Update on Safety Considerations from WHO’s Global Advisory Committee on Vaccine Safety

Melinda Wharton
Chair, Global Advisory Committee on Vaccine Safety

11th International Rotavirus Symposium
5 September 2014
Global Advisory Committee on Vaccine Safety

• Established in 1999 by WHO’s Department of Vaccines and Biologicals
• Mandate is to enable WHO to respond promptly, efficiently, and with scientific rigor to vaccine safety issues
• Provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short term or long term national immunization programs, including providing advice on urgent matters as needed
• Regular meetings in June and December, with additional meetings as needed by teleconference
<p>| June 2006 | December 2006 |
| June 2007 | December 2007 |
| June 2008 | December 2008 |
| June 2009 | December 2009 |
| June 2010 | December 2010 |
| June 2011 | December 2011 |
| June 2012 | December 2012 |
| June 2013 | December 2013 |
| June 2014 | December 2005 |</p>
<table>
<thead>
<tr>
<th>Year</th>
<th>Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2005</td>
<td>December 2005</td>
</tr>
<tr>
<td>June 2006</td>
<td>December 2006</td>
</tr>
<tr>
<td>June 2007</td>
<td>December 2007</td>
</tr>
<tr>
<td>June 2008</td>
<td>December 2008</td>
</tr>
<tr>
<td>June 2009</td>
<td>December 2009</td>
</tr>
<tr>
<td>June 2010</td>
<td>December 2010</td>
</tr>
<tr>
<td>June 2011</td>
<td>December 2011</td>
</tr>
<tr>
<td>June 2012</td>
<td>December 2012</td>
</tr>
<tr>
<td>June 2013</td>
<td>December 2013</td>
</tr>
<tr>
<td>June 2014</td>
<td></td>
</tr>
</tbody>
</table>
SAFETY OF CURRENT ROTAVIRUS VACCINES
Safety of Rotarix and RotaTeq

• Prelicensure studies and early post-licensure data provided no evidence of increased risk of intussusception (June 2007)
• Post-licensure data from Australia suggested a small excess risk of intussusception, although work was ongoing (December 2008)
• Preliminary findings from study in Mexico of 4-5-fold increase in intussusception following dose 1 of Rotarix (September 2010)
• Data from Australia and U.S. provide evidence of increased risk of intussusception associated with both vaccines (December 2013)
Rotavirus Vaccines and Intussusception –
Australian Experience, December 2013

• Intussusception cases identified from national hospitalization databases, supplemented by active hospital-based surveillance from July 2007 through June 2010

• Findings were similar for both vaccines, suggesting that a significant risk of intussusception exists after the first and second dose of both vaccines.

• The average vaccine-attributable risk for intussusception, based on the estimated relative incidence in the 1–21 days after dose 1 and the 1–7 days after dose 2, was estimated to be 5.6 additional cases per 100 000 vaccinated infants.

Vaccine Adverse Event Reporting System:

- Rotateq: from 2006 to 2012, 584 confirmed cases of intussusception were reported for 47 million doses distributed. A cluster of cases was observed between days 3 and 6 after doses 1 and 2.

- Rotarix: 66 confirmed intussusception cases were reported for 7.4 million doses distributed.
Rotavirus Vaccines and Intussusception – U.S. Experience, December 2013 (2)

• Vaccine Safety Datalink:
  – Rotarix: VSD identified a small cluster of cases following Rotarix, with 6 cases of intussusception for 200 000 doses administered.
  – Rotateq: no such cluster was found with Rotateq, with 8 intussusception cases identified (4 each after dose 1 and dose 3) for 1.3 million doses administered.

Rotavirus Vaccines and Intussusception – U.S. Experience, December 2013 (3)

- Post-licensure Rapid Immunization Safety Monitoring system (PRISM)
  - Rotateq: small cluster of intussusception cases identified with an attributable risk of approximately 1 case per 100,000 doses
  - Rotarix: the number of cases is currently too small to allow calculation of an attributable risk for Rotarix
GACVS concluded that the findings support a risk of intussusception following administration of both Rotarix and RotaTeq, especially during first 7 days following dose 1.

Attributable risk estimates vary across studies:
- differences in the background rate of intussusception
- sampling uncertainty in all available estimates
- limitations of the surveillance systems that lead to some uncontrolled biases (e.g. differences in diagnostic tests and case definitions in different settings).

Overall, benefits greatly exceed risks.

IMPORTANCE OF POST-MARKETING SURVEILLANCE
Importance of Post-Marketing Surveillance – June 2006

• WHO is developing a generic protocol for post-marketing surveillance of rotavirus vaccine safety that can be adapted for implementation at the country level.

• WHO will also support the post-marketing surveillance of rotavirus vaccine safety through a network of sentinel countries.

• The Committee noted that plans are under way, under the leadership of the United States Centers for Disease Control and Prevention, to develop and make available a protocol for the post-marketing surveillance of the impact of rotavirus vaccines.

• It strongly recommended that introduction of rotavirus vaccines should be associated with careful consideration of post-marketing surveillance at country level and securing its funding as an essential part of immunization programmes.

Wkly Epidemiol Rec 2006;81(28):274-275
More on Post-Marketing Surveillance (1)

• December 2008: Important to continue to accumulate post-marketing surveillance data on intussusception and other possible adverse effects and to set up surveillance systems for such effects as the vaccines were introduced into increasing numbers of developing countries.

• December 2011: Active surveillance of intussusception in African and Asian countries that plan to introduce rotavirus vaccines should be seriously considered, because the data accrued would provide additional benefit-risk information related to these important vaccines.
More on Post-Marketing Surveillance (2)

• December 2013: “Given possible population differences in risk of intussusception, it is important that rotavirus vaccine introduction in other parts of the world be accompanied by similar active intussusception surveillance studies together with rotaviral disease surveillance so that the benefits and risks can be ascertained with relevant evidence.”
Rotavirus Vaccine Safety

NEW ROTAVIRUS VACCINES
Safety of ROTAVAC – June 2014

• Phase 3 study of 4532 vaccinees and 2267 placebo recipients.
  – No imbalance noted between vaccine and placebo groups with respect to adverse events, death, or intussusception.

• 11 confirmed cases of intussusception, none temporally associated with vaccination.
  – Observed incidence 94 per 100,000 child-years among vaccinated and 71 per 100,000 child-years among placebo recipients
Safety of ROTAVAC – June 2014

• Post-licensure study of at least 45,000 vaccinated infants is planned.

• Important that additional data be collected in order to assess the risk of intussusception as well as to identify any other rare adverse events that might occur.

• Based on the experience with other rotavirus vaccines, the infrastructure of sentinel sites that exists in India should be utilized for continued intussusception surveillance in order to fully characterize the safety profile of this new vaccine.
Conclusions from GACVS

• The available data supports the continued use of Rotarix and RotaTeq.
  – Although a risk of intussusception has been found in several populations, the benefits greatly exceed the risks.

• Ongoing work in several countries will help us better understand the safety profile in regions where currently data are limited.

• The experience with safety surveillance of current vaccines will inform safety assessment of new and future rotavirus vaccines.

• Data on both safety and impact of vaccines on disease are essential for evidence-based decision-making.
Thank you

http://www.who.int/vaccine_safety/committee/en/