Enhanced International R&D Cooperation

20th DCVMN Annual General Meeting

23rd October 2019, Rio de Janeiro, Brazil

Anh Wartel, MD
IVI, Head of Clinical Development and Regulatory Affairs
Presentation Content

• Introduction

• IVI Organization

• Examples of IVI International R&D Cooperation

• Conclusion
• Introduction

• IVI Organization

• Examples of IVI International R&D Cooperation

• Conclusion
DCVMN Goals

- DCVMN has built a **successful track record** of producing **innovative, high-quality, and affordable** vaccines

- DCVMN members’ will is to contribute to improving the health and well being of people in all regions, especially in **developing countries**

- 70% of global vaccines are now produced by large multinationals based in North America and Europe, with the remaining **30%** being produced by **the vaccine industry** in **emerging and developing countries**
  - The vaccine industry in these countries is **growing rapidly**, in volume, innovation, technology sharing, and effective partnerships
  - When it comes to the supply of children’s vaccines, the figures are actually reversed, with **70% of vaccines** being **produced by developing-country manufacturers**

- As developing-country manufacturers continue to **cooperate**, increasing numbers of technology transfer agreements are being sought and negotiated to **speed up access to new vaccines**

- In the Decade of Vaccines, DCVMN members should be able to supply **most of the childhood vaccines**

- Further, vaccines against **neglected diseases** are in the pipeline to better protect low-income countries

**DCVMN Manufacturers as of 2012**

**DCVMN: 37 manufacturers from 14 countries**

BRICS’s Impacts on the Global Vaccine Market

- **Brazil, the Russian Federation, India, China and South Africa (BRICS)** have made considerable progress in vaccine production, regulation and development over the past 20 years.

- By 2014, all five countries had strong initiatives for the development of vaccine technology and had greatly improved their national regulatory capacity.

- Through collaborations with universities, donors, international partners and multinational corporations, vaccine manufacturers in BRICS have not only provided increased production capacity for important underutilized vaccines but also developed novel vaccines for specific use in LMICs.

- Vaccines from the BRICS countries are currently competitively priced because the manufacturing costs in BRICS are relatively low.

- More cooperation between academia, biotechnology firms and public health institutions should also be encouraged.

**Vaccines produced in BRICS, 2013**

<table>
<thead>
<tr>
<th>Country and references</th>
<th>No. of manufacturers</th>
<th>Vaccine types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>3</td>
<td>BCG, BMP, DT, DTP, DTP-Hib, Hep B, Hib, influenza, IPV, OPV 1–3, MMR, MMR–varicella, pneumococcal conjugate, rabies, rotavirus, Td, YF</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>4</td>
<td>BCG, brucellosis, diphtheria, DT, DTP, DTP–Hib, encephalitis vaccine (EnCeVi), Gonococcus, hepatitis (child and adult), influenza (live and inactivated), M, meningococcal A, MM, mumps, OPV, rabies, rubella, tetanus, rabies, tularaemia, varicella, YF</td>
</tr>
<tr>
<td>India</td>
<td>10</td>
<td>BCG, C (inactivated oral), DT, DTP, DTP–Hib, Hib, influenza H1N1, JE (inactivated), meningococcal A conjugate, M, MR, MMR, OPV 1 + 3, OPV 1, OPV 1–3, pandemic influenza (live), Pent., rabies, rubella, seasonal influenza, TD, TT, typhoid conjugate, typhoid Vi polysaccharide</td>
</tr>
<tr>
<td>South Africa</td>
<td>1</td>
<td>Hep B</td>
</tr>
</tbody>
</table>

Kaddar et al. Impact of BRICS’ investment in vaccine development on the global vaccine market. *Bull World Health Organ* 2014;92:436–446
• Introduction

• IVI Organization

• Examples of IVI International R&D Cooperation

• Conclusion
The International Vaccine Institute is dedicated to enabling the world's most vulnerable people to have full, productive lives by accelerating R&D for critical vaccines with partners in Korea, across Asia and around the globe.
IVI is an International Organization dedicated to Global Health

Global Vaccine Research Institute

• HQ and labs at Seoul National University in Seoul, South Korea
• Field programs in 29 countries: Asia, Africa, Latin America
• 12 Nationalities in workforce of ~ 130 staffs

OECD-recognized International Organization (not for profit)

• UNDP initiative
• UN Treaty-based
• First international organization in Korea (1997)
• 36 countries and WHO as State parties
An Extensive Global Network
36 Signatory Countries, 160 Partners, Multiple Programs in 44 Countries

- Dengue Program
  - Colombia
  - Brazil
  - Senegal
  - Guinea Bissau
  - Nigeria
  - Burkina Faso
  - Mali
  - Gabon
  - Ghana
  - Sudan
  - Ethiopia
  - Kenya
  - Tanzania
  - Gabon
  - DR Congo
  - Malawi
  - Mozambique
  - Madagascar
  - South Africa

- Cholera Program
  - Nicaragua
  - Niger
  - Sudan
  - Egypt
  - South Sudan

- Typhoid Program
  - Cambodia
  - Malaysia
  - Indonesia
  - Philippines
  - Cambodia
  - Vietnam
  - Thailand
  - Nepal
  - North Korea
  - South Korea

- Other IVI Programs
  - Mongolia
  - China
  - Kyrgyzstan
  - Pakistan
  - India
  - Sri Lanka
  - Cambodia
  - Malaysia
  - Vietnam
  - Philippines
  - Indonesia
  - North Korea
  - South Korea
  - Mongolia
  - China
  - Kyrgyzstan
  - Pakistan
  - India
  - Sri Lanka
  - Cambodia
  - Malaysia
  - Vietnam
  - Philippines
  - Indonesia
  - North Korea
  - South Korea

Map showing countries with different colors indicating the programs they are part of.
IVI has 160 partners worldwide ranging from Government, Industry, Academia and Civil Society to Intergovernmental Organizations

Major Partners

**Industry**
Tech transfer and vaccine development partnerships with 8 manufacturers from 6 countries

**Korea**
Engage with all sectors, in addition to government ministries and agencies, in host country

**Government**
Partnerships to develop vaccines and build capacity in developing countries

**Academia**
Universities, academic societies, research institutes, medical associations

**Global Health**
Conduct public health research and immunization campaigns in collaboration with WHO, GAVI, UNICEF, CEPI, and health ministries

**Philanthropy**
- Bill & Melinda Gates Foundation, a key supporter since 2000
- Samsung Foundation supports our MERS vaccine development program
Partnerships with Global Networks
**IVI Develops and Delivers Vaccines against Infectious Diseases with Limited Commercial Potential - yet High Public Health Importance**

<table>
<thead>
<tr>
<th>Vaccine Development Pathway</th>
<th>Preclinical 1-3 years</th>
<th>Clinical 6-7 years</th>
<th>Registration 1-1.5 years</th>
<th>Launch Life cycle management</th>
</tr>
</thead>
</table>

**Programs**

- IVI Clinical Sites
  - Preclinical, Animal, Toxicology, Proof of Concept, Process Development
  - Tech Transfer, Trial Sites, Project Management, Trial Execution, Data Management
  - Host Country NRA Strengthening & Coordination, WHO Prequalification
  - Uptake, Access, Health Economics, Vaccination Campaigns

<table>
<thead>
<tr>
<th>Science</th>
<th>Discovery</th>
<th>Development</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epidemiology, Disease Burden Research</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Capacity-building | Training, Technical & Financial Support |
IVI Capacity: Laboratory Science

Clinical Research Laboratory (CRL)
Molecular, clinical, and translational immunology.
Qualifies and validates immunogenicity assays in support of clinical trials.

Vaccine Process Development (VPD)
Vaccine conjugation, bacterial/viral process development, Analytics and formulation.
Identifies and assists vaccine manufacturers with tech transfer

IVI Lab Infrastructure
Animal testing facilities. (mice/rats)
BSL 1-3 rated laboratories.
IVI Capacity: Field Programs

Epidemiology & Public Health Research
Infectious disease surveillance and epidemiologic studies

Policy & Economic Research (PER)
Disease burden, cost-of-illness, and vaccine cost-effectiveness field studies

Policy & Economic Research (PER)
Develops vaccine investment cases for governments, GAVI, and WHO
IVI Capacity: Clinical Trials and Regulatory Affairs

**Development & Delivery (D&D)**
- Plans and conducts regulated clinical trials, vaccine effectiveness studies, and vaccination campaigns
- Facilitates NRA product registration & WHO prequalification
- Engages governments and international bodies on policies related to vaccines and vaccination

**Biostatistics & Data Management (BDM)**
- Data management, statistical analysis, mathematical modelling of infectious diseases.
- Vaccine Adverse Events Information Monitoring System (VAEIMS)
- Centralized Dengue Vaccine Safety Data Monitoring (cVDMS)

**Clinical Development and Regulatory (CD&R)**
- Develops clinical strategy and clinical development plan from phase I-IV including designing studies, executing the clinical studies, and communicating the results to scientific community
- Provides technical and regulatory support to partners

### AEFI cases by adverse event (Top 10)

<table>
<thead>
<tr>
<th>AEFI</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEFI</td>
<td>56</td>
</tr>
<tr>
<td>Itch Fever</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
</tr>
<tr>
<td>Dilation of long bones of upper limb and scapula</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
</tr>
<tr>
<td>Rocky mountain spotted fever</td>
<td>5</td>
</tr>
<tr>
<td>Skin rash</td>
<td>4</td>
</tr>
<tr>
<td>Skin rash in the palms and soles</td>
<td>4</td>
</tr>
<tr>
<td>Sore throat</td>
<td>4</td>
</tr>
<tr>
<td>Purple vasovir skin</td>
<td>3</td>
</tr>
<tr>
<td>Dengue fever virus infection</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
</tr>
</tbody>
</table>

### AEFI cases by gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100</td>
</tr>
</tbody>
</table>
### Vaccines under different stages of development.

- Oral cholera vaccine (Shantha, Eubiologics)
- Vi-DT typhoid conjugate vaccine (SK, Biofarma)
- MERS vaccine (GeneOne)
- Schistosomiasis vaccine
- Chikungunya vaccine
- Non-typhoidal Salmonella vaccine (NTS)
- Shigella vaccine
- Hepatitis A vaccine
- TB vaccine

- Bivalent inactivated oral cholera vaccine is first product licensed and approved by WHO.
- Vi-DT typhoid conjugate vaccine is next vaccine out of pipeline (year 2020).
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<table>
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<tr>
<th>Program</th>
<th>Title</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOMI</td>
<td>Diseases of the most impoverished</td>
<td>$40M</td>
</tr>
<tr>
<td>ViVA</td>
<td>Vi-based Vaccines for Asia</td>
<td>$14M</td>
</tr>
<tr>
<td>TSAP</td>
<td>Typhoid Surveillance in Africa Program</td>
<td>$11.2M</td>
</tr>
<tr>
<td>SETA</td>
<td>Severe Typhoid Fever in Africa</td>
<td>$9.5M</td>
</tr>
<tr>
<td>THECA</td>
<td>Typhoid conjugate vaccine effectiveness in Africa</td>
<td>$18.8M</td>
</tr>
<tr>
<td>Gavi MDG</td>
<td>Gavi support for Madagascar</td>
<td></td>
</tr>
<tr>
<td>Vi-DT</td>
<td>Typhoid Conjugate Vaccine: SKB &amp; BioFarma</td>
<td>$37.5M</td>
</tr>
</tbody>
</table>

**IVI Typhoid Programs 2000 - 2019**
Enteric Fever Vaccine Program

<table>
<thead>
<tr>
<th>Past</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diseases of The Most Impoverished (DOMI): Typhoid, Cholera, and Shigella (~$50M)</td>
<td>• Vi-DT SK preclinical ($5M)</td>
</tr>
<tr>
<td>• Vi-based Vaccines for Asia Initiatives (VIVA) ($14M)</td>
<td>• Vi-DT SK clinical phase I and II ($7.2M)</td>
</tr>
<tr>
<td>• Bivalent (Typhoid-paratyphoid A) vaccine development ($2.1M)</td>
<td>• Vi-DT SK CMC ($7M)</td>
</tr>
</tbody>
</table>

Total projected programmatic funding for Vi-DT: $41.6 million (includes $3.5M from ViVA)
Vi-DT Typhoid Conjugate Vaccine enters Phase III End of 2019

1994-2010

Preclinical stage

- Biological E (B)
- PT Bioforms (A)
- SK Chemicals (A)
- Bharat (licensied 2013)
- Ciba
- Vedanta
- Walvax

(A) VI technology transfer
(B) NVGH technology transfer

- V-CRM
- VI-DT
- VI-IT
- VI-EPA
- Under review

Capeding et al, Vaccine 2018

Safety and immunogenicity of a Vi-DT typhoid conjugate vaccine: Phase I trial in Healthy Filipino adults and children

Martina Rosario Capeding 1, Samuel Tesbome 2, Tarun Sahula 1, Khaliq Ali Syed 1, Donal Byun Kim 1, Ja Yeon Park 1, Jae Seung Yang 1, Yang Hee Kim 1, Jiwook Park 1, Sue-Kyung Jo 1, Yun Chon 1, Sudhosp Kothari 1, Sosn Young Yang 1, Dong Soon Ham 1, Ji Hwa Ryu 1, Hee-Seong Hwang 1, Ju-Hwan Mun 1, Julia A. Lynch 1, Jerome H. Kim 1, Hun Kim 1, Jean-Louis Excler 1, Sushant Sahastrabuddhi 1

1 Research Institute for Emotional Medicine, Manila, Philippines
2 Aravind Eye Care System, Madurai, Tamil Nadu, India
3 All Children's, Texas, Republic of Texas

RESEARCH ARTICLE
Six-month follow up of a randomized clinical trial-phase I study in Indonesian adults and children: Safety and immunogenicity of Salmonella typhi polysaccharide-diptheria toxoid (Vi-DT) conjugate vaccine

Barrie Endyemi Medians 1,2,3, Sudjatmiko Soedjatmoko 1,4, Irin Ranggengga 4, Hordativ Gianardi 4, Mimi Sukarni 4, Sukarni Kosasih 4, Mitha Roesik Sudi 4, Sri Nusiana Hikmati 4, Jae Seung Yang 1,2,3, Jan-Louise Excler 3, Sushant Sahastrabuddhi 1

1. Department of Child Health, Faculty of Medicine Universitas Indonesia, Dr. Cipto Mangunkusumo General National Hospital, Jakarta, Indonesia. 2. Department of Internal Medicine, Faculty of Medicine Universitas Indonesia. 3. Dr. Cipto Mangunkusumo General National Hospital, Jakarta, Indonesia. 4. International Vaccine Institute, Seoul, Republic of Korea. 4 PT, Bio Farma, Bandung, Indonesia

Medise et al, PLoS One 2019
### IVI Cholera Vaccine Programs 2000 - 2019

<table>
<thead>
<tr>
<th>Program</th>
<th>Title</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOMI</td>
<td>Diseases of the most impoverished</td>
<td>$40M</td>
</tr>
<tr>
<td>CHOVI</td>
<td>Cholera Vaccine Initiative + Cholvax supplement</td>
<td>$14.1M</td>
</tr>
<tr>
<td>Shantha</td>
<td>Technology Transfer to Shantha (Sanofi)</td>
<td>CHOVI</td>
</tr>
<tr>
<td>EuBiologics</td>
<td>Technology Transfer to EuBiologics</td>
<td>$19.7M</td>
</tr>
<tr>
<td>Cholvax</td>
<td>Technology Transfer to Incepta</td>
<td>CHOVI</td>
</tr>
<tr>
<td>MOCA</td>
<td>Cholera vaccine effectiveness Mozambique</td>
<td>$3M</td>
</tr>
<tr>
<td>GICC-ECHO</td>
<td>Global Initiative for Cholera Control-Ending Cholera (Mozambique/Nepal) KOICA</td>
<td>$8M</td>
</tr>
</tbody>
</table>

**Diagrams:**
- **DOMI 2000**
- **CHOVI 2006**
- **Shantha 2007**
- **EuBiologics 2010**
- **GDEF 2020**
- **MOCA 2016**
- **Cholvax Incepta 2014**
IVI Cholera Program Activities Overview

**Color Code**
- Supply
- Flexibility of Use
- Introduction

**Activities Overview**
- **IVI**
- **VABIOTECH**
- **SHANTHA Tech Transfer 2008**
  - Shanchol PH 3 Kolkata
  - Dosing interval study India
  - Single dose Study Bangladesh
  - Bridging (PH 4) India
  - Bridging (PH 4) Ethiopia
- **EUBIOLOGICS Tech Transfer 2010 -2011**
  - Euvichol® Toxicity & PH 1 by EuB
  - Euvichol® Bridging trial
  - Euvichol-plus® Reformulation
  - Euvichol-plus® CTC label
- **INCEPTA Tech Transfer 2014**
  - Toxicity study Cholvax®
  - Cholvax® licensure trial
- **BIBCOL Tech Transfer 2020**
- **OCV Pilot Introduction Orissa**
- **Vaccination Malawi, Ethiopia**
- **Reactive campaign Malawi, Nepal**
- **Vaccination Nepal, Mozambique**
- **CHOVI investment case**
- **Modeling Global Roadmap**
- **DOVE**
OCV: Virtuous Cycle of Demand – Supply (eventually)

- 2016: New source of supply (EuBiologics)
- 2018: WHO/UNICEF announce Ending Cholera 2030 Roadmap to reduce cholera deaths by 90% by 2030
- Increased demand, increased supply, decreased disease = “virtuous cycle” – 96M doses requested in 2019!
- New manufacturers entering market due to increased demand
Oral cholera vaccination in Ethiopia
LG Electronics, 45,000 people, 2015

Oral cholera vaccination in Malawi
after flooding
Kia, MOFA 130,000 people, 2015

Oral cholera vaccination in Nepal
Rotary, Kim & Chang, Exim Bank, etc,
38,000 people in 2 campaigns

KOICA GDEF – IVI cholera vaccination in
Mozambique, 190,000, 2018
Korean vaccine ‘Euvichol-Plus’ used
### IVI Vaccines Bring Affordable Innovation to Global Health

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>COST</th>
<th>MANUFACTURER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VACCINE #1</strong></td>
<td><strong>Cost thru PQ: $28M</strong></td>
<td><strong>SHANCHOL PQ 2011</strong></td>
</tr>
<tr>
<td>ORAL CHOLERA VACCINE</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VACCINE #2</strong></td>
<td><strong>Estimated Cost thru PQ: $28M</strong></td>
<td><strong>EUVICHOL, EUVICHOL PLUS PQ 2016, 2018</strong></td>
</tr>
<tr>
<td>Vi-DT TCV (Typhoid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VACCINE #3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Non-typhoidal Salmonella</td>
<td><strong>IVI internal investment preclinical POC;</strong></td>
<td></td>
</tr>
<tr>
<td>• Shigella</td>
<td>Wellcome Trust $3.2M</td>
<td></td>
</tr>
</tbody>
</table>

**IVI internal investment preclinical POC; Wellcome Trust $3.2M**
CNBG and IVI exchange MOU to provide high-quality vaccines to developing countries

Dr. Yuntao Zhang (right), Vice President of the CNBG, shakes hands with Dr. Jerome Kim (left), Director-General of IVI, as they exchange an MOU.

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Conclusion - The Global Value of IVI

• Accelerating the development and introduction of a new-generation Typhoid Conjugate Vaccine and other diseases vaccines through a public-private partnership model

• A proven development model: 36 million IVI Oral Cholera Vaccine doses deployed in 22 countries since 2013
• A dedicated partner of WHO Global Task Force on Cholera Control for Ending Cholera: A Global Roadmap to 2030
• Implementing WASH programs into cholera vaccination campaigns

• Increasing access to the HPV vaccine for young girls and women in developing countries
• Provided training and technical assistance to 18 vaccine manufacturers in 14 countries
• Transferred vaccine licenses to manufacturers in 6 countries

• Over 1,300 medical professionals from 72 countries trained in IVI Vaccinology Courses
• Integrated partner of CEPI, Gavi, WHO, and national development agencies
Thank You!

22 Years Advancing Global Health