One Health and Global Health developments within Intravacc

26th March 2013

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Institute for Translational Vaccinology

RIVM → NVI 2003 → 2011

- Unique Values:
  - Over 100 years vaccinology know-how (since 1894)
  - Independent
  - Big and small scale production infrastructure covering entire value chain
  - Resource institute to the DCVM-Network

- Core tasks:
  - Supplying high quality and affordable vaccines via procurement and production
  - Research and development of vaccines
  - Maintaining scientific knowledge on vaccinology and vaccination strategies for the Dutch Ministry of Health (MoH).
Changes NVI 2009→2013
Establishment of Bbio & Intravacc

**2009:**
- Decision of MoH to stop production at NVI for the Dutch NIP
  (bacterial: DTwP; viral: MMR and Salk IPV)

**2012:**
- Acquisition of Bilthoven biologicals (Bbio) by Serum Institute of India (SII)
  (BCG, D and T, Salk IPV and OPV)

**2013:**
- Major part of R&D → Establishment of **Intravacc** → directly under MoH
- Business Case → towards a PPP construction
Vaccine chain

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Technology Transfer

universities, government and small biotech

- analysis
  - threat to public health
  - (intervention) epidemiology
  - relevant developments
  - cost effectiveness

- (pre)clinical research
  - exploratory microbiology
  - immunology
  - molecular biology
  - animal models

- (pre)clinical development
  - pilot scale process development
  - assay development
  - Formulation clinical development phase I/II
  - compose registration files, GMP, QA and QC

Industry

- clinical production
  - scaling up (clinical) phase III
  - registration production

- vaccination programmes
  - procurement
  - storage
  - distribution
  - implementation and evaluation

TT partners

Bbio/SII

Intravacc

Institute for Translational Vaccinology
InTraVacc has the knowledge and skills to valorise fundamental research in vaccinology.

http://www.intravacc.nl/
# Product development Intravacc

<table>
<thead>
<tr>
<th>product</th>
<th>discovery</th>
<th>preclinical</th>
<th>clinical</th>
<th>marketed</th>
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<tbody>
<tr>
<td>Hib</td>
<td></td>
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<td>marketed in India</td>
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<tr>
<td>MenB</td>
<td></td>
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<td>collab.big pharma</td>
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<td>Pneumo</td>
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<td>license to big pharma</td>
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<td>Sabin IPV</td>
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<td>TT to WHO partners</td>
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<td>Influenza</td>
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<td>TT to WHO partners</td>
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<td>RSV</td>
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<td>open for partnering</td>
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with partners (academia, industry)
## Product development Intravacc

<table>
<thead>
<tr>
<th>product</th>
<th>discovery</th>
<th>preclinical</th>
<th>clinical</th>
<th>licensed</th>
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<td>Needlefree IPV</td>
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<td>Shigella</td>
<td></td>
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<td>FP7</td>
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<td>Universal influenza</td>
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<td>FP7/CTMM</td>
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<tr>
<td>Rota</td>
<td></td>
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<td>Pathfinder grant</td>
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<tr>
<td>C. burnetii</td>
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<td>SVRP</td>
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</table>

with partners (academia, industry)
Bacteriology & Molecular Biology

OMV platform technology

Outer membrane LPS structure

Gal-GlcNac-Gal-Glc-Hep1-Kdo1-GlcNac

galE

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OMV platform technology

Outer membrane LPS structure

Gal-GlcNac-Gal-Glc-Hep1-Kdo1-GlcNac

galE

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Mycobacterium tuberculosis

Bordetella pertussis

Coxiella burnetii

Neisseria meningitidis
Virology and (Clinical)Immunology

RS virus

Influenza

IMPD
Process development

Fact results early development → production scale:
- Do not ‘linear’ translate
- full scale: high costs

Unique Scale up/ scale down for optimalisation process development
Scalable processes: cell culture (USP)

- QbD
- DoE
- PAT
Scalable processes: Purification (DSP)

Trial and Error

but:
To accommodate innovation of the legacy process, Thomassen and coworkers analyzed historical manufacturing data using multivariate data analysis....down scale process
Formulation:

Antigen delivery

Alternative administration

Stabilisation, freeze drying and spray drying

QbD
Analytical Research:
... In addition, the available knowledge in the field of vaccine development and production, is deployed to contribute to the **global accessibility of vaccines**. At this so-called “technology transfer (TT)”, or capacity building Intravacc is working closely with various international partners.
Technology Transfer at Global level at Intravacc

Expertises:
• Micro-carrier technology
• Formulation-technology
• QC
• QA
• GMP
• Animal Husbandry

Vaccines:
• (Oral) Polio
• Measles
• DPT
• Haemophilus Influenzae b
• Influenza
Technology Transfer Hub for Vaccines

WHO: There is a great lack of interested technology providers

→ the establishment of a technology and training platform (a “hub”) was identified as the most promising approach

A hub brings together the appropriate development, clinical and regulatory expertise in a contractor hub, hosting and coalescing all components of the TT project, generating a comprehensive documentation package (SOPs, batch process records, validation procedures, etc.) and associated training modules → turnkey access to a robust TT package cost-effective and time efficient

Requirements:
• free of intellectual property barriers
• suitable manufacturing and quality control experience and infrastructure
• sustainable financial support

M.P. Kieny at all, Vaccine 27 (2009) 631–632
# Technology Transfer since 1970

<table>
<thead>
<tr>
<th>Project</th>
<th>Vaccine(s)</th>
<th>Recipient</th>
<th>Country</th>
<th>Approach</th>
<th>IP-issues</th>
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</thead>
<tbody>
<tr>
<td>Micro-carrier technology (1970-1980)</td>
<td>Viral vaccines</td>
<td>Sanofi, GSK, Sclavo</td>
<td>Several</td>
<td>Turn key</td>
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<td></td>
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<td>(Novartis), Lederly</td>
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<td>Hib Project (1999 – now)</td>
<td>Hib conjugate</td>
<td>Bio Farma SIIL, BE Ltd</td>
<td>Indonesia</td>
<td>Development and transfer of pilot process (hub)</td>
<td>non-exclusive license; fees and/or royalties</td>
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<td>Glovax/SIBP</td>
<td>India/China</td>
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<td>Salk-IPV procurement (2005– now)</td>
<td>Salk IPV</td>
<td>Panacea, BE, SII, Glovax</td>
<td>India, Korea</td>
<td>Bilateral agreements Transfer of IPV related QC testing</td>
<td>none</td>
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<td>ITPIV Project, WHO (2007 – now)</td>
<td>Egg-based inactivated</td>
<td>VACSERA IVAC</td>
<td>Egypt Vietnam</td>
<td>1-generic, hub based 2- bilateral TT agreements</td>
<td>non-exclusive license; modest fees; no royalties</td>
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<tr>
<td></td>
<td>influenza</td>
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<tr>
<td>Sabin-IPV Project, WHO (2008 – now)</td>
<td>new safer polio Vaccine</td>
<td>1. Panacea</td>
<td>India</td>
<td>Development and transfer of process and related QC testing (hub)</td>
<td>non-exclusive license; modest fees; royalties</td>
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<td>2. LG</td>
<td>Korea</td>
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<td>3. CNBG</td>
<td>China</td>
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<td>4. SII</td>
<td>Korea/China</td>
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<td>5. Birmex</td>
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<td>6. Sinovac</td>
<td>China</td>
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Hendriks et al. (2011), Vaccine
Global health/Technology Transfer

- Longstanding experience with technology transfer
- ‘Hubs’ for influenza, polio en Hib vaccines are operational
- but also more generic technologies (e.g. lyophilization, cell culture, animal husbandry etc.)
Application of OMV as platform technology for human as well as animal vaccines

e.g.

- Whooping cough
- Lyme disease
- Q-fever
- (Para)Tuberculosis

*Bordetella pertussis*  *Borrelia burgdorferi*  *Coxiella burnetii*  *Mycobacterium Tuberculosis*

van der Ley P, Human Vaccines 7: 886, 2011
Human vaccines against Q-fever

Q-vax: formalin-inactivated phase I whole cell vaccine

licensed in Australia
highly effective in occupational risk individuals

Drawbacks:
• Production at high biosafety level (BSL-3), using embryonated chicken eggs
• Cannot be used in people with pre-existing immunity: screening of vaccinees required
• General disadvantages of whole cell vaccines: difficult registration for human application
A novel Q fever vaccine based on LPS of Coxiella burnetii

Heterologous expression of *C. burnetii* O-antigen in *Bordetella pertussis* and ‘proof of concept in goats’

**Advantages:**

- No BSL-3 necessary
- Relative easy to culture in defined medium
- O-antigen can be combined with met lipid A mutant (detoxified)

Rotavirus vaccines in Humans

2 Live Oral Vaccines
• GSK Rotarix (2 doses; PhIII Efficacy >85%)
• Merck RotaTeq (3 doses; PhIII Efficacy >90%)

Drawbacks current oral live vaccines:
• Intussusception (1-5/10,000, depending on age [3-12 months])
• Low efficacy in low income countries

Aoki & Dormitzer et al. Science 324, 2009

Relationship between RV Vaccine Efficacy & Per Capita Gross Income

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Rotavirus vaccines in calves

The third major (severe) pathogens for calves
1. E. Coli
2. Corona
3. Rota

Rota disease occurs first 2-3 weeks of life, so immune protection from colostrum

Current bovine Rotavirus vaccine
• BPL inactivated Rotavirus vaccine
• Administered with oil adjuvant

However
• Still limited efficacy
→ Need for improved Bovine Rota Virus Vaccine
Rotavirus vaccine

Need for improved rotavirus vaccines for both:

- Calves
  - improved efficacy

AND

- Human
  - improved efficacy in low income countries
  - preventing vaccine related intussusception

→ One Health R&D within Intravacc: rotavirus vaccine project using Intravacc’s platform technology on Vero cells
One Health approach:

• veterinary vaccines are developed for same or related diseases (e.g. tuberculosis, Influenza, Rota virus, Q-fever). Large animals may be better predictors of immunogenicity, and their use could help identify biomarkers. They can be tested in experimental challenge models and can also often provide proof-of-principle to aid the development of human vaccines.

• there is a need for new approaches to the development of animal models of disease such as transgenic animals or using large animal species (pig, calves, sheep, horse, etc.) that are sensitive to the same pathogens as humans.

• human vaccine research should benefit from synergies with veterinary research for developing pre-clinical vaccine-testing platforms and vice versa.
Dependence of **public and private** sectors is an indisputable and crucial component in the provision of **safe and effective vaccines**, and will probably remain so indefinitely. Eskola and Kilpi, The Lancet, July 2011