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111 years producing immunobiologicals: New challenges

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THE EFFORTS OF A PUBLIC INSTITUTE TO DEVELOP NEW VACCINES

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PORTUGAL, 2012

AGENDA

- OVERVIEW OF IMMUNIZATION PROGRAM IN BRAZIL AND INSTITUTO BUTANTAN
- BUTANTAN DEVELOPMENTS

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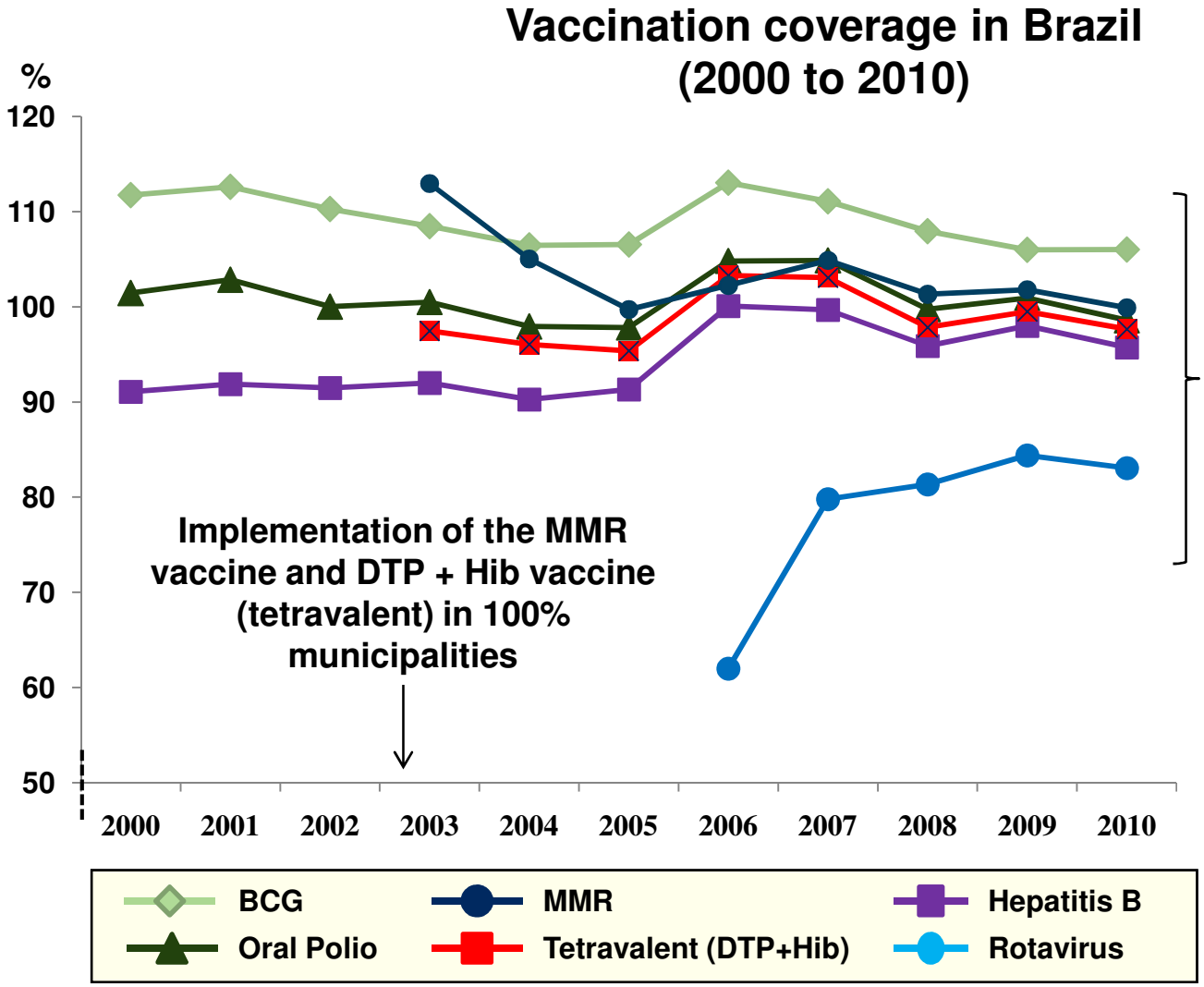
THE IMPACTS OF VACCINATION IN BRAZIL

Children vaccination coverage by type of vaccination

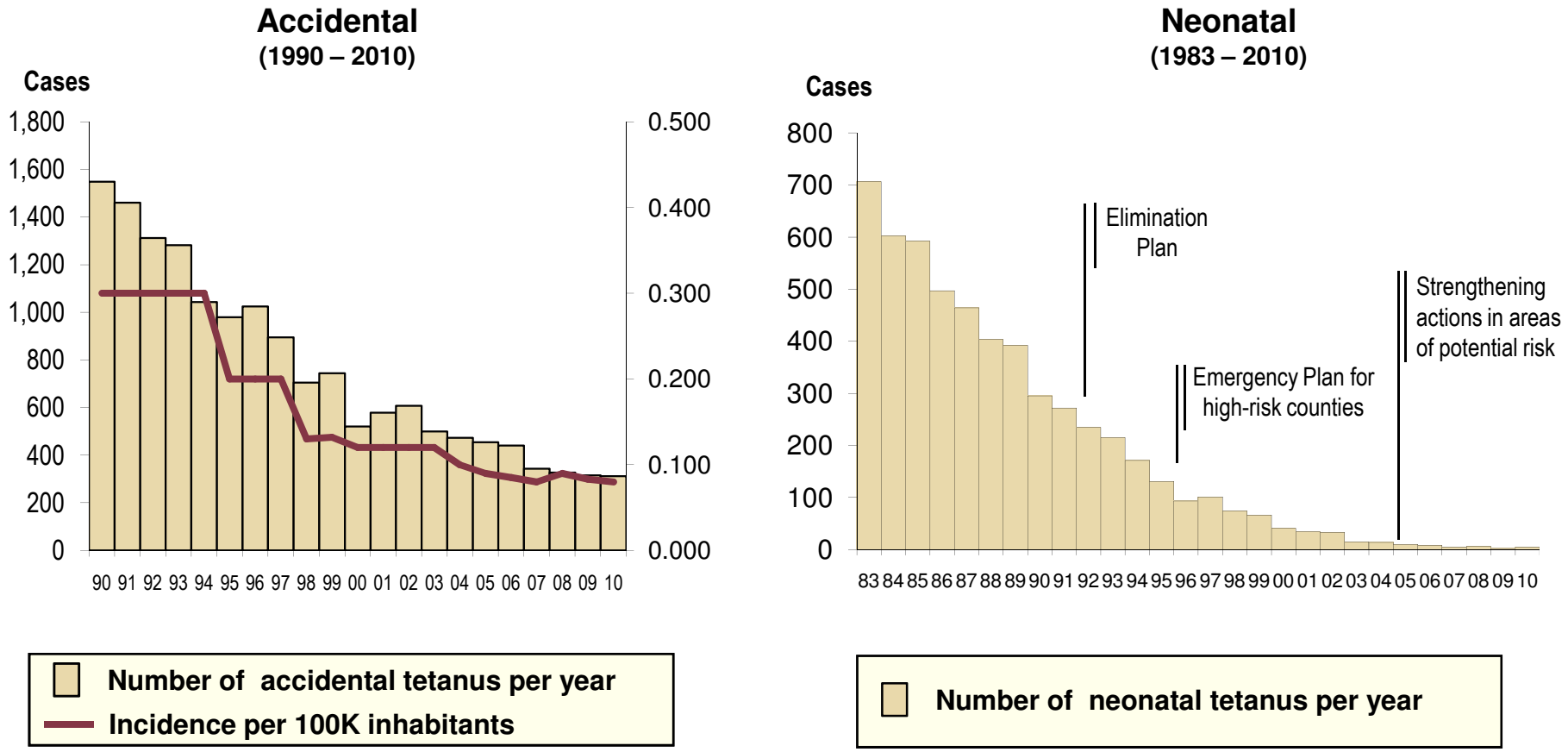


Over 70 million children successfully vaccinated in two decades

THE IMPACTS OF VACCINATION IN BRAZIL

Number of cases for tetanus – accidental and neonatal

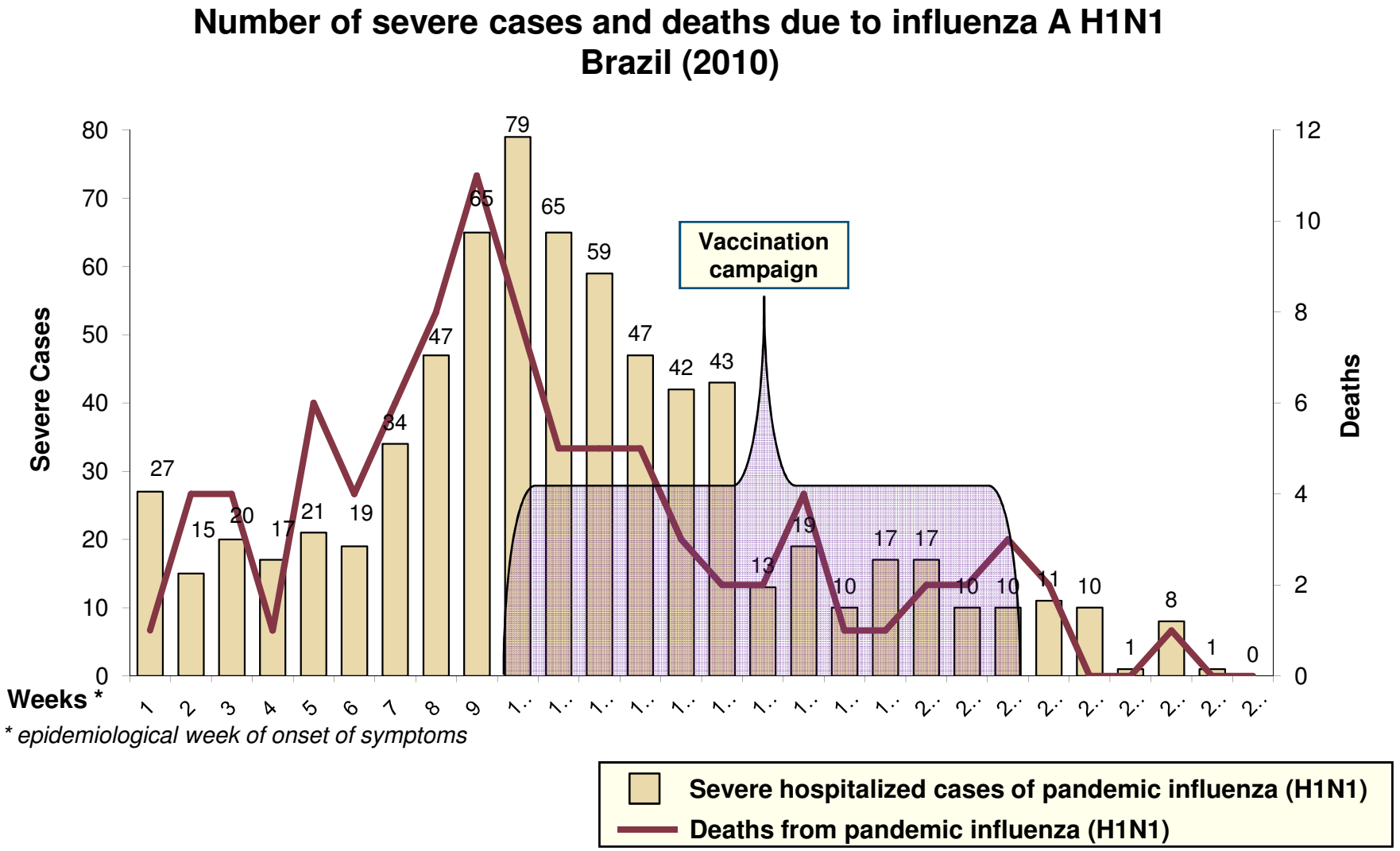
Number of cases – Accidental and neonatal Tetanus



Source: Sinan/SVS/MS, data in 25/08/11Ministry of Health, Brazil , 2010.

THE IMPACTS OF VACCINATION IN BRAZIL

The number of severe cases and deaths due to influenza A H1N1 has been falling since March 2010



* *epidemiological week of onset of symptoms*

Source: Sinan/SVS, Ministry of Health, Brazil , 2010.

BRAZIL HAS BECOME AN INTERNATIONAL REFERENCE IN IMMUNIZATION

Strategy

Brazil decided in the mid 80's to become self-sufficient in vaccines and immunization programs

Decision

This was a State decision rather than a government decision

Why

Too important to depend on availability and pricing

National Immunization Program (PNI) in Brazil

PNI – Founded in 1973

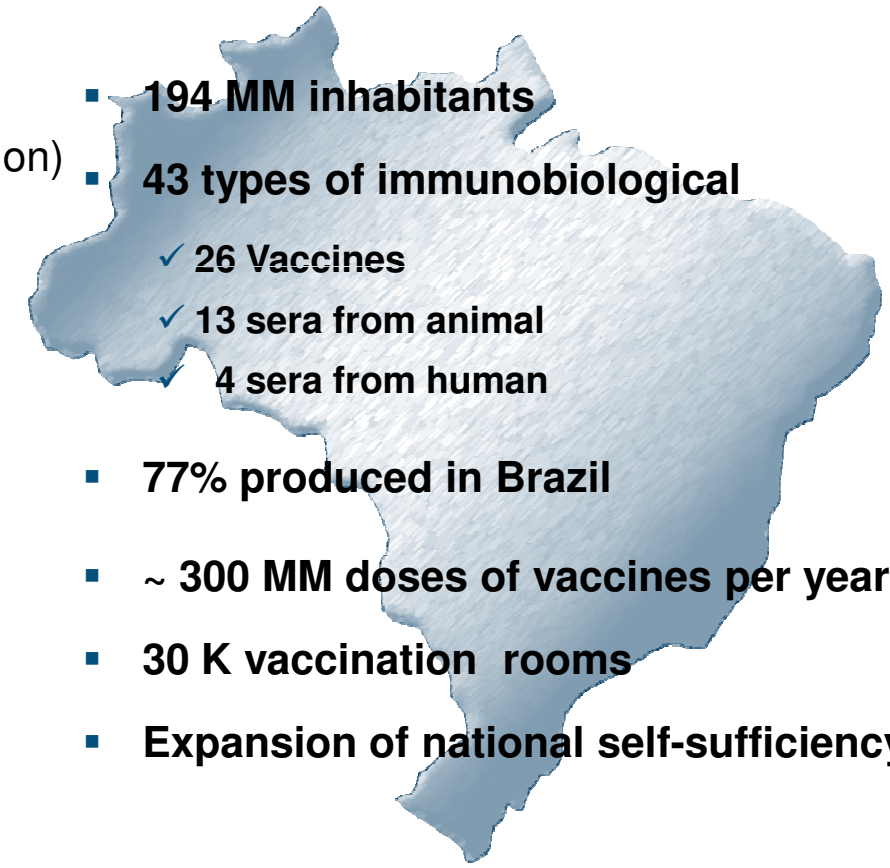
Eradication

- Smallpox
- Poliomyelitis
- Measles (autocne transmission)

Under Control

- Neonatal tetanus
- Accidental tetanus
- Tuberculosis
- Diphtheria
- Pertussis
- Hepatite B
- Influenza
- Pneumococcus

PNI – General Information of Brazil (2011)



- **194 MM inhabitants**
- **43 types of immunobiological**
  - ✓ **26 Vaccines**
  - ✓ **13 sera from animal**
  - ✓ **4 sera from human**
- **77% produced in Brazil**
- **~ 300 MM doses of vaccines per year**
- **30 K vaccination rooms**
- **Expansion of national self-sufficiency**

Source: SVS/Ministry of Health, National Immunizatation Program, Brazil, 2011.

WHAT DO WE ARE?

BUTANTAN – A PUBLIC INSTITUTION OF THE STATE GOVERNMENT OF SÃO PAULO

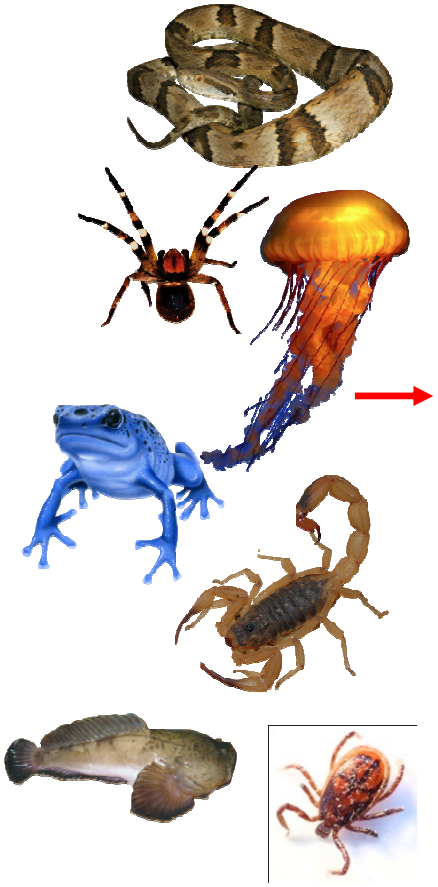
- In 1901 Butantan was established to produce serum against the bubonic plague
  - ✓ Vital Brazil, the first director, investigated antivenoms against snake bites
- Currently, Butantan is the main public producer of vaccines, antivenoms, antitoxins in Latin America
  - ✓ Fully dedicated to develop scientific research and production of immunobiological products for public health

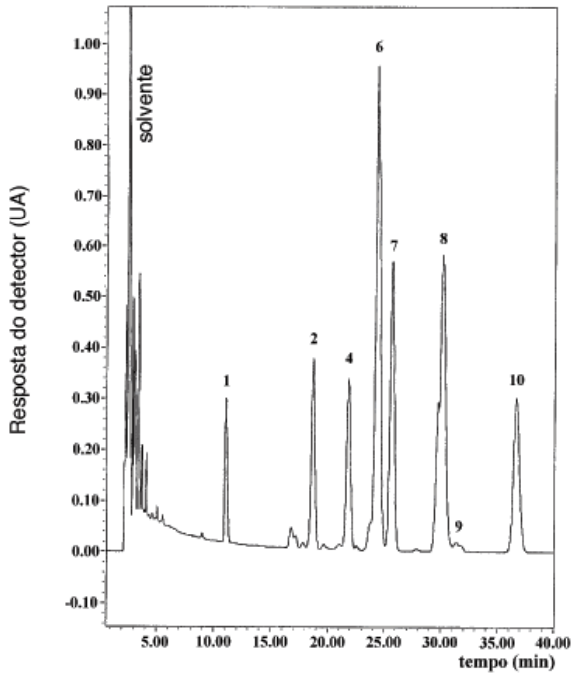
RESEARCH & DEVELOPMENT LABORATORIES

- ~21 scientific labs
- ~180 Researchers
  - ✓ 85% are PhD
- 1 Biotechnology Center
  - ✓ Multiple laboratories
- 1 Hospital (10 hospital beds)
- 1 Central Animal Facility

- Training programs (PAP)
- Graduate studies in Toxicology
- Masters and PhDs

SCREENING OF BIOACTIVE COMPOUNDS OF ANIMAL VENOMS





Pharmacological Activities

- ANALGESIC
- ANTIINFLAMATORY
- ANTI-MICROBIOLOGICAL
- ANTI-COAGULANT
- ANTI-TUMORAL
- NERVOUS SYSTEM ACTION
- ANTI-VENOMS REACTIVITY
- ANTI-HYPERTENSION

Venom Composition by Transcriptomics and Proteomics

Plasma fractioning by chromatography

Plasma fractioning by chromatography

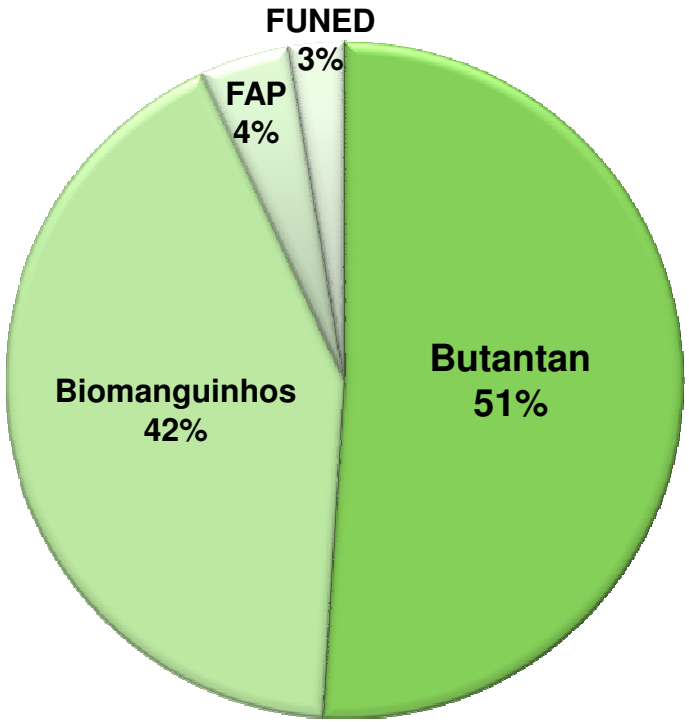
INDUSTRIAL COMPLEX

- **7 Main Industrial Plants (Buildings)**
  - ✓ Anaerobic vaccines (tetanus and botulinic) and Anatoxin Purification
  - ✓ Biological control
  - ✓ Aerobic Vaccine (Diphtheria and Pertussis)
  - ✓ Hepatitis
  - ✓ Influenza
  - ✓ Rabies
  - ✓ Blood Products (under construction)
  - ✓ Control, Serums, Formulation and Filling
- **6 Pilot Plants**
  - ✓ Dengue / Rotavírus (Under Construction)
  - ✓ Recombinant (BCG)
  - ✓ Monoclonal Antibodies
  - ✓ Influenza
  - ✓ Blood Products

WHAT DO WE DO?

NATIONAL SUPPLIERS OF VACCINES FOR THE MINISTRY OF HEALTH

‘Market Share’ per Suppliers[1] (2010)



Note: Part of Butantan’s production was sent to other Institutes, such as Biomanguinhos. Not computed in the analysis

Products (Vaccines)

DTP

DT

dT

Rabies

Hepatitis B

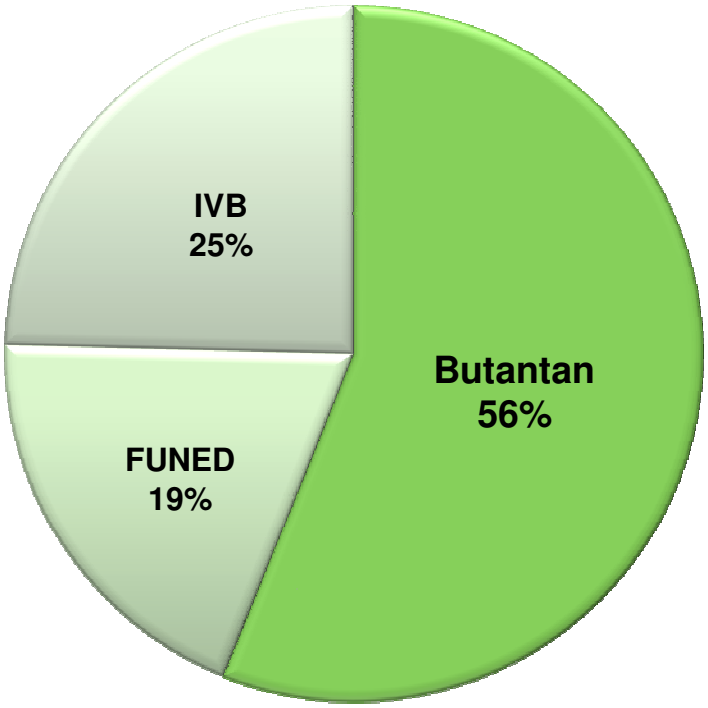
Influenza
(Flu)

[1]Source: Ministry of Health, 2010

WHAT DO WE DO?

NATIONAL SUPPLIERS OF ANTIVENOMS AND ANTITOXINS FOR THE MINISTRY OF HEALTH

‘Market Share’ per Suppliers[1] (2010)



Note: Part of Butantan’s production was sent to other Institutes, such as FUNED and CPPI. Not computed in the analysis

Products (Sera)

Snakes AV

Scorpion AV

Spider AV

Caterpillar AV

Tetanus AT

Diphitheria AT

AntiRabies

Botulism AB & E

[1]Source: Ministry of Health, 2010

VACCINES WITH EXTERNAL COOPERATION

Cooperation	Projects
NIH-PATH	Rotavirus (pentavalent)
NIH-DVI	Dengue (tetravalent)
Sabin Vaccine Institute - George Washington University	Necator - Schistosoma
Children's Hospital Harvard - PATH	Pneumococcus (cellular)
Infectious Diseases Research Institute	Visceral Leishmaniosis (for dogs)
Ludwig Institute for Cancer Research	Adjuvant for ovarian cancer
BR Foods	Lung Surfactant
Universidade de São Paulo – Medical School	Recombinant OncoBCG for bladder cancer
Institut Pasteur – Paris / Novartis - Siena / Albert Einstein College of Medicine	Recombinant BCG-Pertussis

AGENDA

- OVERVIEW OF IMMUNIZATION PROGRAM IN BRAZIL AND INSTITUTO BUTANTAN
- **BUTANTAN DEVELOPMENTS**

WHAT DO WE WANT TO DO?

Presentation and discussion of vaccines projects

Area	Vaccines Projects [1]
Vaccines - Research and improvement	▪ Pertussis$_{low}$ ▪ Adjuvant *Bp*MPLA ▪ Recombinant onco BCG ▪ Silica nanostructure mesoporous – vaccine antigens encapsulated
Vaccines - Collaborative development	▪ Rotavirus (pentavalent) ▪ Dengue (tetravalent) ▪ *Streptococcus pneumoniae* (cellular - SPWCV) ▪ BCG-Pertussis
Vaccines – Basics R&D	▪ Leptospira
Techtransfer	▪ Several vaccines under negociation

[1] *Not exhaustive*

Pertussis$_{low}$ vaccine

Product - Pertussis$_{low}$ vaccine

- **Composition**
  - *B.pertussis* whole cell with lower content of LPS
- **Production Technology**
  - Organic extraction of the cells to reduce LPS content
    - ✓ ~ 70% reduction of LPS
  - "*in line*" process without additional costs
- **Phase of Development**
  - Pre-clinical studies performed in Butantan and in the Netherlands Institute Vaccine (NIV)
  - **Phase I (2012) – Brazil**

Butantan –

- **Challenges:**
  - Scale-up
- **Objectives:**
  - To make available an alternative vaccine for immunization of children, adolescent, pregnant women and adults

Pertussis$_{low}$ vaccine - technical and scientific aspects

New developments in Pertussis Vaccines with Appropriate technologies

Ⓡ = Patents

Whole Cell Pertussis Vaccine

Whole Cell Pertussis
Low LPS content

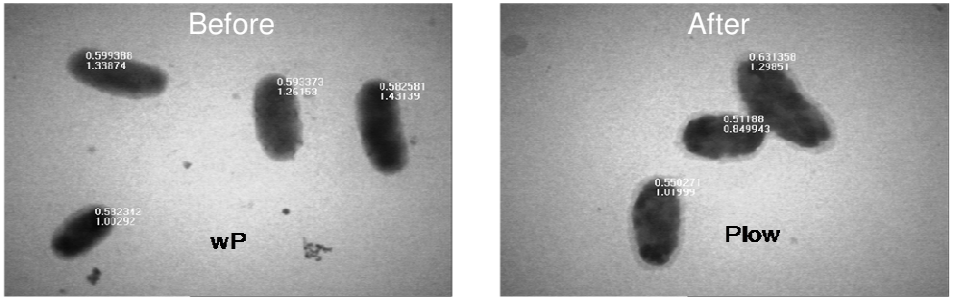
- ~ 70% reduction of LPS
- Less reactogenic
- Low cost

B. pertussis fermentation → **WCP** → **WCP$_{low}$** Ⓡ

Tangential filtration

Organic extraction

Pertussis vaccine before and after organic extration of LPS (P_{Low})



Chromatography

Acellular Pertussis Vaccine Ⓡ

MPLA Adjuvant Ⓡ

Recombinant BCG-Pertussis
Neonatal immunization

Figure 1- Electron microscopy: negatively stained whole cell pertussis vaccine before (wP) and after solvent treatment (Plow). The dimensions of the cells were measured in micrometers.

Adjuvant – Monophosphoryl lipid A (*Bp*MPLA)

Product - Monophosphoryl lipid A (*Bp*MPLA)

- **Composition**
  - *Bp*MPLA derived from LPS of *B.pertussis*
- **Production Technology**
  - Purification of *B.pertussis followed by* LPS hydrolises
- **Phase of Development**
  - **Scale-up**

Butantan –

- **Challenges:**
  - Scale-up
- **Objectives:**
  - To optimize immunolgical response of pre-exisiting and new vaccines
  - To increase production capacity

***Bp*MPLA**

- **Clinical trial**
  - ✓ Pandemic H1N1 + BpMPLA
- **Pre-clinical**
  - ✓ Human rabies
- **Animal Study**
  - ✓ Dog Leishimania
- **In development**
  - ✓ Hepatites B + BpMPLA
  - ✓ Seazonal Influenza + BpMPLA

Recombinant BCG-Pertussis

Neonate vaccine / Onco BCG for Bladder cancer

Product - Recombinant BCG – Pertussis

- **Composition**
  - Recombinant BCG strain expressing the S1 subunit 1 of Pertussis toxin
- **Production Technology**
  - The **rBCG-Pertussis** strain was produced without antibiotic resistance gene[1]
    - ✓ Appropriate for use in humans
- **Phase of Development**
  - **Production of GMP lots**

Butantan –

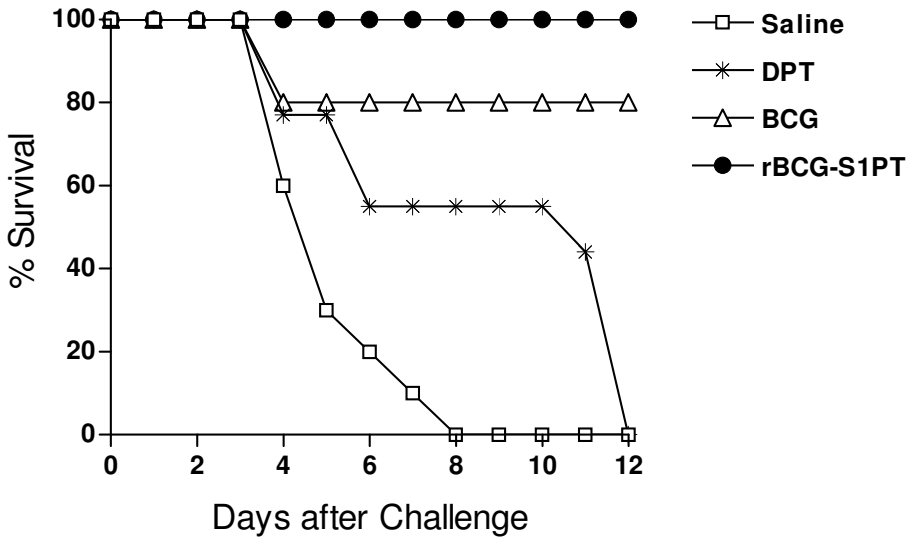
- **Challenges:**
  - To produce the vaccine by fermentation or static culture
  - To perform the clinical trials
- **Objectives:**
  - To immunize infants 0 – 2 months of age
  - To make available a new vaccine for bladder cancer

Nota: [1] Auxotrofic strain for lysine is complemented with a plasmid that expresses the deleted gene plus the heterologous gene – S1PT

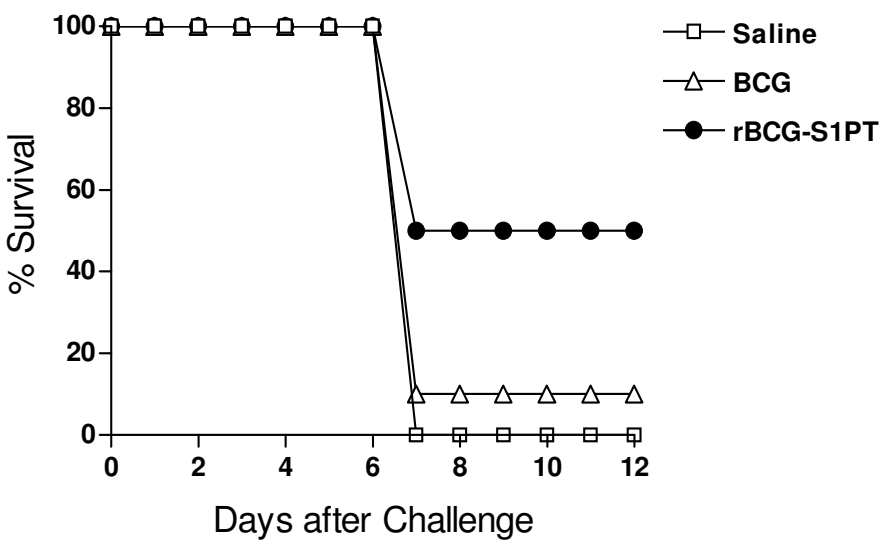
Recombinant BCG-Pertussis - technical and scientific aspects

Protection of neonate mice immunized with rBCG-S1PT against intracerebral challenge with *B. pertussis*

ONE DOSE AT DAY 5



Challenge dose at day 21: 10^6 CFU

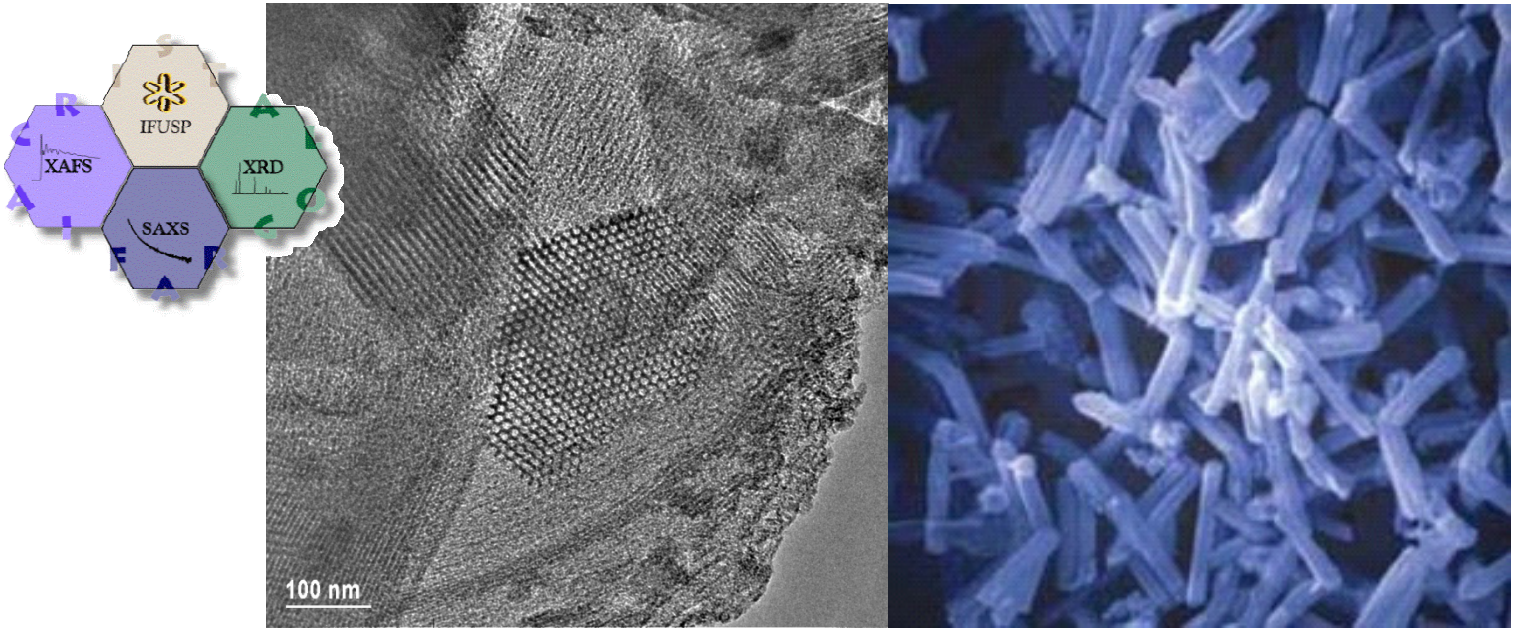


Challenge dose at day 21: $3x10^7$ CFU

Source: Microbes Infect.10:198-202 (2008)

Silica (SBA-15)

Immunogenic complex formed by vaccinal antigens encapsulated by nanostructured mesoporous silica



Features

- The SBA-15 possesses hexagonal porous uniformity (3.1 – 6.5 nm)
- Thermal and hydrothermal stability
- Exhibits potential applications for selective adsorption and catalysis

Rotavirus Vaccine

Product – Pentavelent Rotavirus Vaccine

- **Composition**
  - Attenutated virus
  - Sorotypes: G1, G2, G3, G4 e G9
- **Technology of Production**
  - Cell substrate: Vero cells
  - Reassortment – Human/bovine
  - Nº lots produced: 09 (6 K doses)
- **Phase of Development**
  - **Phase I: 2010**
    - ✓ Results: safe and immunogenic
  - **Phase II: 2013**
- **Partnership**
  - NIH / PATH / BNDES

Butantan –

- **Challenges:**
  - To perform Phase II and III - non-inferiority study
  - To find funding for:
    - ✓ Clinical Trial and laboratory assay – Phase II / III
- **Objective:**
  - Pentavalent low cost vaccine

Dengue Vaccine

Product – Tetravalent Dengue Vaccine

- **Composition**
  - Attenuated virus
  - Sorotypes: DEN1, DEN2, DEN3, DEN4
- **Technology of Production**
  - Cell substrate: Vero cells
  - Recombinant DNA technology
  - Chimeric
  - Nº lots produced: 06 (17 K doses)
- **Phase of Development**
  - **Phase I and II: 2012/2013**
- **Partnership**
  - NIH - DVI (Dr. Steve Whitehead)
  - BNDES / FAPESP

Butantan –

- **Challenges:**
  - To speed up Phase I, II, and III – (to avoid non-inferiority study)
  - To find funding for:
    - ✓ Clinical Trial and Laboratory assay – Phase III
    - ✓ Equipment
    - ✓ Plant
    - ✓ Maintenance of "The Global Solutions for Infectious Disease" support
  - To define target population for immunization
  - Production capacity x national and international demand
- **Objective:**
  - Tetravalent low cost vaccine

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Obrigado

Thank you

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