CAN COMPLETE GENOME ANALYSES EXPLAIN THE HIGH VACCINE EFFICACY OF ROTATEQ™ AGAINST AFRICAN G8 ROTAVIRUS STRAINS?

10th International Rotavirus Symposium, Bangkok, Thailand, September 19-21 2012
G8 rotaviruses

- Genotype G8 is a typical bovine rotavirus genotype in addition to G6 and G10
- The G8 genotype is found in combination with several different P-genotypes (P[1], P[5] and P[11])
- Bovine rotaviruses usually have the following genotype constellation: Gx-P[x]-I2-R2-C2-M2-A3/11-N2-T6-E2-H3
- A limited number of G8 rotavirus strains have been described in other animal species such as sheep, antelope and goat
- G8 has also been detected in humans:
  - Sporadic detection of G8 outside Africa
  - Significant rates of detection in Africa
- Limited number of complete genomes of human and animal G8 rotavirus strains currently available
Clinical trials for RotaTeq™ in Africa

- Conducted in 2007-2009 in Ghana, Mali and Kenya
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- Conducted in 2007-2009 in Ghana, Mali and Kenya
- High prevalence of G8 RVA strains:
  - Mali: 4.7%
  - Ghana: 6.5%
  - Kenya: 23.6%
Clinical trials for RotaTeq™ in Africa

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- High prevalence of G8 RVA strains:
  - Mali: 4.7%
  - Ghana: 6.5%
  - Kenya: 23.6%

- High vaccine efficacy against G8 RVA strains was observed
  - Against G8 rotaviruses: 87.5%, [95% CI: 6.5-99.7]
  - Against genotypes contained in the vaccine: 34.0%, [95% CI: 11.2-51.2]

Tapia et al. 2012
Viruses present in RotaTeq<sup>TM</sup>

<table>
<thead>
<tr>
<th>Strain</th>
<th>VP7</th>
<th>VP4</th>
<th>VP6</th>
<th>VP1</th>
<th>VP2</th>
<th>VP3</th>
<th>NSP1</th>
<th>NSP2</th>
<th>NSP3</th>
<th>NSP4</th>
<th>NSP5</th>
</tr>
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- **Human Wa-like**
- **Human DS1-like**
- **Bovine origin**

- G8 strains were detected in combination with P[6] or P[1] →

Fully heterotypic compared to the G- and P- genotypes of RotaTeq<sup>TM</sup>
Distinct VP7 and VP4 gene segments

Bovine-like RVA

Strains in RotaTeq™
Distinct VP7 and VP4 gene segments

- **Bovine-like RVA**
- **Strains in RotaTeq™**
- **Human P[6]**
Objective

Study the relationship between the complete genomes of wild-type G8 RV strains collected during the clinical trial and RotaTeq™ vaccine strains.
Methods

- Fecal specimens from clinical trials were selected based on the following criteria:
  - Samples that contributed to the per-protocol efficacy analysis
  - Samples representing the genotype diversity in developing countries
  - Availability of sufficient stool sample with positive ELISA results
  - Permission from local institutional review boards to carry out the analyses
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- A total of 8 G8 rotavirus strains collected in Ghana (n=3), Mali (n=4) and Kenya (n=1) were selected for full genome sequencing using 454™ pyrosequencing
3 Distinct G8 genotype constellations

<table>
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<tr>
<th>Sample</th>
<th>VP7</th>
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- 2 different genome constellations in Ghana
3 Distinct G8 genotype constellations

- **2 different genome constellations in Ghana**
- **All Malian and Kenyan strains possessed the same constellation**

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- **2 different genome constellations in Ghana**
- **All Malian and Kenyan strains possessed the same constellation**
- **I2-R2-C2-M2-A2-N2-T2-E2-H2:**
  - Conserved genotype constellation
  - Typically observed among human DS-1-like RVA strains
  - Several gene segments of human DS-1-like and bovine RVA strains share the same genotype, but they can be distinguished phylogenetically
Phylogenetic trees of VP1-3, VP6, NSP1-5

Based on the West-African G8P[6] strains:

- Segments distantly related to human RVA strains
  - VP6, VP1, VP3 and NSP2
Segments distantly related to human RVA strains

- Bovine-like RVA
- Human DS-1-like RVA
- Strains in RotaTeq™
Phylogenetic trees of VP1-3, VP6, NSP1-5

Based on the West-African G8P[6] strains:

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- Segments closely related to human RVA strains
  - NSP1 and NSP3
Segments closely related to human RVA strains

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- **Bovine-like RVA**
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- Segments distantly related to human RVA strains
  - VP6, VP1, VP3 and NSP2

- Segments closely related to human RVA strains
  - NSP1 and NSP3

- Segments most closely related to bovine-like or human RVA strains
  - VP2, NSP4 and NSP5
Most closely related to bovine-like or human RVA strains

Bovine-like RVA

Human DS-1-like RVA

Strains in RotaTeq™
### Genome constellations

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<th>RVA/Human-wt/GHA/Ghan-059/2008/G8P[1]</th>
<th>VP7</th>
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- **Human DS1-like**
- **Human P[6]**
- **Animal origin**

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|-------------------------------------------|-----|-----|-----|-----|-----|-----|------|------|------|------|------|

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- **Bovine origin**
Conclusions and future perspectives

- The close genetic relationship for some of these RVA strains, suggest the (limited) ability of these bovine-human reassortant RV strains to spread from one human to another.
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- Besides VP4 and VP7, other rotavirus proteins may play a role in vaccine induced immunity as suggested by previous studies and the observed high level of cross-protection afforded by RotaTeq™ against heterotypic G8 RVA strains.
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- The fact that RotaTeq™ possesses a bovine RVA genetic backbone may explain the high vaccine efficacy against African G8 RV strains, with a (partial) bovine-like genetic backbone.
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- The close genetic relationship for some of these RVA strains, suggest the (limited) ability of these bovine-human reassortant RV strains to spread from one human to another.
- Besides VP4 and VP7, other rotavirus proteins may play a role in vaccine induced immunity as suggested by previous studies and the observed high level of cross-protection afforded by RotaTeq™ against heterotypic G8 RVA strains.
- The fact that RotaTeq™ possesses a bovine RVA genetic backbone may explain the high vaccine efficacy against African G8 RV strains, with a (partial) bovine-like genetic backbone.
- We are planning to analyze more complete genomes of Kenyan G8 strains to further investigate their genetic backbone and their relatedness to human or bovine-like RVA strains.
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