Influenza vaccine production for Brazil: A classic example of successful North–South bilateral technology transfer

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Abstract

Technology transfer is a promising approach to increase vaccine production at an affordable price in developing countries. In the case of influenza, it is imperative that developing countries acquire the technology to produce pandemic vaccines through the transfer of know-how, as this will be the only way for the majority of these countries to face the huge demand for vaccine created by influenza pandemics. Access to domestically produced influenza vaccine in such health crises is thus an important national defence strategy. However, technology transfer is not a simple undertaking. It requires a committed provider who is willing to transfer a complete production process, and not just the formulation and fill–finish parts of the process. It requires a recipient with established experience in vaccine production for human use and the ability to conduct research into new developments. In addition, the country of the recipient should preferably have sufficient financial resources to support the undertaking, and an internal market for the new vaccine. Technology transfer should create a solid partnership that results in the joint development of new competency, improvements to the product, and to further innovation.

The Instituto Butantan–sanofipasteur partnership can be seen as a model for successful technology transfer and has led to the technological independence of the Instituto Butantan in the use a strategic public health tool.

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1. Introduction

In 2000, the Ministry of Health decided to provide influenza vaccination free of charge to individuals over 60 years of age, patients with chronic diseases, and health-care personnel. The Instituto Butantan – an arm of the São Paulo Office of Health – was charged to develop, produce and register the seasonal vaccine needed to implement this policy decision. The yearly demand for seasonal influenza vaccine was estimated at 25 million doses, to be deployed at 25,000 health centres across the country. A significant challenge to this enterprise was the short time available to import the approved vaccine strains and control reagents from the World Health Organization (WHO), prepare production banks, and carry out the required quality control tests in time for the annual southern hemisphere influenza season that starts in most of Brazil in April.

In parallel, the highly pathogenic avian influenza outbreak that threatened many countries in Asia in 2003 was a powerful argument for Brazil to increase its influenza pandemic preparedness. At that time, it was anticipated that countries without seasonal influenza production capacity, or existing contracts for the supply of vaccine, may have to wait over a year before sufficient pandemic vaccine became available to immunize their population [1,2].

To address these issues, Brazil sought a technology transfer partnership to construct a dedicated influenza vaccine production plant and, in the interim, to formulate and finish monovalent bulk vaccine supplied by an international vaccine producer, who would agree to become the technology provider.

The objectives were to produce 25 million doses of seasonal vaccine per year and to create a stockpile of H5N1 vaccine for use at the onset of a potential influenza pandemic. This paper describes progress towards these goals and discusses Butantan’s experience of the transfer of a complete production process.

2. Selection of the best technology transfer partner

As the production of inactivated influenza vaccine in embryonated eggs is a very standardized process, there is no regulatory uncertainty for manufacturers embarking on such production through technology transfer, provided that the vaccine seeds
(also called vaccine viruses) are generated and tested under the aegis of WHO, and that the plant complies with Good Manufacturing Practice (GMP). Moreover, the basic technology to grow viruses in fertilized hen eggs is well known to virology laboratories and producers of veterinary and human vaccines, and production technology does not vary with the influenza serotype.

For Butantan, a technology supplier would also need to take account of the financial constraints of a not-for-profit organization. For example, the Institute would only be able to pay for the bulk vaccine upon transfer of funds from the Ministry of Health and approval of the vaccine by the National Control Laboratory, i.e., months after receipt of this bulk in Brazil. Exchange rate fluctuations add to this concern.

Butantan selected sanofi pasteur (previously Sanofi Aventis) as its bulk vaccine provider and technology transfer partner for egg-based inactivated split seasonal influenza vaccine and whole virion adjuvanted H5N1 vaccine. Two reasons guided this choice: first, sanofi pasteur’s extensive experience in large-scale influenza vaccine production, and second, the long-standing relationship of this company with Brazil. Indeed, in 1975 it was the only company to accept the challenge to build temporary facilities for the supply of meningococcal serogroup A/C vaccines to control a widespread epidemic in major Brazilian cities.

A production plant was designed to process 125,000 eggs per day to allow for the production of up to 25 million doses of non-adjuvanted trivalent seasonal vaccine. The technology transfer solution agreed by both parties – in addition to addressing logistic, time and financial constraints – comprised oversight of the production plant design and selection of equipment (partly produced in Brazil), supervision of the construction of the plant and its validation, as well as assistance in the selection of an adequate source of eggs and training of senior staff.

3. Construction of the large production plant for seasonal influenza

The Ministry of Health, under an agreement concluded with Butantan in 2004, provided US$ 10 million to purchase the basic equipment, and the State of São Paulo Office of Health agreed to fund the construction of the plant, estimated at US$ 20 million. Significant delays were incurred because of a legal challenge during the tender process, difficulties experienced by the construction company, and the emergence of highly pathogenic H5N1 avian influenza. The latter required Butantan to upgrade its containment facilities and to identify and implement a technical solution to process residual egg shells and chicken embryos so that they could not be used for animal feed. The cost of the plant thus increased to US$ 35 million.

As with its other non-live vaccines, Butantan intends to transfer the monovalent inactivated bulk vaccine produced in the new production plant to its central formulation and filling plants. Two filling lines – one automated and the other manual – can sterilize, fill, cap, label and control 26,000 vials per hour. To save on transport and cold-room storage, each fill-finished vial will contain 10 doses.

Sanofi Pasteur fulfilled all the terms of the technology transfer agreement, including the provision of expert advice, site visits and training for key staff. Sanofi experts were also instrumental in overseeing the building of a large additional fertilized egg production farm near to Butantan.

In September 2010, after final validation by sanofi pasteur, the influenza production plant was ready for production. Starting from 2011, Butantan intends to produce 20–25 million doses of trivalent southern hemisphere seasonal vaccine per year. The development and registration of an adjuvanted formulation would allow for the production of significantly more vaccine, as reported below. This is particularly important in view of the fact that non-adjuvanted H5N1 split inactivated influenza vaccine is poorly immunogenic and requires immunization of vaccines twice with very high doses of haemagglutinin (HA) antigen (90 μg compared to 15 μg for seasonal vaccine). In order to alleviate this problem – i.e. to “spare” antigen in case of a pandemic and maximize the number of persons who can be immunized – multinational vaccine manufacturers have developed much more immunogenic H5N1 adjuvanted vaccine formulations.

4. Establishment of a “pandemic” influenza vaccine pilot plant

In 2008, the Instituto Butantan was selected, along with five other developing country vaccine manufacturers, to receive financial and technical support from WHO as part of an initiative to increase global production capacity for pandemic influenza vaccine [3]. The grant was for the construction and partial equipment of a pilot plant – a standard procedure for all new projects at Butantan – to manufacture experimental lots of H5N1 influenza vaccine, and for the training of key staff of the new production plant. The pilot plant would allow the development of basic technology to produce small vaccine lots for evaluation in animal models and, if produced under GMP, for a Phase 1 clinical trial to ascertain whether the safety and immunogenicity results obtained in human volunteers was similar to those obtained in animals.

The pilot plant was rapidly installed in an existing building adapted for GMP and equipped using funding from WHO, the Brazilian Ministry of Health, the São Paulo State Foundation, FINEP (a Federal Granting Organization), and CNPq (National Research Council). Additional funds invested by the Butantan Foundation were largely used to recruit new staff, who were later relocated to the large production plant.

In order to train the technical production staff, and to conduct the first adjuvantation assays [4] of influenza vaccine produced in Butantan, we first produced small lots of an H3N2 serotype vaccine. We then prepared master and working seed banks for H5N1 reference vaccine viruses (A(H5N1)Vietnam/2003 and A(H5N1)Indonesia/2005). A chromatography procedure was developed to purify whole virion H5N1. This allowed us to evaluate the yields for both split and whole virion vaccine, the immunogenicity of the H5N1 candidate vaccine and the antigen-sparing potential of several adjuvants in mice. Using 10 μg of Butantan’s MPLA (Monophosphoryl lipid A) or alum, we demonstrated that it was possible to successfully immunize mice with 3.75 μg of HA with a balanced humoral/cellular response [5].

To date we have produced seven lots of experimental H3N2 and three lots of H5N1. HA antigen sufficient to enable the rapid formulation of 20,000 doses of H5N1 vaccine were produced and stored at 4 °C.

The unexpected spread of the A/H1N1 influenza pandemic in 2009 moved Butantan’s priority to this novel virus serotype. New master and working virus seed banks were produced, antigen-sparing of our MPLA adjuvant tested in mice, and a small Phase 1 clinical assay carried out in human volunteers. This trial was supported by the Butantan Foundation, the Children’s Hospital, and the Campus Hospital of the University of São Paulo.

Table 1 shows the yield and purity of the H3N2, H5N1 and H1N1 candidate vaccines produced in the pilot plant over the period 2007–2009. The pilot laboratory has now become a permanent facility to develop and test technology improvements and to produce master and working virus seed lots. A quality control section will also be incorporated into the laboratory in the coming months.
5. Matching Brazilian influenza production capacity to evolving public health needs

5.1. Demographics

The population of Brazil is changing fast. From 184 million when the influenza vaccine project started in 2004, the population is expected to reach 204 million in 2040. Demographically, the coming years are expected to show a reduced demand for paediatric vaccines due to lower birth rates. On the other hand, the increase in life expectancy means that the population over 60 years of age will represent about 40% of the total population in 2040. This evolution has an important bearing on vaccine needs and production plant capacity. Indeed, using 15 μg of antigen per dose as anticipated for a non-adjuvanted split inactivated vaccine, Butantan would not be able to meet the demand of the Ministry of Health for seasonal influenza vaccine.

5.2. Northern or southern hemisphere vaccine formulations

Butantan’s production plant will operate for 4–6 months per year to produce southern hemisphere influenza vaccine, and would remain idle for a full semester. It could therefore be envisaged to produce the northern hemisphere formulation during these inactive months, which could be provided to other governments for immunization of their target groups, in exchange for southern hemisphere vaccine. Approval for this strategy remains to be sought from the technology provider (sanoﬁ pasteur).

There are further complexities in the timing and formulation of influenza vaccine in Brazil. Vaccination in the north and north-east currently takes place as elsewhere in the country in April, yet this is four months after the local seasonal inﬂuenza peak. Analysis of an epidemiological survey suggests that vaccination should take place earlier in this region. The exact transmission pathway that determines the origin of the virus is not clearly understood, nor the onset of a significant drop in temperature that sparks inﬂuenza incidence. Even if we could use the northern hemisphere formulation in this region, our inability to meet the demand for the southern hemisphere vaccine would not change, as the north and north-eastern regions only needs 2–5 million doses per year. Further, the difference in protection using one or the other formulation is not well defined [6] as this will depend on the extent to which the viruses have drifted.

5.3. Production of adjuvanted vaccines

Butantan considers that the best option to address potential shortages of inﬂuenza vaccine is antigen sparing through the use of adjuvants. We ﬁrst intended to formulate our inﬂuenza vaccines using aluminium hydroxide. We anticipated that by doing this we would not only be able to maximize production capacity by reducing the HA antigen content per dose, but also to lower the price of the vaccine to make it accessible for the least developed countries. Unfortunately, results of many published animal and clinical assays, mostly for H5N1, show that immunopotentiation by aluminium hydroxide is at best moderate, and most likely dependent on the source of aluminium salts, although the recent establishment of the mechanism of potentiation of aluminium salts [7] should lead to the improved performance of aluminium preparations.

Butantan’s commitment in 1985 to develop a pertussis vaccine that is less reactogenic than whole cell vaccine, allowed us to develop a procedure to remove lipopolysaccharide (LPS, which is responsible for pyrogenicity and inﬂammatory responses) from Bordetella pertussis without damaging the bacterial ultramicroscopic structure or the protection of mice against intracerebral challenge with virulent strains [4]. The resulting detoxiﬁed whole cell diphtheria–tetanus–pertussis (DTP) vaccine – DTPlowv. – was not only safer, but could be up to ﬁfty times cheaper than that of DTaP. Our research had further showed that removal of LPS allowed for the puriﬁcation of MPLA, which is potentially an extremely inexpensive adjuvant.

5.4. Demonstration trial

The 2009 A/H1N1 pandemic called for Butantan to take on an additional temporary role to provide pandemic vaccine to the Ministry of Health by ﬁlling a large number of doses imported as bulk product from international producers. Our proposal to vaccinate grammar school children (7–11 years old) to prevent the spread of seasonal inﬂuenza from schools to families was therefore curtailed. We did, however, initiate a demonstration trial among 5000 children in the São Paulo area. If results of this ambitious trial, conducted following stringent international practices, corroborate the positive impact of similar strategies [8], it might be recommended to immunize about 1 million children in Brazil.

6. Conclusion and plans

Technology transfer is complex. It entails a great deal of responsibilities on the part of the technology provider and technical and managerial capability on the part of the recipient. Above all, technology transfer is a joint venture based on mutual trust and commitment. A major objective must also be for the project to be sustainable, which implies incorporation of new developments into the process and, ultimately, technology independence for the recipient.

In the future, Butantan will seek ways to increase its production capacity in order to meet the demand for inﬂuenza vaccine, either by improving procedures within the large production plant, or by investigating new technologies.

Conflict of interest statement

The authors, all investigators of Instituto Butantan, a Governmental Research Institute, have no conﬂicts of interest.

References


