NATIONAL DEVELOPMENT AND LICENSURE OF A HUMAN MONOVALENT ROTAVIRUS VACCINE (ROTAVIN-M1) IN VIETNAM

DANG DUC ANH
NATIONAL INSTITUTE OF HYGIENE AND EPIDEMIOLOGY, VIETNAM

10th Rotavirus Symposium
Bangkok, Thailand Sep 19-21, 2012
1 Rotavirus vaccine development in Vietnam
Viet Nam: population 91.5 million, area of 330,000km2, birth co-hort: 1.500.000

In the surveillance funded by WHO covering 3 major cities since 1998, rotavirus is the cause of >50% hospitalised children for diarrhea (Nguyen, JID 2001, Van Man JID 2005)

122,000-140,000 hospitalizations and 2900-5400 deaths annually are attributable to rotavirus-related diarrhea (Anh et al, 2006)
Dynamics of the different RV genotypes in Vietnam from 1998-2010

Percentage among RV positives (%)

Source: Nguyen Dang Hien, 2012
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Schedule</th>
<th>Seroconversion rates-Vaccine (%)</th>
<th>Seroconversion rates – Placebo (%)</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotarix</td>
<td>2 doses, 1 month apart</td>
<td>63.3 (54-72)</td>
<td>7.8 (2.6-17)</td>
<td>ND</td>
</tr>
<tr>
<td>N=375</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 doses, 2 months apart</td>
<td>81.5 (73-88)</td>
<td>15.4 (7.6-27)</td>
<td>ND</td>
</tr>
<tr>
<td>RotaTeq</td>
<td>3 doses, 1 month apart</td>
<td>97 (90-100)</td>
<td>18.9 (11-30)</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; year: 72.3 (45.2to97.2)</td>
</tr>
<tr>
<td>N=2036</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

NIHE
Development of Rotavin-M1

- Originated from stool of a child with acute gastroenteritis in Khanh Hoa in 2003
- “Attenuated” by serial passages (x40) in cell culture
- Tested for safety and immunogenicity in mice, rabbits and monkeys
Milestones for Rotavin-M1

**Invention**
1998

**Development**
2003-2008

**Assessment**
2009-2011

**Approval**
4/2012

**Market**
2012-

- RV surveillance
- KH 0118 Vaccine candidate
- Clinical trial
  1: NCT01375907
  2a: NCT01377571
  2b: NCT01502969

**Funding org.**

- WHO
- US-CDC
- MOST-Vietnam
- MOST-Vietnam
- Licencing
- Distribution
2 The clinical trials
Clinical study

Phase 1
Adult volunteers (29)
safety

Phase 2a
Infants (200)
5 groups
Safety, immunogenicity
dose/schedule

Phase 2b
Infants
Phu Tho: (399)
Thai Binh: (400)
Safety, Immunogenicity
Clinical study

- Phase 1: 29 healthy volunteers
  No increase in blood cells counts
  No increase blood urea nitrogen concentration (BUN)
Clinical study

- Phase 2a: 200 infants, divided into 5 groups
  + 1 group with Rotarix™
  + 4 groups with Rotavin-M1

<table>
<thead>
<tr>
<th>Schedule/dosing</th>
<th>2H</th>
<th>2L</th>
<th>3H</th>
<th>3L</th>
<th>Rotarix</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$10^{6.3}$ FFU/dose</td>
<td>$10^{6.0}$ FFU/dose</td>
<td>$10^{6.3}$ FFU/dose</td>
<td>$10^{6.0}$ FFU/dose</td>
<td>$10^{6.0}$ CID/dose</td>
</tr>
<tr>
<td></td>
<td>2 doses</td>
<td>2 doses</td>
<td>3 doses</td>
<td>3 doses</td>
<td>2 doses</td>
</tr>
<tr>
<td></td>
<td>2 month interval</td>
<td>2 month interval</td>
<td>1 month interval</td>
<td>1 month interval</td>
<td>1 month interval</td>
</tr>
</tbody>
</table>
Dose 1

Dose 2

Dose 3

(a) 3L and 3H

Serum 1

Stool

Serum 2

Serum 3

0

30 ± 3

60 ± 3

90 ± 3
Dose 1
0

Dose 2
30 ± 3

Dose 3
60 ± 3
90 ± 3

(a) 3L and 3H

Dose 1
0

Dose 2
30 ± 3

Dose 2
60 ± 3
90 ± 3

(b) 2L and 2H

Serum 1

Serum 2
Dose 1  |  Dose 2  |  Dose 3  
0       |  30 ± 3  |  60 ± 3  |  90 ± 3  

(a) 3L and 3H

Dose 1  |  Dose 2  
0       |  30 ± 3  

(b) 2L and 2H

Dose 1  |  Dose 2  
0       |  30 ± 3  

(c) Rotarix™

Serum 1  |  Serum 2  

Clinical study

- Phase 2a

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<th>Schedule/dosing</th>
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<th>3L</th>
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<td>10^6.0 FFU/dose</td>
<td>10^6.0 CID/dose</td>
<td></td>
</tr>
<tr>
<td>2 doses</td>
<td>2 doses</td>
<td>3 doses</td>
<td>3 doses</td>
<td>2 doses</td>
<td></td>
</tr>
<tr>
<td>2 month interval</td>
<td>2 month interval</td>
<td>1 month interval</td>
<td>1 month interval</td>
<td>1 month interval</td>
<td></td>
</tr>
<tr>
<td>RV-IgA seroconversion (95% CI)</td>
<td>73% (58.88%)</td>
<td>61% (45.76%)</td>
<td>63% (46.79%)</td>
<td>56% (39.71%)</td>
<td>58% (42.73%)</td>
</tr>
<tr>
<td>RV-IgA GMT</td>
<td>76 (44,126)</td>
<td>89 (58,138)</td>
<td>83 (55,126)</td>
<td>71 (35,141)</td>
<td>82 (52,135)</td>
</tr>
</tbody>
</table>

Anh, DD, Vaccine 2012
Vaccine take: percent of children with either RV-IgA seroconversion or shedding of vaccine viruses after any dose.
*Clinical study: Phase 2b

- Participants and location: 799 infants in 2 provinces:
  - 600 infants received vaccine,
  - 199 infants received placebo

- Vaccine dose and schedule
  2 doses, $10^{6.3}$FFU/dose, 2 months interval
  Follow-up period: 1 year

- Age of children at first dose: 8.4 (6-12) week
- Concurrent administration with other vaccines in the EPI program was not done
Adverse events 30 days followings each dose

Day 1-7

- No difference between AE in vaccine and placebo groups
- The main AE are fever, irritability and diarrhea
Adverse events 30 days followings each dose

Day 8-30

- No difference between AE in vaccine and placebo groups
- The main AE are fever, irritability and diarrhea
**RV- IgA antibody responses**

<table>
<thead>
<tr>
<th></th>
<th>RV-IgA GMT</th>
<th>Seroconversion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre (95%CI)</td>
<td>Post (95%CI)</td>
</tr>
<tr>
<td>Vaccine</td>
<td>5.6 (5.4, 7.6)</td>
<td>82 (71,96)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.4 (5, 7.8)</td>
<td>7.6 (6.4, 8.9)</td>
</tr>
</tbody>
</table>
Distribution of RV-IgA titers in vaccine/placebo control groups

65% children with IgA titers ≥80
* RV-IgG titers

<table>
<thead>
<tr>
<th>IgG</th>
<th>Placebo</th>
<th>Rotavin-M1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre (Mo)</td>
<td>Post (M2)</td>
</tr>
<tr>
<td>N</td>
<td>198</td>
<td>173</td>
</tr>
<tr>
<td>GMT</td>
<td>1060</td>
<td>171</td>
</tr>
<tr>
<td></td>
<td>(900-1248)</td>
<td>(136,215)</td>
</tr>
</tbody>
</table>

-RV IgG titers reduced (~6 fold) in placebo groups due to half live of maternal antibody
-RV-IgG increase ~2 fold in vaccine groups
Possible factors affecting antibody responses

- Pre-exposure to rotavirus infection
- Maternal antibody level (RV-IgG) at time for 1st vaccination
- Age of the child at first dose
## Seroconversion v.s RV pre-exposure status

<table>
<thead>
<tr>
<th>Baseline RV-IgA titers</th>
<th>Vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%seroconvert(95%CI)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>485</td>
<td>83 (79, 86)</td>
</tr>
<tr>
<td>≥20</td>
<td>28</td>
<td>50 (33, 67)</td>
</tr>
</tbody>
</table>
Level of maternal antibodies and RV-IgA responses

IgA seroconversion rate and IgA titers after vaccination is inversely proportional to IgG titers at the time of vaccination.
Correlation between age and IgA seroconversion

<table>
<thead>
<tr>
<th>Age group (weeks)</th>
<th>Rotavin-M1</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N seroconvert (%)</td>
</tr>
<tr>
<td>6-7</td>
<td>220</td>
<td>170 (77.3%)</td>
</tr>
<tr>
<td>8-9</td>
<td>199</td>
<td>162 (81.4%)</td>
</tr>
<tr>
<td>10-12</td>
<td>94</td>
<td>83 (88.3%)*</td>
</tr>
</tbody>
</table>

* Significantly different from 6-7.9w age group, Fischer Exact, p <0.05
Correlation between IgA seroconversion, baseline RV-IgG titers and age of infants

Weeks: 6-7, 8-9, 10-12

RV-IgA seroconversion rate (%) vs IgG-Mo GMT
## ImmunoGencity and Efficacy of Rotavirus Vaccines in Vietnam

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Schedule</th>
<th>Seroconversion – Vaccine (95%CI)</th>
<th>Seroconversion – Placebo (95%CI)</th>
<th>RV-IgA GMT-Vaccine</th>
<th>RV-IgA GMT-Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotarix</td>
<td>2 doses, 1 month apart</td>
<td>63.3 (54.3-71.6)</td>
<td>7.8 (2.6-17.3)</td>
<td>77 (55,109)</td>
<td>&lt;20</td>
</tr>
<tr>
<td></td>
<td>2 doses, 2 months apart</td>
<td>81.5 (73.4-88)</td>
<td>15.4 (7.6-26.5)</td>
<td>176 (124,251)</td>
<td></td>
</tr>
<tr>
<td>Rotavin-M1</td>
<td>2 doses, 2 month apart</td>
<td>81 (77-84)</td>
<td>14 (9-19)</td>
<td>82 (71,96)</td>
<td>7.6 (6.4, 8.9)</td>
</tr>
<tr>
<td>N=680</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavin-</td>
<td>3 doses, 1 month apart</td>
<td>56-63</td>
<td></td>
<td></td>
<td>71 (35,141)</td>
</tr>
</tbody>
</table>
Conclusions

1. *Rotavin-M1 is safe for use in young infants*
   - No difference between rates of AE in vaccine and placebo groups in both study sites
   - Few cases of diarrhea observed during observation period but mainly mild as no other AGE related symptoms (fever, vomiting) were observed
   - No cases of intussusception related to vaccine were reported during the 1 year observation period
2. High level of seroresponses among Rotavin-M1 vaccinees

RV-IgA

The IgA seroconversion rate in Rotavin-M1 vaccinated group is 81% compared to 14% in placebo group. This result is comparable to that observed in Rotarix vaccine trial in Vietnam (Anh, Vaccine, 2011)

- More than 50% of children having RV-IgA titers >=80, suggest good immune responses induced by the vaccine

RV- IgG

IgG-GMT decrease 6 fold in placebo group while increase ~2 fold in vaccine group, suggesting good immune response in the presence of maternal antibodies
Maternal antibody level at the time of 1st dose influences the post-vaccination IgA titers and seroconversion.

Modeling of the immunogenicity data (IgA and IgG) suggest that improved immunogenicity by giving vaccine at a later age may be primarily affected by waning of the maternal antibodies.
Licensure of Rotavirin-M1: what it means to rotavirus vaccine introduction to Expanded Immunization Program
What is next?

- Rotavin-M1 was licensed to use in Vietnam in April 2012. Renewal of the license will required generation of clinical effectiveness data.

- Additionally, post-marketing safety data need to be collected, including surveillance for intussusception.

- Demonstration of non-inference on OPV responses also needs to be conducted in order to consider integrating rotavirus vaccine with EPI schedule.
What is the future?

- It is important for Vietnam to produce our own rotavirus vaccine (4 million doses required/year), especially when GAVI support runs out.

- Rotavirus vaccine is in consideration for introduction to EPI program, in addition to rubella and pneumococcal vaccines by 2014-2015.

- The government of Vietnam has a program to promote local pharmaceutical products in order to assure stable and affordable supply.
Rotavin-M1 trial Head-quarter
Thank you for your attention