ACTIVE SURVEILLANCE FOR INTUSSUSCEPTION IN A PHASE III EFFICACY TRIAL OF AN ORAL MONOVALENT ROTAVIRUS VACCINE IN INDIA.

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Active surveillance for intussusception in a phase III efficacy trial of an oral monovalent rotavirus vaccine in India

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Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian children in the second year of life

Nita Bhandari a, Temsunaro Rongsen-Chandola a, Ashish Bavdekar b, Jacob John c, Kalpana Antony d, Sunita Taneja a, Nidhi Goyal a, Anand Kawade b, Gagandeep Kang c, Sudeep Singh Rathore a, Sanjay Juvekar b, Jayaprakash Muliyil c, Alok Arya a, Hanif Shaikh b, Vinod Abraham c, Sudhanshu Vrati e, f, Michael Proschan g, Robert Kohberger h, 1, Georges Thiry i, Roger Glass g, Harry B. Greenberg j, George Curlin g, Krishna Mohan k, G.V.J.A. Harshavardhan k, Sai Prasad k, T.S. Rao l, John Boslego m, Maharaj Kishan Bhan n, *, for the India Rotavirus Vaccine Group 2


Intussusception in southern India: Comparison of retrospective analysis and active surveillance

Susan Jehangir a, Jacob John b, Sangeeth Rajkumar d, Betty Mani c, Rajan Srinivasan d, Gagandeep Kang d, *

Vaccine 32S (2014) A99–A103
ORV 116E Phase III trial plan

Recruit 6800 children at 6 weeks

3 sites – SAS Delhi (3800), KEM Pune (1500), CMC Vellore (1500)

Randomize in a 2:1 ratio vaccine: placebo

Administer 3 doses of TA at 6, 10 and 14 weeks

Designed primarily as an efficacy study and not for measuring rare side effects
6799 enrolled at 3 sites

First $3^{rd}$ at each site (2300)

Remaining $2/3^{rd}$s (4499)

Detailed safety follow-up visit after each dose, **daily for 14 days** to document all AEs

Weekly contacts with participants

Any AEs, SAEs, deaths reported and followed up

Until 2 years of age

All participants had access to study team via call center 24*7 to report AEs
Rotavac trial

Intussusception surveillance primarily for **participant safety**

Criteria for suspecting intussusception were very broad and were decided by expert consensus to ensure no cases could be missed:

- Blood in stool **OR**
- Vomiting more than 3 times in one hour **OR**
- Abdominal lump **OR**
- Abdominal distension

Highly intensive surveillance was done to detect potential cases of intussusception.

- All families were provided a mobile phone
- Had access to study team (call center) - 24*7
- Dedicated team evaluated all cases of suspected intussusception
- Ultrasound done within 8 hours and pediatrician and pediatric surgeon consulted
Independent Adjudication Committee

Screening and evaluation done per protocol by sites

Data submitted to **Independent adjudication committee** made up of a pediatric surgeon, radiologist and pediatrician – not connected with the study

**Adjudication committee** applied Brighton criteria to determine whether a case reported by the site met the level 1 for diagnostic certainty

Committee examined all cases occurring during the follow up period and not cases just in the risk window.

**BRIGHTON CRITERIA**
Major & Minor
By
*The Brighton Collaboration Intussusception Working Group*
*J. E. Bines et al, Vaccine 2004*
Based on the broad criteria for suspecting intussusception:

- Blood in stool OR
- Vomiting more than 3 times in one hour OR
- Abdominal lump OR
- Abdominal distension
Intussusception detection flow chart

Suspected Intussusception 1432

Possible Intussusception 1361

Excluded* 71

Ultrasound (USG) done (1344)

No evidence of Intussusception in USG 1321

Followed up until symptoms resolved

Evidence of Intussusception present in USG 23

Followed up until symptoms resolved

Followed up until symptoms resolved

*Excluded = History of abdominal distension unaccompanied by increase in abdominal girth or another sign or symptom of intussusception

†USG not performed for 17 cases either because the family refused or the event was identified after the child had recovered.
Evidence of Intussusception present in USG 23
Evidence of Intussusception present in USG 23

Not classified: inadequate information for classifying by Brighton criteria
Evidence of Intussusception present in USG: 23

- Transient Intussusception: 12
- Barium reduction: 5
- Pneumatic reduction: 6
- Surgery: 0
Based on Brighton criteria

- Brighton Level 1: 11
- Brighton Level 2: 8
- Not classified: 4

Evidence of Intussusception present in USG: 23

Intervention done

- Transient Intussusception: 12
  - Barium reduction: 5
  - Pneumatic reduction: 6
  - Surgery: 0
Age distribution of intussusception events

The incidence rate of confirmed intussusception is:
- 94/100,000 child-years (Vaccine recipients)
- 71/100,000 child-years (Placebo recipients)

1st confirmed IS case at 36 days among placebo recipients

1st confirmed IS case among vaccine recipients at 112 days

7 day risk window

- USG-evidenced Intussusception
- Brighton Level 1 Intussusception
## Comparison of intussusception detection rates

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Type of surveillance</th>
<th>Total # of participants</th>
<th>Period of follow up</th>
<th>Number of IS case detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>REST trial (Rotateq)¹</td>
<td>Facility based</td>
<td>68038</td>
<td>1 year</td>
<td>27</td>
</tr>
<tr>
<td>Rotarix trial²</td>
<td>Facility based</td>
<td>63225</td>
<td>100 days</td>
<td>25</td>
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<tr>
<td>Rotateq (Africa)³</td>
<td>Facility based</td>
<td>5468</td>
<td>527 days</td>
<td>0</td>
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<tr>
<td>Rotateq (Asia)⁴</td>
<td>Facility based</td>
<td>2036</td>
<td>527 days</td>
<td>1</td>
</tr>
<tr>
<td>Rotateq (Africa)⁵</td>
<td>Facility based</td>
<td>4939</td>
<td>1 year</td>
<td>1</td>
</tr>
<tr>
<td><strong>Rotavac (Ph 3)</strong></td>
<td>Active home based</td>
<td>6799</td>
<td>2 years</td>
<td><strong>11</strong></td>
</tr>
</tbody>
</table>

1. T. Vesikari et al, NEJM 2006
2. G. M. Ruiz-Palacios et al, NEJM 2006
4. K. Zaman et al, Lancet 2010
5. S. A. Madhi et al, NEJM 2010
Discussion

- In the 116E trial, we considered identifying all possible cases of intussusception in this community based clinical trial
  - Enhance participant safety in the trial
  - As an ethical priority

But .....  
- Requires intense effort  
- Result in identification of large proportion of transient cases  
- Cases identified were less severe since none required surgery
This suggests ....

the criteria employed in the trial are inefficient for routine surveillance for intussusception in immunization programs.

nonetheless, monitoring safety will continue to be critical both pre-licensure and after introduction because vaccination safety at the level of the individual child and of programs is necessary to manage rare side effects.
THANK YOU