the purpose of contributing to this debate and talk about the present and future challenges, that we have launched this publication in the certainty that the successful covenants and partnerships that have brought us here will also allow us to move forward towards achieving new victories.

Victor Mezei
President of the Directing Council

Antônio Britto
Executive President
Special thanks to supporting companies

- GSK
- MSD
- Pfizer
- SANOFI Pasteur
Special thanks

To all who devoted their time and knowledge to make this project possible.

Dr. Akira Homma
Scientific advisor of the Institute of Technology in Immunobiológicos Bio-Manguinhos/Fiocruz

Dra. Carla Domingues
Coordinator of the National Immunization Program (PNI) for the Ministry of Health

Dr. Gabriel Oselka
Professor at the Faculty of Pediatrics at USP and member of the Technical Advisory Committee on Immunization (CTAI) at the PNI

Dra. Carla Domingues
Scientific advisor of the Institute of Technology in Immunobiológicos Bio-Manguinhos/Fiocruz

Evelin Plácido dos Santos
Nurse Technical Supporter of Immunization for the Xingu Project at the São Paulo School of Medicine/Federal University of São Paulo

Dr. Eduardo Hage Carmo
Professor at the Faculty of Collective Health at the Federal University of Bahia and former director of the Department of Surveillance of Communicable Diseases for the Ministry of Health

Mirian Martho de Moura
Nurse and former PNI coordinator

Dr. Helena Sato
Technical director of the Immunization Division of the State Health Department of São Paulo
Dr. José Cassio de Moraes  
Adjunct professor at the Faculty of Medical Sciences of Santa Casa de São Paulo and consultant of the Pan American Health Organization (PAHO)

Dr. José Geraldo Leite  
Professor at the Faculty of Medical Sciences of Minas Gerais and member of the Technical Advisory Committee on Immunization (CTAI) of the PNI

Dr. Marco Aurélio Sáfadi  
President of the Department of Infectology at the Brazilian Society of Pediatrics and member of the Technical Advisory Committee on Immunization (CTAI) for the PNI

Dra. Maria de Lourdes de Sousa Maia  
Clinical advisor of the Institute of Technology in Immunobiológicos Bio-Manguinhos / Fiocruz and former PNI coordinator

Dr. Reinaldo de Menezes Martins  
Scientific advisor of the Institute of Technology in Immunobiológicos Bio-Manguinhos / Fiocruz

Dra. Rosana Richtmann  
Infectologist from the Emilio Ribas Hospital and member of the Technical Advisory Committee on Immunization (CTAI) for the PNI

Dr. Renato Kfouri  
Vice President of the Brazilian Society of Immunizations (SBIm)

Maria Izabel Nascimento  
Nurse Coordinator of the Immunization Program of Amazonas
Two centuries of vaccine in Brazil

Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1804</td>
<td>The first vaccination in the country was carried out against smallpox.</td>
</tr>
<tr>
<td>1811</td>
<td>The Court Vaccine Board has been set up to propagate the smallpox vaccine.</td>
</tr>
<tr>
<td>1832</td>
<td>First legislation of vaccine obligatoriness in Brazil.</td>
</tr>
<tr>
<td>1834/35</td>
<td>Smallpox epidemic in Rio de Janeiro.</td>
</tr>
<tr>
<td>1846</td>
<td>Foundation of the Empire Vaccine Institute, from the restructuring of the Vaccine Board, with an extended range of action for the entire Empire.</td>
</tr>
<tr>
<td>1872</td>
<td>Oswaldo Gonçalves Cruz is born in São Luís de Paraitinga, São Paulo.</td>
</tr>
<tr>
<td>1878</td>
<td>Smallpox epidemic in Rio de Janeiro.</td>
</tr>
<tr>
<td>1885</td>
<td>Introduction of the first generation of rabies vaccine.</td>
</tr>
<tr>
<td>1886</td>
<td>Extinction of the Vaccine Institute.</td>
</tr>
<tr>
<td>1887</td>
<td>Smallpox epidemic in Rio de Janeiro. Introduction of the smallpox vaccine in Brazil.</td>
</tr>
<tr>
<td>1889</td>
<td>An outbreak of bubonic plague in the port of Santos leads the government to acquire the Butantan farm, to produce antipest serum.</td>
</tr>
<tr>
<td>1889</td>
<td>Smallpox vaccine became mandatory for children up to six months of age.</td>
</tr>
<tr>
<td>1894</td>
<td>Creation of the Municipal Vaccine Institute in Rio de Janeiro.</td>
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<tr>
<td>1897</td>
<td>First generation of bubonic plague vaccine.</td>
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<tr>
<td>1900</td>
<td>Creation of the Federal Serum Therapy Institute, the first institution to produce serum in Brazil which, as of 1974, was renamed as Oswaldo Cruz Foundation (Fiocruz).</td>
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<tr>
<td>1902</td>
<td>Oswaldo Cruz assumes the General Directorate of the Federal Serum Therapy Institute.</td>
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<tr>
<td>1903</td>
<td>Rodrigues Alves appoints Oswaldo Cruz as General Director of Public Health, a position that currently corresponds to the Minister of Health.</td>
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<tr>
<td>1904</td>
<td>Smallpox epidemic in Rio de Janeiro. Smallpox vaccination law is approved. Vaccine Revolt erupts.</td>
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<tr>
<td>1907</td>
<td>Yellow fever is eradicated in Rio de Janeiro. The Federal Sororapic Institute changes its name to Institute of Experimental Pathology of Manguinhos</td>
</tr>
<tr>
<td>1908</td>
<td>Epidemic of smallpox leads mass population to vaccination sites</td>
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<tr>
<td>Year</td>
<td>Event</td>
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<tr>
<td>1909</td>
<td>Oswaldo Cruz leaves the General Directorate of Public Health, beginning to dedicate himself only to the Institute of Manguinhos, which happens to be called Oswaldo Cruz Institute.</td>
</tr>
<tr>
<td>1917</td>
<td>Oswaldo Cruz dies.</td>
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<tr>
<td>1919</td>
<td>The Oswaldo Cruz Institute incorporates in its structure the Municipal Vaccine Institute that is now called the Federal Vaccine Institute.</td>
</tr>
<tr>
<td>1925</td>
<td>BCG vaccine is introduced in Brazil.</td>
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<tr>
<td>1937</td>
<td>Onset of the production and use of the vaccine against yellow fever, manufactured in Brazil.</td>
</tr>
<tr>
<td>1940</td>
<td>The need to combat the vector mosquito, Aedes Aegypti, is enhanced due to the low efficacy of the vaccine.</td>
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<tr>
<td>1942</td>
<td>Urban yellow fever is eradicated in Brazil.</td>
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<tr>
<td>1950</td>
<td>Implantation of tetanus toxoid (TT) and DTP vaccine in some states.</td>
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<tr>
<td>1953</td>
<td>Epidemics of diphtheria in Brazil.</td>
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<tr>
<td>1961</td>
<td>First experimental campaigns with the oral Poliomyelitis vaccine.</td>
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<tr>
<td>1962</td>
<td>First national campaign against smallpox.</td>
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<tr>
<td>1966</td>
<td>The smallpox eradication campaign was launched.</td>
</tr>
<tr>
<td>1967</td>
<td>Introduction of the measles vaccine for children aged 8 months to 4 years.</td>
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<tr>
<td>1968</td>
<td>Vaccination with the BCG vaccine is started.</td>
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<tr>
<td>1970</td>
<td>The Public Health Campaign Superintendency (SUCAM) was created as a result of the merger of the National Department of Rural Endemics, from the Campaign for Smallpox Eradication and Malaria Eradication.</td>
</tr>
<tr>
<td>1971</td>
<td>Implemented in Brazil the National Control Plan for Poliomyelitis. Latest cases of smallpox in Brazil. Begins the production of lyophilized BCG vaccine by the Instituto Butantã.</td>
</tr>
<tr>
<td>1972</td>
<td>Start of the Measles Vaccination Program.</td>
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<tr>
<td>1973</td>
<td>International certification of smallpox eradication in Brazil.</td>
</tr>
<tr>
<td>1974</td>
<td>Expanded Immunization Program created. Meningococcal meningitis epidemic in Brazil.</td>
</tr>
<tr>
<td>1975</td>
<td>Beginning of the dosage registration system of applied vaccines. National System of Epidemiological Surveillance and Immunizations is established. National vaccination campaign against meningococcal meningitis.</td>
</tr>
<tr>
<td>1976</td>
<td>Unit of Fiocruz in Bio-Manguinhos implanted in Brazil, which is a center for the production of vaccines against meningococcal meningitis A and C.</td>
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<tr>
<td>Year</td>
<td>Event</td>
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<tr>
<td>1977</td>
<td>Vaccines are defined as mandatory for children under 1 year of age in Brazil. Approval of the Vaccination Book template.</td>
</tr>
<tr>
<td>1980</td>
<td>Mandatory vaccination against smallpox extinct. Start of the National Day Against Childhood Paralysis in Brazil.</td>
</tr>
<tr>
<td>1981</td>
<td>National awareness campaign on yellow fever launched.</td>
</tr>
<tr>
<td>1982</td>
<td>Fiocruz launches the first batch of the Brazilian measles vaccine.</td>
</tr>
<tr>
<td>1984</td>
<td>Vaccination of children 0 to 4 years old against poliomyelitis, measles, diphtheria, pertussis and tetanus is initiated throughout the country.</td>
</tr>
<tr>
<td>1986</td>
<td><strong>Creation of Zé Gotinha,</strong> a character symbol of the campaign for the eradication of poliomyelitis in Brazil.</td>
</tr>
<tr>
<td>1989</td>
<td>Last case of poliomyelitis recorded in Brazil.</td>
</tr>
<tr>
<td>1990</td>
<td>SUCAM and EPSU extinct, which result in Funasa.</td>
</tr>
<tr>
<td>1994</td>
<td>International certification of poliomyelitis eradication in Brazil.</td>
</tr>
<tr>
<td>1996</td>
<td>National Vaccination Campaign against hepatitis B, involving schoolchildren and dentists.</td>
</tr>
<tr>
<td>1997</td>
<td>National Vaccination Campaign against measles, in children under five years of age.</td>
</tr>
<tr>
<td>1998</td>
<td>Vaccination against hepatitis B throughout Brazil.</td>
</tr>
<tr>
<td>1999</td>
<td>Measles Eradication Plan is implemented. First year of vaccination campaign for the elderly - against influenza, tetanus and diphtheria. Vaccine against <em>Haemophilus influenzae</em> b for children under 2 years is implanted.</td>
</tr>
<tr>
<td>Year</td>
<td>Description</td>
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<tr>
<td>2000</td>
<td>Basic calendar for vaccination of indigenous peoples implemented.</td>
</tr>
<tr>
<td>2001</td>
<td>Vaccination of women in childbearing age intensified in order to eliminate the occurrence of neonatal tetanus.</td>
</tr>
<tr>
<td>2003</td>
<td>South American Vaccination Day with the purpose of accelerating the eradication of measles and the control of diseases that can be prevented by means of vaccines. Agreement for the manufacture of the triple viral vaccine against measles, rubella and mumps signed by the Ministry of Health.</td>
</tr>
<tr>
<td>2004</td>
<td>Basic Vaccination Calendar established. Six priority vaccines by the Technology and Science Department (DCT) presented for development over the next three years: pentavalent (against diphtheria, pertussis, tetanus, hepatitis B and <em>Hemophilic influenza</em>), against human and canine rabies, immunization of Meningitis A and B, and against canine leishmaniasis.</td>
</tr>
<tr>
<td>2005</td>
<td>Distribution of the new Child’s Booklet by public and private maternity hospitals.</td>
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<tr>
<td>2006</td>
<td>Contra rotavirus vaccination incorporated into the Child Vaccination Baseline. “National Day of Chickenpox Prevention” instituted to be held annually on August 5.</td>
</tr>
<tr>
<td>2008</td>
<td>National vaccination campaign against rubella.</td>
</tr>
<tr>
<td>2009</td>
<td>The World Health Organization reports that the influenza A (H1N1) pandemic has spread among humans.</td>
</tr>
<tr>
<td>2011</td>
<td>Expansion of vaccination ranges against influenza and hepatitis B.</td>
</tr>
<tr>
<td>2012</td>
<td>Inclusion of the inactivated vaccine against poliomyelitis. Replacement of the tetravalent vaccine by the pentavalent one.</td>
</tr>
<tr>
<td>2014</td>
<td>Incorporation of the human papillomavirus (HPV) vaccine for girls aged 11 to 13 years in the national calendar.</td>
</tr>
<tr>
<td>2015</td>
<td>Expansion of HPV vaccination range for girls from 9 years of age.</td>
</tr>
<tr>
<td>2017</td>
<td>Expansion of the target audience for six vaccines: viral triple, viral tetanus, adult dTPa, HPV (now including boys), Meningococcal C and hepatitis A. Outbreak of wild yellow fever in Minas Gerais and Espírito Santo and occurrences in some cities of Rio de Janeiro and São Paulo are recorded.</td>
</tr>
</tbody>
</table>

Sources: Revista da Vacina (Ministry of Health) and book of the 30 years of the National Immunization Program
Breakthrough in immunization

Mirian Martho de Moura


“I started working with immunization in 1981, when I coordinated the Poliomyelitis eradication campaign in the State of São Paulo. At the time, there was no structured program in the state and even in Brazil the coverages were low, around 50%. It was a period in which many measles and diphtheria deaths occurred.

The parameters of storage and conservation of vaccines and of the entire cold chain, from production to application at the healthcare centers, were not well established in the world. As immunobiologics lost effectiveness, there were cases of diseases in vaccinated persons.

Disposable materials were not yet used. The syringes were made of glass and the metal needles were sanded at the end of the day. Disposables were only used in the State of São Paulo in 1987, in the campaign against measles. There was an epidemic. There were so many cases that we counted only the number of hospitalizations. At the same time, AIDS cases were growing in São Paulo and in the country.

Our goal was to vaccinate 15 million people up to 15 years against measles. A lot of people did not believe it would work. However, we reached a coverage of almost 90% and, thus, we managed to control the disease, which began to decrease in a short time. In 1990, we won a UNICEF Prize for the results of the campaign. It was a milestone.

In 1991, I assumed the Coordination of Immunizations and Self-sufficiency in Immunobiology (CIAI). I had the opportunity to draw up with other professionals, that same year, the first Manual of Norms and Procedures for Vaccination and, in 1992, to organize the National Campaign on Measles Vaccination, initiating the control of the disease in the country. The Program of Control for Adverse Effects of the PNI.

These steps were taken thanks to the work of a very committed team that contributed to make PNI a strong and quick program in the introduction of vaccines, with a quality for storing, training and enabling.”
An epidemiological revolution

The World Health Organization (WHO) estimates that around 2 to 3 million deaths worldwide are prevented each year as a result of vaccination. In the same period, approximately 116 million children around the world receive the basic vaccines and, along with them, protection against a large number of infectious diseases, many of them being fatal.

On the other hand, diseases such as AIDS, lung cancer and hepatitis C make about 2 million victims a year in the world. In Brazil alone, prostate and breast tumors account for almost 30,000 deaths per year. These are diseases with a high incidence and high mortality rates, for which there are still no vaccines available. But, great efforts are being made worldwide, especially by the research industry, to reverse this situation.

The numbers and results of immunization are huge and point to a consensus among experts as to their power: vaccines represent one of the greatest success stories of modern medicine. In the last decades, possibly no other public health program has achieved results that are so relevant, on a large scale and across all age groups, to improve the quality of life of populations.

More than that: from the 18th century, when the first smallpox vaccine was developed, until the present date immunization has promoted a real revolution in the history of human health. Diseases such as smallpox itself, pandemic for more than 3,000 years and responsible for a trail of half a billion deaths in the last century, according to the World Health Organization (WHO), have been swept away. Poliomyelitis, devastating by its personal, social and economic impacts, was eradicated in Brazil in 1994 and is about to disappear from the world.

The same can be said of measles, rubella, and neonatal tetanus - diseases that the new generations have hardly heard of. Others, if not yet eliminated, are controlled or in an abbreviated form, such as diphtheria, bacterial meningitis, and diarrheal diseases caused by rotavirus. In terms of public health impacts, these are benefits equivalent to those occurred with the access of the populations to the treated water, according to the comparison made by the president of the Department of Infectology of the Brazilian Society of Pediatrics, Marco Aurélio Sáfadi.

Whether in the world or in Brazil, immunization efforts have been - and continue to be - one of the most important tools for reducing mortality and disease morbidity, reducing hospitalizations and preventing severe and often disabling sequelae, such as those caused by poliomyelitis.
Behind the whole structure surrounding the immunization area is a basic concept: investing in prevention is better than treating. And the results prove this traditional thesis.

In 1930, infectious and parasitic diseases accounted for 45.7% of deaths in Brazil. In 2005, they accounted for only 5.2% of deaths with defined causes and, in 2010, the index fell to 4.3%, according to the Ministry of Health.

Going back a bit in time, we see that both in Brazil and in the world, children were, in general, the group most affected by these diseases and, therefore, also the main targets of the local and world vaccination programs promoted by the World Health Organization (WHO).

In the 1980s, prevalence and deaths from the most common diseases in children up to 5 years old - measles, polio, rubella, congenital rubella syndrome, meningitis, tetanus, whooping cough and diphtheria - revolved around 153,000 cases and 5.5 thousand deaths in Brazil. In 2009, after successive vaccination campaigns, 2,000 cases and 50 deaths were recorded.

The vaccines currently available in the world enable the prevention and control of 26 diseases or infectious agents, contributing to a drastic reduction in the occurrence and magnitude of epidemics. In Brazil, the National Immunization Program (PNI) of the Ministry of Health includes 19 vaccines that are available through the Unified Health System (SUS) and protect against about 20 diseases.

### Vaccines available in the National Immunization Program

#### CHILDREN
- BCG
- Hepatitis B (dose at birth)
- Penta (DTP/Hib/HepB)
- VIP (Poliomyelitis inactivated vaccine) *
- VOP (Oral poliomyelitis vaccine) *
- VORH (Human rotavirus oral vaccine)
- Pneumococcal 10-valent
- Yellow fever
- Viral triple (Measles, mumps and rubella)
- DTP (Bacterial triple) - diphtheria, tetanus and pertussis
- Meningococcal C (conjugated)
- Influenza (annual campaign) 6 months to <5 years
- Tetraviral (Measles, mumps, rubella and chickenpox)
- Hepatitis A
- Human papillomavirus 6, 11, 16 and 18 (recombinant) - HPV

#### ADOLESCENT AND ADULTS
- Hepatitis B
- dT (Adult double) - tetanus and diphtheria
- Yellow fever
- Viral triple (measles, mumps and rubella)
- dTpa (Pregnant and health professionals)
- Influenza (Priority Groups)

#### ELDERLY
- Hepatitis B
- dT (Adult double) - tetanus and diphtheria
- Yellow fever
- Influenza (annual campaign)

* Vaccines poliomyelitis sequencing scheme (VIP and VOP): 1st and 2nd doses (VIP), 3rd dose and booster (VOP) Source: Ministry of Health
The WHO estimates that, in the 20th century, the morbidity of preventable diseases - the rate of infected persons in the population - fell by 90% to 100% as a result of immunization.

Although vaccines promote individual protection against disease, they play an even greater role in the population: by reducing the number of people who transmit diseases, they reduce the circulation of viruses and bacteria and thus protect the entire community. This is what experts call indirect protection.

Apart from improving the health of the population, vaccines also have a major economic impact, reducing costs with treatment and medical care. In the evaluation of epidemiologist and current director-president of the National Agency for Sanitary Surveillance (ANVISA), Jarbas Barbosa, mass immunization is one of the public health actions that has one of the best cost and effectiveness ratios, being one of the cheapest means to prevent diseases and avoid deaths, when compared to other types of interventions.

Researchers at Johns Hopkins University in the United States have calculated the costs that countries will lose from investing in disease prevention with immunization programs. By analyzing data from 94 low and middle income countries and projecting vaccination rates for the period of 2011-2020, they concluded that for every US$ 1.00 invested in vaccines, countries save US$ 16.00 - a figure they no longer shell out, for not having to deal with illnesses and their consequences.

And 10 types of vaccine-preventable infections were included: Hemophilic influenza type b, hepatitis B, human papillomavirus, Japanese encephalitis, measles, Neisseria meningitis serogroup A, rotavirus, rubella, Streptococcus pneumoniae, and yellow fever.

Their conclusion applies to Brazil and to all countries striving to broaden the access of their populations to vaccines: “Even though these are estimates that assume coverage will expand and improve, our findings are important in encouraging donors and governments to continue investing in immunization programs,” said Sachiko Ozawa, the study’s author.
The value of vaccines

- Millions of lives saved
- Protection of the whole society
- Reduction of healthcare costs
- Eradication and elimination of diseases such as poliomyelitis, measles and rubella

Source: IFPMA (International Federation of Pharmaceutical Manufacturers & Associations)
The Decade of Vaccine

The World Health Organization (WHO) has instituted the period from 2010 to 2020 as the Decade of Vaccine, a worldwide effort to make access to vaccines universal. The goal is to extend the benefits of immunization to everyone on the planet by the end of the decade. Supported by some 200 countries and considered one of the largest and most ambitious public health actions, the initiative has a Global Plan of Action for Vaccines that sets out six strategic objectives that countries must meet in the 10 years to reach the goals:

1. All countries undertake to prioritize immunization;
2. Individuals and communities understand the value of vaccines and require immunization as their right and responsibility;
3. The benefits of immunization are equally extended to all persons;
4. Strong immunization systems are part of a good health system;
5. Immunization programs have sustainable access to the provision of resources, quality supplies and innovative technologies;
6. Research and development of local, regional and global innovations maximize the benefits of immunization.
1878
First vaccine developed against smallpox

1885
Rabies vaccine

1886
Vaccine against cholera

1927
Tuberculosis vaccine (BCG)

1935
Yellow Fever Vaccine

1948
DTP vaccine (diphtheria, tetanus, and pertussis)
Two centuries of research and innovation

Vaccine history in the world

1963 Rubella vaccine
1963 Measles Vaccine and Poliomyelitis Vaccine
1969 Hepatitis B vaccine
1969 Rubella vaccine
1986 Pneumococcal (heptavalent) vaccine
2000 Pentavalent vaccine
2001 Rotavirus vaccine (attenuated and new immunological)
2006 Human Papillomavirus (HPV) Vaccine
2006
A technological revolution

The focus of research on the prevention of the major threats that have devastated and ravaged mankind by laboratories worldwide have played a crucial role in the eradication, elimination and control of a large number of infectious-contagious diseases. In addition to saving and protecting millions of lives by placing them safe from these diseases, they have made room for other diseases that challenge health authorities around the world, such as the prevention of some forms of cancers caused by viruses, cervix and liver.

This outstanding public health performance, which is the result of more than 200 years of research and development (R&D) in the field of immunization, while benefiting from the scientific findings that have taken place in all areas, has also promoted them, consolidating a technological revolution that has sped up in recent decades. And that has enabled the whole world to unite around global eradication campaigns, such as those promoted by the World Health Organization (WHO) in relation to poliomyelitis and measles.

There are currently hundreds of vaccines being tested and developed around the world - around 300 in the United States alone, according to estimates by PhRMA, the American association of the research industry. The rapid development of science has opened doors and revealed new processes through which vaccines can act and become more effective and safe, expanding the perspectives also for the rise of other products and the fulfillment of needs that have not yet been solved.

At the same time, however, when it beckons with a potential universe of promise, the scientific and technological development achieved so far has made the research, development and production of vaccines even more complex and burdensome - a process that by itself is already long and risky, in addition to demanding high financial investments.

One example: the worldwide trend of producing multivalent conjugate vaccines - which protect against various diseases from a single product - places researchers in the face of much greater challenges than there was to produce a traditional inactivated vaccine focused on the prevention of only one disease.

Regulatory requirements, which provide the safety and efficacy parameters that guide vaccine research, development and production processes, have also become more sophisticated and more rigorous over time. To meet them, often
manufacturers will have to perform something around 500 quality control tests for a single vaccine.

The complexity of the vaccine production process is such that the World Health Organization (WHO) estimates that the discovery of a vaccine to its licensing takes an average of 10 to 15 years. And out of every 10 new candidates being tested, only one will actually reach the market.

Much of the difficulty is due to the unpredictability of the microorganisms used in the production of vaccines and the uncertainty about how the human body will react to them. Some vaccines under test can produce, for example, an adequate immune response, but cause adverse reactions. Others may be safe, but ineffective in disease prevention.

And all this unfolds in a succession of steps that unfold from research and discovery: the development process involves the production of a vaccine that is economically viable for the world; the clinical development stage includes numerous steps in which it is necessary to demonstrate the safety of a vaccine and to measure its protective effect in humans; the testing phase requires numerous tests to ensure the purity, potency and stability of the product being developed.

However, thanks to breakthroughs in several research areas and also in the field of immunization, it is now possible to produce safer and more effective vaccines. In addition, it is changing the perspective with which researchers think and produce vaccines. Currently, in addition to disease prevention, scientists are also looking for therapeutic vaccines, which stimulate the body to react and fight certain diseases, including chronic infections or degenerative diseases.

From the first generation of vaccines, when bacterial or disease-causing viruses were inoculated into the population after undergoing inactivating or inactivating treatments, to modern DNA vaccine research that works with the genetic material of the virus or bacteria, researches took a quantum leap in this field.

Great challenges and unmet needs still persist. Researchers and scientists around the world continue to seek ways to produce, for example, a vaccine against HIV, hepatitis C or zika and chikungunya. However, with the horizon that opens up with new vaccine development techniques and strategies, these findings become more likely.

As it is characteristic of the vaccine area since the earliest days of immunization, all still depends on further research, studies and research. It is this continuous effort that allows a vaccine, even after release or years of use, to continue to be improved, whether it be to increase its effectiveness or to reduce any adverse reactions.
This happened innumerable times in Brazil, thanks to the onslaught of national science. Renowned immunization research institutes have been gradually absorbing innovative technologies and, once they have gained scientific knowledge and production capacity, they have developed a research to improve products.

There have been cooperation agreements between Brazilian scientists and international companies for more than 40 years, allowing innovative technologies to be internalized by our researchers. One example is the hepatitis B vaccine, which has been improved and had its cost of production significantly reduced after it was incorporated into local science.

Immunizing agents against meningitis A and C also began to be produced by Brazil in the 1970s, based on a cooperation agreement with the Mérieux Institute in France. Vaccines against yellow fever, measles and poliomyelitis were further developed.

This has been the great asset of Brazilian science, through public laboratories, as emphasized by Scientific Advisor of the Bio-Manguinhos/Fiocruz Institute, Reinaldo de Menezes Martins. He acknowledges that national collaborations with innovation are modest, but highlights the success of technology transfer in this area. It not only makes the improvement of immunization feasible, but also helps to overcome the challenge of supplying a country of continental proportions and a very populous one, as it can significantly reduce the cost of each dose. This collaboration between the public and private sectors tends to extract the best from each one, for the benefit of the Brazilian society.
Technology transfer

The partnership between the pharmaceutical industry and official government laboratories has been a successful practice in which the private sector invests in research for the creation and development of a particular technology and then transfers it to the public sector.

There are currently seven projects for technology transfer in progress in the country, five of which are in the Productive Development Partnerships (PDP) model and two in the Technological Project model, where technology is transferred without the drug being provided by the private sector in the Intermediate phases of the process.

Technology transfer for vaccine production has been much more successful than other partnership agreements involving other categories of drugs. Out of the 110 PDPs approved by the Brazilian government between 2009 and 2013, only 23 are providing medicines to the Ministry of Health. Another 24 were excluded or suspended and the others did not show any progress.

When the universe of vaccines is observed in relation to other models of partnership, the scenario changes completely. All seven projects are progressing consistently, with indicators of a likely outcome of success in the near future.

According to Reinaldo de Menezes Martins, Bio-Manguinhos / Fiocruz Scientific Advisor, the biggest challenge of partnerships is to meet deadlines for technology transfers. This would require a robust financing in a timely manner and new forms of public sector management, which needs modernization and promptness without giving up control. According to Martins, “the creation or development of infrastructure and human resources of high qualification is indispensable”.

See below table for vaccines, public laboratories and pharmaceutical companies holding the technologies.

### Transferência de tecnologia para produção de vacinas

<table>
<thead>
<tr>
<th>YEAR</th>
<th>PRODUCT</th>
<th>PUBLIC LAB. PÚBLICO</th>
<th>PARTNER 1</th>
<th>PDP PHASE</th>
<th>DESCRIP. PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Influenza H1N1 vaccine</td>
<td>Butantan</td>
<td>Sanofí</td>
<td>IV Phase</td>
<td>Internalization of Technology</td>
</tr>
<tr>
<td>2010</td>
<td>Meningococcal C Conjugate Vaccine</td>
<td>Funed</td>
<td>Novartis</td>
<td>Technological Project</td>
<td>PDP</td>
</tr>
<tr>
<td>2010</td>
<td>Pneumococcal Vaccine 10 Valente</td>
<td>Bio-Manguinhos</td>
<td>GSK</td>
<td>Technological Project</td>
<td>PDP</td>
</tr>
<tr>
<td>2012</td>
<td>Hepatitis A Vaccine</td>
<td>Butantan</td>
<td>MSD</td>
<td>III Phase</td>
<td>PDP</td>
</tr>
<tr>
<td>2012</td>
<td>Tetaviral vaccine</td>
<td>Bio-Manguinhos</td>
<td>GSK</td>
<td>III Phase</td>
<td>PDP</td>
</tr>
<tr>
<td>2013</td>
<td>Adsorbed Diphtheria, Tetanus and Pertussis Acellular Vaccine (Immunotherapy)</td>
<td>Butantan</td>
<td>GSK</td>
<td>II Phase</td>
<td>PDP Project</td>
</tr>
<tr>
<td>2013</td>
<td>HPV vaccine</td>
<td>Butantan</td>
<td>MSD</td>
<td>III Phase</td>
<td>PDP</td>
</tr>
</tbody>
</table>

Source: DECIIS/SCTIE/MS. Updated on 03/19/2017
The National Immunization Program

An exceptional program

The National Immunization Program (PNI) of the Ministry of Health is an exception in the spectrum of public health actions in Brazil. Since it was created in 1973, it left with small and punctual scratches from the economic crises that devastated the country. The program has maintained for more than four decades a cohesive technical staff that advises it. It underwent 10 presidents of the Republic and 26 ministers of health without losing the status of priority or going through discontinuity and political influences.

There are many well-justified reasons why the PNI should be considered an international reference in public health and why it has undergone the last decades without much surprise. One of them is the ability to extend vaccination to all municipalities in the country and offer, through the Unified Health System (SUS), free vaccines exclusively funded by public resources to the entire population.

In support of this good performance, there is a legal aid that guarantees financial support to the program, whatever the government is, and that contributed to the funds destined to grow over time. “Even if there is contingency in the budget of the Ministry of Health or the Federal Government, investments in vaccines cannot be cut,” says PNI coordinator Carla Domingues.

In order to make its structure feasible and maintain it, the program has an annual budget of R$ 4.3 billion - bigger than the global budget of capitals such as Aracaju, Florianópolis, Natal and Vitória.

Development of PNI financial resources

Source: CGPNI/DEVIT/SVS
The impacts of immunization in the country also draw attention, even before the implementation of the PNI. One example was the eradication of smallpox in 1973, as a consequence of a global campaign led by the World Health Organization (WHO). To get an idea of the devastating effect of smallpox, the WHO estimates that more than half a billion people died in the last century from the virus. The disease was pandemic for more than 3,000 years until the 1970s, killing about 30% of those affected. The program, moreover, was born in the wake of this successful initiative, in which Brazil anticipated several countries. In overall terms, the disease was only considered eradicated from the planet seven years later.

Good results have also been achieved in the fight against poliomyelitis, known as childhood paralysis. Of the 11,545 cases registered in the 1970s, the disease progressively declined due to vaccinations - the only way to prevent it - until it disappeared completely in 1989. It was during the campaigns against poliomyelitis that the popular character named Zé Gotinha emerged, which is a symbol of this endeavor and became synonymous with vaccination.

In 1994, Brazil received from the Pan American Health Organization (PAHO) the Certificate of Eradication of the Indigenous Transmission of the Wild Poliovirus, together with the other countries of the American continent.

Pertussis and diphtheria were diseases that practically disappeared from the Brazilian map. In the first case, the incidence was around 10.6 per 100 thousand inhabitants. When immunization reached 100% of the population, the proportion of cases fell to 0.32/100 thousand inhabitants in 2010. Diphtheria dropped from 495 cases to 56 between 1991 and 1999.

When mass vaccination against type b meningitis was started in 1999, Brazil had 1,700 cases per year and an average annual incidence of 23.4 cases per 100,000 children under one year. With the vaccine, there was a reduction of more than 90% in the number of cases, incidence and deaths.

After conquering these important public health milestones, Brazil is currently seeking to control infections caused by diseases that still have a major impact on the population health and on the public healthcare system finances. This is the case of type b hemophilic influenza (a bacteria that mainly affects children up to 5 years old), rubella, congenital rubella syndrome, hepatitis B, influenza (influenza) and pneumococcal infections.

A study conducted between 1992 and 2006 by a group of researchers from Brasília, Rio de Janeiro and Salvador showed that, in addition to preventing or controlling diseases, immunization also promotes a reduction in the problems they may cause.

To reach this conclusion, they compared data from the SUS on hospitalizations of the elderly due to influenza complications before and after 1999, when this group was regularly immunized. “After the campaigns, hospitalization rate fell from 22 in 1,000 elderly people per year to 0.75 in 1,000 elderly people per year,” says Eduardo Hage Carmo, a professor at the Institute of Public Health for the Federal University of Bahia, and one of the participants in the study.
The reduction in the number of disease cases in Brazil was inversely proportional to the increase in vaccine coverage.
Impacts of immunization in the control of preventable infectious diseases in Brazil

Diseases eliminated or in the process of elimination
• Smallpox
• Poliomyelitis
• Measles (in the Americas)
• Congenital Rubella Syndrome
• Neonatal Tetanus

Reduction tendency
• Accidental Tetanus
• Diphtheria
• Hib Meningitis (type B Hemophilic influenza)
• Streptococcus pneumoniae meningitis
• Diarrheal rotavirus diseases

Controlled Transmission
• Meningitis and Meningococcal Disease

Source: Dr. Rosana Richtmann, Infectologist of the Emílio Ribas Institute. 2017

Diseases preventable by vaccines in Brazil
• Chicken pox (varicella)
• Mumps
• Whooping cough
• Cholera
• Dengue fever
• Diphtheria
• Meningococcal disease
• Pneumococcal disease
• Yellow fever
• Typhoid fever
• Influenza (flu)
• Diseases caused by Hemophilus B
• Hepatitis A
• Hepatitis B
• Herpes zoster
• HPV
• Poliomyelitis
• Rage
• Rotavirus
• Rubella
• Measles
• Tetanus
• Tuberculosis

Source: Ministry of Health
A public healthcare machine

The characteristics of Brazil - a country with continental dimensions and with great geographical, social and economic contrasts - have made the National Immunization Program (PNI) a superlative project in all aspects and, above all, a good logistics articulator.

Just remember we are talking about taking vaccines to 210 million people living in densely populated metropolises, but also those isolated in the middle of forests. And that, to be vaccinated, they depend on transports like boats and airplanes.

Even so, the PNI reaches levels of vaccine coverage between 80% and 90%, higher than that of many countries. Of course, there are disparities that vary from region to region. However, the result is considered quite an achievement, given the difficulties of access that are imposed, as observed by José Cassio de Moraes, a consultant with the Pan American Health Organization (PAHO).

PNI is also one of the immunization programs that offers the largest number of vaccines to the population and includes all the basic ones recommended by the World Health Organization (WHO). There are 19 in total, aimed at children, adolescents, adults and the elderly, as well as pregnant women and groups with special health conditions, such as those with low immunity.

In 2017, the PNI plans to distribute 300 million doses of vaccines and serum. To do so, it has the structure that public health services routinely assign to primary care: 36,000 rooms distributed in 26 states, the Federal District and more than 5,500 municipalities. The campaigns mobilize, each time, a legion of 250,000 nurses, technicians and auxiliaries who concentrate their efforts in this period to guarantee the immunization of the largest number of people. However, vaccination services are also available year-round at the Basic Health Units (UBS). There are more than 10,000 UBS spread throughout Brazil that make it possible for the population to access PNI immunizations at any time of the year, not only during campaigns.

The infrastructure is part of the Family Health Program, which was created almost 25 years ago and currently provides care to more than half the Brazilian population through basic care, as well as monitoring and encouraging adherence to PNI vaccines.

The operation of this public health machine results from a network of interactions involving the federal, state and municipal governments, official laboratories and research industries, medical societies, specialists, national and international entities and vaccination technicians.
“The PNI is one of the largest social inclusion programs in the world. A rural child receives the same vaccines as a child from the private clinic,” says epidemiologist and sanitary veterinarian Jarbas Barbosa, director of the National Agency for Sanitary Surveillance (ANVISA).

In recent years, the program has been prompt in introducing new vaccines into the official vaccination schedule and has further broadened the target age groups for vaccination. In 2017, the Ministry of Health expanded the publics of six vaccines: Hepatitis A, viral Tetra (measles, mumps, rubella and varicella), HPV, Meningococcal C, adult dTpa (diphtheria, tetanus and whooping cough) and Viral Triple (measles, mumps And rubella).

This is an important strategy in terms of extending coverage. However, it requires an intense work of awareness of the population, as it is not part of the Brazilian vaccination culture to understand that immunization must occur throughout life and not only in childhood, as observed by pediatrician and epidemiologist José Geraldo Leite, professor of the Faculty Of Medical Sciences in Minas Gerais and collaborator for the Technical Advisory Committee of the program.
In search of self-sufficiency

One of the pillars of support for the National Immunization Program (PNI) is the search for the country’s self-sufficiency in vaccines. To this end, in 1985 the Ministry of Health created the National Immunobiological Self-Sufficiency Program (PASNI), which establishes a coordinated action between public producers and partnerships with universities, research centers, institutes, universities, national and international organizations and private initiative. In addition to an articulated action among the seven official laboratories.

The incentive to national production functions as a kind of stony clause governing PNI’s decisions regarding the incorporation of new vaccines. It establishes that a new immunobiological will only become part of the official immunization schedule if a technology transfer agreement is established that will enable public laboratories to manufacture it in the country. These partnerships have made the production of new, modern and effective vaccines possible and are a great support for actions to control, eradicate and eliminate diseases.

The scientific advisor of the Institute of Technology in Immunobiological Bio-Manguinhos, Akira Homma, believes that partnerships for technology transfer and local production expand the population’s access to vaccines and contribute to the country’s training and scientific capacity. For example, it is the world’s largest producer of yellow fever vaccines, according to Rosana Richtmann, and self-sufficient in immunobiologicals against influenza.

According to PNI coordinators estimates, about 75% of the 300 million doses of vaccines that the program has committed to distribute in 2017 will leave public laboratories, especially the Butantan Institute in São Paulo and the Bio-Manguinhos Institute of Immunobiologicals, in Rio de Janeiro.

The two institutions jointly produce 16 different types of vaccines and maintain 17 other immunobiologicals at different stages of development and production.

**Public Laboratories**

- Institute of Immunobiological Technology Bio-Manguinhos (RJ) - production of vaccines and serum;
- Butantan Institute (SP) - production of vaccines and sera;
- Vital Brazil Institute (IVB), Rio de Janeiro - production of serum;
- Paraná Institute of Technology (TECPAR) - production of canine anti-rabies vaccine;
- Ezequiel Dias Foundation (FUNED), Minas Gerais - production of sera;
- Immunobiological Research and Production Center (CPPI), Paraná - production of serum;
- Ataulpho de Paiva Foundation (FAP), Rio de Janeiro - production of BCG vaccine against tuberculosis.
Human vaccines produced by public laboratories

Bio-Manguinhos/ Fiocruz Institute

10 VACCINES
1. Meningococcal AC (polysaccharide)
2. Hemophilic influenza (Hib) (conjugated)
3. Diphtheria, tetanus, pertussis and Hemophilic influenza B (conjugate) - tetravalent DTP and Hib
4. Pneumococcal 10-valent (conjugated)
5. Yellow fever (attenuated)
6. Poliomyelitis 1, 2 and 3 (attenuated orally)
7. Poliomyelitis 1, 2 and 3 (inactivated)
   Human Rotavirus
9. Measles, mumps, rubella (triple viral - TVV)
10. Measles, mumps, rubella and varicella (viral tetravalent - MMRV)

At different stages of development
1. DNA vaccine to prevent yellow fever
2. Vaccine against meningitis caused by meningococcal serogroup B
3. Meningitis vaccine C
4. Human Vaccine Against Leptospirosis
5. Bivalent vaccine against schistosomiasis and fasciolosis
6. Vaccine for the prevention of yellow fever and malaria
7. Vaccine for dengue prevention
8. Defective recombinant influenza viruses as platforms in the development of bivalent vaccines against influenza and swine circovirus
9. Pandemic influenza virus vaccines

Butantan Institute

6 VACCINES
1. Diphtheria, tetanus and pertussis adsorbed vaccine (DTP)
2. Diphtheria and adult tetanus adsorbed vaccine (dT)
3. Diphtheria and infant tetanus (DT) adsorbed vaccine
4. Hepatitis B (recombinant) Adsorbed Vaccine
5. Trivalent seasonal influenza vaccine (fragmented and inactivated)
6. Rabies vaccine (inactivated)

Vaccines being developed
1. Dengue
2. Rotavirus
3. Pneumococcus
4. DTPlow
5. Heptavalent vaccine
6. Recombinant BCG-pertussis - neonatal vaccine against whooping cough
7. Recombinant Onco-BCG - bladder cancer treatment
8. Hemophilus - new conjugation method for vaccine

Technology transfer
1. HPV, in partnership with MSD - for girls aged 9 to 13 years
2. Hepatitis A in partnership with MSD - for children up to 1 year
3. dTpa in partnership with GSK (GlaxoSmithKline) - for pregnant women
Four times a year, teams of six to 12 doctors, nurses, nutritionists and dentists linked to the Xingu Project of the São Paulo School of Medicine for the Federal University of São Paulo (Unifesp) travel from São Paulo to the Xingu Indigenous Park, located in the region Northeast of the State of Mato Grosso, in the southern portion of the Brazilian Amazon. There, they vaccinate and provide healthcare to 54 villages of 19 indigenous ethnic groups living in the northern part of the park, known as Baixo Xingu.

Since the program was created in 1965, at the request of then-Park Director Orlando Villas Boas, immunization was prioritized to avoid a repetition of a devastating event: in 1954, a measles epidemic - introduced by contact with the white man - about 20% of the population of the Upper Xingu. Smallpox also made many victims in the region.

Since the distances are great, the expeditions last about 40 days and are supported by four base poles distributed throughout the Baixo Xingu region, which have their own generator and freezer for vaccine conservation, as well as permanent health teams. Without them, it would be impossible to keep the vaccines at the necessary temperatures to preserve their effectiveness.

Therefore, for everything to work out, each trip is carefully prepared at least 30 days in advance. This is the minimum period for assembling the special logistics that involves, in addition to the cold network, needs for inland and fluvial transportation, experienced boaters and fuel, among other demands, which vary according to the time of the year, as the climate in the region includes droughts and heat above 35°C and torrential rains, when the technicians walk in the forest, with water by their waist.

The 3,174 Indians assisted by the program of the São Paulo School of Medicine at the Federal University of São Paulo (Unifesp) receive before the rest of the country all the vaccines that are part of the national immunization schedule. Yet, the vaccinated age groups and the number of doses vary according to the specificities and the contact history of each people.

“The flu vaccine is given to the entire population from the age of six months because the indigenous are quite vulnerable to this disease. The results of the program are very good. Vaccination coverage ranges from 92% to 98% and for many decades there has been no
HOW VACCINES CHANGED A COUNTRY
records of vaccine-preventable diseases in Baixo Xingu*, says Evelin Plácido dos Santos, a nurse and technical supporter of the Xingu Project since 2006.

In contrast, children still die as a result of diarrhea and respiratory diseases. And the people of the Xingu, as a whole, face the threats stemming from changes in eating and living habits, such as diabetes, hypertension, high cholesterol, obesity and cardiovascular disease.

Unlike the rest of Brazil, where coverage accounting is done by the number of vaccine doses applied, in the Xingu, vaccination record is nominal. It turns out that, for cultural reasons, the Indians change their name over the years and the community’s indigenous health workers are key in identifying the people who need to be vaccinated.

As a matter of fact, the role of these agents goes far beyond immunization. It is they, who help the technical team to understand, respect and integrate the cultural and social rules of the indigenous population in the work.

“The technician who goes to Xingu has to establish a dialogue that integrates traditional medicine with indigenous people and to work with people who provide health services in the community, such as the shaman, midwife and the raizeiro, who knows medicinal plants. For the indigenous, diseases are not separated from spiritual matters. We always need to know if they are being treated by the shaman and also integrate, for example, the prenatal care of a pregnant woman with the local midwife*, explains the nurse.
Hitches of the matter

Coverage

Getting to all Brazilian states and municipalities is one of the strengths of the National Immunization Program (PNI) of the Ministry of Health, but maintaining a homogenous vaccination coverage is one of its main challenges.

Coverage is the indicator that expresses the proportion of the population that was vaccinated and that measures whether the target audience and immunization goals were met and whether the strategy worked. The more people who get a vaccine, the greater the vaccine coverage.

Brazil has high rates of vaccination, especially in the first years of life, when coverage reaches almost 100% of children. However, there are municipalities in which it does not reach even 40% of the population that should be vaccinated, according to the estimates of the infectious disease of the Emilio Ribas Institute, Rosana Richtmann.

The problem of low-coverage “zones” is that, in addition to affecting local residents, they put the entire Brazilian population at risk. The increase in the number of unprotected people can cause outbreaks of diseases that were already under control, or prevent them from being controlled.

Part of the coverage discrepancies has to do with regional differences. To reach the 20,000 inhabitants of Atalaia do Norte in Alto Solimões, in the state of Amazonas, vaccines leave Manaus and cover a fluvial distance of 1,623 kilometers, making more than 40 hours of travel.

### Percentage of municipalities that have adequate coverage in 75% or more of the vaccines of the basic vaccination calendar*, 2014

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage of municipalities with adequate vaccination coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>North</td>
<td>35.56</td>
</tr>
<tr>
<td>Northeast</td>
<td>40.3</td>
</tr>
<tr>
<td>Southeast</td>
<td>57.13</td>
</tr>
<tr>
<td>South</td>
<td>47.94</td>
</tr>
<tr>
<td>Midwest</td>
<td>53.53</td>
</tr>
<tr>
<td>Brazil</td>
<td>47.7</td>
</tr>
</tbody>
</table>

* Vaccines considered: BCG, Rotavirus, Pentavalent (DTP + Hin + Hep B), Poliomyelitis, Meningococcal, Pneumococcal, Viral Triple, Yellow Fever and Influenza
“When we set off to immunize the population of Ipixuna (interior of Manaus) we travel more than 70 hours by car and by boat,” explains nurse Maria Izabel Nascimento, Coordinator of the Amazon Immunization Program.

It would be difficult in the northern region to vaccinate riparian populations and indigenous communities, and even so race against time so that vaccines will not lose effectiveness without the Armed Forces support for health actions in the state of Amazonas. This partnership between the Ministry of Health and the Armed Forces provides helicopters, small airplanes, boats and even ships that work as fluvial vaccination rooms.

Even in São Paulo, which historically has coverage rates above 90%, some localities, such as the Ribeira Valley in the south of the state, are accessible only by boat. In order to guarantee vaccinations in some other municipalities, the only option is to use itinerant buses.

It is important to remember that the logistics that takes care of Brazil during campaign times is repeated several times a year, either because some vaccines require booster doses or because they have different immunization schedules, as is the case with the seasonal influenza vaccine.

The problem, however, is not always geographical. In the evaluation of the General Coordinator of the PNI, Carla Domingues, the hitch of the matter is not properly in the difficulty of the population to initiate the vaccination scheme, but mainly to complete it. “Not everyone will return to the health center to receive booster doses,” she says.

Another important aspect to be emphasized is that, historically, the perception regarding vaccination coverage in Brazil has always been associated with the governmental actions of prevention, translated by mass campaigns, to reach populations in the most distant places of the Brazilian territory and where logistics become a challenge to be overcome by health workers. It turns out that, probably due to sheer ignorance on the part of the population, people believe that the moment to take a vaccine is only during the official campaigns when, in fact, the prevention can take place throughout the year.

To remove these barriers, some ideas that the technicians discuss goes through simple solutions, such as opening the stations on Saturdays, when the population is more available to get vaccinated. Another way is to mobilize associations of residents, municipal councils and “approaching the population,” as pointed out by the clinical advisor of Bio-Manguinhos/Fiocruz, Maria de Lourdes de Sousa Maia, former PNI coordinator.

Recently, the National Health Surveillance Agency (ANVISA) has opened a debate to establish a sanitary standard that could define the minimum requirements for the provision of vaccination services in pharmacies, drugstores and other establishments, thus increasing coverage, especially during campaigns of immunization.

In Amazonas, where, in addition to distances, nature also influences the results of vaccination - such as floods and droughts that make navigation unfeasible - those responsible for the program have found a good strategy to facilitate the population’s access to vaccines. “We try to match the vaccination dates with the days when people will receive the Bolsa Família (Brazilian Government social assistance program), explains Maria Izabel do Nascimento.
Many audiences, many challenges

The Ministries of Health and Education recently renewed the Health in School Program and signed a partnership to expand the immunization of children and adolescents against HPV and meningitis C. Adolescents are one of the most refractory publics according to the evaluation of PIN technicians.

The idea is that schools work together with health teams to strengthen the membership of this group, which do not have the habit of seeking the health system.

The result of the difficulty can be measured in figures: more than half of the Brazilian municipalities have low vaccination coverage against HPV, which means about 5.5 million girls from 9 to 14 years old with the incomplete vaccination scheme.

In 2017, in addition to increasing the vaccination of adolescents, the program also intends to immunize 3.6 million boys against HPV. To reach young people, the Ministry will also change their way of communicating. They use games in the campaigns and still long to count on the help of bloggers.

In São Paulo State, health authorities work together with the adolescent, women’s and sexually transmitted diseases department of the State Health Secretariat and with the Education Department, HPV vaccine in the country to the prevention of cervical cancer.

“We also do publicity in public places. We distribute informative material in blood banks, subway and train stations,” explains Helena Sato, technical director of the Immunization Division of the State Health Secretariat.

With the support of gynecology and obstetrics, pediatrics and immunization societies, the program also aims to reverse the difficulty of vaccinating pregnant women. One of the problems to overcome is the mistaken belief that vaccines can harm the fetus.

45% of girls, ages 9 to 14, did not take the second dose of the HPV vaccine.

Source: SIPNI/CGPNI/OEVIT/SV/SVS/MS (2014 to 2016 - Jan/Oct)
The cold network

The chain or cold network is the heart of any mass immunization program. In order not to lose effectiveness and safety, most vaccines need to be stored at temperatures ranging from 2 to 8°C for 24 hours a day, from leaving the breeding laboratories to being applied in the population.

It is a complex structure, governed by rules and technical regulations that must be observed in the storage, distribution, transport and manipulation of immunobiological. And the importance of this is evident when we remember that before arriving at the population, the vaccines travel a long truck route, through cold rooms, freezers and refrigerators of the Federal Government and states, until arriving at vaccination rooms in the municipalities.

In general, the chain works well and ensures safety for the population, once any change in the conservation of vaccines must be reported to the PIN. But, as with other aspects of the program, the conditions of maintenance and renewal of this chain - which includes refrigerators, freezers and refrigerated means of transport - are not homogeneous in all states and municipalities.

Recently, the Ministry of Health invested R$ 106 million in improving the cold chain. One of the actions planned is to carry out a broad mapping to identify needs and vulnerabilities and thus guide investments in this area.

According to José Cassio de Moraes, a consultant with the Pan American Health Organization (PAHO), the program’s extensions have also brought new demands on the cold network. The increase in the number of vaccines incorporated into the official calendar and the expansion of the target audience to be reached require a greater storage capacity.
Incorporation and sustainability

The National Immunization Program (PNI) has a common dilemma in all areas of health: how to reconcile the development of new technologies and vaccines and the need to offer them to the population with a budget that, although constant and safe, is finite and limited.

Equating the innovation and financial sustainability binomial is one of the main current challenges of the PNI and a situation that tends to become increasingly present as science advances and the epidemiological profile of the world and Brazil are transformed.

The development of new technologies requires more and more investments and the future comes with the need to provide answers for the prevention of chronic diseases, which become more common as the population ages.

Although the PNI has become known throughout the world for the provision of a wide range of vaccines, not all those currently in the country’s private clinics are available in the Unified Health System (SUS).

“We have not yet offered the elderly population, which vaccinates in the public network, all the resources available in the private network, such as vaccines against pneumonia”, says Renato Kfouri, vice-president of the Brazilian Society of Immunizations.
Innovation and access

From the 1960s, the world witnessed an unprecedented scientific development in the field of immunization. New technologies enabled the emergence of a large number of vaccines, and many of those that were in use underwent important modifications, which made them more modern, safe and effective.

The accumulation of scientific knowledge promoted in parallel a great expansion of population access to vaccines, allowing the immunization to be extended to other groups, such as the elderly and adolescents. He also promoted the emergence of vaccines with "new concepts", according to the professor of the Faculty of Pediatrics at USP, Gabriel Oselka.

“This scientific contribution gave rise to combined vaccines, which enable the prevention of multiple diseases with a single vaccine. It opened up several possibilities for improving immunobiologics, promoting the emergence of safer products with better results and fewer adverse effects", says the researcher.

An example: Until the 1960s, vaccines were produced with dead or attenuated viruses or bacteria. This group is considered a first generation vaccine against smallpox, measles, poliomyelitis, among others.

Although attenuated vaccines remain in use, to increase safety without compromising efficacy researchers have also begun to use increasingly smaller fractions of these agents. In the second generation, vaccines began to only contain the proteins of these microorganisms capable of provoking a response from the immune system. Vaccines such as toxoid tetanus and diphtheria belong to this category.

Other classes of vaccines, called conjugates, such as Hepatitis B and HPV, became possible only after the development of genetic engineering, opening a new field of studies and protection for the population.

The recently launched dengue vaccine itself is an important epidemiological landmark to prevent the onset of an incurable virus and can lead to serious complications. It is a way to prevent the disease, especially its more severe forms, and can prevent thousands of deaths. According to the Ministry of Health, Brazil recorded 802 thousand cases of the disease in 2016.
Third generation vaccines, called DNA vaccines, work with sequences of the genetic material of the virus or bacteria to be combated and with agents capable of transporting them into our cells, called “DNA vectors”.

“Results such as these have only become possible because of a huge global research and study effort involving companies around the world. A concentrated effort and enormous complexity. Nowadays, the safety requirements are extremely strict and to introduce a new vaccine, one is required to follow a multitude of regulatory obligations”, says Oselka.

In the evaluation of Akira Homma, Scientific Advisor at the Bio-Manguinhos/Fiocruz Institute of Technology in Immunobiologicals, the development of vaccines is also a high-risk endeavor. The breakthrough of immunization requires very high and continuous investments in research and development over a long period of time and with uncertain return, because it is not possible to know in advance whether the results will be satisfactory.

Each project includes several stages and steps until a vaccine can be approved for human use and many experiments and attempts fail along that path.

To get an idea, according to researchers Stanley A. Plotkin, Paul A. Offit and Walter Orenstein from the University of Pennsylvania, in the book entitled “Vaccines,” the varicella vaccine took about 25 to 30 years to be approved; the HPV vaccine also demanded the same time; in the case of the rotavirus vaccine, it took between 14 and 16 years and, until the population could have access to a combination of pediatric vaccines, from 10 and 12 years had to pass by.

According to Oselka, the vaccine industry is very dynamic worldwide. The constant search for greater efficacy and safety impels the research and development of new immunobiologics continuously, allowing more people to have access and benefit from the immunization.
New vaccines, new audiences

In the 1970s, only four vaccines were required and given to children in the first year of life: BCG, DTP (diphtheria, tetanus, and whooping cough), against measles and poliomyelitis. However, with scientific and technological development, new vaccines have emerged or have been perfected.

Since 1990, Brazil has adopted the multi-vaccination strategy to complement the basic plan for the first years of life, progressively expanding the immunization program. Hepatitis B vaccines, as well as the double and triple viral vaccine (measles, rubella and mumps) became part of it.

In 1999, the country adopted the 1st vaccination campaign of the elderly, with immunization against influenza. At the same time, some vaccines have been replaced by more modern versions, such as the diphtheria and tetanus vaccine, a substitute for the tetanus vaccine.

Currently, 19 vaccines are incorporated into the PNI, protecting the population against more than 20 types of diseases. Publics also expanded, as well as the age groups benefited, forming a complex calendar that includes vaccines from birth to the old age, going through all stages, such as gestation.

Evolution of the incorporation of vaccines and audiences in the national calendar

Decade of 1970

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Target population 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus Calmette Guerin (BCG)</td>
<td>At birth</td>
</tr>
<tr>
<td>Oral poliomyelitis vaccine (OPV)</td>
<td>2, 4 and 6 months. Reinforcement at 15 months and 4 years</td>
</tr>
<tr>
<td>Diphtheria, Tetanus and Pertussis (DTP)</td>
<td>2, 4 and 6 months. Reinforcement at 15 months</td>
</tr>
<tr>
<td>Measles vaccine</td>
<td>9 months</td>
</tr>
</tbody>
</table>

Decades of 1980-1990

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine</th>
<th>Target population</th>
<th>Comments 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Hepatitis B vaccine</td>
<td>13 municipalities Western Amazon</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>2nd dosage of measles vaccine</td>
<td>15 months old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triple viral vaccine</td>
<td>1 year old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>By vaccination campaigns (1 to 11 years of age)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>Hepatitis B vaccine</td>
<td>&lt;1 year old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shortages in the country started in 1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Hemophilic influenza B (Hib)</td>
<td>&lt;1 year old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seasonal influenza in the elderly</td>
<td>In the elderly (65 years)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>expanding in 2000 (60 years)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Decade of 2000

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine</th>
<th>Target population</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Triple viral vaccine</td>
<td>1 year old</td>
<td>Exclusion of monovalent vaccine</td>
</tr>
<tr>
<td></td>
<td>Tetravalent vaccine (DTP + Hib)</td>
<td>&lt;1 year old</td>
<td>Replacement of triple bacterial (DTP) and monovalent (Hib)</td>
</tr>
<tr>
<td>2006</td>
<td>Human rotavirus oral vaccine</td>
<td>20 to 49 (women)</td>
<td>1m15 days (D1) and 5m15 (D2)</td>
</tr>
</tbody>
</table>

Source: Ministry of Health
# Decade of 2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine</th>
<th>1 Target population</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Pneumococcal 10-valent conjugate vaccine</td>
<td>&lt;1 year old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meningococcal conjugate C vaccine</td>
<td>&lt;1 year old</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>Hepatitis B vaccine</td>
<td></td>
<td>Expanding for people from 20 to 24 years old</td>
</tr>
<tr>
<td></td>
<td>Seasonal influenza vaccine</td>
<td></td>
<td>Children 6 months to 2 years; pregnant women; health</td>
</tr>
<tr>
<td>2012</td>
<td>Hepatitis B vaccine</td>
<td>25 to 29 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viral triple</td>
<td></td>
<td>VIP / VOP sequential scheme</td>
</tr>
<tr>
<td></td>
<td>Seasonal influenza vaccine</td>
<td></td>
<td>substituted the tetravalent one</td>
</tr>
<tr>
<td>2013</td>
<td>Tetraviral (Measles, rubella, mumps, varicella)</td>
<td></td>
<td>Expanding for people from 30 to 49 years</td>
</tr>
<tr>
<td></td>
<td>Human rotavirus oral vaccine</td>
<td></td>
<td>Expanding for men and women up to 49 years</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A</td>
<td></td>
<td>Extension for puerperal women, comorbidities and people with special conditions</td>
</tr>
<tr>
<td></td>
<td>dTpa</td>
<td>15 months old</td>
<td>Replacing the 2nd dose of viral triple</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>&lt;1 year old</td>
<td>1m15 days (D1) 2nd dose up to 7m29d (more opportunity for vaccination)</td>
</tr>
<tr>
<td>2014</td>
<td>Seasonal influenza vaccine</td>
<td>1 year old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td></td>
<td>Pregnant woman between the 20th and 36th week of gestation</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>11 to 13 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vacina influenza sazonal</td>
<td></td>
<td>Children 2 to 5 years</td>
</tr>
<tr>
<td>2015</td>
<td>HPV</td>
<td>9 to 13 years old HIV + women (9 to 26 years old)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Ministry of Health
Anti-vaccine movement

A movement contrary to the use of vaccines has begun to gain strength in Brazil, especially through social media. Fearful of adverse reactions, even if there is no scientific evidence about them, mothers and other tutors are failing to get their children to even receive the basic vaccines from the national immunization calendar.

Experts believe that the movement is a consequence, to a certain extent, of the very success of vaccines and immunization programs around the world. The eradication of many diseases made the threat they pose to society forgotten, prompting many to question the need for immunizations.

This has had repercussions in the press and worried the Ministry of Health, as it is not only an individual issue, but a public healthcare issue. If vaccination coverage decreases in the country, eradicated diseases or those with a low incidence might return and cause outbreaks.

Recently, the United States has had an outbreak of measles, a disease that could be prevented with vaccination. This phenomenon is attributed to the propagation of the anti-vaccine movement.

According to experts, tutors discreetly and occasionally anonymously share in social media information with no scientific basis on possible harm to health and adverse reactions from vaccines. This strategy is adopted to avoid negative repercussions and, thus, reduce the risk of denunciations to the Guardianship Council.

There are cases of mothers who admit to hide from their own husbands the decision not to vaccinate their children. This attitude is even encouraged by antiviral activists, especially regarding pediatricians and children’s schools.

They are also advocating the use of alternative therapies, such as homeopathy and supposedly medicinal oils, to strengthen the immune system of children. The healthy appearance, as well as caring for the little ones’ feeding, completes the view that vaccines would pose an unnecessary risk - although there is no scientific evidence for this.

To restrain the movement, the medical profession has reinforced the explanations to mothers and other tutors that the vaccines available in the country have the effectiveness and safety proven by robust studies and verified by the control of the sanitary bodies.
The Vaccine revolt

At the beginning of the twentieth century, a movement marked actions to combat infectious diseases. At that time, unlike today, populations, for absolute lack of knowledge, refused to take vaccines believing that they did not bring any benefit, but, on the contrary, could pose many health risks.

At the time, the then capital of Brazil, Rio de Janeiro, grew with no structure. The population was advancing towards the hills, forming slums with no sewage network or garbage collection. The lack of basic sanitation has favored the proliferation of contagious diseases such as yellow fever, bubonic plague and smallpox. The latter, alone, killed more than 3,500 people in 1904.

The situation was alarming and forced the then president Rodrigues Alves to create a broad revitalization project for the city, which began in the central region. Hence, the biologist and sanitarian Oswaldo Cruz was appointed as head of the National Department of Public Health.

Revitalization included demolition of slums, fighting mosquitoes, rodents and other animals that could transmit disease, in addition to the Compulsory Vaccination Campaign. In it, people were vaccinated compulsorily, with the use of violence in some cases. The Mandatory Vaccine Act was instituted on October 31st, 1904, with the implementation of the campaign in the following month.

Needy and with little education, the population of Rio de Janeiro did not understand the importance of the vaccine to prevent potentially fatal diseases. Driven also by the economic crisis, residents began to destroy trams, the main means of transportation in the period, as well as buildings, trains, shops and police stations. This episode became known as the Vaccine revolt.

The popular uprising caused the government to suspend the law on November 16, 1904, removing the compulsory vaccination. It took the intervention of the army and the navy, as well as the police, to restrain the population and end the revolt.

After that, the vaccination was resumed. In 1906, two years after the revolt, only nine deaths were recorded from smallpox, and in 1910 only one victim was recorded. After more than 300 million fatalities in the 20th century, smallpox was officially declared extinct by the World Health Organization (WHO) in 1980.
The future of vaccines

The great amount of knowledge accumulated in the area of immunization opens up to the future of Brazil and of the world huge possibilities for new vaccine lines to be developed, as a response to needs that are not yet met today.

There are currently about 300 ongoing immunization surveys in the United States under PhRMA, which represents the pharmaceutical research industry in that country. It is not yet possible to predict which of these studies will succeed, or when the vaccines will be available in the market, but the lines of research reveal the nature and the tendency of the efforts, and for which diseases the concern of the global scientific community is turned to.

One of the great current areas of research that mobilizes scientists, researchers and companies worldwide is the prevention of various types of cancers. What is sought is to advance and prevent other forms of the disease, as it is happening today through the vaccine against HPV, which protects against cervical cancer, and the vaccine against hepatitis B, which prevents liver cancer.

There are currently lines of studies against tumors of the prostate, breast, colorectal, ovary, pancreas and digestive system, among others. All these diseases have registered significant advances around the world, with worrying mortality rates. Brazil also faces this problem and would certainly greatly benefit from the prevention of these diseases through immunization.

“Researchers are deepening studies to better establish the nexus between the occurrence of viruses and the development of cancer,” says Eduardo Hage Carmo, a professor at the Institute of Collective Health for the Federal University of Bahia.

The Bio-Manguinhos/Fiocruz Scientific Advisor, Reinaldo de Menezes Martins, adds that there is no way to say that there are insoluble problems, as immunological technologies are being improved more and more. “Challenges drive innovation. We are still in the control stage of infectious diseases caused by microbial agents. Even greater difficulty will exist to apply vaccination to non-infectious diseases, such as the various forms of cancer. There are many genetically based diseases that, apparently, only gene therapy will be able to avoid or control, and thus, immunology and genetics need to work in interaction, or as alternatives.”

What is being sought is to prevent other forms of cancer, as is the case today with the vaccine against HPV, which protects against cervical cancer, and the vaccine against Hepatitis B, which prevents liver cancer.
In the field of infectious diseases, where immunization science and technology have achieved their greatest victories to date, there are still needs and difficulties that challenge the world and are also the focus of global attention. This is the case of research for the production of vaccine against zika and chikungunya, which make large numbers of victims in Brazil and worldwide. And still against malaria, schistosomiasis and Chagas disease.

Despite all technological advances, efforts to produce vaccines against HIV, hepatitis C and respiratory syncytial virus, one of the main causes of infection in newborns and children, have persisted for decades.

The fight against HIV, for example, concentrates researches for both the development of preventive vaccines and post-infection treatments. These are extremely complex studies, since the virus has one of the most sophisticated mechanisms for surviving the body's natural defenses. However, breakthroughs have been recorded. Some studies have already passed the early stages. There is a growing hope that, one day, AIDS can be fought with a definitive weapon.

**New perspectives**

**Malaria.** According to the international humanitarian organization, Doctors with no Boundaries, in 2015, 214 million new cases were registered worldwide and an estimated 490,000 people have already died from the disease. Malaria must have its first vaccine licensed in 2018.

**Schistosomiasis.** It is one of the most socioeconomically devastating parasitic diseases, second only to malaria. According to the World Health Organization (WHO), about 200 million people are living with schistosomiasis worldwide, and the high ratio has a strong connection to precarious sanitation, reaching endemic areas in more than 70 countries including 19 states of Brazil.

After 30 years of development, the Oswaldo Cruz Foundation (Fiocruz) is carrying out final tests in humans of the Brazilian vaccine against schistosomiasis, called the Sm14 Vaccine. If the results are positive, it is ready for use in 2017. The initiative has been chosen as an investment priority of the World Health Organization (WHO).

**Chagas disease.** It is estimated that about 12 million people worldwide suffer from the disease. Of those, three million in Brazil alone, according to the Ministry of Health.

Studies for the development of the vaccine against Chagas disease have been coordinated for 20 years by the Federal University of São Paulo (Unifesp) and a Brazilian vaccine capable of stimulating the immune system against the parasite that caused the disease was successfully tested in a therapeutic manner in experiments with mice.

The increase of the elderly population and the search for a healthy aging bring new demands that should also be contemplated by the researches. One of the necessary responses is how to deal with immunosenescence, loss of the body’s ability to respond to infections and immune memory, especially vaccination - a condition that occurs gradually over the years.

In addition, science maintains a constant effort to improve, through incremental innovations, existing vaccines. Whether by improving production processes or reducing the risk of adverse reactions. Another trend is to increase the number of vaccines that can be conjugated to a single product effectively and safely.

Currently, there is technology available to compose up to six products. Conjugate vaccines help improve population adherence to immunization and increase coverage, as people will have to go only once to the health clinic to get a shot.

Along the same lines, research that seeks to obtain vaccines that are more effective, long-lasting and that produce fewer adverse effects, such as influenza, must be taken only once a year.

Efforts are not lacking and they occur around the world in an extraordinary concentration of brains and talents aimed at increasing survival and improving the quality of life of the population at the global level. This is an enormous undertaking, of a size equivalent to the challenge that scientists face.

The average for a radical innovation in vaccines to be successful easily surpasses a decade of research. What is being studied today can reach the market perhaps only as a benefit of the next generation. Despite this, the effort is always transformative, with a significant impact in reducing the incidence of diseases and mortality rates, and in many cases, it can result in the total eradication of the disease. The wait is not easy and the efforts are gigantic, but the benefit to society is equally great.
Is it possible to summarize in a few words what vaccines represent for our society?

The achievements of science in the field of vaccines are so expressive and transforming that we have forgotten how the world was before them. Smallpox, for example, killed more than 300 million people in the last century - that’s equivalent to one Brazil and a half. However, do you hear anyone talking about smallpox today? Or measles? This disease infected more than 300,000 people in the United States alone in the 1960s, causing hundreds of deaths. Today, however, no one cares about measles. This was only possible thanks to the vaccines. They succeeded in eradicating or significantly reducing diseases that were at the top of the list of world health concerns. Often, such diseases led to the global ranking of concerns in general, because an illness has an impact on the economy, politics and international relations, as well as on the family routine, transforming the routine of entire families when a body becomes ill.

Today, data from the World Health Organization show that more than three million deaths are prevented every year thanks to the adoption of a calendar of basic vaccines worldwide, which protect people from more than 20 diseases. We are talking about the older vaccines, which have already been established even in countries with low levels of development.

It is estimated that the number of deaths avoided could increase by at least 50% if other, more modern vaccines were not neglected.

Thus, in a few words, vaccines are capable of transforming history, removing barriers that seemed insurmountable, and enabling society to become less vulnerable and advance more safely.
Will this kind of transformation continue to occur in the next few years? What are the current challenges in the field of vaccines?

The researches of the previous decades defined the transformations recently generated by vaccines and of which we can now enjoy. We can imagine the same thing regarding the future when we look at current research. There are more than 300 immunizers in different phases of clinical trials around the world. Dozens of studies are looking for a preventive vaccine against HIV and others are aimed at treating the already infected patient. Imagine a world free from AIDS. Maybe, we are not that far away. Among sexually transmitted diseases, HPV was a huge concern, especially among women, as it can progress silently to cervical cancer. Currently, this scenario is already beginning to change. The creation of recent vaccines is already protecting the new generations from many strains of the disease, with an expected impact on the incidence of the disease.

In total, there are more than 120 infectious diseases and 105 different types of cancer that are the target of the vaccines currently under development. Dengue, herpes, ebola, Alzheimer’s disease, type 1 diabetes, multiple sclerosis, celiac disease, gout, rheumatoid arthritis, kidney cancer, lung cancer, breast, pancreas, prostate and ovary cancer are some examples. It is important to highlight those advances in vaccines against bacteria. The misuse of antibiotics, among other problems, has favored the creation of bacteria increasingly resistant to drugs today available in the market. It is understood that many of these infectious diseases need effective preventive treatment, as their combat may be close to becoming unfeasible. Therefore, there are many lines of research in this area.

It may take a few years for one to come up with a transformative novelty, perhaps another 20 years, as has already been expected in other cases. The global average for vaccine release, considering the period between the beginning of its creation and the end of the phase III trials, when the drug is submitted to sanitary agencies approval, varies between 10 and 15 years. Nevertheless, regardless of the waiting time for the studies to advance, each vaccine presented to the market always has a transforming potential.
Why do vaccines take so long to develop?

Because the technology applied is very sophisticated. If the pharmaceutical industry is widely observed, it is safe to say that the biggest challenge facing us today is the development of biological medicines. This is because their production process is very delicate, complex and sophisticated, in which small variations in the manufacturing conditions can influence the final product. Making the drug is already extremely complicated, but before that there is an even bigger challenge, the challenge of radical innovation, where scientists need to figure out how to make the drug. Multicenter studies are required for several consecutive years to achieve consistent results that ensure patient safety and efficacy. The specific field of vaccines deals with all of this. As with other biological medicines, vaccines work with living organisms and DNA manipulation. This is still extremely challenging these days, but it has been on the routine of immunization research for decades. Therefore, creating vaccines means being on the boundaries of science, working with many more questions than answers and facing many more failures than victories.

So, is dealing with the creation of vaccines an activity with many uncertainties?

Innovation in any area is by nature a risky activity, filled with uncertainties. We do not know when the discovery will take place, not even if it really will happen someday. Million-dollar investments are needed to bring cutting-edge technology to highly skilled researchers in structures that often require foundations in many countries. The pharmaceutical industry deals with this challenge, sometimes with the support of public laboratories or with funding from state-owned banks, but often only with its own resources. It is not uncommon to find researchers who have been conducting several lines of research for more than 30 years to stop a disease. The cost of this is gigantic. However, the gains to society, when a vaccine is finally created, can be fairly transformative. The effort is worth it. And someone needs to assume this responsibility.
HOW VACCINES CHANGED A COUNTRY
Beginning of operation in Brazil: 1908

Headquarters in Brazil: Estrada dos Bandeirantes 8464, Rio de Janeiro, RJ

Since 1988, when we registered the hepatitis B vaccine (recombinant) Engerix® B, GSK has distributed vaccines nationwide. Today, we are present in 80% of the vaccination schedules for children and adolescents in Brazil.

In addition to serving the private market, we have established solid partnerships with the Brazilian government for the control of poliomyelitis, measles, mumps, rubella, chickenpox, pneumococcal diseases, Haemophilus influenzae type b, rotavirus, meningococcal diseases, diphtheria, tetanus and pertussis.

UNICEF also highlights the reduction of child mortality in the country by 77%, along the last 20 years. The Fund cites a “combination of strategies” responsible for such reduction, including health services in communities, improved sanitation condition, promotion of breastfeeding and expansion of immunization.

Our portfolio of potential new vaccines covers diseases that still have a serious impact around the world, including Herpes Zoster, Malaria, HIV, Tuberculosis and Ebola.
Start of operation in Brazil: 1952

Headquarters in Brazil: São Paulo, SP.

For 125 years, MSD has been committed to the discovery and development of vaccines capable of preventing numerous diseases such as measles, mumps, rubella, varicella, rotavirus, hepatitis A and B, herpes zoster, pneumococcal disease, as well as cancers and diseases related to human papillomavirus (HPV). Currently, the company has one of the broadest portfolios of immunization for pediatric and adult use.

Present in Brazil since 1952, MSD is dedicated not only to inventing vaccines and offering services capable of improving and saving lives of the population, but it also seeks ways to increase the population’s access to its products. One of the company’s more achievements in this regard was the availability of the HPV vaccine, which can prevent about 90% of genital warts and 70% of cervical cancers, free of charge to millions of girls and boys through a technology transfer agreement signed by MSD with Butantan Institute.

MSD actively collaborates with the continued medical and scientific education in the country by sharing information on the impact and importance of prevention and health care, from birth to the later stages of life.
Start of operation in Brazil: 1952

Headquarters in Brazil: São Paulo

Pfizer has been strengthening its vaccine area, both by expanding the portfolio and by encouraging the discovery of innovative immunizers. This is one of its priority areas for investments in Research and Development, which is reflected in a diversified pipeline, contemplating molecules that in the future may help in the fight against challenging diseases, such as infections by resistant bacteria, namely Staphylococcus aureus and Clostridium Difficile.

The company’s trajectory in vaccines was driven by the acquisition in 2009 of Wyeth Laboratories, a company with a tradition in this segment that, throughout the 20th century, played a decisive role in worldwide epidemics, such as smallpox. It was also the primary supplier of the first oral trivalent vaccine against poliomyelitis and the vaccine against typhoid fever in World War II. Another key contribution was the development of the pneumococcal conjugate vaccine, considering the strong impact of pneumococcal diseases in the world.

By acquiring Wyeth, Pfizer had the opportunity to use its commercial and global scale capability to expand the distribution of the 13-valent pneumococcal conjugate vaccine, which protects against the most prevalent pneumococcal serotypes in the world. Launched in Brazil in 2010, initially for infants and children, currently Prevenar 13 is indicated for Brazilians of all ages and traded in more than 120 countries.

The company’s efforts are also focused on the fight against meningitis, characterized by the ease of contagion, rapid evolution and high lethality. The acquisition of the Nimenrix vaccine in 2015 to prevent meningococcal disease associated with the ACWY serogroups of the bacterium Neisseria meningitides is one of the company’s responses to this challenge.
Start of operation in Brazil: 1974

Headquarters in Brazil: São Paulo, SP

Sanofi Pasteur, one of the world’s leading vaccine manufacturers and distributors, arrived in Brazil in 1974, following a request from the Brazilian government to provide doses of the vaccine against meningitis. At the time, 90 million Brazilians were immunized, ending the epidemic.

With more than 1 million euros invested per day in research and development of vaccines, the company currently offers a wide range of vaccines for the immunization of Brazilians, such as the vaccine against influenza, rabies, poliomyelitis and, since 2016, offers the first and only vaccine against dengue.

Our main goal is to protect people against infectious diseases through safe and effective vaccines. We have a broad portfolio of immunizations that protect against 20 bacterial and viral diseases.

Over the years, Sanofi Pasteur has established several partnerships with the Ministry of Health and public laboratories in Brazil to respond to the country’s main public health needs. We have technological partnerships for influenza vaccines, rabies and inactivated poliomyelitis vaccine.

Our more than ten-year partnership with the Butantan Institute has made it the first public laboratory in South America to manufacture the influenza vaccine, which immunizes about 50 million Brazilians against the disease each year.

The agreement with Bio-Manguinhos, the Institute of Immunobiological Technology of the Oswaldo Cruz Foundation (Fiocruz), has allowed the introduction of the inactivated vaccine against poliomyelitis (VIP) by the Sanofi Pasteur in the National Immunization Program.

Sanofi Pasteur is proud to have significantly contributed to the constant improvement of the country’s public health through disease prevention. The company will follow its commitment so that fewer and fewer Brazilians will suffer or die from an infectious disease that can be prevented by vaccination.