

Review

Vaccine research, development, and innovation in Brazil: A translational science perspective

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ARTICLE INFO

Keywords:

Vaccines
Innovation
Translational sciences
Brazilian immunization program

ABSTRACT

This article examines the Brazilian innovation policy for vaccines and its impact on infectious diseases, with emphasis on advances in translational science. The results indicate significant progress, with a rapid increase over the past two decades in the number of vaccine research groups, indicating scientific excellence. Advances and gaps in technological development and in public–private partnership initiatives were also identified. We stress the crucial role of partnerships, technology transfer, and targeted policies that could accelerate Brazil's participation in global vaccine research and development. We propose that new strategies should be urgently conceived to strengthen the links between the scientific and technological policies, the National Health System, and the National Immunizations Program in Brazil to provide access to low-cost vaccines to address major public health challenges. We also discuss the lessons learned from the Brazilian experience in the implementation of governmental policies on vaccine innovation that could be applicable to other developing countries.

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1. Introduction

The global scientific and technological capacity for innovation in vaccines for infectious diseases has advanced rapidly. Innovative strategies have resulted in new and effective vaccines against hepatitis B virus, *Haemophilus influenzae* type b, *Streptococcus*

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pneumoniae, *Neisseria meningitidis*, and human papillomaviruses, as well as new combination vaccines, such as the pentavalent vaccine [1].

At the same time, international demand for vaccines has increased. Many of the poorest countries are now incorporating new vaccines, with financial support from the GAVI Alliance. Support from the Bill & Melinda Gates Foundation (BMGF) and other international organizations, such as WHO and UNICEF, has contributed to significant advances in immunization and eradication strategies and to spectacular progress in National Immunizations Programs worldwide. Many countries have already attained high immunization coverage, saving the lives of millions of children and helping to reach Millennium Development Goals [1,2].

Moreover, in a global context of economic crisis, permeated by sharp social inequalities, there is increasing awareness among policymakers of the crucial role that vaccines can play in improving the life conditions of the poorest populations because of their high public health impact and cost-effectiveness. In fact, WHO estimates that immunization against vaccine-preventable diseases currently averts nearly 2.5 million deaths per year worldwide, and that an additional 2 million deaths could be prevented by improving access to existing vaccines [1,2]. Successful international immunization strategies—such as the eradication of smallpox, the significant reduction of polio's incidence, and the rapid decrease in measles deaths—illustrate well the global impact of vaccines.

Heightened awareness of vaccines' impact and increased global demand for vaccines have highlighted a need for strategies to strengthen local capacity for vaccine research and development in emerging economies, such as Brazil. Brazil has participated actively in many international immunization initiatives, with policies supporting the development of national capacity as well as free, universal access to vaccines. The national scenario for vaccine research, development, and production has significantly changed over the past five years in Brazil. Many of the proposals made by the scientific and technological communities to increase use of vaccines have already been successfully implemented in the national Health Industrial Complex Program, an outcome of the new technological and industrial policies in Brazil, established by the Brazilian government in 2008. In this Program, many important areas with technological gaps were identified to receive investments in order to overcome constraints and make possible to respond to the country's needs and to strengthen the National Health System (SUS).

2. Materials and methods

We provide here an analytical evaluation of vaccine policies in Brazil and their outcomes, based on updated information from government documents, published papers, and national and international databases. We also indicate the national capacity for translational research [3], describing the national policies and strategies conceived to translate findings in basic research more rapidly and efficiently into medical practice and public health, accelerating the use of innovative vaccines.

3. The National Immunizations Program: universal and free access

The mass vaccination campaign to eradicate smallpox from 1966 through 1973 created the social and political foundations for the emergence of a "culture of immunization" in Brazil [4], which resulted in the successful and internationally recognized Brazilian National Immunizations Program (NIP). The new social norms and the vaccine culture of the 1970s contrasted dramatically with the

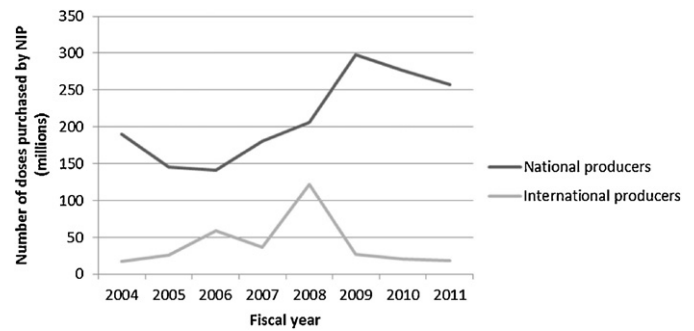


Fig. 1. Amount of vaccine purchased from national and international producers by Brazil's NIP, 2012. Note: Increased international purchase in 2008 is mostly due to measles-rubella vaccine for national campaign on rubella eradication.

Source: Elaborated from data provided by the National Immunizations Program, Ministry of Health, Brazil.

previous occurrence of episodes of intense popular resistance to vaccination—as exemplified by “The Revolt Against the Vaccine” that occurred in 1904 in Rio de Janeiro during a smallpox vaccination campaign directed by Dr. Oswaldo Cruz.

This change in the social perception on immunization led to new governmental policies and the creation in 1976 of Bio-Manguinhos, a federal institute for vaccine manufacture at the Oswaldo Cruz Foundation. Now a large complex for vaccine development and manufacture, Bio-Manguinhos maintains rigorous quality management and is one of the main vaccine providers for the NIP. State governments have also built vaccine-manufacturing facilities, such as the Butantan Institute in the state of São Paulo and the Ezequiel Dias Foundation in Minas Gerais. With the new 1988 Brazilian Constitution, which introduced free, universal access to health care as a civil right, these public manufacturers became crucial players in the support to the NIP and the new SUS.

The Brazilian NIP is recognized as one of the most comprehensive and effective immunization programs among emerging countries and is comparable to the immunization programs of developed countries. It was a pioneer in the introduction of rotavirus vaccine in 2007 and of pneumococcus 10-valent conjugate vaccine and meningococcal C conjugate vaccine in 2010. These vaccines—and the almost-universal vaccination against influenza pandemic H1N1 in 2009—indicate the technical and operational capacity of the NIP and the Ministry of Health. In 2012, the NIP is introducing inactivated polio vaccine, hepatitis A vaccine, and tetravalent MMR + varicella vaccine.

National public producers supply more than 90% of the vaccines purchased by the NIP (Fig. 1). This is a successful outcome of the strategies conceived and implemented by the National Vaccine Self-Sufficiency Program. Brazil provides universal vaccination free of charge for all, targeting children, adolescents, the elderly, and indigenous populations. It also provides access to most of the vaccines in the international market. This policy has resulted in the successful global eradication of smallpox and in the elimination of autochthonous cases of polio, measles, and rubella in the country. Moreover, all states have established special clinics for immunization of persons at special risk, such as those who are immunodeficient.

The NIP's rapid growth is also remarkable. Its budget for vaccine purchase has grown exponentially since 1995, reaching US\$ 800 million in 2012, as indicated in Fig. 2.

This strategy utilizes the government purchase power by which, at the moment of introduction of a new vaccine into the NIP it is also negotiated with the vaccine provider its technology transfer of production. The adoption of this strategy continuously for years has maintained a sustainable supply to the NIP, improving the technological capacity and the qualification of national

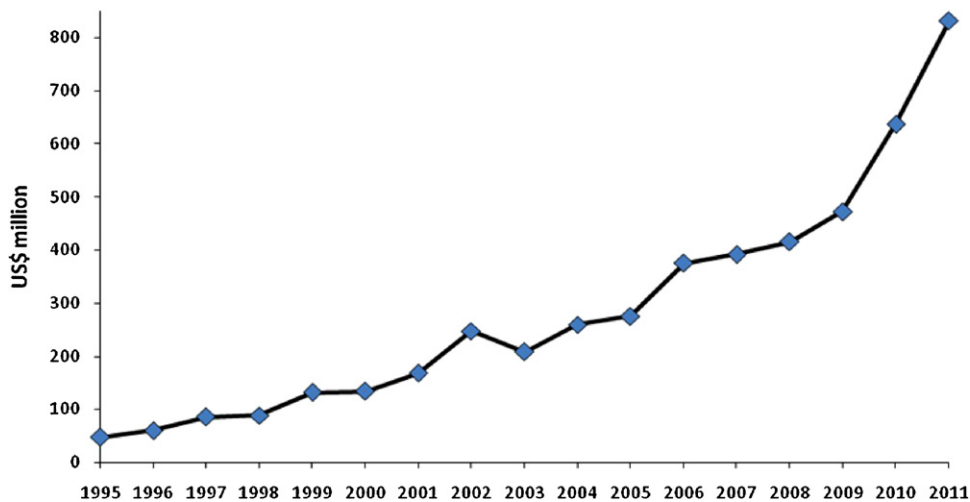


Fig. 2. Evolution of expenditure with purchase of vaccines in the NIP Brazil, 1998–2011 (in US\$ million). Updated in 16/03/2012. Not included here the government expenditure with emergency purchase of Influenza A (H1N1) vaccine in 2010: US\$ 700 million, provided through complementary sources of funding.

Source: Elaborated from data provided by the Brazilian National Immunizations Program, Ministry of Health.

manufacturers, as well as the infra-structure for vaccine development and production.

4. Converging policies

There has been a convergence of policies supporting the NIP, and major forces have critically contributed to work to advance innovation, technological development, production capacity, and implementation of vaccine programs in Brazil. While NIP's operation and implementation were improving, other major activities were simultaneously strengthened, such as the producers' technological development and capacity of production, the quality control and assurance system, and the national epidemiological surveillance system. These four driving forces, although coordinated by different government structures, were supported and developed in a similar fashion, and together they assured a strong structure and organization for Brazil's immunization program.

The Brazilian National Regulatory Authority (ANVISA), a main component of this strategy, is well organized and structured. WHO has recognized that Brazil has established all essential regulatory functions, such as registration of products, laboratory testing, and lot release system through the National Institute of Quality Control for Health (INCQS), with the analysis of field trial protocols and approvals, inspections for Good Manufacturing Practices, and pharmacovigilance. The Ministry of Health created a National Committee on Pharmacovigilance for Vaccines and other Immunobiologicals that includes ANVISA, INCQS, and the National Health Surveillance Secretary. The committee meets regularly, with *ad hoc* participation of outside experts.

The epidemiological surveillance system is also well organized and structured and works in a network system with state public health laboratories. Epidemiological information is available online and is also published monthly. The yellow fever surveillance system includes surveillance of monkeys' deaths in all regions.

5. Vaccines: the global market and opportunities in Brazil

At the global level, vaccines are a fast-growing segment of the pharmaceutical market, although they still represent only a small component of it. Recent advances in biotechnology, from

recombinant DNA, have opened a broad range of perspectives for vaccine innovation.

This scenario has motivated multinational companies to move their investments into new innovative vaccines, such as recombinant hepatitis B, conjugate heptavalent pneumococcal vaccine and HPV, which are more profitable and expensive, produced mainly for use in developed countries. Some of them have recently stopped production of traditional and less expensive vaccines, essential for developing countries [6–8].

Because more than 75% of global vaccine production is concentrated in a few multinational corporations, this trend has affected global vaccine supplies. It has led to an impasse that has especially affected the poorest developing countries.

Public and private manufacturers in emerging economies such as Brazil are making significant efforts to overcome this impasse by increasing the production of traditional vaccines of lower added value that are essential for resource-limited countries. Several authors have emphasized the increasing participation of manufacturers from developing countries, including Brazil, in the global traditional vaccines market, around 60% in 2010 [6–8].

In fact, most of the vaccines procured by UNICEF and the Pan-American Health Organization (PAHO), through the PAHO Revolving Fund/WHO, are provided by the Developing Countries Vaccine Manufacturers Network (DCVMN). Bio-Manguinhos, as a member of DCVMN, is prequalified by WHO and is exporting yellow fever vaccine through United Nations agencies.

At the international level, BMGF and other international organizations, such as WHO, are playing an important role in helping to overcome these gaps in global vaccine supply. Innovative financing mechanisms have also been conceived to support vaccination in the poorest countries [9]. These include the International Finance Facility for Immunization (IFFIm), developed by GAVI, and the Advance Market Commitment, developed by G-8 countries, to stimulate production and innovation.

Brazil is now an important market for human vaccines in the developing world, mainly as a result of significant public purchases by the NIP. The two main national producers, Bio-Manguinhos/Oswaldo Cruz Foundation (FIOCRUZ) and the Butantan Institute, supply 83% of the NIP demand for vaccines for human use [5]. The main international suppliers are GlaxoSmithKline and Sanofi Pasteur (Sanofi-Aventis vaccine division), followed by Wyeth (Pfizer), MSD, and Novartis.

Table 1
Development of bacterial vaccines in Brazil, 2012.

Vaccine	Phase of development	Institute(s)/Enterprise(s)
Meningococcal B	Phase II	Bio-Manguinhos
Meningococcal C	Phase II	Bio-Manguinhos
Meningo C conjugated/meningo B OMP	Preclinical	Butantan Institute
Pentavalent vaccine (DPT+) Hib + hepatitis B (HB)	Phase III	Bio-Manguinhos/Butantan I.
Pneumococcal vaccine cloned antigen/conjugated polysaccharides	Preclinical	Butantan Institute
DNA vaccine TB	Preclinical	USP/Ribeirao Preto
Combined BCG/hepatitis B vaccine	Phase II	Butantan Institute
Pertussis “low”	Phase II	Butantan Institute
Leptospiral recombinant	Preclinical	Bio-Manguinhos/GonçaloMuniz
Microspheres/oral adjuvants	Development	Butantan Institute

Source: FIOCRUZ, Bio-Manguinhos, Vaccine Development Database (2012).

6. Vaccine innovation: an update on national capacity

The policies supporting the NIP have resulted in a significant increase in the national capacity for scientific and technological research, clinical trials, and technological development of vaccines, through technology transfer agreements and joint developments, following public–private partnerships. A new legal frame has been supporting the innovation, technological, and industrial policies in Brazil: the Innovation Law, the Sectorial Funds legislation, the Law for Incentives, and several other legal instruments, which we have described in a previous publication [5].

These policies have been supported by new funding initiatives aiming to strengthen the scientific and technological capacity of national manufacturers. In the past two decades, several national and state funding agencies started to support vaccine research and development in universities and research institutes: in the Ministry of Science and Technology, the National Research Council (CNPq), and the Financier for Studies and Projects (FINEP); in the Ministry of Health, the Secretariat for Science and Technology, and the Department for Science and Technology; at the National Bank for Social and Economic Development; and at the state level with state funding agencies for research and development (FAPs). Recently, an innovative national program—Science without Frontiers, coordinated by the Ministry of Science and Technology—has provided significant funding to stimulate international scientific cooperation, including cooperation on vaccines. We describe here some of these initiatives and outcomes.

6.1. Scientific and technological research

Brazilian scientific production ranks 13th in international comparisons and has increased tenfold during the past two decades. This trend of growth exceeds that observed in established G-7 countries, according to a recent Thomson Reuters report [10]. This report also indicates that Brazil, relative to the rest of the world, performs exceptionally well in biology and biomedical disciplines,

accounting for 18.4% of global scientific production in tropical medicine based on the analysis of 10,500 scientific journals. This outcome is the result of long-standing, consistent scientific and technological policies coordinated by the Ministry of Science and Technology to build capacity and provide funding for biomedical research and development.

As a consequence of these policies, the number of vaccine research groups increased exponentially in the past two decades and there are now 65 Brazilian research and development groups involved with different aspects of vaccine research, including immunology, virology, scale-up, and clinical research. About 200 vaccine projects have been reported, most of them in the predevelopment stage, according to databases of national and state funding agencies (CNPq, FINEP, Ministry of Health, and FAPs). These projects have resulted in publications in international scientific journals [11–14].

6.2. Technological development

Significant efforts have been put in place to promote technological development in vaccines and overcome the main gaps in this area, which has been identified by the Brazilian government and policy analysts as a critical issue [15–17]. These efforts have focused on identifying new vaccine candidates; supporting centers for research excellence; strengthening the laboratory and clinical infrastructure; building new laboratories and other facilities for animal research and experimentation; establishing internationally acknowledged norms and criteria for accreditation of research laboratories and clinical centers involved in vaccine research; organizing research networks focused on discovery and innovation; and stimulating international and national multicentric networks related to new vaccine innovation.

The technological development of vaccines for infectious diseases in Brazil has been mainly conducted by public research institutes and universities, through technology transfer and joint development with multinational enterprises. The biotechnology

Table 2
Development of viral vaccines in Brazil, 2012.

Vaccine	Phase of development	Institute(s)/Enterprise(s)
Inactivated tetravalent dengue vaccine	Preclinical	Bio-Manguinhos/GSK
Dengue recombinant tetravalent vaccine	Phase I	NIH/Butantan Institute
Dengue recombinant	Preclinical	Bio-Manguinhos/Oswaldo Cruz I.
Dengue yellow fever vector	Preclinical	Bio-Manguinhos
Reduced-dose yellow fever vaccine	Licensing	Bio-Manguinhos
Yellow fever subunit vaccine (transient expression in plant systems)	Preclinical	Bio-Manguinhos/Fraunhofer Center of Molecular Biology
Inactivated yellow fever vaccine 17 DD	Preclinical	Bio-Manguinhos/Federal University of Rio de Janeiro
Genetic yellow fever vaccine (LAMP fused antigens) – patented	Preclinical	Aggeu Magalhaes FIOCRUZ, Johns Hopkins University
Recombinant yellow fever vaccine 17 DD – patented	Preclinical	Bio-Manguinhos
Preventive HIV vaccine	Preclinical	Medical School/USP
Therapeutic HIV vaccine	Phase II	Medical School/USP

Source: FIOCRUZ, Bio-Manguinhos, Vaccine Development Database (2012).

Table 3
Development of vaccines against parasitic diseases in Brazil, 2012.

Vaccine	Phase of development	Institute(s)/Enterprise(s)
Malaria recombinant	Preclinical (Initial)	Oswaldo Cruz I./Bio-Manguinhos
Hookworm	Preclinical	Bio-Manguinhos/Sabin Institute
Leishmania recombinant	Preclinical (Initial)	Bio-Manguinhos
Schistosomiasis SM14 – patented	Phase I	Oswaldo Cruz I./Ludwig I. for Cancer R./Ouro Fino

Source: FIOCRUZ, Bio-Manguinhos, Vaccine Development Database (2012).

Table 4
Technological transfer for viral and bacterial vaccines in Brazil, 2012.

Vaccine	Phase of transfer	Institute(s)/Enterprise (s)
10-Valent pneumococcal	Initial	Bio-Manguinhos/GSK
Rotavirus	Intermediary	Bio-Manguinhos/GSK
Measles, mumps, rubella (MMR)	Intermediary	Bio-Manguinhos/GSK
Influenza	Final	Butantan Institute/Sanofi Pasteur
Meningococcal C conjugate	Initial	FUNED/Novartis
Hib conjugate	Concluded (2006)	Bio-Manguinhos/GSK
Measles	Concluded (1985)	Bio-Manguinhos/Biken
OPV	Concluded (1985)	Bio-Manguinhos/Biken

Source: FIOCRUZ, Bio-Manguinhos, Vaccine Development Database (2012).

industry is relatively new in Brazil. About 120 companies are now operating in Brazil, most of them with links to major universities and research institutions. Tables 1–4 list ongoing and completed projects.

The efforts to transfer these technologies have required a comprehensive evaluation of various aspects of this transfer. Factors evaluated include scientific interest and feasibility, aspects of intellectual property, conditions of the market, the establishment of systems of seed-lots, production of consistent lots, quality control and assurance, certification of laboratories in Good Manufacturing and Biosafety Practices, clinical studies for validation of trial data, and registration at ANVISA [23].

A good example illustrating the success of recent policies to strengthen national capacity in this area is research currently being conducted by two of FIOCRUZ's institutes, Bio-Manguinhos and Oswaldo Cruz Institute. This research is part of international collaborations using the yellow fever virus as a vector for different vaccines, such as those for dengue and HIV (see Table 2), and related research [11].

Table 5
Technological platforms for vaccines in Brazil, 2012.

Platform	Goals	Institute(s)/Enterprise(s)
Center final processing	Final processing immunobiologicals Increase capacity/export (PAHO Revolving Fund, UNICEF, GAVI)	Bio-Manguinhos (Santa Cruz, Rio de Janeiro)
Recombinant antigen production tobacco plants	Production viral protein envelope yellow fever virus Hookworm antigen	Bio-Manguinhos (Fortaleza, CE)/Fraunhofer Sabin Institute
Technological platform/plant animal experimentation	Translational research neglected diseases	Center for Technological Development in Health CDTS/FIOCRUZ
GMP Pilot-Plant	Scale-up studies Develop produce experimental lots for clinical studies (viral, bacterial, biopharmaceutical)	Bio-Manguinhos FIOCRUZ Rio de Janeiro
Production	Plant bacterial conjugate vaccine	Novartis/Recife PE (first in Latin America)
Production	Meningococcal C conjugate vaccine (12 million doses/year)	FUNED/Novartis Belo Horizonte, MG

Source: FIOCRUZ, Bio-Manguinhos, Vaccine Development Database (2012)

Another important initiative is The National Institute for Science and Technology in Vaccines (INCTV), originated from the Millennium Institute for Vaccine Technologies, coordinated by FIOCRUZ's René Rachou Research Center. This work concentrates in seven vaccine development areas: dengue, influenza, Chagas disease, leishmaniasis, leptospirosis, malaria (*Plasmodium vivax*), and toxoplasmosis.

Finally, there is an understanding that these technology transfer initiatives must be agile and supported by national policies providing the financial resources for sustained development. New vaccine technologies require a long period of development before the final product is ready for use.

6.3. Technological platforms and production

The limitations of existing platforms were an important constraint in Brazil for technological development. Several initiatives are now in place to create adequate technological platforms, through national and international collaborations and significant investments. These platforms are supported in Brazil by the national Health Industrial Complex Program and by the Brazilian Growth Acceleration Program (PAC), with investments in infrastructure. Table 5 lists some of these initiatives.

6.4. Clinical trials

Brazil has a long-standing scientific capacity for clinical trials of vaccines and other pharmaceutical products, in international cooperation with the National Institutes of Health (NIH), the National French Agency for AIDS and Viral Hepatitis Research (ANRS) and other international scientific networks. Brazil's inclusion in multicenter studies is paramount to the growth of the sector and the safety of Brazilian patients.

A National Network for Clinical Research supported by the Brazilian government has been created, with participation of universities and research institutes. FIOCRUZ contributes to this network with Bio-Manguinhos' Unity for Clinical Research (ASCLIN) (with the reduced-dose yellow fever vaccine, needle-free vaccine delivery, and other trials) and with the Evandro Chagas Institute for Clinical Research (IPEC), which has recently conducted vaccine trials in national and international collaborations, the H1N1 trial in HIV patients [18] with support from the National STD/AIDS/Viral Hepatitis Program in the Ministry of Health, and the HPV trial for prevention of cervical cancer, in collaboration with Merck.

Brazil is a leader in conducting clinical research in Latin America, according to data from the Clinical Trials registry database

[19] managed by the US National Library of Medicine (NLM) at the NIH. The database currently holds registrations from more than 130,000 trials for pharmaceuticals and vaccines from more than 170 countries. In 2011, a search for clinical trials and Brazil recorded about 500 trials in this registry. This includes trials in different stages—pre-recruitment and recruitment of patients, in progress and complete, both for pharmaceuticals and vaccines. Brazil ranks second among the BRICS (Brazil, Russia, India, China, South Africa) in the total number of clinical trials in this database, with 2,821 records, compared with 2,939 for China, 1,996 for Russia, 1,918 for India, and 1,462 for South Africa [20].

In this Clinical Trials database, a search for vaccines, infectious diseases, and Brazil found 64 trials in 2011, ongoing and completed. This indicates that in spite of the national capacity for clinical trials, the number of vaccine trials in Brazil it is still low. The Brazilian government has defined vaccines as a high-priority area and is making significant efforts to increase funding in this area, in the National Clinical Research Network, supported by the Health Industrial Complex Program, a component of the national technological and industrial policies.

In spite of the existing constraints, significant progress has been made in this area. Several international multicentric HIV vaccine trials were conducted in Brazil from 1995 to 2009 [21]. Funding for clinical research has also been provided by national sources, mainly by the Research Unit in the National STD/AIDS Program [22]. In 1991, WHO identified Brazil—along with Thailand, Rwanda, and Uganda—as high-priority sites for conducting HIV vaccine trials. In 1992, Brazil launched the first HIV Vaccine Plan in a developing country, which has been regularly updated. The recent HIV Vaccine Plan 2008–2012 [23] emphasizes the importance of strengthening the clinical trials capacity for HIV vaccines.

The national regulatory agency, ANVISA, is making an effort to support this new government policy and to expedite its process of evaluation, overcoming existing constraints and delays, so that trials already approved by recognized bodies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) can pass through a simplified analysis in Brazil. This will help to increase the country's participation in international multicentric studies, bringing investment, scientific knowledge, and benefits for patients. The National Commission for Ethics in Research (CONEP), is also working to accelerate its evaluations.

7. Ethics, regulation, and quality: the legal environment for vaccines in Brazil

Brazil and other developing nations have benefited from the ethical, regulatory, and quality guidelines for vaccines that have been developed internationally, particularly those from the Council for International Organizations of Medical Sciences (CIOMS), the WHO's Expert Committees on Biological Standardization (ECBS), and from regional initiatives and organizations. WHO has also contributed to improve international vaccine quality and to strengthen national regulatory agencies. The Developing Countries' Vaccine Regulators Network (DCVRN) has also played an important role in strengthening regulatory procedures among member countries. To comply with these more strict regulatory requirements, significant investments have been made in Brazil for modernization and infrastructure necessary to vaccine development. Maintaining an adequate regulatory system, with timely registration and approval of vaccines, is a major challenge in many developing countries, especially with new, complex manufacturing platforms for novel technologies. Regulatory concerns can be a significant issue, particularly for pandemic vaccines [24].

In Brazil, there are now adequate and well-established national structures for ethical, regulatory, quality, and intellectual property

evaluations. ANVISA, which regulates pharmaceuticals, vaccines, and other health products, has in the past two decades significantly increased its requirements and has received international certification. This regulatory activity is supported by INCQS, located in FIOCRUZ, and by the National Institute of Metrology (INMETRO).

In regard to vaccine prequalification, it is important to note that the Brazilian government emphasizes the prequalification process conducted by the WHO Vaccines Department. Two vaccines from Brazil have already been prequalified by WHO: those for meningococcal meningitidis serogroups A and C and for yellow fever.

The National Institute of Industrial Property (INPI) is the Brazilian Patent Office and is responsible for enforcing national intellectual property legislation. Some vaccine technological developments have recently been patented in Brazil (see Table 2). A recent study [25] indicates that the majority of biotechnology patents (87.2%) were filed by nonresidents, with USA being responsible for 51.7% of all patents deposited in Brazil. Pfizer, Novartis, and Sanofi were the largest applicants in Brazil, with 339, 288, and 245 biotechnology patents filed, respectively. For residents, the largest applicant was the governmental institution FIOCRUZ, which filed 69 biotechnology patents within the period analyzed. Nevertheless, the incorporation of intellectual property rights (IPR) evaluations into the vaccine field is complex and will require strengthening local capacity to deal with IPR issues in technology transfer agreements and in public–private partnerships.

Vaccine research proposals with genetically modified organisms (GMOs) are submitted for evaluation by the National Technical Commission on Biosafety (CTNBio), a collegiate organization linked to the Ministry of Science and Technology, supported by a network of 313 local biosafety committees (CiBios) in research institutes and universities.

In clinical studies, proposals are evaluated by CONEP, supported by a network of 645 local ethical committees (CEPs) in universities and research institutes.

8. Conclusion

It is important to anticipate the scenario for innovation in the context of the Decade of Vaccines [1] and accelerate vaccine research and development in Brazil and other emerging economies. The main challenge is to define adequate strategies to explore and maximize these countries' scientific and technological capacities and to strengthen international collaborations, with the support of BMGF and with technical support from other international organizations, such as WHO and PAHO.

The global market for traditional vaccines is increasingly relying on manufacturers in emerging nations, particularly from India, Korea and China, with an increasing participation in innovative products [6]. In contrast, manufacturers in developed nations are moving into more profitable new vaccines that require sophisticated and expensive manufacturing technology [24].

In this scenario, it is crucial to strengthen, from a translational sciences perspective, the innovation capacity of vaccine manufacturers in emerging economies, such as Brazil, to stimulate the development of vaccine candidates in their pipelines. To meet this goal, new public–private partnerships should be stimulated, supported by sustainable funding initiatives and incentives, such as the Advance Market Commitment, created by developed nations (G-8) and by BMGF.

This review indicates significant national efforts in Brazil to incorporate vaccine innovation into technological and industrial policies and strategies for economic competitiveness. Brazil has outstanding academic institutes and an emerging and flourishing biotechnology industry. In addition, it is the world's seventh-largest pharmaceutical market, with a large government purchase power

for health products and an increasing public budget for vaccine purchase.

Nevertheless, important gaps persist, mainly related to innovation and technological development of vaccines. Coordinated policies, supported by the new Health Industrial Complex Program, will be necessary to accelerate public–private partnerships, technology transfer agreements, and targeted projects.

This approach will require effective governance structures. These structures are needed to coordinate the diverse financing sources, facilitate the flow from basic research to the final product, and integrate the activities involved in the technological routes and in the production cycle, building adequate partnerships at each stage. The Brazilian National HIV Vaccine Plan 2008–2012 [23] describes some of these governance strategies, which could create conditions to ensure the country's participation as a global provider of vaccines and other biological products.

One of the main challenges for the future is the need to accelerate qualification programs supporting the national production of vaccines. This will enable manufacturers to meet international standards for the development and exportation of new vaccines, reaching international markets beyond the Brazilian NIP. This is a very important issue that tends to be underestimated because of the great weight on technology transfer partnerships (which prevent exportation during the period of contract validity) and the size of the Brazilian market, favored by significant public purchase. Domestic vaccine manufacturers should have vaccine exportation as an explicit goal as well.

Lessons learned from the Brazilian experience could be applicable to developing countries. First, there is a need to understand the importance of international technology transfer to build national capacity, avoiding a naïve approach based exclusively on autochthonous and self-sufficient development. Second, there is a need to concentrate on essential vaccines and to avoid an extensive vaccine development portfolio. Third, there is a need to build political support from scientific and civil society organizations to promote a favorable social perception of vaccines, which should be viewed as a public good and not just as a source of profit. Finally, there is a need to establish a clear and complementary division of labor between public and private manufacturers, which has been key to the success of the Brazilian NIP.

In conclusion, this review tries to highlight the need to strengthen links between scientific and technological policies, the National Health System and the National Immunizations Program. These links will accelerate access to new, high-quality, affordable vaccines, which are essential for public health and global sustainability, and contribute to a new era of innovation in the Decade of Vaccines.

Conflict of interest

The authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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