Key elements for the sustainable production of influenza vaccine in Brazil in the framework of the Global Action Plan for Influenza Vaccines

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GAP INFLUENZA VACCINES

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ABBREVIATIONS AND ACRONYMS

Anvisa	National Sanitary Surveillance Agency
APEX	Brazilian Agency for the Promotion of Exports and Investment
API	Active Pharmaceutical Ingredient
Ascom	Communication Office of the Ministry of Health
CENADI	National Centre for Storage and Distribution of Immunobiologicals
CITEC	Committee for Incorporation of Technology
CONITEC	National Committee for Technology Incorporation in SUS
DMIHT	Department of Management and Incorporation of Health Technologies
FC	Federal Constitution
Fiocruz	Oswaldo Cruz Foundation
GAVI	Global Alliance for Vaccines and Immunization
GCCD	General Coordination of Communicable Diseases
GCNPI	General Coordination of the National Immunization Programme
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
HIC	Health Industrial Complex
ICHID	Industrial Complex and Health Innovation Department
LACEN	Central Public Health Laboratory
NIHQC	National Institute of Health Quality Control
NIC	National Influenza Centre
NIP	National Immunization Programme
NHSS	National Health Surveillance System
PAHO	Pan American Health Organization
PDP	Production Development Partnerships
RVML	Respiratory Virus and Measles Laboratory
Sinan	case registry database
SUS	National Health System
SHS	Secretariat of Health Surveillance
SSTSI	Secretary of Science, Technology and Strategic Inputs
TACI	Technical Advisory Committee on Immunization
UNDP	United Nations Development Programme
WHO	World Health Organization

1 Introduction

In 2006, the World Health Organization (WHO) launched a Global Action Plan for Influenza Vaccines to reduce the global shortage of influenza vaccines for influenza seasonal epidemics and pandemic and to increase equitable access to pandemic vaccines and to contribute to international pandemic preparedness efforts, through three main approaches:

1. the increase seasonal influenza vaccine use;
2. the increase the global capacity for vaccine production to deal with a potential pandemic, and strengthen the competence of national regulatory authorities;
3. the develop new, more effective and more stable influenza vaccines with a higher yield and lower production times.

In this context, the Pan American Health Organization (PAHO) conducted a study in Brazil on the key elements needed for the sustainable production of influenza vaccine, in the framework of the Global Pandemic Preparedness Plan. The study aimed to improve understanding of Brazilian health policy environment, production and surveillance capacities in relation to a pandemic scenario, which may provide useful information for the sustainability of the influenza vaccine production. Note that this study was conducted with no certainty of an imminent pandemic; neither PAHO nor the Brazilian Government has received a formal alert relating to such a pandemic.

Influenza vaccination was introduced into the Brazilian vaccination schedule of the National Health System (SUS) in 1999, through the National Immunization Programme (NIP) of the Ministry of Health. Initially, it aimed to cover the population over 65 years of age, as recommended by WHO.

Since there was no domestic production of influenza vaccine at that time, it had to be purchased from an international supplier. In an attempt to cut the cost of the vaccine and eventually to develop a sustainable and high quality national production capacity, the Ministry of Health signed an agreement with the Butantan Institute to acquire both the vaccines and the production technology *(1)*.

As in other technology transfer projects in the health sector in Brazil, the Butantan agreement foresaw that the vaccines would be supplied by an international partner until the Brazilian producer was able to produce an influenza vaccine. In parallel, Butantan began to implement the simpler production processes for influenza vaccine, eventually introducing more complex steps until it was fully able to produce the active pharmaceutical ingredient, and had a full command of the skills needed when producing a vaccine.

For the 2016 influenza vaccination campaign, 53 million doses were needed to immunize the priority groups: children aged between 6 months and 5 years, pregnant and breastfeeding women, health care workers, indigenous people, people aged 60 years or more, the prison population and prison workers, and people suffering from chronic noncommunicable disease or other specific clinical conditions. Butantan produced 88% of the vaccines needed by the NIP (47.2 million doses).

The inclusion of new target groups, or the development of a pandemic scenario, could require a higher vaccine production capacity. It is particularly important to align the annual production schedule to WHO's prevision of the strains needed in the vaccine as early as possible, so that the amount of vaccine needed to immunize the Brazilian population is ready by March. Impact studies are therefore needed on the increased production that may be required from Butantan, together with an understanding of the sustainability elements and

their relation to the different key agents in the country, so that all actors are aware of the measures that would need to be taken in a pandemic scenario.

2 Goals of the study

The general goal of the present study was to understand the key elements for sustainable influenza vaccine production in Brazil in relation to a potential pandemic.
More specific goals were:

- to develop a questionnaire to collect information on the key elements of sustainable domestic production of influenza vaccine;
- to conduct interviews with chosen agents involved in vaccine production, quality assurance, regulation, promotion, finance and influenza surveillance;
- to make recommendations on the key elements of sustainable domestic production of influenza vaccine, based on discussions at a workshop attended by the key agents interviewed.

3 Methodology

This study comprised six main steps, as described below, aimed at achieving the general and specific goals.

1. Survey and analyse the main policies, standards and technical recommendations on immunization in Brazil.
2. Identify the individuals in charge of Brazilian public institutions involved in developing policies on access to vaccines, influenza surveillance and vaccine production. People involved in the production, regulation and promotion of measures related to influenza vaccine production in Brazil were considered as key persons.
3. Develop and validate a structured research questionnaire (Annex 1), to investigate the situation in Brazil. The questionnaire was divided into five parts: the political and health system framework; specific information regarding planning for the acquisition of influenza vaccines; communication related to influenza vaccine; development of the product and local production; and product approval and regulation. A similar study in Mexico was used as a reference in creating this questionnaire[a].
4. Conduct interviews using the structured questionnaire (this was done in June and July 2016).
5. Convene a workshop attended by representatives from all the institutions interviewed and representatives of PAHO and WHO, to discuss the study's findings and make recommendations on sustainable production of influenza vaccine in Brazil.
6. Compile data and draw up the final report, detailing the project's main findings by study area and recommendations from the workshop.

[a] Technical Report of consultations with the Mexican Secretary of Health on key elements of sustainability for local production of influenza vaccine within the context of global pandemic preparedness = Reporte técnico de la consulta con la Secretaría de Salud sobre los elementos clave para la sostenibilidad para la producción de vacuna contra influenza en el país en el marco del Plan Mundial de Preparación ante una Pandemia. Mexico City : PAHO, 2016. ISBN 978-92-75-07453-4 (bilingual edition) Not available on line (publish date December 2016).

A list of the people interviewed and their contact information is given in Annex 2. People from the following institutions and departments under the Ministry of Health were interviewed.

1. Secretariat of Health Surveillance (SHS)
   - General Coordination of Communicable Diseases (GCCD)
   - General Coordination of the National Immunization Programme (GCNIP)

2. Secretariat of Science, Technology and Strategic Inputs
   - Industrial Complex and Health Innovation Department (ICHID)
   - Department of Management and Incorporation of Health Technologies (DMIHT)

3. Brazilian National Sanitary Surveillance Agency (Anvisa)

4. Oswaldo Cruz Foundation (Fiocruz)
   - Respiratory Virus and Measles Laboratory (RVML) - National Influenza Centre (NIC)
   - National Health Quality Control Institute (NHQCI)

4 Theoretical and regulatory framework

The 1988 Brazilian Federal Constitution recognizes the right to health of the Brazilian population, and requires the State to provide the conditions needed to fully exercise this right, in the form of actions to promote, safeguard and restore health. The Federal Constitution also places an obligation on the State to develop and enforce economic and social policies aimed at reducing illness, and to provide universal access to the country's health services and initiatives.

In this context, the national health system was created in the 1980s. Law no. 8.080/90 *(2)* defines this system as the collection of health services and initiatives provided by federal, state and municipal public institutions and bodies, whether through direct public administration, indirect administration or as foundations maintained by the Government. The same law defines epidemiological surveillance as the actions that provide awareness, detection or prevention of any change in the determining and conditioning factors of individual or collective health, for the purpose of recommending and adopting prevention and control measures for disease. It also defines sanitary surveillance as the collection of initiatives capable of eliminating, reducing or preventing health risks, and of intervening in sanitary problems arising from the environment, from the production and circulation of goods, and from the provision of services of interest to health.

The National Sanitary Surveillance Agency (Anvisa) was created to provide regulatory support. It is currently involved in regulation, operating authorization and registry, oversight and monitoring, education, research and activities in the National Sanitary Surveillance System, as laid out in Law no. 9.782/1999 *(3)*.

The National Immunization Programme was created in the 1970s, before the enactment of the Brazilian Federal Constitution, with the goal of coordinating immunization initiatives that had previously been uncoordinated and had had limited coverage.

Law 6.259/1975 *(4)* and Decree 78.231/1976 *(5)* set out the national vaccination policy for the control, elimination and eradication of vaccine-preventable diseases in the country, emphasizing continuous vaccination activities and institutional strengthening of the NIP *(6)*.

Currently, the NIP is coordinated by the Ministry of Health, together with the states and municipalities. Its notoriety comes from its scope, which provides vaccination for millions of Brazilians and, above all, its results, which include the eradication of poliomyelitis and the elimination of the circulation of native rubella virus. It has also succeeded in reducing vaccine-preventable diseases, and helped to reduce infant mortality rates and increase life expectancy *(6)*.

Brazil offers a large number of free vaccines, including 15 for children, five for adolescents, and five for adults and the elderly *(6)*.

The 2009 influenza pandemic was a global outbreak of a swine influenza variant. The virus was identified as a new strain of the already known influenza A subtype H1N1, the virus responsible for most cases of influenza among humans. On 25 April 2009, WHO declared that the epidemic was an "international public health emergency", which meant that all countries should increase surveillance; this was subsequently elevated to the level of pandemic alert.

In 2010, populations at higher risk of disease, complications and death were given vaccine against influenza A H1N1 (2009); some 98 million Brazilians were immunized.

In 2010, the target audience for the national influenza vaccination campaign was extended to include pregnant and breastfeeding women, health care workers, indigenous people, the prison population, children aged between 6 months and 5 years, and people with various illnesses (Figure 1).

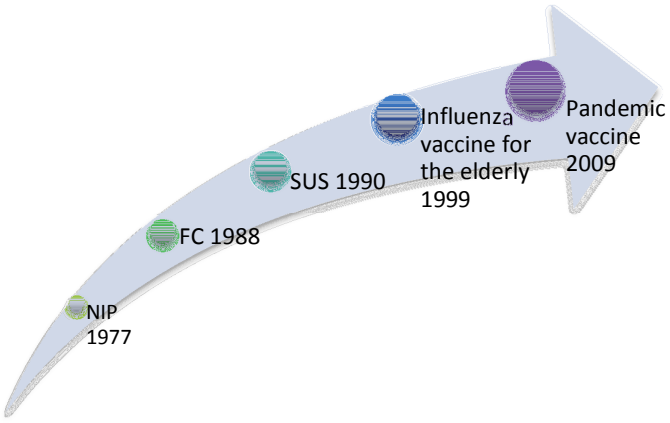

Figure 1. Historical timeline of events relating to production and distribution of influenza vaccine

Activities within the scope of the NIP have produced important results over the years, with continuous development of new strategies for fighting illness; among the more recent are the eradication of measles and the elimination of neonatal tetanus. In addition, there has been control of diphtheria, pertussis and tetanus, hepatitis B, meningitis, yellow fever, serious forms of tuberculosis, and rubella and mumps in some states, as well as eradication of poliomyelitis *(6)*.

The NIP is in line with WHO's recommendations on immunization policies, and receives technical, operational and financial support from the United Nations Children's Fund (UNICEF) as well as contributions from Rotary International and the United Nations Development Programme (UNDP) *(7)*.

New vaccines proposed for incorporation in the NIP are assessed by the National Committee for Technology Incorporation in SUS (CONITEC). According to law 12.401/2011 *(8)* on scientific evidence and health technology assessment techniques, CONITEC "has the purpose of advising the Ministry of Health on the powers relating to the incorporation, exclusion or modification of health technologies by SUS, and on the constitution or alteration of clinical protocols and therapeutic guidelines" *(9)*.

The decision to introduce new vaccines is also considered by the Technical Advisory Committee on Immunization (TACI) (10), which provides technical and scientific support to the SHS in relation to immunization. On the basis of TACI discussions, SHS submits proposals to CONITEC for additions to, exclusions from, or modifications of the vaccine schedule.

In recent years, the following vaccines have been included in the programme: oral vaccine against human rotavirus (2006); 10-valent pneumococcal vaccine (2010); meningococcal vaccine C (conjugate) (2010); adsorbed pentavalent vaccine against diphtheria, tetanus, pertussis, hepatitis B (recombinant) and *Haemophilus influenzae* type b (conjugate) (2012); inactivated poliomyelitis vaccine (2012); measles, mumps, rubella, and varicella vaccine (2013); human papillomavirus vaccine; hepatitis A vaccine; tetanus, diphtheria and acellular pertussis vaccine (2014) *(6)*.

While public health needs and quality of life are the primary considerations in the decisions, finance is also an important criterion. Analysis of the available budget is important when a new vaccine is being considered for inclusion in the annual vaccination calendar.

In support of the NIP, the public production of immunobiological products – which nowadays account for the majority of vaccines and sera distributed free of charge to the public – is of utmost importance. This production, by Brazilian public companies, is supported by both State and external investments, including strategic partnerships, such as technology transfer and Production Development Partnerships (PDPs) *(11)*.

The strategy of using the State's purchasing power to boost public production has been implemented by the Ministry of Health since 2008 *(12)* and has contributed to the strengthening of the Industrial Economic Health Complex *(13)*.

Technology transfer from the French company Sanofi Pasteur to the Butantan Institute was a result of these various factors. The transfer of the influenza vaccine technology took place over a period of 14 years, starting in 1999. Eventually, knowledge of the entire production process was transferred to Butantan *(1)*.

This model has subsequently been improved by the Ministry of Health, with the support of the PDP, and used to develop domestic production of compounds considered to be strategically important for the country *(14)*. This has led to savings of US$ 3.02 billion in the public procurements of 23 products made by the Ministry of Health between 2011 and 2016.

It is expected that these projects will eventually lead to savings of US$5 billion, according to the Ministry of Health *(15)*.

At the end of the influenza technology transfer process, a Revocation and Discharge Agreement was signed by Sanofi Pasteur and Butantan; this was considered a milestone in the development of Brazilian industry, science and technology. The agreement states that Butantan is able to produce influenza vaccine of guaranteed quality. Moreover, after inspecting the production lines and packaging process, Anvisa granted a certificate of Good Manufacturing Practices (GMP).

Currently, Butantan has an agreement with Sanofi Pasteur, valid until 2018, for the purchase of influenza vaccines, if necessary, and to obtain technical assistance to increase production capacity.

Audits by the Brazilian Government have attested to the importance of this initiative for the country. The technology transfer for influenza vaccine has allowed Brazil "to reduce the cost of vaccine doses purchased from international laboratories, to master the production technology and quality control of immunobiologicals and to replace the import of the product by domestic production".

In addition to the national strategy to strengthen the health industrial complex (HIC), the annual epidemics of influenza and the risk of a pandemic make epidemiological surveillance of the influenza virus of paramount importance. The influenza epidemiological surveillance network coordinated by WHO started in 1948 and currently includes some 110 national influenza laboratories in over 82 countries, supported by four reference centres, in London, Atlanta, Melbourne and Tokyo.

In Brazil, there are three national influenza laboratories: the Adolfo Lutz Institute in São Paulo, the Oswaldo Cruz Foundation (Fiocruz) in Rio de Janeiro, and the Evandro Chagas Institute in Belém *(16)*.

Influenza virus strains collected in various parts of the world are classified and catalogued. Since 1977, the recommendation for the composition of the influenza vaccine has included three viral strains: two type A, of the H1N1 and H3N2 subtypes, and one type B *(17)*.

The domestic production of influenza vaccine depends on the dissemination of information about circulating strains in the northern hemisphere. Anvisa publishes each year a Collegiate Directorate Resolution, which specifies the composition of the influenza vaccines to be used in Brazil in the following year’s vaccination campaign. The resolution published by Anvisa is consistent with WHO recommendations for the southern hemisphere.

Only influenza vaccines that comply with the specifications and composition described in the Anvisa standards can be produced, marketed or used. The resolution also forbids the use of any other virus strains in the influenza vaccines in the country.

5 Summary of findings by field of study

5.1 Political milestones and the health system

Currently, 95% of the vaccines distributed in Brazil are produced in national public laboratories. National policies encourage technological development and the development of infrastructure for the manufacture of immunobiologicals in line with regulatory requirements. The Ministry of Health promotes initiatives for technology development, financing of production plants and research into strategic inputs. There is also political interest in ensuring the sustainability of the population's access to necessary vaccines and avoiding dependence on the external market.

International recommendations on influenza affect national policies, since Brazil follows WHO guidelines. However, the country has autonomy to decide on national campaigns and the use of vaccines. TACI performs the necessary analysis and adapts the general recommendations to the Brazilian reality.

In addition to the NIP, which is well established in the country, national and regional purchasing and distribution policies promote the production and purchase of products manufactured in the country.

Priority groups have been established for vaccination against seasonal influenza as part of the national vaccination campaign. All the groups recommended by WHO are included, such as children aged 2–5 years, women who have recently given birth, indigenous people and the prison population.

Risk groups in the event of an influenza pandemic have also been defined in line with WHO recommendations. In the 2009 pandemic, the 20–39-year age group was added to these risk groups, resulting in a total of 98 million Brazilians being vaccinated.

The structure of the national vaccination campaign against seasonal influenza, and the surveillance and control policies, would support the actions required in the case of a pandemic. The primary purpose of the annual campaigns is to reduce the severity of the disease and related deaths, since vaccination tends to reduce transmission of the virus in general.

Vaccines distributed free by the NIP are available to the population at health care facilities. There is adequate infrastructure in these facilities for vaccination activities. The vaccine distribution system also works satisfactorily.

Since 2012, Brazil has invested in improving the quality of its vast cold chain network, which currently has 36 000 vaccination rooms, 317 regional units and 27 state units. In 2016, 53million people were vaccinated against influenza. In a routine situation, the 36 000 vaccination rooms receive all immunobiologicals included in the immunization calendar. In all, 15 vaccines are made available for children, five for the adolescents , and five for the adults and elderly. Some 400 million doses are purchased annually for use in the NIP, with a total budget of 3.5 billion Brazilian reals (approximately US$1 billion).

The deadlines for the acquisition of influenza vaccine from the domestic producer are met and allow the annual campaign to start on time. However, although the final result is achieved, not all doses of the vaccine are available from the public producer before the start

of the campaign. This means that complex logistics are needed to distribute the vaccine, as Butantan makes partial deliveries throughout the campaign.

The acquisition process for influenza vaccine is long and complex. It starts in September, with the announcement of the recommended strains by WHO, and ends shortly before the start of the national campaign. The delay caused by internal procedures in the Ministry of Health means that Butantan has to start production without a signed contract.

It should be noted that the price of the vaccine is not considered an obstacle to the free vaccination of risk groups, according to the SHS. Further, the SHS considers that the Government has no political interest in nominating a second national (back-up) producer of influenza vaccine. The high investment costs do not justify a second production plant for public service, even in the event of a pandemic, especially since Butantan has the capacity to triple production to meet the domestic market needs in the event of a pandemic.

When the influenza vaccine was included in the NIP vaccination calendar in 1999, no health technology assessment study was carried out, since at that time there was no body responsible for preparing opinions on incorporation of new products. The Committee for Incorporation of Technology (CITEC) of the Ministry of Health was set up by Decree No. 2.587/2008 and the National Committee for Technology Incorporation in the SUS was regulated by Law 12.401 (replacing CITEC) in 2011.

No health technology assessment studies have been conducted in Brazil, or analysed by the Brazilian authorities, comparing the trivalent and tetra-valent vaccines, because there is currently no interest in changing the vaccine provided by the NIP. It is, nevertheless, important to understand the cost-benefit of the trivalent influenza vaccine that is currently being used in the immunization programme; this is recognized by the Department of Management and Incorporation of Health Technologies (DMIHT) and the Secretariat of Science, Technology and Strategic Inputs (SSTSI) as a challenge.

Another challenge, according to DMIHT, is the lack of cost-effectiveness studies of the trivalent influenza vaccine after each seasonal immunization campaign. However, these studies are difficult to conduct because the vaccine used for the campaign may not match the circulating strains, since there is little time between information on the circulating strains becoming available, production of the vaccine and release for use and distribution by SUS. There are doubts as to the possibility of changing the effectiveness of the vaccine at each change in the composition of the strains, with the potency, especially in those cases in which the strains composing the vaccine differ from those currently in circulation. The tetra-valent influenza vaccine is available in Brazil in the private sector and, according to the SHS, a preliminary analysis has already been carried out of the investments and resources that would be needed to incorporate it in the vaccination calendar. This analysis compared the private market price of the tetravalent vaccine with the public price of the trivalent vaccine currently made available by the NIP. The cost of the tetravalent vaccine was higher than that of the trivalent vaccine. Negotiations were carried out to find out the real cost of tetravalent vaccine for the public market.

CONITEC has so far received no request to incorporate the tetravalent vaccine from companies holding the registration or from the NIP. The NIP has no plans to replace the

trivalent vaccine with the tetravalent one, because of the available data from international studies showing a higher cost of the tetravalent vaccines compared to their–effectiveness[b].

There have also been no studies of production aspects or regulatory impact of the tetravalent vaccine in relation to the investments needed to make the necessary industrial adjustments.

5.2 **Surveillance**

The two coordinators of the SHS (the GCCD and the General Coordination of the National Immunization Programme (GCNPI)) consider that the virological and epidemiological surveillance system in Brazil is well established and adequate, and is supported by specific regulations, sentinel centres, and human and technological resources. The reporting by states and municipalities to the Ministry of Health of information from epidemiological surveillance is also considered accurate and timely.

Regarding influenza diagnosis, laboratory results are usually available within three or four days; the maximum allowed is seven days. However, there is a need to improve complementary analysis of the influenza virus (virus isolation, antigenic analysis, etc.).

The data collection system is adequate for epidemiological surveillance, but there is need for continuous monitoring and supervision by the Ministry of Health in order to maintain this status.

The data reported to the Ministry of Health include information on population risk factors as well as surveillance information. Weekly epidemiological reports are made, based on data analysis of the influenza information systems, Sinan Web Influenza and Sivep-flu.

Surveillance data are also aggregated and reported to the PAHO FluID platform every two weeks.

A study is beginning in the countries of the Americas on the burden of influenza. The disease burden study will use not only notification information and sentinel systems, but also other databases, such as hospital records and mortality registers.

Political decision-making is often based on the impact of a disease, but it is also influenced by other factors, such as press reports of increasing numbers of cases and related deaths, and pressure from the population.

According to the SHS, the number of vaccine doses that need to be produced to meet the needs of the Brazilian population in the case of a pandemic can be estimated. The data to support the estimation will be based on population estimates, results of epidemiological surveillance and information from national databases, such as the mortality information system, the live births information system and the case registry database (Sinan).

During a pandemic, or during a national or international public health emergency, the resources of the Ministry of Health for the prevention and treatment of influenza should be supplemented with additional resources to meet the needs of the population.

[b] http://www.who.int/phi/DAY2_05_Hendriks_PM_SaoPaulo2015.pdf

The Respiratory Virus and Measles Laboratory (RVML)**,** of Fiocruz is the national reference laboratory for the surveillance of influenza, and is seeking to become a WHO collaborating centre for influenza[c]. RVML has a regular and effective working relationship with WHO on issues related to the surveillance of circulating influenza strains. The management of the laboratory has direct contact with the WHO team responsible for influenza. There is regular and effective communication with WHO regarding the time for submission of strains and reports are submitted two or three times a month in the epidemic period. Outside this period, reporting is done as necessary.

RVML also has a regular and effective working relationship with the SHS (through GCCD and the General Coordination of Public Health Care Laboratories (CGLAB)), allowing the smooth conduct of activities under its responsibility. However, there is a need for better communication with Butantan, to provide it with information about what vaccine formulation will better match the circulating strain so that the production can start in time to provide the NIP with the vaccines to start the national campaign on time.

In the view of RVML, although the time available for production of seasonal influenza vaccine is short, earlier dissemination of the circulating influenza strains in Brazil would not reflect reality. Indeed, the incidence and prevalence of influenza are higher in the south and southeast of the country from June to August. It is therefore necessary to monitor the circulation of influenza until August.

It is worth noting that, contrary to what was previously thought, the strains circulating in north and northeast Brazil are not those circulating in the northern hemisphere, but are the same strains that circulate in the south, southeast and centre-west of the country. As regards seasonality, in the north and northeast the virus is most often found between April and June, and in the south, southeast and centre-west from June to October.

Brazil does not send many virus samples to WHO for the purposes of seasonal virus definition, for several reasons. Australia is crucial for the definition of the southern hemisphere vaccine composition; strain typing is carried out there on a large number of samples, its surveillance network contributes significantly, and there is WHO collaborating centre in the country.

From the perspective of RVML, the main challenge is to develop an influenza vaccine that is effective against all strains, since the difficulties of assessing and producing seasonal vaccines each year are numerous. RVML supports several academic studies, but does not carry out research to develop influenza vaccines.

RVML considers that reporting to WHO on unusual strains or strains with pandemic potential takes place in a regular and timely manner and there are currently no challenges that need to be highlighted. There is also effective communication with members of the WHO Global Influenza Surveillance and Response System, both through weekly reports of influenza activity during the season, and for provision of other relevant information. However, there is a need to improve the surveillance process in Brazil, so that more representative and viable virological samples are analysed effectively by RVML, thus increasing the chances of detecting new circulating strains.

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[c] The interview to relevant stakeholders to get information on this aspect was conducted on the basis of a questionnaire developed using the WHO document, "Terms of reference of national influenza centres" *(19)*.

The receipt of clinical samples by NICs for isolation of the influenza virus is inadequate at certain times of the year, including during outbreaks. There are problems in the influenza laboratory surveillance network, which are aggravated by the difficult logistics in some parts of the country for clinical samples to arrive to the laboratories for testing. The heterogeneity of the shipments causes the samples to suffer with variation of temperatures which may contribute to the reduction of the isolation rate. The problems are more pronounced in the transport of virus samples between the collection points and the Central Public Health Laboratories (LACENs) than between the LACENs and the NICs (as a result of the direct action of GCCD and CGLAB/SHS in this transport). However, there is a need for constant monitoring of the LACENs by the Ministry of Health, so that the flow of sample routing to the NICs is followed as recommended, considering the technical aspects and established deadlines. The LACENs network is decentralized; all states of the Federation have LACENs, which are linked to the state health departments, and which provide state-wide coverage.

In general, the country's three NICs experience difficulties with sampling, the logistics of sample receipt and a shortage of human resources. In addition, these laboratories provide very different diagnostic services. LVRS / Fiocruz, as a national reference laboratory, can be overloaded with more complex request such as resistance tests and complete genome analyses.

The RVML performs in-depth analysis of the circulating strains, including isolation, genetic sequencing, serology, resistance analysis, phylogenetic analysis and strain evolution. However, financial resources for updating some of these tests and for carrying out the analyses are limited; there are regular resources for only 50% of the analyses, but RVML manages to type 70% of the samples received. Initial identifications are carried out at LACENs.

At the LACENs, in general, improvements have been noted recently in the organization and maintenance of activities, including the standardization of routine work. However, there is a continuing need for technical training, because of the high turnover of human resources in the laboratories.

In the RVML, the laboratory employees and technicians are aware of WHO deadlines and requirements for reporting to the Global Influenza Surveillance and Response System. However, the number of employees is insufficient to meet the current demands, training to use the new technology/methodology and materials are also necessary.

The RVML promotes and hosts training on epidemiological surveillance for the national network of laboratories and for other countries in the region, usually at the request of PAHO. However, it does not have sufficient resources of its own for this training and so must seek external resources for technical training.

It is worth highlighting that the last project approved for modernization of RVML was in 2010; since then, there have been no new projects for improvement of laboratory facilities or acquisition of equipment. The 2010 project did not include actions needed to meet the requirements to become a WHO collaborating centre. The project to become a collaborating centre is a medium- to long-term one, and is being discussed by Fiocruz and the Ministry of Health.

5.3 **Communication**

The SHS maintains a solid relationship with the other stakeholders involved in communication to the public about influenza vaccination, and each participant understands his or her role. The media plan for the annual vaccination campaigns is defined by the Communications Office of the Ministry of Health (Ascom), at the request of GCNPI and GCCD. The plan is then consolidated and validated by all stakeholders.

After the communication strategy has been validated, campaigns and advertisements are created by private companies contracted by the Ministry of Health with the guidance of Ascom. In general, trained personnel in the Ministry of Health efficiently conduct communications activities for the influenza vaccination campaign.

There is a need for institutional coordination, primarily with the Primary Care Coordination of the Ministry of Health, to refine and integrate the communication strategies in other areas.

Ascom is responsible for measuring the effectiveness of communication about the influenza vaccination campaign, and also monitors access to communication channels (press, advertising and social networks).

The vaccination measurement graph (Figure 2) allows the number of people vaccinated to be tracked in real time, using the mascot of the vaccination campaigns, *Zé Gotinha*. The effectiveness of the campaign is also measured by reading comments on social networks, and monitoring the number of downloads of information materials. General opinion surveys are also conducted to update the communication strategies.

Public campaigns are assessed regularly and feedback given to the parties involved. This allows specific aspects of the communication strategies that need special attention to be strengthened during the campaign. These interventions have had positive results, increasing participation in vaccination campaigns.

Ascom also directs and intensifies communication activity when poor compliance is noted in a given area. Positive results have also been noted with actions of this nature.

Effective communication in the vaccination campaign is linked to the uptake by the population. A survey has been commissioned by the SHS to identify factors associated with vaccination against influenza and contribute toward improving the uptake by the population during seasonal vaccination campaigns.

Ascom uses epidemiological and other scientific data in defining communication strategies. The importance of establishing focus groups that include laypeople and advertising agencies is recognized.

Public campaigns in the press and advertising and social networks are regularly assessed by Ascom.

At the end of the campaign, an impact report is produced that is forwarded to the NIP as feedback.

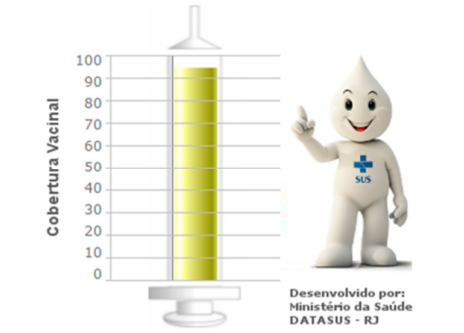

Figure 2. Vaccination measurement graph

5.4 **Production**

According to the Industrial Complex and Health Innovation Department (ICHID) and the SSTSI, the HIC has policies that encourage national production of strategic inputs for SUS, such as vaccines. However, there is a need to harmonized existing regulations and reduce overlap of responsibilities between the entities involved. It is also important that the institutions recognize these policies to induce the production of strategic inputs for SUS.

One of the main challenges according to ICHID is to improve the coordination of the network of institutions that produce goods for use in the public sector. This would allow a better distribution of resources, based on Ministry of Health guidelines, so that important projects with a low economic return, such as products for neglected diseases, could be appropriately addressed. There is also a need to organize the network at federal level, in order to improve expertise and organize initiatives at a local level.

There are also challenges related to: maintaining the continuity of the management within manufacturers; maintenance of constant training for managers and technicians; and modernizing industrial structures to comply with current sanitary regulations in the face of budget constraints. Among other challenges, manufacturers need to understand the diversity of legal status among producers (public, private, etc..) that determine the kind of support from the Ministry of Health.

Public producers rely on support from the Federal Government through specific programmes of the Ministry of Health. The Development Program of the Health Industrial Complex (PROCIs); the National Economic and Social Development Bank (BNDES); the Ministry of Science, Technology, Innovation and Communications (MSTIC) of the States of the Federation, contribute in the development of strategic orientations for public producers.

In general, there are challenges in maintaining and linking projects with the existing priorities and policies of the Ministry of Health. In addition, the resources available for development and innovation are limited, despite the existing initiatives, and they need to be managed and applied as efficiently as possible to meet the demands of the sector.

The ICHID/SSTSI supports the decisions of the national regulatory body as regards requirements for obtaining a GMP certificate, as well as other Anvisa requirements for record-keeping. It supports investments by public institutions to meet the sanitary standards in force, including providing budgetary resources. It sees the implementation of the regulatory requirements by the public producers as a challenge, since there is a need to

combine management strategies, monitoring, evaluation and constant awareness to maintain the GMP certificate.

In the view of the ICHID/SSTSI, the total number of doses of vaccine requested by NIP is a challenge, as Butantan is still in the final stages of escalating productive capacity. The transfer of the influenza vaccine technology was monitored directly by ICHID/SSTSI from 2013. In 2014 the transfer was completed and the ICHID/SSTSI reported that it had completed its follow-up, as regulated by Ordinance No. 2.531/2014. It should be noted that no executive project or term of commitment was signed, as advocated in PDP regulations, since this project was established in 1999 before the legislation came into force.

No analysis was conducted by ICHID/SSTSI to understand the impact on the production at Butantan of a tetra-valent vaccine if this was introduced in the NIP.

There are initiatives by the Federal Government to train staff to produce vaccines (for example Decree No. 8,269/2014, which established the National Programme of Knowledge Platforms). However, there are challenges in implementing these initiatives, mainly because of budget limitations.

There are discussions involving the Ministry of Development, Industry and Foreign Trade, the Ministry of Health, and the Ministry of Science, Technology, Innovation and Communication, to strengthen the HIC and provide a stimulus for exports, so that public laboratories, including Butantan, can increase production and take a share of the foreign market. Discussions are also being held with the Brazilian Agency for the Promotion of Exports and Investments (APEX) regarding export of vaccines, including to Mercosul.

In addition, there is an official commitment – in the terms of commitment for PDP projects in vaccine development – to serve the countries of the Global Alliance for Vaccines and Immunization (GAVI).

According to the ICHID, public laboratories should be more professionally managed, and should work with business plans within the market, so that they do not have to rely on public resources for financial support.

Ordinance No. 2531/2014 (14) allows the technical and managerial capacity needed for a particular technology to be transferred from the private or public institution that holds it to another public institution. Thus, the knowledge needed to produce influenza vaccine could be transferred to a second public producer, if this was seen to be in the interests of the SUS.

The ICHID considers that, although Butantan has a GMP certificate from Anvisa for the production of influenza vaccine, it could be a challenge to maintain it for different reason like; the difficulty in obtaining financial resources for necessary modernisation; the public nature of Butantan, which imposes specific deadlines for public purchases.

Butantan Institute considers that production costs in Brazil are high, especially the cost of supplies, raw materials and equipment, which are often imported. Unscheduled price rises resulting from changes in the exchange rate can have a significant impact. Furthermore, the selling price to the Ministry of Health is established in reals (R$) and the difference arising from fluctuations in the exchange rate is usually borne by Butantan.

Some complications are external and not predictable. It could occur that the Ministry of Health request vaccines which were not anticipated, out of the vaccination campaigns. This forces Butantan to start the production without the financial support of the Ministry of Health which has an impact on the final product cost. Sometimes contracts with Ministry of Health are signed in the month when the vaccination campaign begins, forcing Butantan to commence production using its own resources and making unscheduled purchases, which raise costs.

The reference points in negotiations with the Ministry of Health are international market prices, as reflected in the revolving fund of PAHO, and prices of purchases made in previous years. According to Butantan, because of inflation, public procurement prices have been continuously decreasing and are now lower than those of the revolving fund, which are considered among the lowest in the world. This has meant that there is no financial surplus that can be invested in the manufacturing process, such as development of back-up production lines, or in research and development.

The demand from the Ministry of Health has increased in recent years. This has had an impact on the production plant, which had originally a capacity to meet only one-third of current demand, under normal production conditions. There were thus need for more investment to improve the existing production lines, and to build new ones.

The demand for influenza vaccine from the NIP in 2016 was 54 million doses; local production by Butantan was 47.3 million doses, about 88% of the total needed. There is a need for additional investment to expand the plant to meet 100%of PNI demand. Butantan's current maximum capacity is 55 million doses per year for the seasonal trivalent vaccine. The demand for the 2017 campaign is estimated at 60 million doses (data from Butantan, 5 August 2016).

A technical assistance contract is still in effect with Sanofi Pasteur to help develop production and human resources to meet the demand from the NIP.

Butantan itself does not carry out studies to incorporate technologies into its industrial plant. Sanofi Pasteur has made a number of assessments and transferred the results to Butantan under the technology transfer agreement. The assumption is that, in a technology transfer process, the private partner performs a cost-benefit analysis when it defines the technologies to be transferred. As a result, Butantan does not need to validate or assess new processes and equipment. This is an advantage of the technology transfer process, which provides faster access to new productive technologies.

In the Butantan production facilities, the areas of formulation, filling and packaging are used for the production of other vaccines as well as the influenza vaccine. However, the API (monovalent) production area is a dedicated area. The fact that there is no dedicated area for all operations requires efficient and robust production planning and control in order to avoid problems with scheduled deliveries.

Another important challenge is the supply of embryonated eggs for the IFA production process. Although Butantan has two aviaries, egg costs are high and account for about 60% of the total cost of the vaccine. The chickens that lay the eggs for vaccine production are slaughtered at the end of the production period and the aviaries are unused for six months each year, increasing the cost of this critical input.

Butantan is considering investigating the use of adjuvants to increase productivity. However, the costs related to the necessary clinical trials are seen as high.

Income from the sales of products to the Ministry of Health by public producers are not automatically ploughed back into infrastructure improvements or encouragement of domestic production. However, public investments have been made to increase the production capacity of Butantan's manufacturing plant. The original capacity was 20 million doses per year, while current capacity is sufficient to meets the demand from the NIP of 55–58 million doses per year. Butantan has made efforts in recent years to obtain financial resources to start a second production line for formulation, filling and packaging.

There is a need to define state and federal policy for developing public production and promoting research and development in order to meet future demand. There is also a need to adjust fiscal policies or provide tax exemptions to encourage domestic production. For example, imported equipment is costly, and there is currently no exemption from tariffs for public producers.

The current contracts with the Ministry of Health do not provide for investment of the revenue from vaccines in research and development. Such investment is currently less than 2% of the revenue from influenza vaccine sales, according to Butantan senior management.

There is no plan for systematic training of staff using sales income. Training is provided as needed, but is dependent on the availability of funds from various sources.

There are no mechanisms for retention of staff trained at the Butantan Institute and the Butantan Foundation[d]. Because of the high concentration of pharmaceutical industries in and around São Paulo, where Butantan is located, there is a systematic loss of skilled technicians in the private market. One reason for this is that salaries in the public sector are not competitive with those paid by the pharmaceutical industry. Butantan has initiatives, which are dependent on the availability of resources, to promote the development skills of personnel through training.

Butantan has staff in its Clinical Trials and Pharmacovigilance Division who are trained in the design and implementation of clinical trials for vaccines and are responsible for the clinical development programme of all Butantan vaccines. This division undertakes activities related to the design, implementation and management of clinical trials and ensures compliance with Anvisa requirements in relation to the preparation, approval and implementation of clinical protocols. However, more personnel are needed in this area.

Another challenge in relation to the conduct of clinical trials, is the high cost of preparation, monitoring and final analysis. In Butantan's view, there is no need to reduce the health and ethical approval times for clinical trials. There is a need for more direct involvement of the Clinical Research Centre of the National Clinical Research Network[e] to meet the existing SUS needs for clinical research and help reduce the costs of such research.

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[d] The Butantan Foundation is a legal institution of private law that provides administrative support to the Butantan Institute (a public institution governed by public law).

[e] The Network was established in 2005, as a result of a joint initiative by the Ministry of Health and the Ministry of Science and Technology, in order to encourage research attuned to the needs of the Brazilian National Health System.

There is no vivarium at Butantan and no infrastructure for preclinical studies in conformity with Good Laboratory Practice (GLP). Currently, tests are outsourced to private vivarium.

Butantan has strategic alliances with public and private entities to obtain knowledge and technology; for example, it exchanges experiences of conducting clinical trials with clinical research centres in national public universities. However, the exchange of experience with other national vaccine producers is at an early stage, and there is no formally established network.

Butantan undertakes only passive pharmacovigilance of its products, using information received by Consumer Services and from the NIP. In the hope of receiving prequalification status from WHO, the Butantan Institute is considering establishing active monitoring of adverse events in the distribution and marketing stages.

After-sales monitoring of the influenza vaccine is carried out by the NIP (passive monitoring). In projects involving transfer of technology to PDPs and other entities in the private sector, monitoring is done jointly with the private entity, and may be passive or active.

Butantan reports that national policies influence development and infrastructure used to manufacture biological products in accordance with regulatory requirements. Butantan follows Anvisa regulatory requirements, which are based on national health surveillance policy.

Butantan uses the SUS lists of strategic products as a reference in decision-making on products to be developed or produced.

Butantan's institutional mission is to assist the NIP and meet the demands of the state of São Paulo. However, there is growing pressure to act internationally and provide assistance to other countries in the region. It is also necessary to align with WHO prequalification requirements for potential exportation.

Butantan requested prequalification for the influenza vaccine from WHO in May 2016; it has so far not received a response.

5.5 **Product approval and regulation**

The National Institute of Health Quality Control (NIHQC) is a unit of the Oswaldo Cruz Foundation. It acts as a national reference point for the quality control of products, environments and services related to health surveillance. and provides training. The NIHQC is linked to the Ministry of Health and participates in the National Health Surveillance System (NHSS), with autonomy to carry out monitoring activities. It is accredited by WHO, and is responsible for analysing the release of all vaccines produced in the country or abroad, from direct purchases or the PAHO revolving fund.

Being part of the NHSS, it works in conjunction with Anvisa, and with state and municipal health secretariats, among others. Among its activities are the implementation of analytical laboratory initiatives provided for in health legislation or requested by official bodies, and the issuance of opinions on scientific and technical issues related to health surveillance.

The NIHQC is an important national player in supporting vaccine production, both in analysing batch releases with regard to methodologies, technologies, management and distribution of inputs and also in providing training and human resources development.

Quality control is performed for all batches of vaccines purchased by the NIP, whether from domestic production or imported, to comply with monitoring policy and ensure the quality of vaccines distributed in the domestic market. A document analysis of batch-to-batch production protocols and analysis of production and quality controls are carried out in accordance with approved sampling procedures. Because time is often short, parallel batch releases may be carried out, in accordance with international regulations.

The NIHQC is the only national laboratory with the necessary structure, equipment, and human resources to carry out quality control; it also has a vivarium and other complex structures. Its quality control activities on batch releases of vaccines and serums are recognized and legitimized by the service responsible in the Brazilian Ministry of Health.

From the questionnaire answered by the NIHQC, it is clear that there is a regular and effective working relationship with the Brazilian Government (through various departments of the Ministry of Health, Anvisa, and others). There are, however, challenges in maintaining consistent and non-bureaucratic routines necessary for the flexible release of batches to the NIP. Moreover, differences in understanding of the existing regulations should be reduced to avoid having a negative impact on important activities in the regulated sector and on the vaccine distribution programme.

The NIHQC's role comes at the end of the production chain and it therefore works with short time scales. Batch release analysis should be carried out around February to allow the vaccines to be delivered in time for the national campaign in April. The normal time scale is five days for document analysis and 30 days for laboratory testing of vaccines. No differences were found in the times needed for testing of batch releases of vaccines produced nationally and those imported.

The vaccine produced by Butantan is forwarded to the National Centre for Storage and Distribution of Immunobiologicals (CENADI), which takes samples according to an approved procedure and forwards them to NIHQC. The NIHQC carries out the analyses and sends the results to the NIP. If the results are acceptable, the NIP then authorizes CENADI to proceed with distribution.

There is a regular and effective working relationship with the Butantan Institute on matters relating to the approval and release of batches and to the reporting. There is also the possibility of performing quality control releases in parallel of the production, which allows quick analysis in an event of a pandemic.

All internal and external clients of the NIHQC are familiar with the workflows that have been built up over the years, especially after the creation of Anvisa. Collegiate directive resolution No. 73/2008 (18) is the standard that sets the workflow and the role of each of the players. Under this legislation, the NIHQC also became responsible for the release of vaccines imported into the private market. A workflow has also been defined for vaccines produced for export.

The reference materials for the influenza vaccine and the standards and specific serum used in the tests are imported. WHO assists in the process of acquiring these materials.

The NIP has access to the NIHQC computer system, which manages information about the batches released or rejected in real time. When batches are rejected, approved procedures are used. A report is issued, to which the NIP has access, and Anvisa is informed about actions that should be taken. These actions may delay the start of the vaccination campaign. NIHQC participates in and guides the investigation process with Butantan in cases of rejection of batches for non-conformities. An investigation is conducted by the producer to understand the production processes to detect the non-compliance, on a case-by-case basis. Investigation activities pose a challenge to NIHQC especially in the identification of the non-compliance.

The quality control analysts are familiar with the production process of the influenza vaccine and have attended training courses outside the country in recent years.

If changes are made that have an impact on production processes, as a result of which Anvisa needs to change its records, the NIHQC is informed. Good communication is needed between all parties in order to avoid disruption to the workflow.

At present, there is no specific demand for the NIHQC to act as a focal point for training in the region. However, in the past it has been involved in exchanges of individual professionals and has run training at the request of PAHO. The NIHQC is available to participate in technical training initiatives for other countries in the region that are active in quality control of vaccines in the public sector.

A monograph on analysis of influenza vaccine is being prepared for publication by the Brazilian Pharmacopeia. It does not contain anything that would require a change in the current process of carrying out the main tests; only the standards relating to the annual strains will change. Because of the productive collaboration between Butantan and Sanofi Pasteur, the European Pharmacopoeia is currently followed for routine analysis.

The NIHQC participates in discussions on adverse events arising from the use of the influenza vaccine. This participation is regulated by a joint ordinance of SHS, Fiocruz/NIHQC and Anvisa.

The demands of the vaccination campaigns are continually increasing, generating an increased demand for quality control. However, there is no financial compensation for this, and no stimulus to incorporate new technologies, increase human resources or buy more reagents to respond to this increased demand.

If the NIP adopts the tetravalent vaccine, the quality control methodology will need to be re-evaluated. The NIHQC does not participate in the discussions on the incorporation of new technologies in the NIP. There is a bottleneck in the emergence of new technologies and receipt by the Institute of funding for modernizing its equipment and facilities and for training staff.

All vaccine quality control activities are carried out by the NIHQC. There is no outsourcing of quality control to private or public laboratories.

There is no workplan to respond to an increased demand for quality control analyses of the influenza vaccine in the event of a pandemic. The NIP need to develop this workplan. The main challenge affecting the release of batches by NIHQC is compliance with work schedules for the production and delivery of vaccines by Butantan to CENADI. Only in this way can the batch releases be tested without delaying planned immunization initiatives.

The Brazilian agency responsible for health surveillance and regulation of health technologies and services, Anvisa, is prequalified by WHO. However, prequalification requires effective pharmacovigilance, clinical research, inspection, registration and batch release process. Coordinating all areas of Anvisa to maintain its prequalified status is a great challenge. It should be noted that, as part of the prequalification process for Anvisa, NIHQC is evaluated, even though Anvisa has no control over NIHQC.

There is an effective working relationship between Anvisa and public producers of vaccines in Brazil. Public institutions need to constantly ensure that they comply with health regulations, in order to maintain their GMP certification. This process is helped by the fact that Anvisa carries out effective performance evaluation for compliance with GMP in conjunction with its health surveillance services to states and municipalities, and maintains a dialogue with producers through the regulatory technical committees, which are in continuous contact with the producers.

The transfer of the technology for influenza vaccine production to Butantan was monitored by Anvisa. Anvisa considers that the transfer was completed successfully.

If Butantan changes its infrastructure in order to meet the total demand for seasonal vaccine, or to meet the demand generated by a pandemic, there may be a need to revalidate the GMP. A change in registration may be necessary if there is an increase in the size of the production batch.

If the influenza vaccine produced by Butantan is prequalified by WHO, it will be important for the Institute to maintain its GMP status, so that it can supply products for the PAHO revolving fund. Public producers in Brazil know the regulatory requirements for vaccine production in the country and also for the submission of a dossier of prequalification by WHO.

The current Butantan influenza vaccine is up to date and is valid until December 2017. Six months before registration of the vaccine, Butantan must request revalidation. This activity has been carried out properly since Butantan started production of the influenza vaccine.

The updating of the vaccine to include new strains requires post-registration amendment, as occurs in other regulatory agencies in the world. As from 2016, Anvisa stopped requiring efficacy data for updating strains. All countries now require more robust and active pharmacovigilance when strains are updated, rather than an immunogenicity study, which uses an unrepresentative sample.

The use of a mock-up is an interesting strategy for speeding up the registration process for a pandemic vaccine. A mock-up is a vaccine that contains all components except the IFA. In the case of influenza vaccine, registration is carried out using a generic strain and, if there is a need to produce a vaccine to deal with a pandemic, a post-registration update to include the

circulating strain is requested. It should be noted that the mock-up request must follow all registration requirements (GMP and pilot batches).

The mock-up registration strategy was used in the most recent H1N1 pandemic in the USA. Anvisa currently does not have regulations for registering products for use in emergency situations and these would need to be drafted.

As an alternative to increasing production capacity, the packaging of the vaccine could be transferred to another local producer, since packaging is a critical bottleneck in the production process.

Preliminary analyses by the Butantan team have shown that no structural changes would be necessary to produce the tetravalent vaccine rather than the current trivalent vaccine. A new GMP certification would not be needed. It would need only a change in product registration, as a result of the insertion of another strain in the formulation.

6 Recommendations to increase the sustainability of influenza vaccine production in Brazil

Recommendations for the sustainable production of influenza vaccine in Brazil were drawn up on the basis of the interviews. These were supplemented at a workshop held on 5 August 2016, attended by the interviewees and representatives of WHO.

At the workshop, WHO stressed the importance of increasing world production capacity of influenza vaccine in preparation for a pandemic. The global capacity for seasonal vaccine has increased since 2006; in 2015, it was 1.46 billion doses. In a pandemic scenario, a production of about 6.3 billion doses should be achievable, for several reasons. First, seasonal vaccine includes three antigens; in the case of a pandemic vaccine, all production would be geared to a single antigen, which would allow production capacity to be tripled. In addition, the gradual increase in the use of tetravalent vaccines rather than trivalent ones, and the increased use of adjuvants that allow a lower dose of antigen to be used, would contribute to achieving the 6.3 billion doses.

Butantan has reported that it can expand its production of pandemic vaccines**,** to reach 400 million doses in 2018–19. Butantan is also conducting studies to develop pandemic vaccines and adjuvants to improve performance.

The recommendations made to increase the sustainability of influenza production in Brazil fall into five categories:

- political and institutional factors;
- infrastructure;
- human resources;
- evidence and technical capabilities;
- regulatory standards.

6.1 Political and institutional factors

The Ministry of Health is interested in promoting sustainable production, as well as policies that encourage technological development and maintain for the manufacture's infrastructure in accordance with regulatory requirements. There is a political interest in ensuring access to

immunobiologicals products, specifically for the NIP, as well in preparing the country for a pandemic scenario, in line with recommendations made by WHO.

The NIP is well established and active and is presented as an example of the success of national public policy, with high levels of adherencein all groups define for vaccination. The mechanisms of surveillance, control and distribution of vaccines throughout the country are appropriate for actions that may be required in a pandemic scenario.

There are policies to stimulate the national production for SUS (such as vaccines). These are considered among the main elements of sustainability, since they give priority to long-term actions of technology transfer, technological development and internal supply of products free of charge to the population by the Ministry of Health.

One of the most important challenges in ensuring the sustainability of influenza vaccine production by Butantan is the lack of long-term contracts with the Ministry of Health. Current Brazilian legislation makes no provision for such contracts and purchases must be agreed each year based on vaccine prices around the world, in particular those of the PAHO revolving fund. This causes difficulties for Butantan, which as a result has not been able to invest in long-term actions, such as research and technical training.

6.2 **Infrastructure**

There is a clear need for investment to modernize some structures related to production and to support quality in the production of vaccines. Thus, investments are needed, not only in Butantan, but also in the quality control and surveillance network laboratories (LACENs and NICs), to allow them to purchase new equipment and modernize their facilities to keep up with technological developments.

A positive factor is the extended network of laboratories currently implementing activities related to the epidemiological and virological surveillance system. However, the need for modernization of the infrastructure should be considered, as well as the improvement of flow and techniques for transporting samples.

The LACENs highlight various problems, such as a small number of staff available for testing and management. The Ministry of Health transports samples from the LACENs to national reference laboratories. There is a need for improved management in these laboratories to ensure the regular submission of samples.

The NIC is seeking to become a WHO collaborating centre, and has an ongoing project for this purpose. There is a need to maintain financial support to ensure the continuation of this project. It would be important in ensuring a greater input from Brazil in the definition of circulating strains in the southern hemisphere for vaccine production, which today is very much based on Australian samples.

As a national producer, Butantan will need to adjust (equipment purchase, validation, and training) its second filling line (the current filling capacity is 1.1 million doses/day, and it might be duplicated with the second line installed) and its API production (monovalent eggs) – the current production bottlenecks – in short term, in order to increase its production capacity to meet the annual demand of seasonal vaccines and also pandemic vaccine. To do so, it must has an external contribution of financial resources.

6.3 Human resources

The recruitment, retention and training of human resources are one of the main challenges for sustaining national production of influenza vaccine. There is a need to construct a systematic training plan for the completion of strategic projects in the medium and long term. In addition, routine training is required for manufacturing operations, quality control and surveillance, which do not have a continuous flow of financial resources.

In recent years, there has been fierce competition for jobs in pharmaceutical companies in the region in which the Butantan Institute is located. These jobs have more attractive salaries, which has made it difficult to retain skilled personnel.

Despite all the difficulties, the transfer of technology and routine training have led to safe, high-quality production and laboratory output and to technical cooperation. The company is open to cooperation with other countries in the region.

6.4 Evidence and technical capabilities

In this area, there are two main factors of note. The first is the transfer of technology from Sanofi Pasteur, which was completed in 2014. This transfer is one of the main elements that is promoting sustainability in domestic production, since one Brazilian producer now holds all the production technology and uses it independently.

The second factor is currently a significant challenge, and concerns the obtaining of information on circulating influenza strains in order to begin production of the seasonal vaccine. This information is available in September, while the national immunization campaign generally starts in April. As the production process takes over six months, there is a high risk that Butantan cannot meet the needs of the NIP in a timely manner. It would therefore be preferable to have information on circulating strains before September, so that vaccines could be made available in advance of the campaign and with less production risk.

This has to be considered in direct relation to the provision of a better service to the north and northeast of the country, where influenza virus begins to circulate before the start of the annual campaign. The NIP may wish to consider reviewing its vaccination strategy, with a view to providing vaccines on different dates in different regions of the country, depending on the seasonality of the virus.

There is a need for better communication between the RVML and Butantan so that Butantan receive information analysed by RVML immediately during the seasonal influenza virus in Brazil. Advance information about the strains circulating in the country would provide greater security for Butantan in starting up production (it starts production on one of the strains before it is officially announced by WHO in September). It should be noted that RVML/Fiocruz reports to the Global Influenza Surveillance and Response System on a regular basis.

One of the main challenges for laboratory surveillance in providing the strain information timely, is the lack of investment to modernize the RVML. This laboratory plans to become a WHO collaborating centre, which would greatly increase the reliability of information on circulating strains in Brazil. A Brazilian national influenza centre would help ensure that the situation in Brazil is better represented in the annual definition of vaccine strains.

Another challenge is that the LACENs, which have the responsibility for collecting and sending samples of circulating viruses to reference laboratories, such as the RVML, do not do this regularly and tend to focus on the end of the season.

Butantan has been working to develop new formulations with the use of adjuvants, a strategy supported by WHO. Butantan already tests adjuvants that are available on the market. Anvisa should assess the safety and effectiveness of these adjuvant formulations for licensing on the domestic market. The SSTSI is willing to collaborate with Butantan, should the need arise, by contacting international suppliers of adjuvants.

However, the greatest challenge to the continuity of this initiative is ensuring the continuous supply of the resources needed for the laboratory tests and clinical studies required, including in children. Butantan understands that it has to comply with regulations for the production of an adjuvant vaccine, but there are no systematic budgetary resources for research and development.

Another important element of sustainability, mainly for the pandemic vaccine, is the availability of embryonated eggs for the production of IFA. Butantan currently has two suppliers, which provide eggs from September to April. However, from May to July each year, both suppliers remove their stocks of chickens, because of the high maintenance costs. This may be a complicating factor if a pandemic occurs in the months in which chickens are not available. This situation could be avoided if vaccines were produced throughout the year, e.g. if Butantan could produce vaccines for export to the northern hemisphere, as a prequalified WHO producer.

6.5 **Regulatory standards**

Butantan meets Brazilian regulatory standards for the health sector and is currently GMP-certified by Anvisa for the IFA production lines for formulation and filling. However, Butantan must respect timing requirements and regulatory standards to retain its GMP certificate and to keep its registration for product supply up to date.

It is proposed that Anvisa should draw up regulations for the registration of products in an emergency situation. As an example, it would be possible to evaluate a mock-up for a monovalent pandemic vaccine. To this end, Butantan submit document to the attention of Anvisa, with comment on specific resolution regarding registration of products in a case of a pandemic.

As an alternative to increasing production capacity in Butantan, it was suggested to evaluate the possibility of a second public producer packaging the vaccine. Butantan can currently increase production of the vaccine, but cannot deal with the packaging of this expanded production. The SSTSI may therefore consider analysing the existing network of public immunobiological producers to determine whether they could provide support to Butantan.

The tetravalent vaccine is already available in Brazil on the private market, but counts for only a small proportion of vaccinations (95% of vaccinations are carried out in public health centres). Because of its high cost compared with the trivalent vaccine, the NIP has not yet incorporated it into the annual calendar, and it has not been incorporated as a new technology in the SUS. Should the NIP decide to incorporate the tetravalent vaccine, an impact study would needed. It is recognized that future technical advances may make the production of

tetravalent vaccine more acceptable, at which time the production plant may need to be adapted.

There is a consensus about the possibility of parametric batch release, which according to the NIHQC is already being done. However, Anvisa has suggested that WHO should participate in developing a protocol specifying the minimum parameters that Butantan should follow for batch release. Batch release procedure requires an in-depth assessment of the consistency of production.

7 Conclusions

Brazil is one of the few countries with favourable conditions for the sustainable production of influenza vaccine. The search for sustainability in the production of influenza vaccines in Brazil, especially in the event of a pandemic, needs to be stimulated. Actions aimed at sustainability should be continually monitored by the institutions involved with vaccine production.

The finalization of the technology transfer for influenza vaccine to Butantan was a great step forward for Brazil. Butantan is now capable of carrying out all stages of manufacture of the influenza vaccine, from production of IFA to the finished product. This fact greatly contributes to the long-term sustainability of production in Brazil, since a public institution is the holder of the technology for the manufacture of a vaccine considered strategic for the health of the population.

However, at present production is not sufficient even to meet the demand of NIP for seasonal vaccine; the production capacity of Butantan is practically equal to the demand for seasonal vaccine, so that any setbacks in the production process would lead to a shortfall.

The great demand for vaccines in Brazil is related to the existence of a public health system, SUS, which provides vaccination free of charge. In 2016, the Ministry of Health spent around R$ 5.3 billion (approximately US$ 1.8 billion) on the NIP, out of a total projected budget of R$ 103 billion (US$ 34.3 billion) for the year.

Vaccine coverage is high. The risk groups to be vaccinated against influenza in the annual campaigns are clearly defined, and in the 2016 campaign, coverage of over 80% of all risk groups was achieved.

The public health system promotes the development of national production and public policies support the financing of public production facilities, such as Butantan. In this way, the country promotes the sustainability of national production, and dependence on imported vaccines is declining. The country has solid institutions that support the public producer with regard to regulation, guarantees and quality control.

Anvisa and NIHQC/Fiocruz monitor the activities of batch release, changes in production facilities, and the registration and post-registration formalities required for a vaccine that is changed every year, to reflect the strains in circulation. The regulatory agency operates in accordance with the recommendations of WHO, providing reassurance to the population that the vaccines are safe, effective and of high quality, which contributes to greater vaccination coverage.

The communications strategies used by the Ministry of Health to raise the awareness of risk groups also contributes to the high vaccination coverage achieved by NIP. The importance of communicating with the population and the need for constant training of health workers in the vaccination rooms, as well as other SUS policies for basic care, are recognized by the Brazilian Government.

In general, the elements needed to ensure sustainable production of vaccine against seasonal and pandemic influenza are present in Brazil. Nevertheless, there are challenges related to coordination and the need for better infrastructure, a strengthened regulatory framework, and scientific evidence in support of a long-term strategy.

In a pandemic scenario, Butantan would be responsible for supplying the appropriate vaccine; it is expected that it would be able to produce triple the number of vaccine doses currently produced.

Investing in infrastructure is a more economical, and thus more viable, alternative than increasing the scale of production. Therefore, it is desirable that the Butantan Institute extent its plant to support the demand for seasonal vaccine and pandemic. Carrying out research on adjuvant formulations for registration will increase the production and ensure high production quantities in pandemic situation.

The network of official Brazilian laboratories could be used for shared production in certain situations, under the coordination of the Ministry of Health.

Above all, it is prevalent that there is technical and institutional support of other instances related to the production of a vaccine to meet the vaccine coverage.

Annual vaccination campaigns against seasonal influenza are important in reducing the impact of a possible pandemic, as they protect against each season. Resolving challenges in the production of seasonal vaccine will also facilitate the production of pandemic vaccine.

Some of the approaches proposed to the challenges identified here need to be evaluated by senior staff of the Ministry of Health and other institutions, since they have an impact on general policy. These include negotiations to obtain budgetary resources for research and development and for clinical studies for new formulations, as well as administrative solutions to speed up the contractual arrangements to supply vaccines.

The Brazilian experience of producing influenza vaccine can provide useful lessons for other developing countries seeking to produce influenza vaccines in a sustainable way, within the framwork of the Global Action Plan for Influenza Vaccines.

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Annex I - Questionnaire

PART I – Political Framework and Health System

Interviewed public institution: SVS/DEVIT
General Coordination of the National Immunization Program (CGPNI)
General Coordination of Transmissible Diseases (CGDT)
Members of the Consultancy Technical Committee on Immunizations (CTAI)

Sustainability Element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is the collection of clinical samples from patients to isolate the influenza virus during the year proper, especially during outbreaks and in the seasonability?		x		x		There is a challenge in optimizing the times for sample collection, shipment, and processing and reporting the results from virus isolation to WHO, as Brazil's participation is low compared to Australia, for example, referring to information volume.
Is there political interest to produce the vaccine in the country? Specify.	x			x		Currently, 95% of the vaccines distributed in the country are produced in national public laboratories. It does not represent a specific challenge, as there is political interest. Brazil adopts conducts to foster the national medicine production, especially highlighting the production of vaccines and sera, in order to decrease the dependence on the foreign market. There is a challenge to keep the fostering and fund the production, which basically occurs in public institutions.

Sustainability Element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there political interest to prepare the county for a possible influenza pandemic referring to vaccine production?	x			x		There is interest in ensuring the sustainability of the population access to the needed vaccines and not depending on the foreign market. There is a challenge in planning and providing the needed resources to prepare the country for a possible influenza pandemic referring to the vaccine production.
Do the international influenza-related recommendations affect the national policies?	x				x	Brazil follows the recommendations from WHO, but adjusts such recommendations to the national condition, as well as to the performance of the national vaccination campaigns.
Is there coherence between the national policies and the significant WHO programs?	x				x	There is coherence; however, the CTAI might adjust the general recommendation to the reality in the country.
Do the national and regional purchase and distribution policies promote the production and purchase of products made in the country?	x				x	The national purchase and distribution policy promotes the production and purchase of products made in the country, as it fosters and support the national production.
Do the national campaign for vaccination against seasonal influenza and the control policies contribute to prepare for a pandemic?	x				x	The national campaign mainly aims to reduce the disease severity and the related deaths, as the vaccination actions tend to minimize the influenza virus transmission in the country.

Sustainability Element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						Furthermore, the control policies already set enable a fast response to work under a pandemic condition. Regional policies do not contribute a lot to promote the production and purchase of products made in the country, as the purchases of Brazilian products acquired by the Strategic and Rotary Fund of PAHO are negligible.
Were priority groups for vaccination against seasonal influenza set and is it part of the national campaign for vaccination against seasonal influenza?	x				x	All groups prescribed by WHO are part of the group included in the national vaccination campaign, also adding the following groups: children from 2 to 5 years old, puerperal females, indigenous populations, and prison population.
Is the vaccine price an obstacle for the free vaccination of the risk groups?			x		x	Currently, the budget defined by the Brazilian government determines the financial expenses to purchase the influenza vaccine for all persons fitted in the risk groups defined by the Ministry of Health.
Is there a proper infrastructure installed in the health services in the country, with due maintenance to perform the vaccination activities?		x		x		Since 2012, Brazil has invested in qualifying its wide cold network, where there are currently 36 thousand vaccine rooms, with 317 regional units and 27 state units. A total of 53 million persons were vaccinated against influenza in 2016.

Sustainability Element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Are the terms for purchasing vaccines from the national producer complied with and do they enable the annual campaign in the country to be started according to the annual vaccination calendar?		x		x		The long term to formalize the contractual instrument by the Ministry of Health (internal procedures to purchase vaccines) requires that *Butantan* begins its production without a legal instrument (contract) signed by the parties. Furthermore, the vaccine production process is long and complex, beginning in September with the release of strains by WHO and the publication of the Anvisa resolution to release such production. However, the production is only complete before the beginning of the national campaign, considering the productive time required to produce the vaccine. Thus, it can be said that the goals of vaccination coverage proposed for the risk groups are met. However, as the producer does not inform the total number of doses to the MOH by the beginning of the campaign, such fact requires a complex logistic operation to be performed to ensure a timely and ongoing vaccine supply to all vaccination rooms in the country.
Is there a vaccine distribution system for the health services in the country and is such system efficient?	x				x	There is a consolidated and validated system for years. CENADI (*Central de Nacional de Armazenamento e Distribuição de Imunobiológicos*), located in RJ city, is responsible at federal level.

Sustainability Element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Are the vaccines freely distributed by the National Immunization Program available for the population in health services? Specify.	x				x	The 36 thousand vaccination rooms receive all immunobiologicals available in the PNI. Fourteen different vaccines are made available for children, 5 are available for teenagers-adults, and 3 are available for the elderly. A total of 400 million doses are purchased annually, in a total budget of 3.5 billion reais in the PNI.
Are vaccines available for private purchase in the private health services? Specify.	x					The influenza vaccines available in the Brazilian private market are imported, and companies Sanofi-Pasteur and GSK are the manufacturers. The quadrivalent influenza vaccine is also available. It has to be said that the Brazilian vaccine market is currently 95% public. The interviewee does not know about the challenges existing in the private health services to inform.
Have risk groups for pandemic influenza established in the country, according to the recommendations from WHO?	x				x	It is added that the population from 20 to 39 years old, besides the risk groups set in the recommendations from WHO, were vaccinated in the 2009 pandemic, totalizing 98 million Brazilians.
Is there an understanding about commercial agreements being able to affect the influenza vaccine supply in Brazil? Specify.	x				x	There is no knowledge in commercial agreements that affects the freedom for purchasing vaccines in both public and private areas in Brazil. However, it is known that, if such thing occurs, such agreements may affect the influenza vaccine supply in Brazil.

Sustainability Element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Are there initiatives in the scope of the federal government to promote the development of trained personnel to produce vaccines?			x		x	Fostering training in the production area is not an attribution of the SVS (PNI and CGDT).
Are there national policies incentivizing technological development and provision of infrastructure for manufacturing immunobiologicals according to the regulatory requirements?		x		x		The Ministry of Health fosters initiatives for technological development, production plan funding, and incentive to researches on inputs deemed as strategic.
Is there stimulation for the local producer to export the product to attend other countries in the region and other countries indicated by WHO?			x		x	The SVS (PNI and CGDT) does not have specific actions to promote such stimulation.
Has an ATS study been already conducted in the country referring to the quadrivalent vaccine compared to the trivalent one?			x	x		It is stressed that it is important to learn the cost-effectivity relation of the quadrivalent vaccine compared to the one of the trivalent vaccine.
Have initial studies been conducted referring to the investments and resources needed (budgetary impact) to incorporate the quadrivalent vaccine in the vaccination calendar?	x			x		The PNI has already performed a budgetary impact evaluation, comparing the prices of the quadrivalent vaccine in the private market to the public prices of the trivalent vaccine. No negotiations have been already conducted to learn the real public cost of the vaccination with quadrivalent vaccine in the country.

Sustainability Element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Have studies been already conducted on the production and regulatory impact of the incorporation of the quadrivalent vaccine in the PNI's vaccination calendar (investment needed for the national public producer of trivalent vaccine to promote the production of quadrivalent vaccine)?			x		x	The possible replacement of the trivalent vaccine with the quadrivalent one needs a more precise debate based on solid technical-scientific evidence about the advantages of the quadrivalent vaccine compared to the trivalent one, considering costs and results.
Is there governmental political interest in licensing a second national producer (backup producer) of influenza vaccine to support the production under pandemic condition?			x		x	The high costs of the investment would not justify having a second plant to attendance in case of pandemic. The MOH infers that the national producer (*Butantan*) has capacity to attend a demand increase caused by a pandemic.
If the answer above is positive, is such second producer already involved in the debates on the national production of influenza vaccine?			x		x	Not applicable.

PART II – Specific evidence subsidizing the planning for purchasing influenza vaccine

Interviewed public institutions:
SVS/DEVIT
General Coordination of the National Immunization Program (CGPNI)
General Coordination of Transmissible Diseases (CGDT)

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there a virological/ epidemiological surveillance system in the country (sentinel centers and human and technological resources)?	x			x		There is currently an established and sufficient epidemiological surveillance, supported by a specific regulation. The timeliness of the laboratory results in Brazil is from 3 to 4 days (agreed reference: up to 7 days). The existing complementary analyses, which need more assiduity (viral isolation, antigenic analyses, and others), need to be improved in surveillance for influenza diagnosis.
Is there a correct and timely report to the Ministry of Health referring to influenza surveillance?	x				x	Not applicable.
Is the data collection system according to the objectives of the epidemiological surveillance?	x			x		Such system needs ongoing monitoring and supervision by the Ministry of Health.
Do the data reports to the Ministry of Health include information on the populational risk factors, besides the surveillance information?	x				x	The epidemiological reports from the Brazilian Ministry of Health are weekly and refer to analyses of data from the influenza information systems: Sinan Web Influenza and Sivep-gripe.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is the information aggregated to and reported in international platforms? Specify.	x				x	PAHO's FluID platform is fed fortnightly.
Is it possible to determine the disease burden in the country from the treatment of the collected data?		x		x		It is possible to perform a disease burden analysis; however, a study to understand the disease burden for influenza is being initiated with countries in the Americas. It is important to stress that not only the notification or sentinel information systems are used for a disease burden study, but hospitalization and mortality databases are also studied.
Does the information on the influenza impact influence the political decision-makers?	x			x		Yes, but the decision-making is also influenced by other factors, such as linking the increase in the number of cases and related deaths by the press, as well as the pressure by the population.
Can the SVS estimate the quantity of vaccine doses that will need to be produced to attend the Brazilian population in a pandemic?	x				x	Yes. The data are based on populational estimates from IBGE, together with epidemiological surveillance data and data present in the national databases (SIM, Sinasc, Sinan, among others).
Is there guidance to obtain financial resources to purchase vaccines in a pandemic?	x			x		In a pandemic and in cases of national and international health emergency, the resources from the Ministry of Health must be complemented with resources from the Brazilian National Congress.

Interviewed public institution: NIC – LVRS – Fiocruz

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there a regular and effective work relationship with WHO in issues related to epidemiological surveillance of circulating strains?	x				x	The LVRS has direct contact with the WHO team responsible for influenza, including the coordinator, Dr Wenqing Zhang.
Is there regular and effective communication with WHO referring to the timely submission of strains?	x				x	Frankly, the limit for submitting strains to WHO is always the end of July, as there is no time after that for using such information in the meeting on the vaccine composition in September. There is a report 2 or 3 times/month during the epidemic period between LACEN and NIC. Out of such period, the report is performed when needed.
Is the term needed for notification to WHO by the NIC on which strains are circulating in both hemispheres, as well as the definition by WHO and the further communication to the producers about which strains must compose the vaccines, consistent to the production times and the correct beginning of the annual vaccination campaign of the PNI?	x			x		Despite the time for vaccine production being exiguous (considering the announcement of the strains in September and the beginning of the national vaccination campaign in March/ April), the LVRS considers that a result anticipation to make the knowledge on the influenza strains viable would not correctly reflect the strains that circulated from June to August in the country, in the Southern and Southeastern regions, which present the highest incidence. In the LVRS's point of view, the development of an influenza vaccine that is effective to fight all strains must be considered, as the challenges found to evaluate and produce seasonal vaccines annually are

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						numberless. It was stressed that the LVRS/ Fiocruz currently does not perform R&D activities for new vaccines.
Is there an effective communication with WHO for the immediate report of uncommon and/or potentially pandemic strains?	x				x	The report from the LVRS to WHO currently does not present challenges to be highlighted and happens timely. However, there is need for improving the epidemiological surveillance process for the LVRS to analyze more representative and viable samples, thus increasing the odds for detecting unknown circulating strains.
Is there an effective communication with the members of the Global Influenza Surveillance Network of WHO in the weekly influenza activity reports during the seasonability period and also in other information significant for surveillance and control?	x				x	There are no challenges in such matter.
Is there a regular and effective work relationship with the Brazilian government (several sectors of the Ministry of Health, Anvisa, Fiocruz, among others)? Specify.	x				x	There is a regular and effective work relationship with the Secretariat of Health Surveillance of the Ministry of Health (General Coordination of Transmissible Diseases-CGDT and General Coordination of Public Health Laboratories-CGLAB). It was informed that the LRVS is not audited by Anvisa.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there a regular and effective work relationship with the national vaccine producer (*Instituto Butantan*)? Specify.			x	x		There is need for improving the communication between the LVRS and *Butantan*, which, in collaboration, is enabled to obtain a better representativity of the national strains in times consistent to the production requirements and in meeting the regular beginning of the national campaign of the PNI/ MS.
Do the NIC's collaborators/ technicians know the WHO's times and requirements for reporting the information to the Global Influenza Surveillance Network?	x			x		The current number of collaborators is not sufficient to meet the current demands, and a training contribution is also deemed as necessary to update and follow the technological evolution of the equipment.
Is the reception of clinical samples from the patients to isolate the influenza virus during the year proper, especially during outbreaks and in the seasonability period? Specify the responsibilities of LACEN and other NIC.			x	x		The reception of clinical samples from patients for isolating the influenza virus during the year by the NIC is sometimes improper, including in outbreak periods and seasonability. There are issues in the laboratory influenza surveillance network, aggravated by the difficult logistic existing in several regions of the country for the clinical samples to reach the laboratories for testing. The submission heterogeneity causes the samples to suffer with the temperature variation, which can contribute to reduce the isolation rate. It is verified that the issues are more marked between the collection sites and the LACEN. Shipment issues are not so evident between the LACEN and the NIC,

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						mostly due to the direction actuation of the Ministry of Health (CGDT) in such purpose. Furthermore, there are irregularities in the definition and submission of the necessary number of samples. It is currently considered that 2 of the 9 existing NIC submit samples regularly. Difficulties in sampling, logistics for receiving samples, and reduced workforce are verified in the NIC. Furthermore, there are NIC very involved with demands for basic diagnosis, which is the case of the NIC located in SP state. Such fact causes other NIC (LVRS/ Fiocruz) to be overcharged with more complex analyses, such as resistance and full genome analyses, for example. Isolation, genetic, serological, and resistance activities are conducted in the LVRS/ Fiocruz, besides training activities for the laboratory network in the country, LACEN, PAHO, and several countries in the Americas. A better activity organization and maintenance has been recently verified in the LACEN, even with work standardization with practice handbooks. However, personnel's training is still required, as there is great human resources rotation in the laboratories.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Are there initial identifications of types and subtypes of the circulating viruses? Specify the responsibilities of the LACEN and other NIC.	x			x		The initial identifications are performed in the Central Public Health Laboratories (LACEN) in the states and DF. The LVRS performs conclusive and deterministic analyses of the circulating lines, besides sequencing, phylogenetic analysis, and strain evolution. There is need to improve the sample quality. Furthermore, there is also need to streamline laboratories and train personnel.
Does it work as a focal point for epidemiological surveillance training for the region?	x				x	It promotes and holds training for the national network of influenza epidemiological surveillance laboratories and also for the countries in the region, usually by solicitation by PAHO/ WHO (For example, training to investigate virus resistance against oseltamivir).

* NIC – National Influenza Centre. LVRS - Laboratory of Respiratory Viruses and Measles

Interviewed public institution: SCTIE/DGITS

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Was the incorporation of the influenza vaccine based on ATS studies?			x	x		No ATS study was conducted, as the MOH did not have an instance responsible for elaborating opinions on new products in 1999, the year when the influenza vaccines was inserted in the national immunization calendar. It is worthwhile to remember that the Commission on Technology Incorporation (CITEC) of the Ministry of Health was regulated by the Administrative Rule no. 2,587/2008 and that the National Commission on Technology Incorporation in SUS was regulated by Law 12,401/2011 (replacing CITEC). However, it is important to learn the cost-result relation/ outcome of this vaccine.
Is a cost-effectivity study, as well as a regulatory evaluation of the influenza vaccines at each seasonability, conducted to subsidize the campaign performance?			x	x		This is a significant challenge, as the times are very exiguous among the learning about the circulating strains, the production, the release for use, and the distribution by SUS. Furthermore, the vaccine effectivity (together with the yield/ strength) is changed at every change in the strain composition, mainly in cases when the strains that compose the vaccines are not the same circulating strains. Thus, it is significant to learn the cost-result relation/ outcome of this vaccine.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Has the CONITEC already received any solicitation to incorporate the quadrivalent vaccine?			x		x	CONITEC has not received any solicitation to incorporate the quadrivalent vaccine from the register-holding company, neither from the PNI. The PNI still does not present any intention of using the quadrivalent vaccine instead of the trivalent one due to the treatment cost-effectivity relation.
Has any solicitation to incorporate the quadrivalent vaccine already been evaluated by the CONITEC?			x		x	CONITEC never evaluated a solicitation to incorporate the quadrivalent vaccine.
Are there ATS studies available that can subsidize the CONITEC to make a decision about the incorporation of the quadrivalent vaccine instead of the trivalent one?			x	x		There is need to evaluate studies that show the higher effectivity of the quadrivalent vaccine instead of the trivalent one, as well as to evaluate the costs of both vaccines for a cost-effectivity analysis. The CONITEC indicates that the evaluation to incorporate a technology that changes its composition annually is complex, as annual evaluations would be also required. Otherwise, the evaluations performed with data from the previous seasonability would be full of biases.
If there are available ATS studies that can subsidize the CONITEC to make a decision about the incorporation of the quadrivalent vaccine instead of the trivalent one, are the annotations of such studies favorable to the incorporation?			x		x	There are no ATS studies conducted in Brazil or analyzed by the Brazilian authorities to compare both vaccines, as there is currently no interest in changing the vaccine provided by the PNI, based on the existing studies.

PART III – Communication for vaccination against influenza

Interviewed public institution: SVS/DEVIT
General Coordination of the National Immunization Program (CGPNI)
General Coordination of Transmissible Diseases (CGDT)

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there a solid relationship among the parties involved in public communication and does each of them known its functions? Specify.	x				x	The annual campaigns are developed by the communication sector of the Ministry of Health from a solicitation by the SVS (PNI and CGDT) and the final validation of the communication strategy is also performed by the SVS.
Are there trained personnel for communication?	x				x	The Communication Advisory Body (Ascom) is the responsible sector in the MS.
Is any measurement of the results referring to communication about influenza performed?	x					The Ascom of the Ministry of Health is the sector responsible for performing measurements and, therefore, no specific challenges are known.
Are there mechanisms to learn the general opinion on the communication and update strategies?	x				x	Public satisfaction surveys (opinion surveys) are conducted. According to the SVS, the Ascom conducts opinion surveys and

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						monitors the access to the communication channels.
Is the communication strategy integrated to other policies (with clear behavioral goals for the priority groups)?		x		x		There is need for an intrasectoral articulation, mainly with the SUS's basic care. There is also need for an articulation with sectors of the Secretariat of Health Care (SAS) that deal with the health of the risk groups considered in the vaccination campaign against influenza.
Are solid methodologies and tools based on scientific data used to define the communication strategy?			x			The Communication Advisory Body (Ascom) of the Ministry of Health is the responsible sector and, therefore, no specific challenges are known.
Are the public campaigns regularly evaluated and is there a feedback for the involved parties?	x					The Communication Advisory Body (Ascom) of the Ministry of Health is the responsible sector and, therefore, no specific challenges are known.
Is there awareness in the population and among the health workers about the benefits of the vaccination against seasonal influenza?	x					The communication is linked to the population adherence. A survey solicited by the SVS is ongoing to understand the vaccination-related awareness of the persons, and its results are still not available.

PART IV – Product development and local production

Interviewed public institution: SCTIE/DECIIS

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Are there policies to stimulate the national production of inputs strategic for SUS (such as vaccines) in the scope of the Health Industrial Complex (CIS)?	x			x		There are policies to stimulate the national production in the scope of the CIS; however, there is need for updating and adjusting the existing rules to maintain harmonization among them. The policies have to contribute for lower attribution superposition levels among the involved parties. There is also need for recognizing the policies within the institutions acting to obtain a higher resolubility in the applied strategies. One of the main challenges is the disarticulation of the network of public producing institutions, which many times compete among themselves for projects with higher economic level, and there is also need for organizing such network at federal level in order to optimize the expertise and organize the initiatives to meet the country's needs for producing strategic inputs.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						Furthermore, there are also challenges related to the discontinuation in the management of such public institutions, the need for training managers and technicians to manage strategic projects; and the budgetary restriction to support the streamlining of the manufacturing structures to comply with the sanitary regulation in effect; among others.
Do the public producers have support from the federal and/or state government for investments? Specify.	x			x		The public producers have support from the federal government in specific programs of the Ministry of Health (For example: Procis – Program for Developing the Health Industrial Complex and fostering edicts), BNDES, MCTI, and the federal states they are linked to, even by their agencies for fostering industrial development and innovation. There are challenges to maintain the articulation with the priorities and policies already in effect in the Ministry of Health. Furthermore, the resources are limited

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						for development and innovation activities (in spite of the existing initiatives) and also need to be more efficiently managed to meet all the demands in the sector.
Does the Ministry of Health (interviewed sector) support the decisions of the national regulatory body to keep the Good Manufacturing Practices (GMP) certificate in effect, as well as other requirements to maintain the product register in the country?	x			x		The MOH supports the decisions of the national regulatory body, as it supports the investment to public institutions to comply with the sanitary rules in effect, including the budgetary resources in such sector. However, the implantation of the regulatory requirements is deemed as a challenge, as there is need for allying the management, monitoring, evaluation, and awareness strategies existing to keep the GMP certificate.
Has the technology transfer contributed to the national production of influenza vaccine?	x			x		There is the challenge of meeting 100% of the national demand by *Butantan*, which is in the final phase of the production capacity escalation. There is also need for timely mapping the demand based on the circulating strain in order to better operate the national public production park.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Has the Ministry of Health supported the technology transfer between the private partner and *Butantan* for the national production of influenza vaccine?	x			x		The MOH has supported this technology transfer, mainly by using the purchase power of the Brazilian State from a technology transfer project that, based on the Brazilian purchase law (Law 8,666/63), has enabled the purchase of inputs strategic for health to attend SUS (PNI) from the public institution that received the technology. The technology transfer was a technological project started by *Butantan* in 1999, and has been directly followed by the MOH just since 2013, as a project similar to the Partnerships for Production Development (PDP) and its regulation in effect (Administrative Rule no. 837/2010 and Administrative Rule no. 2,531/2014). The technology transfer was concluded in 2014. It is highlighted that there were no executive project and commitment term according to what is prescribed in the PDP rule, as this project was set in 1999, before such rule took effect.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Has the Ministry of Health followed such technology transfer?	x			x		Yes, in part. The DECIIS/ SCTIE began to follow this technology transfer project since 2013. The follow-up by SCTIE was finished after the internalization of what was learned.
Has a previous analysis been conducted with the public producer about the production impact in the case of incorporating the quadrivalent vaccine in the PNI's vaccination calendar (investments needed for the national public producer of trivalent vaccine to promote the production of quadrivalent vaccine)?			x	x		The technological horizon monitoring is not conducted by this sector and there is no internal orientation for protocol changes by the PNI to change from trivalent vaccine to the quadrivalent one. Thus, the conduction of studies on cost-effectivity or cost-benefit relation for the quadrivalent vaccine will be expected.
Are there initiatives known in the scope of the federal government to promote the development of personnel trained to produce vaccines?	x			x		There are known initiatives in the scope of the federal government to promote the development of personnel trained to produce vaccines (for example, Decree No. 8,269/201, which instituted the National Program of Knowledge Platforms). However, there are challenges in implementing such initiatives, mainly referring to budgetary limitations.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there stimulation for the local producer to export the product to attend other countries in the region or other countries indicated by WHO?	x			x		There are discussions involving the Ministry of Industry, Foreign Trade, and Services (MDIC), the Ministry of Health (MS), and the Ministry of Science, Technology, and Innovation (MCTI) to develop and strengthen the CIS, determining a stimulation to export for the public laboratories (with *Butantan* among them) to be able to widen their production and their share in the foreign market in order to become sustainable. There are also discussions with the Brazilian Agency for Export and Investment Promotion (APEX) in order to export, even to Mercosur. Furthermore, there is a record of a commitment to attend countries from the GAVI Alliance (Global Alliance for Vaccines and Immunization) in the Commitment Terms of other vaccine projects, for example. According to the DECIIS, the public laboratories need to turn their management professional and to work with business plans considering a market logic to be sustainable and to be qualified to supply PAHO/ WHO, for example.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there known political interest in licensing a second national producer (backup producer) of influenza vaccine to support the production in case of pandemic?			x		x	Discussion on this subject is currently unknown; however, the production capacity of the current producer (*Butantan*) has to be widened to attend the additional demand in case of pandemic. It has to be registered that Administrative Rule No. 2,531/2014 sets the technological portability, defined as being the *"technical and managerial capacity of transferring certain technology from the private entity or public institution that holds it to other public institution"*. Thus, with a public interest in licensing a second producer at any time, the technology holder might transfer the knowledge to other public producer to enable the production in a second public production park, always aiming to attend SUS's interests.

Interviewed public institution: *Butantan*

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is the production area certified in Good manufacturing Practices (GMP)?	x			x		The general activities to keep GMP, the changes in the sanitary regulation with impact on the production area, the needed financial resources, and the public nature of the activities of *Butantan* represent challenges, incurring in specific terms. It is highlighted that *Butantan* (IB) has applied for prequalification by the World Health Organization (WHO) in May/2016, referring to the influenza vaccine.
Is there a work plan based on the cost analysis for production, product price, and investment return?	x			x		There are challenges related to currency exchange alterations in the market, mainly for importing pharmaceutical degree raw materials and equipment. This is due to the fact that the production is almost fully dependent on the foreign market (the embryonated egg is an exception, being produced in Brazil; however, the specific corn to feed the chickens is imported). Furthermore, the sale price for the

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						MOH is set in reais in the established contract and the difference in currency exchange is supported by the IB. There are other intercurrences that are not included in the IB governance (for example, purchase instrument, if it is an agreement or contract). The contracts with the Ministry of Health are signed in the month when the campaign begins, forcing the IB to begin production with its own resources and to perform non-scheduled purchases, raising costs. The vaccine price is fixed and there is price-adjustment policy to minimize the inflation impact and to invest in plant adjustments. There are also no investments set in contract to invest in plan adjustment of backup production lines. The demand from the MOH is dynamic and has increased in the recent years. This has impact in currently operation production plant

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						certified by Anvisa, which has capacity to attend 1/3 of the current demands, under normal production conditions. There is need for defining stated and federal policies for developing the public production and fostering the ongoing and future R&D actions. There is also need for adjusting fiscal or exemption policies to stimulate the national production. An example refers to the purchase of imported equipment, which is expensive, as there is no tariff exemption for public producers.
Is a part of the sale revenue redirected to research and development (R&D)?		x		x		The current contracts with the MS do not set clauses for reinvesting part of the revenue with vaccines in R&D; therefore, this is not the case of a systematic redirectioning of obtained investments. Currently, the investment in R&D is lower than 2% of the revenue with sales of influenza vaccine.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is a part of the sale revenue redirected to improvement in the plant infrastructure?	x			x		The current purchase policy in public producers does not set automatic resources for infrastructure and fostering of the national production from the signing of supply contracts. However, investments were made to increase the production capacity of the manufacturing plant, which was originally designed for 20 million doses/year and currently attends a demand from the PNI at the level of 55–58 million doses/year.
Is a part of the sale revenue redirected to personnel training and learning?	x			x		Training programs are defined according to the capacity of the financial resources, but there is no systematized training plan to train personnel. However, as the production needs require ongoing training, they depend on the availability of resources obtained from several sources. A technical assistance contract with the private partner Sanofi-Pasteur is still in effect (until 2018) in order to aid to develop production and human resources techniques.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is the technology to be incorporated in the manufacturing park selected based on a cost-benefit analysis referring to investments, operational costs, commercialization time, and product approval?	x			x		There is difficulty in finding available technologies in favorable conditions for the IB. There is no great flexibility to choose the equipment to be incorporated, as the technology transfer contract for the influenza vaccine determines that *Butantan* must follow Sanofi-Pasteur's production templates. It is inferred that Sanofi-Pasteur performed a cost-benefit analysis when it defined the technologies to be incorporated to the manufacturing park in the product development step.
Is more than one product produced in the facilities destined to produce the influenza vaccine?				x		Yes, for formulation, filling, and packing areas. The production area for API (monovalents) is dedicated. The fact that there is no dedicated area requires an efficient production planning and control. There is need for obtaining financial resources to license the production in a second production line in the formulation, filling, and packing areas.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Are there mechanisms to retain trained personnel?			x	x		There is a systematic loss of trained human resources to the private market, mainly in the recent years referring to the personnel in *Butantan Foundation* (juridical institution in Private Law that supports certainButantan's activities). The wages paid by *Butantan* are not competitive compared to the ones in the private pharmaceutical industry.
Are there trained personnel to design and implement clinical trials for vaccines?	x			x		There is a Division of Clinical Trials and Pharmacovigilance, responsible for the clinical development program of all vaccines from the Butantan. It performs activities related to design, implementation, and management of clinical trials. There is need for increasing the personnel in such area. The high costs to elaborate and follow trials and final analysis, which depend on the ongoing clinical study phase, constitute a great challenge to the Butantan. There is need for reducing the

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						sanitary and ethical approval times for clinical trials. There is need for an effective actuation by the National Clinical Research Network (RNPC), as the Clinical Research Centers created in the country with public resources are not operating in order to attend the existing demand for conducting clinical research by SUS.
Are there strategical alliances with public or private entities in order to obtain knowledge and technology (for example, to conduct clinical trials, postcommercialization surveillance, product, distribution, etc)?	x					There are strategic partnerships with Clinical Research Centers located at national public universities. The postcommercialization surveillance is conducted by the PNI (passive surveillance), but such surveillance (active and passive) is shared in the case of technology transfer from Partnerships for Production Development (PDP) and other technological knowledge transfer projects from a private entity.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Do the national vaccine producers participate in a network for exchanging expertise, training, etc.?			x	x		The expertise exchange among the national vaccine producers is deemed as incipient. There is no formally established network.
Are there institutional initiatives to promote the development of personnel trained to produce vaccines?		x		x		*Butantan* has initiatives focused on specific demands, depending on the availability of resources.
Is there an active pharmacovigilance system to monitor adverse events during the distribution and commercialization?			x			There is only passive pharmacovigilance (PNI and SAC). The establishment of active pharmacovigilance programs is being discussed in the perspective of the vaccine prequalification by WHO.
Are there infrastructure and an animal facility installed to conduct preclinical studies according to the GMP?			x	x		Besides the need for assembling an animal facility itself, there is need for assembling/ adjusting the laboratories according to the GMP in order to conduct studies with animals. The tests are currently conducted in private animal facilities in third parties.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Do the national policies influence on the development and infrastructure to manufacture biologicals according to the regulatory requirements?	x			x		The Butantan uses the lists of strategic products of SUS as reference to make decisions on the products to be developed and/or produced in its production plant. *Butantan* follows the regulatory requirements from Anvisa, set based on the national sanitary surveillance policy.
Is there stimulation for the national producer to export the product to attend other countries in the region and other countries indicated by WHO?			x	x		The institutional mission is to act to nationally attend the PNI; however, there is growing pressure for an international actuation. An alignment with WHO's requirements for prequalification is needed.
Does the production of influenza vaccine scheduled for 2016 represent 100% of the quantity demanded by the PNI?			x	x		In 2016, the demand solicited by the PNI was 54 million doses and the local production by the IB was 47.3 million doses. The current capacity of the IB is from 34 to 55 million (maximum) doses/year for the seasonal trivalent vaccine (campaign to attend the

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						Southern Hemisphere). The demand for the 2017 campaign will be 58 million.
Is there need for additional investments to expand the manufacturing unit to attend 100% of the current national demand of the PNI?	x			x		No comments.
Is the term needed for the NIC to notify WHO about the circulating strains in both hemispheres, as well as for WHO to define and later inform the producers about the strains that must compose the vaccines, consistent to the production times and the correct start of the annual vaccination campaign of the PNI?			x	x		There is need for improving the communication flow with WHO and NIC, in order to enable *Butantan* to receive the monitoring results in real time to produce seasonal vaccines. Currently, the vaccine production is late, considering that the Northern and Northeastern regions in the country present seasonability different (earlier) than the one in the remaining country referring to virus circulation. Thus, it would be optimal to learn the circulating strains in the beginning of August (and such learning currently occurs just in the second fortnight of September) and to prevent *Butantan* to start the production at risk

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						condition by not knowing the strains indicated by WHO. Furthermore, there is the direct reception of the WHO's report that defines the uncommon strains and Brazil poorly participates in its definition at WHO. There is still need for aid from WHO to make strains and reagents available timely, as the strain suppliers prioritize the European, America, and Australian markets and private producers. Referring to the surveillance of circulating strains in the country, there is need for improving the communication between *Butantan* and NIC (LVRS/ Fiocruz), which is the national reference laboratory for influenza laboratorial surveillance. *Butantan* could receive the information on the strains circulating in Brazil faster, online, directly from the LVRS/ Fiocruz, even before the

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						CDC and WHO. There is need for promoting a better communication among governmental instances (*Butantan*, Anvisa, and Federal Revenue Service) to address vaccine specificities and to reduce the time for customs clearance of strains.
Is there an effective communication with WHO for immediately receiving the information on uncommon and/or potentially pandemic strains?	x				x	No comments.
Would be there need for additional investments to increase the production capacity in case of pandemic?	x			x		This will depend on the demand and the time required to make the vaccines available, as well as on the strain yield.
Does *Butantan* have a mechanism to learn the quantity of vaccine doses that will need to be produced to attend the Brazilian population in a pandemic?			x		x	The definition of the vaccination groups and, consequently, of the number of persons to be vaccinated, is set by the MOH.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Was a study on the critical points (bottlenecks) conducted in the production process for influenza vaccine? Specify.	x			x		The egg production is performed in a farm specialized to breed chickens; however, due to the high cost for maintenance, the farm concentrates its production in certain months in the year, when eggs are specifically produced and kept to attend the influenza vaccine production. The inputs needed to produce adjuvants (as, for example, squalene) are imported. The maximum reception capacity is 268 thousand eggs daily, which limits the final quantity of vaccine doses produced daily. The imports of transgenic strains (used to produce pandemic vaccine) require release from CTNBio as they are genetically modified organism. There is need for duplicating the reception capacity and the egg incubation, duplicating the production line of monovalent eggs, and then developing an adjuvant to increase the yield, for the vaccine

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						production to be able to be triplicated to attend the national demand of about 150 million vaccine doses in case of pandemic. There is also need for expanding the formulation and filling areas to attend the pandemic demand (acquiring a second filler, as well as other pieces of equipment that can become production bottlenecks if they cannot work in proper conditions to attend the entire production demand). It is highlighted that 1 million doses/day for all vaccines (hepatitis B, DTP, adult double, sera, HPV) are produced in the formulation and filling, and there is no second line. Thus, there is need for adjusting the production plant (which was initially planned to attend 1/3 of the current demand) to attend the national demand for influenza vaccine.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there a plan for mitigating problems related to such critical points?		x		x		There are projects being developed for improvement in the production, formulation, and filling areas, but they are not formalized as an official mitigation plan.
Is there a qualified supply chain including all suppliers of the production process?	x				x	No comments.
Is the supplier of embryonated eggs for inoculation qualified and does it correctly meet the solicited demands?	x			x		The supply of embryonated eggs meets the quantity demanded by *Butantan*. In case of pandemic, there would not be eggs available to meet the demand, as the producer is scheduled to breed chickens just to meet the seasonability demand and the chickens are slaughtered after that. One way of turning the chicken breeding viable during the entire year is *Butantan* being prequalified by WHO and beginning to also produce influenza vaccines for the Northern Hemisphere, selling for the Rotary Fund or directly to the countries.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there a backup supplier of embryonated eggs qualified to meet *Butantan*'s demand if needed?	x					There are a total of two suppliers for the seasonability period (there is no egg production in June, July, and August, as the vaccine production is currently exclusive to attend Brazil).
Is the production of monovalent eggs, as well as of the active pharmaceutical input (API), stable and does *Butantan* performs its production activities well, regardless of the international private partner, referring to bulk production?	x			x		There is domain of the technological knowledge for production. However, the production planning, compliance, and control are still a challenge due to the process complexity.
Was the technology transfer, with consequent knowledge transfer, complete from the producing site of the private partner to the producing site of *Butantan*?	x				x	The technology transfer was finished in 2011, and Anvisa granted the GMP certificate to the API production area of *Butantan* in 2012. *Butantan* received the GMPC for the formulation/ filling area in 2014. There is currently a Technical Assistance Contract with Sanofi-Pasteur in effect, in order to aid the IB to expand the production up to the quantity demanded by the PNI/ MOH.

PART V – Product approval and sanitary regulation

Interviewee public institution: Anvisa

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is Anvisa prequalified by WHO?	x			x		The prequalification requires convergence and good performance in the pharmacovigilance, clinical research, inspection, register, and lot release areas. Thus, the coordination of all areas of Anvisa to keep the prequalified status by WHO is a great challenge. Furthermore, the INCQS is also included in the prequalification scope.
Is there an effective work relationship between Anvisa and the Brazilian public vaccine producers?	x			x		The public institutions must constantly improve the culture of compliance with the sanitary regulation. Anvisa has an effective actuation in evaluating the compliance with the Good Manufacturing Practices together with the local visas. Furthermore, the follow-up performed by the Regulatory Technician Committees (CTR) have provided higher contact with the producers.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						It was highlighted that *Butantan* must keep its GMP certification status by Anvisa in order to be able to supply products to WHO in case of prequalification.
Do the Brazilian public vaccine producers know the regulatory requirements for producing in the country?	x				x	No comments.
Do the Brazilian public producers know the requirements for submitting a prequalification dossier to WHO?	x				x	This is a standard submission, as it happens in the USA and Europe. It is highlighted that *Butantan* recently applied for prequalification at WHO which have already answered by asking for explanations about the submitted documentation.
Does *Butantan* have valid Good Manufacturing Practices Certificates (GMPC) for the API production and finished product areas referring to influenza vaccine?	x			x		The challenge is keeping the GMP certification status. As *Butantan* works in the limit of its current capacity, the interest in increasing the productivity to attend a pandemic scenario might require structural changes that can impact on its current GMP certification status.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Does the influenza vaccine from *Butantan* present an updated register? Specify the register validity.	x				x	Valid until 12/2017. *Butantan* must apply for the register revalidation six months before its expiry. This activity has been performed easily.
Does the change in strains composing the influenza vaccine require an annual regulatory analysis?	x				x	The strain update requires a postregister change, as it is performed for the other regulatory agencies worldwide. Anvisa has not been requiring efficacy data for strain update (which must occur annually) since 2016. As a propositional action, the use of a mockup (prototype) regulatory instrument can be evaluated to aid in urgency scenarios, such as a pandemic, within the regulation strategy for product registration under emergency condition. In such case, *Butantan* would present a documentation obtained from a mock-up product and just few documents would be required in a time of necessity, reducing the time for a regulatory analysis in an emergency time. Such strategy was used in the last H1N1 pandemic episode in the USA. It is important

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						to highlight that Anvisa does not have a regulation to register products for use under emergency situations and that, therefore, the elaboration of such regulation would be needed. All countries began to require a more robust and more active pharmacovigilance and not an immunogenicity study including a poorly representative sample anymore to update the strains.
Did the technology transfer (TT) involved in the production of influenza vaccine in *Butantan* have follow-up by Anvisa for its conclusion?	x				x	Anvisa considers the TT as concluded and there are no related challenges. Depending on *Butantan*'s strategy for the scaling, it might have impact on the GMP (change in infrastructure) and/or the register (increase in lot size).
Will a possible production of quadrivalent vaccine demand changes in the production infrastructure and the emission of a new Good Manufacturing Practices Certificate (GMPC) to *Butantan*?						The production of quadrivalent vaccine will not necessarily imply structural changes. This is valid for the tetra- or monovalent vaccine (in a pandemic scenario).

Interviewed public institution: INCQS

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there a regular and effective work relationship with the Brazilian government (several sectors of the Ministry of Health, Anvisa, among others) for releasing influenza vaccine lots? Specify.	x			x		There are challenges related to the maintenance of coherent and non-bureaucratic routines needed to agilely release lots to the PNI. Furthermore, divergences on the understandings of the existing regulation must be minimized in order to not make significant activities difficult (for example, import release). Referring to the strains needed to produce vaccine, these are only known in September every year. However, the INCQS must conduct analyses in February for the vaccines that must be delivered in the national campaign in April.
Is the workflow for lot release defined and known among the involved parties? Specify.	x			x		Strictly speaking, everyone knows the related works that were being build and adjusted along the years, mainly after the creation of Anvisa and with the prequalification by the World Health Organization (WHO). RDC 73/2008 set the workflow and the role of each actor. From such rule, the *National Institute of Health Quality Control* (INCQS) also began to be responsible for releasing imported vaccines to the private market and there was also the definition of the workflow of vaccines produced for export. Thus, the INCQS is the institution indicated by

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						Anvisa as responsible for releasing the use of all vaccines in Brazil, either such vaccines being supplied by public or private sectors. The activity flow begins with the vaccine production by *Butantan*, which forwards it to the *Central Nacional de Armazenamento e Distribuição de Imunobiológicos* (CENADI). Samplings are conducted at CENADI, according to a procedure approved for quality control analyses for lot release and sample storage for retention. Later, the INCQS performs the analyses and submits the result to the National Immunization Program (PNI). The PNI is who authorizes the CENADI to proceed the distribution. The INCQS performs the release of each lot, but does not conduct laboratory tests for all lots necessarily. For producers which quality history is already known, the INCQS performs a documental analysis in order to ensure and control the production quality. The conducted laboratorial tests are dedicated to investigate the vaccine strength, safety, sterility, and contamination. The documental normal times for vaccine release and laboratory analysis is 5 business days (documental analysis) and 30 days (laboratory analyses). No differences have been verified

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						between the release times for nationally produced lots and imported lots. It has to be recorded that the PNI has access to the INCQS's computerized system, which manages the information on released/ rejected lots in order to learn about the available lots for the national vaccination campaign in real time. The challenge found refers to the need for an effective compliance with the work timetables for the lot release terms to be enforced and to not negatively impact on the planned immunized actions. Furthermore, there is difficulty in purchasing reference materials to conduct laboratory tests. There is scarcity in the internal market and consequent need for import. The INCQS also indicates that the term for informing the strains that will compose the vaccine in the Southern Hemisphere is the bottleneck not only in the production process, but also in the performed quality control, as the INCQS retards in receiving the reference material to conduct the vaccine testing (standards, specific sera). The suppliers are: NIBSC (National Institute for Biological Standards and Control) (British regulatory agency) and TGA (Therapeutic Goods Administration) (Australia).

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is there a regular and effective work relationship with the *Instituto Butantan* on issues related to lot release and report of approved or disapproved lots? Specify.	x			x		The existing relationship is isonomic, tuned, and based on the existing regulation. There is facility in performing quality control releases concurrently with the public producers, which enables rapidity in the analyses under crisis situations. The report of disapproved lots is performed annually. Strictly speaking, the INCQS should participate in the certification/ validation process of *Butantan*'s production processes.
Is the lot sampling defined based on national or international regulation? Specify.	x				x	The monograph present in the Brazilian pharmacopoeia is preferentially used, when existing. When it does not exist, the Anvisa's resolution that presents a list of other pharmacopoeias that can be used (RDC 37/2009) is used. Referring to the influenza vaccine, the laboratory analyses are conducted based on the European pharmacopoeia.
Is the flow of activities needed for lot disapproval defined? Specify.	x			x		Approved and defined procedures are used for lot disapproval. The PNI has access to an issued report to not use the vaccine, and Anvisa is informed for actions that must be performed. The INCQS informs the PNI and Anvisa and the latter ones inform the producer (*Butantan*) if any lot is reproved.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						Butantan must report to the INCQS always when there are reproved lots in the plant, for the latter to learn about eventual issues that were detected and possibly internally corrected. Such report is pivotal, as the INCQS many times only releases influenza vaccines by documental analysis.
Does the INCQS participate in/ orientate the investigative process with *Butantan* in cases of lot disapproval to correct non-conformities? Specify.	x			x		An investigation is performed with the products to understand the production processes to detect non-conformities in each case. There are found challenges, inherent to the investigation activity.
Do the quality control analysts known the production process of the influenza vaccines to aid to detect non-conformities?	x				x	The analysts studied in courses on the influenza vaccine abroad in the recent years and have been using such knowledge specifically. They have support from PAHO/ WHO to perform the referred courses.
Is the INCQS informed on changes that have impact on the production processes that can be altered due to a change in the registers at Anvisa?	x			x		It is necessary to keep a good communication in order to avoid interruptions in the workflows. The INCQS is usually called to discuss the critical issues that affect the product quality.
Is there a work plan set for an increase in the analysis demand in case of pandemic?			x	x		There is none ongoing, and a formal indication is needed for beginning specific actions. Such actions imply increasing the purchase capacity and the input storage (reagents, vaccines for testing) and reorganizing the activities of the laboratories to acommodate the demand increase.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
						In case of pandemic, there is possibility of conducting analyses concurrently with the production in order to speed the lot release up when the lots are finished.
Is there awareness about the supplier chain for inputs for vaccine production? Specify			x		x	Such activity is consistent to the responsibilities of the vaccine producer. The INCQS is only aware of who the suppliers are from the quality assurance documents.
Does the INCQS work as a focal point for training on quality control analysis for the region?			x		x	Nowadays, there is no ongoing specific action for such aim, but there was already one action for several products in the past, with great impact on the vaccine area. There is an interchange of isolated professionals, but the INCQS is available for future proposals to participate in training actions for technicians in the countries in the region. Such actions aided in training technicians to reinforce the public institutions for the demands, as the example of Cuba, with funding from PAHO/ WHO. The INCQS has been available to aid other countries in the region to obtain prequalification in production or quality control laboratories.

Sustainability element	Status			Does it represent a challenge in its specific context?		Comments
	Yes	Ongoing	No	Yes	No	
Is the influenza pharmacopoeial methodology updated/ validated?		x			x	The monograph for the Brazilian pharmacopoeia is being elaborated for a further publication. Its review does not have impact in the process to evaluate the main conducted tests. The standard is changed due to the used strains. The currently followed pharmacopoeia is the European one, due to the process of technology transfer from Sanofi-Pasteur.
Does the INCQS participate in discussions in cases of adverse events?	x			x		The Joint Administrative Rule no. 92, from 10/09/2008, addresses the setting of an articulation mechanism among Anvisa, the SVS, and the INCQS on the pharmacovigilance of vaccines and other immunobiologicals in the scope of the Unified Health System and defines their competences. In cases of adverse events, there is a joint discussion among INCQS, *Butantan*, PNI, CGDT, and Anvisa.

Annex II - List of interviewed institutions and responsible persons

Institution			Responsible Person/ Title
Ministry of Health	Secretariat of Health Surveillance (SVS) - Department of Surveillance of Transmissible Diseases (DEVIT)	General Coordination of the National Immunization Program (CGPNI)	Carla Magda (Coordinator)
			Fabiano (Manager)
		General Coordination of Transmissible Diseases (CGDT)	Sérgio Nishioka (Coordinator)
			Walquiria Aparecida Ferreira de Almeida
	Secretariat of Science, Technology, and Strategic Inputs (SCTIE)	Department of the Health Industrial and Innovation Complex (DECIIS)	Joselito Pedrosa (Deputy Director) Gabriela Oliveira (Deputy Coordinator)
		Department of Management and Incorporation of Health Technologies	Clarice Petramale (Director) Vania Canuto (Coordinator)
	Press Office		Renato Strauss
			Anclar Patric
Anvisa	General Management of Medicines and Biologicals (GGBIO)		Daniela Cerqueira Marreco (Manager)
	General Management of Sanitary Surveillance and Inspection (GGFIS)		Mariana Adelheit Von Collani (Manager)
Fiocruz	Influenza Laboratory (National Influenza Centre)		Marilda Mendonça Siqueira (Head) Fernando Couto Motta (Vice-Head)
INCQS			Eduardo Leal (Director)
Instituto Butantan			Marco Antonio El Corab Moreira
			Paulo Lee Ho

Timetable - WHO Project: Key sustainability elements for producing influenza vaccine in Brazil

Activity		Finish Date (in weeks)													
		5/23 to 5/27	5/30 to 6/3	6/6 to 6/10	6/13 to 6/17	6/20 to 6/24	6/27 to 7/1	7/4 to 7/8	7/11 to 7/15	7/18 to 7/22	7/25 to 7/29	8/1 to 8/5	8/8 to 8/12	8/15 to 8/19	8/22 to 8/26
Data collection															
Validation of the questionnaire for interviews		x	x												
Interview with key governmental actors and involved public institutions															
PNI/ **SVS**/ MS	BSB				x										
Influenza Surveillance/ **SVS**/ MS	BSB				x										
DEGITS/ **SCTIE**/ MS	BSB					x									
CGBQB/ DECIIS/ **SCTIE**/ MS	BSB					x									
CTAI Member	BSB				x										
GGMED/ GPBIO/ **Anvisa**	BSB										x				
INCQS	RJ					x									
Fiocruz Lab. **(NIC)**	RJ					x									
Press Office/ **MOH**	BSB										x				
Visit to *BUTANTAN*: Brazilian public institution that produced trivalent influenza vaccine	SP					x									
Technical report on the project															
Survey and analysis of the technical policies, rules, and recommendations in effect in Brazil		x	x												
Meeting with key actors															
Organization coordination (invitations, materials...)								x	x						
Creation of PPT presentation										x					
Holding the meeting												x			
Comment incorporation											x				
Final technical report															
Report circulation for comments											x		x		
Comment incorporation													x		
Report conclusion													x		
Support to the publication process														x	
Support to translation to English and Spanish														x	x

Legend: CTAI - Consultancy Technical Committee on Immunizations (Ministerial Administrative Rule no. 232, from 11/25/2012); DECIIS - Department of Health Industrial Complex and Innovation; DEGITS - Department of Management and Incorporation of Health Technologies; MS - Ministry of Health; NIC - National Influenza Center; PNI - National Immunization Program; SCTIE - Secretariat of Science, Technology, and Strategic Inputs; SVS - Secretariat of Health Surveillance; BSB - Brasilia; RJ - Rio de Janeiro; SP - São Paulo.