Annex 4

Vaccine Product Research & Development efforts at IVR

Initiative for Vaccine Research

Contents

- Why is crucial for IVR to contribute to Product Research and Development?
- What are the comparative advantages of IVR in this area?
- What have we achieved in the past years?
- What have we learnt?
- Where are our efforts leading us to?
Why is it crucial for IVR to contribute to Product Research & Development?

- Support for **key products** that lack R&D investment and leadership
- Catalyze R&D processes by participating in important steps
- Promote and **nurture collaborations** with key stakeholders
Measles Aerosol Project

- Foresaw the potential of a new route of administration for measles & other vaccines:
  - mobilized support from the BMGF & others
  - generated the critical "virtual team"
  - led a systematic review of evidence
  - offered an alternative safer & easier to use method

- Mobilized a network of support for the MAP:
  - effective partnership with CDC & ARC
  - global access framework in place – MoUs with SIIL & 3 device companies
  - nearly 200 experts involved in the project
  - collaborations with SVI, ISAM, AktivDry.

Measles Aerosol Project

- Successfully implementing a development plan with limited financial resources:
  - pre-clinical studies completed
  - phase 1 studies ongoing- preliminary data suggest good safety & immunogenicity.
  - plans to start PIVOTAL trial in early 2008

- Generating additional knowledge:
  - regulatory pathway for aerosol vaccines
  - usability criteria for device selection
  - optimal SOPs for PRNT
  - method to assess vaccine potency retention
  - contribution to development of other formulations
**Preliminary results- Phase I trial, India**

17-35 yo healthy measles immune, 3 sites, 20 subjects per site

<table>
<thead>
<tr>
<th>Day-30</th>
<th>Fold rise (95% CI)</th>
<th>Fold change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=2000</td>
<td>5.0 (2.9-8.7)</td>
<td>&lt;=0.2</td>
</tr>
<tr>
<td>2001-6000</td>
<td>2.3 (1.5-3.6)</td>
<td>0.26 to 0.99</td>
</tr>
<tr>
<td>&gt;6000</td>
<td>0.9 (0.7-1.2)</td>
<td>1 to 3.99</td>
</tr>
<tr>
<td>Overall</td>
<td>2.2 (1.8-2.9)</td>
<td>&gt;=4</td>
</tr>
</tbody>
</table>

All increase day 0 to 28.
Day 28 to 90 depends on site with increase in Chennai, decrease in Kolkata.
Day 0 and 28 don’t differ by site but day 90 do.

Adjusting for day 0 when comparing sites by day 28 gives no difference by sites (p=0.14) (Unadjusted also no difference p=0.09)
Why is it crucial for IVR to contribute to Product Research & Development?

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Meningitis Vaccine Project

- **Initiated efforts** towards a new vaccine to fight epidemic meningitis & mobilized partners:
  - brought the need for a new vaccine to the attention of partners
  - mobilized the key funding resources to launch the MVP

- **Laid the ground for a tailored product profile & innovative product development design:**
  - fostered an analysis of the costs to develop the vaccine
  - sought countries & experts input on optimal target price
  - envisioned the need for an alternate development strategy
  - suggested a tailored vaccine could be produced for less than $US 0.50 per dose
Meningitis Vaccine Project

**Bridging across partners to establish a sound development & regulatory plan:**
- phase I successfully conducted in India
- phase II underway in two key sites in Africa
- advanced planning for Phase II/III studies in 4 key African sites, 1 Indian site
- guidelines on technical specifications for QC & production of Men A conj

**Ensuring a harmonious & sustainable capacity building and access strategy at all levels:**
- strengthening regulatory oversight of African countries
- inter-site collaboration
- triggering conduct of large carriage studies across the African belt
- enriching discussion on choice of schedules

MVP Vaccine Development
Country Level Activities

- Technology Discovery & Transfer
- Pre-clinical Development
- Clinical Development
- Process Development
- Licensure
- Demonstration
- Introduction
**MVP Phase I – Safety, Immunogenicity & Immune Persistence Results**

- The group A conjugate vaccine, PsA-TT, was safe and immunogenic in Indian adults.
- PsA-TT induced higher SBA and ELISA Ab levels than the licensed PsA/C polysaccharide vaccine, with significant differences between the Group A GMCs.
- PsA-TT boosts tetanus responses.
- SBA persisted at significantly higher levels for the PsA-TT than for the polysaccharide group.

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**Why is it crucial for IVR to contribute to Product Research & Development?**

- Support for key products that lack R&D investment and leadership.
- Catalyze R&D processes by participating in important steps.
- Promote and nurture collaborations with key stakeholders.
Global Adjuvant Development Initiative

- **Identified access to adjuvants as a major bottleneck to development of new vaccines:**
  - presented the challenge to major vaccine-development funding agencies.
  - proposed structure and mechanism for public-sector adjuvant development initiative.

- **Serving as a hub for this activity:**
  - links to public-sector vaccine development groups: provides pipeline for use of adjuvants
  - no ties to specific products: neutral broker
  - in-house expertise on adjuvant research, development and production

Global Adjuvant Development Initiative

- **Promote access to critical information:**
  - organized conference series on adjuvants and formulations
  - established database of adjuvants in clinical trials
  - provide advice to vaccine developer partners on selection of adjuvants and

- **Created the Global Adjuvant Development Initiative:**
  - partnership with IDRI on downstream development
  - project with Wellcome Trust on upstream development
  - network of public-sector adjuvant users (AdjuNet).
Global Adjuvant Development Initiative

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Facilitating technology transfer:
- seeking inputs from country level.
- support by all WHO teams involved in pandemic preparedness and response
- identifying appropriate production technology to suit national preparedness plans
- canvassing current in-house expertise on influenza vaccine research, development, production, and delivery.

Producing pandemic influenza vaccine:
- strategies to increase in country supply of influenza pandemic vaccines
- in collaboration with governments, industry and, NGOs

Addressing a WHA resolution, developed the Global pandemic influenza Action Plan to increase vaccine supply (GAP):

Guiding the establishment of critical partnerships:
- guidance document: "Technologies for pandemic influenza vaccine production"
- facilitating partnerships with IP and technology holders
- coordinating reviews on clinical development of pandemic vaccines and, on broad-spectrum influenza vaccines

Increasing production capacity
- management of large multinational grants for developing-country vaccine production capacity building
- six grants to be awarded to developing country producers in 3 regions.
Modelling the potential production yield of two influenza vaccines in a fixed size production facility

- **Live attenuated**
  - No need for syringes and needles.
  - Minimal health-care-worker burden

- **Inactivated**
  - Need for availability of syringes and needles.
  - Requires qualified health-care-workers

Establishment of large-scale seasonal influenza vaccine production capacity: Timeline and cost

- **IIV**
  - Egg cell line
  - Butantan, IVAC
  - Biofarma? Thai MOH?
  - Thai MOH?

- **LAIV**
  - Tissue Culture cell line
  - New cell line

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Investment Required (US$ millions)</th>
<th>Time Required to Establish Seasonal Vaccine Production (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIV Egg</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>IIV Tissue Culture Established cell line</td>
<td>100</td>
<td>8</td>
</tr>
<tr>
<td>IIV Tissue Culture New cell line</td>
<td>1000</td>
<td>12</td>
</tr>
<tr>
<td>LAIV Egg</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
What have we learnt?

- IVR is in a privileged position to act as a hub for partnerships/collaborations in RPD.
- WHO's mandate permits better understanding of country needs & priorities.
- WHO outreach promotes sustainable capacity building.
- Despite perceived large bureaucracy, IVR had efficiently led the PR&D processes.
- IVR team comprises a broad expertise

![Checkmark]

- Some reference/specialized groups may be better positioned to implement some of the more upstream activities.
- WHO need to streamline some of the contractual processes.
- In some circumstances, it is more cost effective to use specialized resources already located with our partners

Where are our efforts leading us to?

- We need to finalize the projects that are ongoing.
- We must capitalize on lessons learnt and use them to develop broad guidance/tools
- We should be vigilant and identify other "orphan" products that may require our involvement
- We must, in a continuous and proactive way help partners to link efficiently with other teams of WHO and our partners
We understand the value of effective partnerships !!!!

Building partnerships is critical

They help to ensure that we effectively nurture vaccine R&D steps with vaccine introduction strategies and, sustainability approaches at early stages in the development process.