

Clinical research for the Brazilian National Immunization Program

Pesquisa clínica para o Programa Nacional de Imunizações

Investigación clínica para el Programa Nacional de Inmunizaciones

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Introduction

The Brazilian National Immunization Program (PNI, acronym in Portuguese) was created in 1973 with the aim of coordinating the country's immunization activities¹.

Brazil is a country of continental dimensions, with a well-characterized geographic diversity and dry land borders on several other countries of South America, making it more vulnerable to epidemics, which can reach the country and spread quickly. This makes a strong PNI extremely important for the country's states and municipalities, capable of achieving and sustaining high and homogenous vaccination coverage rates¹.

No other measure except for safe drinking water is known to have such an impact as vaccines on reducing morbidity and mortality in the population². This can be proven by the reduction in infant mortality rates and in the incidence of vaccine-preventable diseases globally and in Brazil since the advent of vaccination. Figure 1 compares the incidences of some vaccine-preventable diseases before and after the introduction of vaccination. All the diseases showed a significant drop in incidence, proving the benefit of vaccination.

Brazil's PNI stands out in Latin America, comparable to programs in developed countries, due to the effort in implementing increasingly complete vaccination schedules that meet the recommendations by medical societies and especially the country's epidemiological profile, seeking high and homogeneous vaccination coverage rates³.

PNI is a high priority for the Brazilian government, as demonstrated by the program's growing budget, which exceeded BRL 5 billion (USD 1.2 billion) in 2019⁴. And since it is a government priority, it is not subject to discontinuity or budget cuts, which is important, guaranteeing the program's continuity regardless of the country's political situation.

One of the program's challenges has been to maintain its sustainability in the supply of immunobiological products. The year 1985 witnessed the launch of the National Program for Self-Sufficiency in Immunobiologicals, with the objective of expanding domestic production and the diversity of vaccines in the country. A National System for Quality Control in Immunobiologicals was created, as well as a successful partnership between the PNI and the public vaccine manufacturing laboratories, which is still in force¹.

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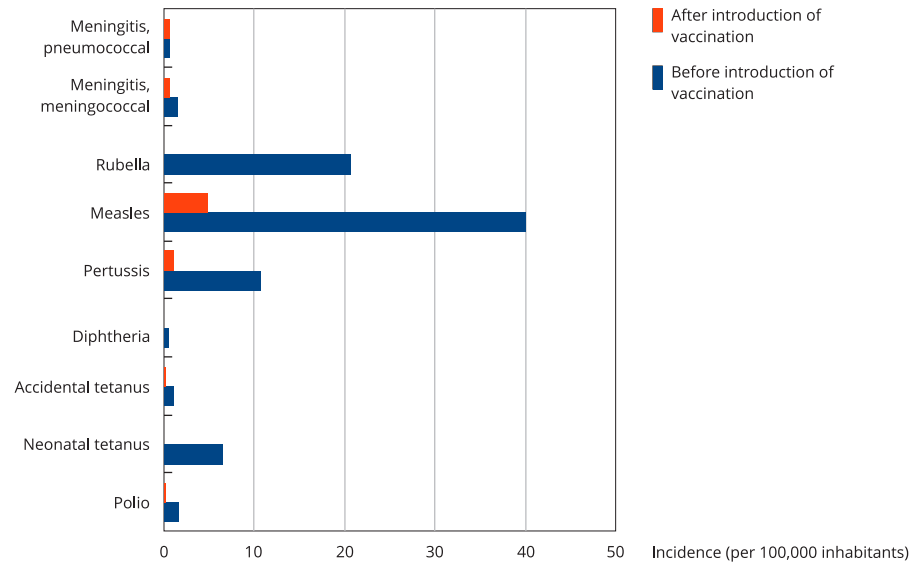
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Figure 1

Comparison of incidence (per 100,000 inhabitants) of certain diseases before and after introduction of vaccination in Brazil.



Source: Department of Immunization and Communicable Diseases, Health Surveillance Secretariat, Brazilian Ministry of Health (DEIDT/SVS/MS).

PNI is about to celebrate its 47th year and faces new and different challenges. While the program previously focused on the pediatric population, it is increasingly determined to work with diverse age groups and now serves from newborns to the elderly. Obviously, autonomy in relation to vaccination of this new population requires the PNI to innovate its strategies, which involve communications plans, especially in the current age of social networks ³.

These challenges have grown with the increase in the program's target public, with the new age groups, the success in controlling previously common diseases, and globalization bringing new diseases, all leading to increasing diversity and quantity of vaccines now supplied by the PNI. This picture increased the complexity of the vaccination calendar and its uptake by health professionals, especially in the vaccination rooms ³.

We also experience difficulties accessing certain communities, whether due to public security issues or religious beliefs, along with the power of social networks as a source of medical information, often spreading fake news, certainly the program's most recent challenge.

In order to tackle so many different challenges, the PNI will definitely need to launch various strategies with diverse partnerships.

This context involves the need to provide answers backed by scientific evidence to the demands for expanding the program with new immunobiological products, whether combined vaccines or new vaccines, besides furnishing data to support answers for the scientific community, users, anti-vaccination groups, and/or to combat fake news.

Demonstrating the efficacy and safety of new vaccines or their combinations can facilitate and improve adherence by users and the medical and scientific community, fostering trust and thus better participation in indications and follow-up. Parents may also feel more comfortable with combined vaccines (several antigens applied in the same injection), decreasing the number of injections and visits to the health unit, thus decreasing the costs for the both health system and families.

Clinical research emerges in this scenario as a fundamental tool for generating scientific knowledge. Clinical research within the Brazilian Unified National Health System (SUS) has proven effec-

tive, not only because of the target population, but also due to the participation by different professionals who see themselves involved and discussing science in their daily work. This partnership with the SUS has proven to be a strategy that promotes the expansion of knowledge and training for healthcare professionals, besides generating benefits for the country's public laboratories and strengthening its health policies. However, the challenges, given the conditions in the health units due to the inadequate physical space and the discouragement weighing on the health professionals, have been obstacles faced by researchers in these units. In recent times, the lack of safety for health professionals and users and the armed conflicts in the communities often lead to delays in the immunization schedules, since the safety of participants and health teams takes precedence over any other procedures.

In addition to all these difficulties, there is the issue of regulatory and ethical timeframes, often out-of-step with the urgent responses that public health requires, even using all the feasible legal mechanisms to speed up this stage.

The costs of fieldwork and materials for biological tests, among other needs, rely on sponsors (e.g., Immunological Technology Institute, Oswaldo Cruz Foundation – Bio-Manguinhos/Fiocruz), various government departments (e.g., Department of Science and Technology, Brazilian Ministry of Health – Decit/MS – and PNI), and health agencies such as the World Health Organization (WHO), among others. However, any delay in the timetable complicates the balance (already fragile) between costing and financing.

This article aims to analyze the development of clinical research in the sphere of public health services in order to support scientifically based decisions in Brazil's PNI.

The experience at Bio-Manguinhos

There are currently seven public laboratories that produce immunobiological products in Brazil: Bio-Manguinhos, Butantan Institute, Ataulpho de Paiva Institute, Paraná State Institute of Technology (Tecpar), Ezequiel Dias Foundation, Vital Brazil Institute, and Paraná State Center for Immunobiological Production and Research ⁵.

The priority for production by these laboratories is to meet the demand of the SUS, and when there is surplus production it can be supplied to institutions like the WHO, Pan American Health Organization (PAHO), and the United Nations Children's Fund (UNICEF). The vaccines must undergo the prequalification process required by WHO ⁶. Through the GAVI-Vaccine Alliance, a partnership of public and private stakeholders that unites governments from developing countries and donor countries, the WHO, UNICEF, World Bank, the vaccines industry in industrialized and developing countries, civil society, Bill & Melinda Gates Foundation, and other private benefactors, the vaccines are distributed to more than 70 countries, with the objective of improving access to vaccination, increasing vaccination coverage of children living in the world's poorest countries ⁷.

The technology leaders feature the Fiocruz, affiliated with the Brazilian Ministry of Health. Fiocruz is responsible for developing the research and manufacturing a major share of the vaccines used in the PNI, under the SUS ⁸. The unit of Fiocruz responsible for development, manufacturing, and clinical trials with vaccines is the Bio-Manguinhos. Other immunobiological and pharmaceutical products produced by Bio-Manguinhos, but which are beyond the scope of this article, are also the object of clinical trials conducted by the Institute.

Bio-Manguinhos has a Clinical Advisory Board (ASCLIN), connected directly to the Board of Directors, responsible for conducting the clinical trials with the vaccines and the other products manufactured by the institution, with studies ranging from phase I to phase IV (pharmacovigilance), always targeted to meeting demands the SUS and involving multiple technical units of Fiocruz in the development of these research projects. The ASCLIN, created in 2004, has already carried out at least 19 trials with vaccines, providing a strategic service to the PNI by conducting research aligned with the program's demands and needs, ensuring the population's access to increasingly safe and effective immunobiological products.

Among the studies by Bio-Manguinhos, several have backed important decisions by the PNI, such as changes to the vaccination calendar, with the recommendation of non-simultaneous administra-

tion of the yellow fever and triple viral vaccines due to the interaction (with lower efficacy) between the two vaccines when applied at the same time or less than 30 days apart in children under 2 years of age⁹. Another example was the recommendation of the use of a fractional dose of the yellow fever vaccine to contain outbreaks/epidemics, based on a dose-response study by Bio-Manguinhos¹⁰.

Studies on the duration of immunity with the yellow fever vaccine, showing that especially in children, a single dose is not sufficient to provide lasting protection, backed the decision by the PNI to not initially follow the recommendation by WHO for a single dose of the vaccine and to maintain a booster dose at 4 years in children and a booster dose (10 years after the first dose) in adults. This recommendation remained in force until the yellow fever outbreak in Brazil in 2017, which forced the PNI to at least temporarily follow the WHO recommendation of a single dose of yellow fever vaccine. The recommendation of a booster at 4 years in children will be resumed in 2020, as provided by *Memorandum n. 130/2019* issued by the Health Surveillance Secretariat of the Brazilian Ministry of Health (SVS/MS)¹¹.

Bio-Manguinhos is currently conducting two studies with the yellow fever vaccine, which will serve to answer questions from the PNI: one cohort study with in a yellow fever-free area with a low migration rate to assess the 10-year duration of the yellow fever vaccine and another with the new stage of the dose-response study that will assess participants 10 years after application of the vaccine's fractional dose. The latter will serve to base the decision by the PNI on when (and if) to revaccinate the population that received the fractional dose in the 2018 campaigns. The data currently show protection up to 8 years after application of the fractional dose of the yellow fever vaccine¹².

Expertise was thus built over the years in conducting controlled clinical trials and pharmacovigilance studies for the PNI. Since this scenario differs from usual clinical research, various lessons were learned, giving us a greater command over conducting clinical research for the SUS and for describing it with propriety. However, such learning and improvement are a continuous process, never exhausted.

How to conduct clinical research in a health unit under the SUS

Conceptually, a clinical trial aims to produce evidence on drug safety and efficacy and is governed by ethical principles based on the *Declaration of Helsinki*, which should be the basis for approving and conducting clinical trials¹³.

Ethical conduct is the guiding thread for all such projects and is ensured by prior approval of the study protocols by the Institutional Review Boards (IRBs) of the institutions conducting them. Clinical research also follows good clinical practices (GCP), a set of regulations, guidelines, and ethical and scientific quality standards by which studies involving human subjects should be conducted, always guaranteeing the research participants' rights and well-being, as well as the data's credibility¹⁴.

The resolution by the Collegiate Directorate of the Brazilian Health Regulatory Agency (Anvisa), *RDC n. 9/2015*, which sets the procedures and requirements for conducting clinical trials with drugs in Brazil, defines the clinical study site as a public or private organization, legally established and duly registered with the National Registry of Healthcare Establishments (CNES) and in which clinical trials are carried out¹⁵.

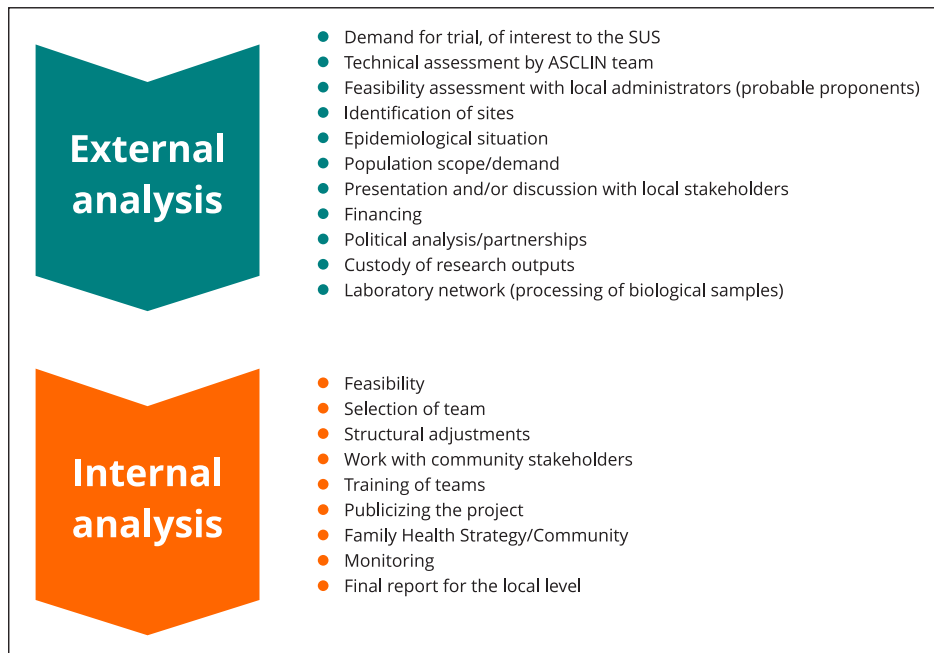
In addition, according to the Document of the Americas and the aforementioned *RDC n. 9/2015*, such study sites should have adequate installations for conducting the clinical protocol in terms of physical infrastructure, equipment, instruments, and human resources, and should also be adequate for the clinical study's population, for example, elderly, children, or persons with special needs, among others. These sites may or may not be affiliated with a university or teaching and research institution. In the case of studies involving vaccines for the PNI, the ideal setting is the vaccination rooms, mostly located in primary healthcare units^{13,15}.

The conduction of a clinical trial should take two interdependent scenarios into account, one external and the other internal. Assessment failures in either of them can compromise the trial's success. Figure 2 illustrates the main stages in this process.

In the sphere of clinical research on vaccines for the SUS, the first stage is assessment of its relevance for the health system. The partner research unit is analyzed to determine the best design and

Figure 2

Process for conducting a clinical trial in the Brazilian Unified National Health System (SUS).



ASCLIN: Clinical Advisory Board, Immunological Technology Institute, Oswaldo Cruz Foundation.

the best site (state/municipality) to conduct the study, taking into account epidemiological factors, the target age bracket, logistics, and other aspects.

Harmonization is thus necessary with the implementing agencies such as State and Municipal Health Departments, which can be the figures proposing the study, with participation by part of their organization such as coordinators of program areas, local immunization programs, primary health-care, the Family Health Strategy (FHS), and community health workers (CHW).

The trial's success requires the project's uptake by local stakeholders, and the research should be presented, debated, and agreed upon in a meeting of the Municipal Health Council. However, this alone will not guarantee either the absence of noise in communication or adherence to the project. Thus, permanent linkage with two-way interaction between the study and this segment of society, seeking permanent construction of new knowledge, is essential to the project's success. Planning and carrying out a trial with participation by organized civil society, aligned with local policymakers and healthcare teams, is what has guaranteed the studies' success.

An example of a research project conducted along these lines is the study on the duration of immunity with the yellow fever vaccine (a 10-year cohort) in a yellow fever-free area, which is being carried out by Bio-Manguinhos in three municipalities (counties) in the state of Paraíba in Northeast Brazil. The study started in July 2016 in the municipality of Alhandra and was later extended to Conde and Caaporã, with a total of 4,761 participants recruited. During the planning stage it was necessary to identify, mobilize, and establish partnerships with various institutions such as the State Health Department, local governments and health departments, the Federal University of Paraíba, the Paraíba Society of Pediatrics and Immunizations, and the Regional Medical Board, among others. Participation by social movements and the FHS has been essential for conducting the study, with sup-

port and mobilization by local CHW. There were 111 ACS in 18 communities in the 3 municipalities in the recruitment of 2,005 adults and 2,756 children. Since the study will last 10 years, partnership and support from these professionals continues to be essential for the study's continuity (data from the Bio-Manguinhos Clinical Advisory Board, unpublished).

Part of the planning should include a diagnosis of the scenario for the project's activities, including the study site's coverage and influence areas and local stakeholders. Mobilization requires local stakeholders with established credibility, a relationship of trust within the community, and inclusion of research participants in discussions of the project whenever possible in order for the study not be seen as the recruitment of "guinea pigs", but as part of society's participation in the sustainability of the SUS.

The necessary budget resources for conducting the study should be guaranteed, and such resources should be specified in the documents submitted to the IRB. The guarantee of a project's continuity is tied to good clinical practices, emphasizing the ethical principles of nonmaleficence and beneficence for study subjects ¹³.

Another key point is the project's internal communication within the study site itself. It is necessary to involve the site's entire team in the study in order for adherence to be effective. It is often difficult to convene the health unit's entire workforce for a presentation of the project. In such cases, separate meetings should be held with the strategic areas, such as the reception, pediatricians (in studies with children), nursing staff, and others. Another strategy to ensure internal familiarity with the study is to use online postings to message exchange groups (e.g., WhatsApp) of the unit's health professionals, news flashes on the health unit's website, and posters, of course. All the communications materials should be submitted to and approved by the IRB ¹⁴.

As for infrastructure, a primary healthcare unit often lacks the structure required for conducting a clinical trial. Therefore, a situational diagnosis (feasibility study) of the units is done, and if applicable, improvements are made to the infrastructure to adjust them to good clinical practices. Examples of adjustments that are often necessary include installation of internet, allowing access to the programs for e-CRF (*Electronic Case Report Form*), GECLIN (a system of the Clinical Advisory Board that allows remote management of clinical trials), adaptation of rooms to accommodate participants, and collection and storage of material, among others. Some sites experience difficulties in guaranteeing Internet access with the necessary quality. This can happen even in large state capitals like Rio de Janeiro. To minimize this problem, Bio-Manguinhos developed an e-CRF in partnership with the Brazilian Federal Data Processing Service – SERPRO (<http://www.serpro.gov.br>), totally in Portuguese, customizable, and now already in an offline version.

Another strategic area is the cold chain, which must store the investigational and reference products in the case of an intervention study. It does suffice to have exclusive cold storage facilities validated for the clinical trial. It requires rigorous temperature control with traceability and the possibility of immediately detecting failures, since many units do not have their own power generators. The immediate detection of temperature excursions, for example, allows mobilizing the contingency plan for such situations and is one of the study's documents, serving to mitigate possible failures ¹⁶.

The selection of human resources is another fundamental stage in this process. Ideally, priority should be given to staffers already working in the health unit and that have available work hours for the project, or who have worked there previously (e.g., retired staff). Our experience shows that working with a team that is familiar with the site and the target population makes the difference in executing a clinical trial.

A key point is the additional gain for the unit where the clinical trial is carried out, which is evident in both our team's experience and the testimony of health professionals that have worked in the projects. Performing clinical research activities has particularly positive impacts for the local team, with improvements in the work process and new perspectives for these professionals in their role in society. In the authors' experience, various professionals that have worked in clinical trials began or resumed their academic lives after the experience with clinical research.

Difficulties and challenges

As seen here, there are various challenges for Brazil's PNI and for everyone that supports the Ministry of Health and the SUS. Increasingly efficient and rapid strategies need to be developed that allow the response for the population and the scientific community to be based on robust and reliable data.

Clinical research has thus become an increasingly necessary and effective tool for meeting the demands of the PNI. The possibility and knowledge for conducting trials locally that respond to the program's strategic demands is an extraordinary gain, since it generates specific scientific information for our products, our population, and our reality.

However, conducting clinical trials according to good clinical practices in primary healthcare units in the SUS has posed a huge challenge. Over the years, clinical trials by Bio-Manguinhos reached 7 states in Northeast Brazil, 2 in the North, 2 in the Central, 3 in the Southeast, and 2 in the South, plus the Federal District, covering 58% of Brazil's states, thus reflecting another important contribution to public health by including other regions outside the more developed South and Southeast in the clinical research scenario, showing that it is possible to do quality work and generate improvements both in the primary healthcare units where the trials took place and for the professionals working in them.

Important factors hindering clinical trials in regions farther from large cities involve logistic and budget issues, since the costs of moving teams, samples, and inputs increase the project's budget. However, efforts have been made for clinical trials to reach different regions of the country, which is often necessary for the project's epidemiological profile.

Another sensitive point is the recruitment of human resources for these regions, due to the lack of professionals trained in clinical research outside of large cities. However, this shortage has been overcome with training and follow-up of local professionals, qualifying teams for future projects.

Aligning the ethical and regulatory timetables with relevant studies for public health and raising the necessary funds are necessary factors for more effective research work with faster turnaround.

The physical space for the study is also a challenge, since we are competing for routine patient care in the health unit, where the study flows almost never correspond to the health unit's routine reality. However, we have managed to overcome these obstacles through partnership with the health units, by revising the work flows and optimizing the spaces, adapting them to good clinical practices. This process involves purchasing equipment and furniture for each study, usually donated to the health unit at the end of each trial, which generates a cost.

Given the above, the ASCLIN, in partnership with the Municipal Health Secretariat of Rio de Janeiro, has invested in assembling fixed study sites in some health units in the SUS. These are spaces designed for and dedicated exclusively to clinical trials, rigorously meeting the requirements of good clinical practices. There are currently two such study sites in operation, one in the Heitor Beltrão Municipal Health Center in the Tijuca neighborhood and the other in the Lincoln de Freitas Filho Polyclinic in Santa Cruz, both in the city of Rio de Janeiro. The latter also has a laboratory for processing clinical samples, with biosafety level 2 (BSL-2)¹⁷.

Conclusion

Clinical research in units of SUS is a strategic tool for the PNI, generating scientific knowledge on the program's vaccines and thereby maintaining trust within the population and among the program's health professionals.

Conducting a clinical trial in a primary healthcare unit also provides opportunities for improvement of the work processes, since all the studies have to be performed according to good clinical practices. It also contributes to training health professionals in clinical research, potentially increasing Brazil's contribution to research projects.

The opportunity to conduct clinical research for the PNI has emerged as a tool for strengthening health policies in the SUS, since it demonstrates the efficacy and safety of epidemiologically relevant new vaccines while promoting the expansion and availability of products that meet the Ministry of Health's demands.

The trials conducted thus far have furnished reliable data on the use of new health guidelines and management, as shown by the studies on the duration of immunity with the yellow fever vaccine, demonstrating that especially in children, a single dose is not sufficient for lasting protection.

As challenges for conducting studies in some regions of the country, we need to improve the logistic and budget conditions, including rigorous control of the cold chain, human resources training, etc. In general, clinical research for the SUS has become increasingly robust, making valuable contributions to the Ministry of Health and strengthening policies with the public laboratories, including Bio-Manguinhos.

There is still a long road ahead with the establishment of partnerships, which should include neighborhood associations, community health councils, stakeholder mobilization, professional societies, and study subjects as the main challenge. New strategies and policies will need to be established and reinforced for this purpose.

Thus, clinical research in the scope of PNI, aligned with the interests and demands of the Ministry of Health, means an important step for research progress in Brazil, raising interest and promoting the health sector's development while improving health quality for the Brazilian population.

Contributors

All the authors contributed to the article's conception, writing, and revision and approval of the final version.

Additional informations

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Conflict of interests

All the authors work at Bio-Manguinhos, which produces vaccines for the Brazilian National Immunization Program (PNI).

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