The Oswaldo Cruz Foundation - Fiocruz
Ministry of Health - Brazil

Technology Transfer
Hib GSK to Bio-Manguinhos/Fiocruz

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WHO Headquaters
30 November-01 December 2010
Vaccine production - intense science & technology basis – must do technology innovation

- The vaccine development is very complex: takes long time, multi-disciplinary teams, high cost and the return of investment is uncertain;
- Requires specialized Human Resources, special facilities and equipment, experienced team and proper management;
Bio-Manguinhos - Strategy for Tecnology Innovation

a) Self development projects

b) Joint Technological Development projects

c) Transfer of Technology Agreements
a) SELF DEVELOPMENT PROJECTS

- Meningococcal serogroup C conjugated – Clinical study - phase 2;
- Meningococcal serogroup B – OMV – Clinical study phase 2;
- Pneumococcal – common protein; conjugation;
- Dengue chimera – 17D as backbone;
- Malaria chimera – 17 D as backbone;
- Yellow Fever inactivated
b) JOINT DEVELOPMENT PROJECTS

- Pentavalent DTP/HBV+Hib – Butantan Institute
- Leptospiral recombinant – proof of concept, IPqGM;
- Leishmanina recombinant – proof of concept, IPqGM;
- Dengue inactivated - GSK
GSK/FIOCRUZ dengue inactivated vaccine development

- Objective = collaborative development of a dengue vaccine that will offer sustainable control of dengue in Brazil and rest of the world

- Contribution of both GSK & FIOCRUZ => all steps of the vaccine devt, including R&D & Clinical devt

- Considering the epidemiological situation in Brazil, we will play key role in the clinical development of the dengue vaccine

- Production in Brazil of the dengue vaccine for Mercosul
**GSK/FIOCRUZ dengue inactivated vaccine development**

- **Why developing a purified inactivated vaccine?**
  - No viral interference with inactivated antigens
  - Shorter immunization schedule/ rapid onset of protection
  - Development considered less complex than for a live-attenuated vaccine
  - No environmental risk

- **Purified inactivated vaccine is considered highly feasible:**
  - Technical & preclinical proof of principle demonstrated by the WRAIR
  - Two examples of highly effective inactivated flavivirus vaccines: JE and TBE vaccines

- **Use of GSK Adjuvant Systems is considered:**
  - Use of adjuvant system to enhance immune response & to provide rapid onset of durable protection
  - Acceptable risk/benefit profile of GSK AS demonstrated for GSK’s adjuvanted HPV and influenza vaccines
    - ~10 Mios (HPV) and ~70 Mios (influenza H1N1) doses administered to date
Status of GSK/FIOCRUZ Dengue inactivated vaccine development

- Preclinical evaluation began in 2009
- Starting Phase I clinical trials in 2011

GSK is committed to develop this vaccine as rapidly as possible:
- GSK aims at starting clinical endpoint studies in 2014
- Timing of any file submission must be agreed with Authorities

Epidemiological studies in Brazil:
- GSK & FIOCRUZ development of site of studies 2010
c) Technology Transfer: Govt commitment

- Long term policy and multi-year forecast;
- Brazilian Public Market - very large - industrial scale of production is required;
- Guarantee of the market and competitive price;
- Financial support for new facility and modernization of facilities;
- Existance of a functional NRA;
- Government’s policy:
  - Use of buyer power;
  - Whenever a new vaccine is introduced into NIP the local production and TT is considered.
BM - Technological Transfers / Partnerships

1900 – Federal Serotherapeutic Institute
- 1976 – creation of Bio-Manguinhos

1937
Yellow Fever Vaccine: Rockefeller Foundation

1976
Meningitis polysaccharide sg A and C: Mérieux Institute

1980
Measles: Biken Institute

1982
Attenuated poliomyelitis, Oral: JPRI

1999
Haemophilus influenzae, type b: GSK

DTP + Hib: Butantan Institute

2002
2003
Rapid Test HIV diagnostic: Chembio
Interferon Alpha 2b human recombinant: Heber Biotec
Erythropoietin human Recombinant: Cimab

2004
2007
Meningitis polysaccharide A and C: Finlay Institute

2008
2009
Pneumococcus Dengue: GSK
NAT: Qiagen
DPP Imunoblot
Rapid HIV-2: Chembio
BM Portfolio

Vaccines
- DTP+Hib (5 doses)
- DTP/HBV + Hib (5 doses)
- Hib (1 and 5 doses)
- Yellow Fever (5, 10 and 50 doses)
- Meningitis Polysaccharides A+C (10 and 50 doses)
- OPV (25 doses)
- Measles (05 doses)
- Triple Viral MMR (10 doses)
- Rotavirus (1 dose)
- Pneumococcal conjugate 10 valent (1 dose)

IVD Reagents
- HIV-1 IFA (100 and 500 tests)
- HIV-1 and 2 Rapid Test (20 tests)
- Chagas Disease ELISA (384 tests), and IFA (600 tests)
- Canine Leishmaniasis ELISA (384 tests) and IFA (2,000 tests)
- Human Leishmaniasis IFA (600 tests)
- Human Leptospirosis ELISA (96 tests and 192 tests)
- Schistosomiasis Helm Test (100 test and 500 tests)

Biopharmaceuticals
- Interferon Alpha 2b Human Recombinant (3, 5 and 10 MUI)
- Erythropoietin Human Recombinant (2,000 and 4,000 UI)
The Hib vaccine Technology Transfer

- Bio-Manguinhos features:
  - Technological capability – production of Meng A/C
    polissacharides vaccine; conjugation group; clinical studies;
  - Adequate facilities and equipments – large freeze-drying facility;
  - Structure, organization and budget for long term implementation - team organized to receive technology;
  - selection of the most adequate technology and proposal;

- Must be a WIN-WIN model
c) Hib vaccine Technology Transfer: GSK features

- Modern and update technology
  - Scientific and technology knowledge;
  - Operational and functional production operation;
  - Compromise to make full technology transfer;
    - entire organization must agree and cooperate;
    - Organization of a specific group dedicated to TT.
- Must be a win-win model
GSK/BM --- The Win-win model

The TT provider (according to BM view)
- Expansion of market;
- Guarantee of market while the technology transfer is in process;
- Economic benefit and revenue assurance for long term;
- Long term planning for production operation;
- Production facility – use of full production capacity;
- Perception on social awareness and international recognition;
- Brand Marketing;
- Royalty up to 5% with a full local production of Hib vaccine.

Bio-Manguinhos/Fiocruz
- Accelerate incorporation of technology of production;
- Guarantee of vaccine supply – avoid shortage;
- Incorporation of modern technology platforms;

The cost per dose drops as the steps of TT is performed and further price drops whenever the TT is fully accomplished
Hib Technology Transfer - Step wise transfer -

✓ Agreement/Oct 1998 - GSK just got license for Hib in Brazil

➢ 1st step – importantion of bulk material and formulation, filling freeze-drying and quality control 1999-2003;
  • training in quality control and assurance training;
  • modernization of facilities and new equipments;
  • training in production: conjugation step at GSK

➢ 2nd step – Conjugation of polyssacharides and tetanus toxoid using imported materials 2003-2006;
  • local conjugated vaccine production;
  • training in polyssacharides production: up stream and down stream;
  • validation of new facilities
Hib Technology Transfer - Step wise transfer

- 3rd step – Production of polyssachhararides and conjugation using locally produced tetanus toxoid 2004-2006;
  - Local produced tetanus toxoid: validation of facilities, methodologies and production;
  - Production of three consecutive lots for clinical uses;
  - Development of protocol for non-inferiority clinical study

- 4th step – Noninferiotatey study using the 2nd step vaccine as control 2005-2007;
  - Protocol approval by Ethical Committee;
  - Preparation of the site of study – 1000 volunteers;
  - Organization and implementation of the clinical study;

- 5th step – License at ANVISA in 2007
  - Preparation of the documentation for licensing by ANVISA;

- 6th step – pharmacovigilance
  - Organization and implementation of pharmacovigilance
Bio-Manguinhos & TT - Tangible and intangible benefits

- Institutional strengthening
  - Administration and managerial capacity;
  - Focus on results;
  - Better visibility;

- Accelerate the incorporation of new technology of production;
  - Increase of specialized professionals;
  - New laboratories, new equipments;
  - Strengthen the technological capacity;
  - Strengthen the infrastructure;

- New products & developments:
  - Tetravalent (DTP + Hib);
  - Pentavalent (DTP/HB+Hib);
  - Development of heptavalent (DTP/HB/IPV/MenC + Hib)
HAEMOPHYLUS INFLUENZAE B MENINGITIS AFTER THE IMPLEMENTATION OF A MASS VACCINATION PROGRAM

Figura 5 - Meningite por *Haemophilus influenzae* b: coeficiente de incidência e cobertura vacinal em crianças menores de um ano, RS, 1995-2001

Thank you!

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HIB VACCINATION IN BRAZIL

- In Latin America, Hib vaccination was first introduced in Uruguay in 1994, followed by Costa Rica and Chile.
- The Hib vaccine was incorporated into the national immunization program of Brazil in mid 1999.
- Hib vaccine was incorporated universally in mid 1999 to children <2 years old, with gradual expansion to the target age of 4 years old, in 2002.
- In 2002, the tetravalent vaccine protecting against diphteria-tetanus-whole cell pertussis (DTP) and Hib infections was established to children <1 year old.
- Current vaccination schedule:
  - three doses of DTP+Hib administered at 2, 4 and 6 months of age.
- In Brazil, there are currently three vaccines:
  - Vaccine against Hib
  - Tetravalent (DTP+Hib)
  - Pentavalent (DTP+HB+Hib)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Administered Doses in 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Against Hib</td>
<td>85,894</td>
</tr>
<tr>
<td>DTP+Hib</td>
<td>8,784,242</td>
</tr>
<tr>
<td>DTP+HB+Hib</td>
<td>17,043</td>
</tr>
</tbody>
</table>

A comparison of incidence rates in the prevaccine ($10.8 \times 10^5$) and post-vaccine ($2.3 \times 10^5$) periods shows a 78% reduction in the risk of Hib meningitis in Goiás.

In Curitiba, southern Brazil, the incidence of meningitis dropped from 35.5 to $9.7 \times 10^5$ (72% reduction), one year after the introduction of the vaccine.

In Salvador, northeastern Brazil, 69% reduction was observed after the first year of vaccination.

Five years after the introduction of Hib conjugate vaccine, Hib meningitis incidence decreased from 2.39 to 0.06 cases per 100,000 population (98%) overall, and from 60.9 to 3.1 cases per 100,000 population (95%) in children <1 year of age.

# Impact of Hib Vaccination

Impact of vaccination against Hib on meningitis in children <5 years old in Brazil

<table>
<thead>
<tr>
<th>Study</th>
<th>Years post-vaccine introduction</th>
<th>Incidence per 100,000</th>
<th>Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takemura &amp; Andrade, 2001 J Pediatr 77, 387-92</td>
<td>1 year</td>
<td>35.4</td>
<td>72.6%</td>
</tr>
<tr>
<td>Ribeiro et al., 2003 J Infect Dis 187, 109-16</td>
<td>1 year</td>
<td>2.6</td>
<td>69.0%</td>
</tr>
<tr>
<td>Kmetzsch et al., 2003 J Pediatr 79, 530-6</td>
<td>2 years</td>
<td>36.5</td>
<td>90.7%</td>
</tr>
<tr>
<td>Simões et al., 2004 Rev Saude Publica 38, 664-70</td>
<td>2 years</td>
<td>10.8</td>
<td>78.7%</td>
</tr>
<tr>
<td>Ribeiro et al., 2007 Vaccine 25, 4420-28</td>
<td>5 years</td>
<td>25.4</td>
<td>97.5%</td>
</tr>
</tbody>
</table>

*<1 year of age

Ribeiro et al., Haemophilus influenzae meningitis 5 years after introduction of the Haemophilus influenzae type b conjugate vaccine in Brazil. Vaccine, 2007, 25, 4420-28
**Hib VACCINATION IN BRAZIL**

*H. Influenzae* serotype distribution and incidence of meningitis due to *H. influenzae*

Data: SINAN/SVS/MS [www.saude.gov.br/svs](http://www.saude.gov.br/svs)
IAL-São Paulo with permission of Dr Ma. Cristina Brandileone
Brazil and NIP’s figures

- Territory – 8,51 million km² (47% Latin America);
- Population - > 190 million;
- Newborn – 3,200 million/year;
- 26 provincial states + Federal District (Brasilia);
- 5,565 municipalities;
- National Immunization Program
  - 17 vaccines; > 30 in CRIES;
- 36,000 Immunization offices (public + private + indéan vaccination center); 30 CRIES offices;
- Routine and National Days of Vaccination – NDV;
- Cold Chain: Central; Regional; Local
National Immunization Program

- 1973 – creation with 6 vaccines (DTP; BCG; measles; OPV);

- Universal access of vaccination – Universal access - Children; adolescents; adults and elderly

- Continuous support and continuous expansion:
  - 2008 – R$ 800 million (US$ 420 million);
  - 2009 – R$ 1,200 million (US$ 720 million);
  - 2010 – R$ 3,0 billion (US$ 1,750 billion), including H1N1*;

- * may not required for 2011
National Immunization Program - Poliomyelites incidence and OPV coverage - National Days of Vaccination (NDV)

* VOP: Vacina oral contra poliomielite.

Fonte: Ministério da Saúde - SI-PNI.
National Immunization Program – Measles incidence and vaccination coverage

Fonte: Secretaria de Vigilância em Saúde/MS/Brasil
NPI, MoH & TECHNOLOGICAL INNOVATION

STRATEGIC IMPORTANCE OF VACCINES

- EPIDEMIIOLOGICAL IMPACT – ELIMINATION OF POLIO, MEASLES, RUBELLA
- IMMUNOPREVENTABLE DISEASES AT LOWEST NOTIFICATION

- NEW AND IMPORTANT VACCINES IN PIPELINE –
  - HPV
  - DENGUE, MALARIA RSV, HIV/AIDS,
    New combinations

- NEW IMPORTANT VACCINES:
  - EMERG DISEASES, EPIDEMIC;
    PANDEMICI;
  - TECHNOLOGICAL IMPROVEMENTS;
    BETTER YIELDS; LOW COST PRODUCTION

✓ THE EXISTANCE OF NATIONAL TECHNOLOGICAL CAPABILITIES FOR PRODUCTION AND INNOVATION GARANTTEE THE SUPPLY OF THE ESSENTIAL VACCINES
✓ 1982 - THE NATIONAL SELF-SUFFICIENCE PROGRAM WAS CREATED
Bio-Manguinhos’ figures

✓ Main immunobiological producer for the Brazilian MOH programs (only federal laboratory): vaccines, IVD reagents, biopharmaceuticals

✓ 1.180 employees - 10% of Fiocruz workforce: 32% - Production, 22% Quality Control and Assurance, 11% R&D, 3% Maintenance & Engineering Production, 32% Management

✓ 2 post-doctors, 42 doctors, 124 masters, 193 post-graduated

✓ 25.000 m2 of lab facilities in 10 buildings