EEROVAC

4TH EUROPEAN EXPERT MEETING
ON ROTAVIRUS VACCINATION

23-25 March 2015
Santiago de Compostela SPAIN



Organizing and Scientific Committee

Chairman

Federico Martinón-Torres
Hospital Clínico Universitario de Santiago de Compostela, Spain

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Endorsed By:

4th European Expert Meeting on Rotavirus Vaccination (EEROVAC)
Santiago de Compostela, Spain, 23–25 March 2015

Welcome

Dear collegues, Dear friends

Welcome to the 4th European Expert Meeting on Rotavirus Vaccination (EEROVAC)! A unique opportunity to interact directly with, and learn from, those who generate the evidence that moves the science behind Rotavirus Vaccination.

Rotavirus still is a leading cause of severe acute diarrhoeal disease and dehydration in infants and young children throughout the world, with most symptomatic episodes occuring in young children between 3 months and 2 years of age. High mortality and morbidity rates persist, irrespective of hygienic and sanitary conditions, which leaves vaccination as the principal strategy with a possible impact on prevention.

Since the commercial availability in Europe in 2006 of two live, oral, attenuated rotavirus vaccines, several deep changes have ocurred in the field. Worldwide, 78 countries have adopted this recommendation and implemented rotavirus vaccines in their paediatric immunisation programmes, but only a limited number of the European countries have done so (Austria, Belgium, Finland, Germany, United Kingdom, Estonia, and Luxembourg). In the UK, only one year after the introduction of the vaccine, a 69% reduction in the number of cases has been observed. However, the number of countries vaccinating against rotavirus in Europe is still far behind the actual burden, rationale or scientific evidence. Hopefully this meeting will help to find the right path forward for universal vaccination against rotavirus in Europe.

All the proceedings will take place in Santiago de Compostela, a historic town with a strong cultural background and university tradition, always keen to welcome everyone. The administrative, social and commercial capital of the Autonomous Community of Galicia, Santiago is listed as a World Heritage City by UNESCO in recognition to its multicultural nature and as the final destination of a thousand-year-old pilgrimage route that, since the 9th century, has transformed this finis terrae into a meeting place. Tradition is still alive and the continent's spirituality still looks towards Compostela, as shown by the thousands of visitors coming in pilgrimage. With such rich cultural vibrancy and a five-hundred-year-old University, Santiago has much to offer.

To those who are joining EEROVAC again: thank you; to the newcomers: welcome. We are looking forward to meeting you in Santiago!

Federico Martinón-Torres

FACULTY

Christian Agboton. *GSK Vaccines, Wavre, Belgium*
Vesna Blazevic. *University of Tampere, Finland*
Tessa Braeckman. *University of Antwerp, Belgium*
Patricia Bruijning-Verhagen. *University Medical Center Utrecht, Netherlands*
Ron Dagan. *Soroka University Medical Center, Israel*
Adam Finn. *University of Bristol, UK*
Carlo Giaquinto. *University* of Padova, Italy
Roger Glass. *Fogarty International Center, Bethesda, USA*
Harry Greenberg. *Stanford University School of Medicine, USA*
Vanessa C. Harris. *University of Amsterdam, Netherlands*
Hans-Iko Huppertz. *Prof. Hess-Kinderklinik Bremen, Germany*
Baoming Jiang. *Centers for Disease Control and Prevention, Atlanta, USA*
Xi Jiang. *Cincinnati Children´s Hospital Medical Center, USA*
Pier Luigi Lopalco. *European Centre for Diase Prevention and Control, Stockholm, Sweden*
Federico Martinón-Torres. *Hospital Clínico Universitario de Santiago de Compostela, Spain*
Osamu Nakagomi. *Nagasaki University, Japan*
Toyoko Nakagomi. *Nagasaki University, Japan*
Laurence Nicolas. *Sanofi Pasteur MSD, Lyon, France*
Doris Oberle. *Paul-Ehrlich Institut, Germany*
Umesh Parashar. *Centers for Disease Control and Prevention, Atlanta, USA*
John Patton. *Laboratory of Infectious Diseases, Bethesta, USA*
Daniel C. Payne. *Centers for Disease Control and Prevention, Atlanta, USA*
Pierre Pothier. *National Reference Center Enteric Viruses, Dijon, France*
Franco Maria Ruggeri. *Istituto Superiore di Sanità, Rome, Italy*
Pierre Van Damme. *University of Antwerp, Belgium*
Timo Vesikari. *University of Tampere, Finland*

MONDAY 23 MARCH

19.00 Opening ceremony and opening remarks
Federico Martinón-Torres

19.15 Opening keynote lecture: The continuing rotavirus vaccine story
Timo Vesikari

20.30 Welcome reception "Vinos y Tapas"
Pazo de San Lorenzo
Robleda de San Lorenzo, s/n.
GPS coordinates: latitude 42.8780002 longitude -8.557738

TUESDAY 24 MARCH

SESSION I: EUROPEAN PROGRESS FROM DECISION MAKING TO INTRODUCTION
CHAIR: CARLO GIAQUINTO AND HANS-IKO HUPPERTZ

9.00 Introduction: The RV vaccination map
Carlo Giaquinto

9.10 ECDC analysis of the decision making process
Pier Luigi Lopalco

9.40 UK experience in introduction of universal RVimmunization
Adam Finn

10.00 Germany - The road to STIKO recommendation and afterwards
Hans-Iko Huppertz

10.15 How France reversed its position on rotavirus vaccination
Pierre Pothier

10.30
11.00 Coffee break and Poster viewing

SESSION II: CURRENT RV VACCINES
CHAIR: PIERRE VAN DAMME AND FEDERICO MARTINÓN-TORRES

11.00 Post-marketing experience in industrialised countries with Rotateq®
Laurence Nicolas

11.30 Observing rotavirus vaccines deployment worldwide: lessons learned
Christian Agboton

12.00 Rotavirus vaccine impacts and effectiveness in the US
Daniel Payne

12.20 Vaccine effectiveness in Europe
Tessa Braeckman

12.40 ESPID/ESPGHAN Recommendations for rotavirus vaccination in Europe. Update 2014
Pierre Van Damme

13.00
14.30 Lunch bag and Poster viewing

SESSION III: EFFECT OF ROTAVIRUS VACCINATION
CHAIR: TIMO VESIKARI AND OSAMU NAKAGOMI

14.30 RV Serotypes before and after RV vaccinations in Europe
Franco Ruggeri

15.00 Long-term shedding and formation of Rotateq® double reassortants
Timo Vesikari

15.20 Vaccination of pre-term infants
Patricia Bruijning-Verhagen

15.40
16.00 Coffee break and Poster viewing

SESSION IV: ADVERSE EFFECTS
CHAIR: ROGER GLASS AND ADAM FINN

16.00 Intussusception experience from the US
Umesh Parashar

16.20 Intussusception experience from Japan
Toyoko Nakagomi

16.40 Intussusception experience from Europe
Doris Oberle

17.00 Overall Discussion

SESSION V: BEST COMMUNICATIONS – SHORT ORAL PRESENTATIONS
CHAIR: FEDERICO MARTINÓN-TORRES AND RON DAGAN

17.15 The impact of rotavirus vaccination on outpatient pediatric emergency room visits and hospitalization in southern Israel in children <5 years
Ron Dagan

17.30 Rotavirus genotypes and the indigenous children of Brazilian Midwest in the vaccine era, 2008 to 2012
Adriana Luchs

17.40 Bed occupancy for rotavirus gastroenteritis before and after the implementation of the vaccination program with Rotateq® in Finland
Susanne Hartwig

17.50 Measuring the quality of life lost due to rotavirus gastroenteritis in children and their families in the UK
Robin Marlow

18.00 Rotavirus disease revisited: snapshot prior to vaccine introduction in Norway
Tone Bruun

18.10 Epidemiology of group a rotaviruses in Brazil, 1996-2013: impact of universal vaccination with the monovalent vaccine
Jose Paulo Gagliardi Leite

18.20 Intussusception following rotavirus vaccination in the Valencia region, Spain
Silvia Pérez-Vilar

21.30 Dinner

WEDNESDAY 25 MARCH

SESSION VI: ROTAVIRUS VACCINE RESEARCH
CHAIR: OSAMU NAKAGOMI AND UMESH PARASHAR

9.00 Rotavac: The indian neonatal rotavirus vaccine
Roger Glass

9.20 Non-live whole virus vaccine
Baoming Jiang

9.40 Non-live VP8 vaccine
Xi Jiang

10.00 Non-live VP6 vaccine
Vesna Blazevic

10.20
10.40 Coffee break and Poster viewing

SESSION VII: ROTAVIRUS RESEARCH
CHAIR: HARRY GREENBERG AND FRANCO RUGGERI

10.40 Role of the intestinal microbiota in the uptake of rotavirus vaccines
Vanessa C. Harris

11.00 Interferon and rotavirus
John Patton

11.20 The humoral basis of heterotypic immunity to rotaviruses in people
Harry Greenberg

12.00 **Closing remarks**
Federico Martinón-Torres

23-25 MARCH

POSTERS EXHIBITS

1. Frequency and characteristics of rotavirus infections in The Basque Country
   Javier Arístegui

2. Impact on children and parents of rotavirus infections in The Basque Country
   Javier Arístegui

3. In vivo adjuvant effect of rotavirus VP6 on norovirus-specific antibody responses
   Maria Malm

4. Effectiveness of rotavirus vaccines, licensed but not funded, against rotavirus hospitalizations in the Valencia region, Spain
   Silvia Pérez-Vilar

5. Comparing hospitalisation caused by rotavirus infection in the very young children pre- and post-vaccination using a belgian follow-up study
   Bernd Benninghoff

6. A review of Rotarix™ 10 years after its introduction: delivering the promise of protection against rotavirus diarrhoea
   C. Agboton

7. Impact of rotavirus vaccination on childhood seizures hospitalization
   J. Pardo-Seco

8. Shedding and clinical significance of RotaTeq® vaccine viruses
   Maria Hemming

9. Infants rotavirus vaccine coverage in the area of Aragon in Spain
   M. I. Lostal Gracia

10. May be salivary Rotavirus-IgA a more reliable correlate of protection than serum IgA for rotavirus vaccines?
    J. Gómez-Rial

ABSTRACTS

SESSION I: EUROPEAN PROGRESS FROM DECISION MAKING TO INTRODUCTION

ECDC analysis of the decision making process

Pier Luigi Lopalco
Head of Scientific Assessment Section
European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

Decision making process for introducing new vaccines in the vaccination schedule is a complex process influenced by epidemiological, economic, as well as political and social drivers. In the European Union (EU) there is no common approach to introduction of new vaccines, since vaccination policies are of exclusive competence of individual Member States (MS). According to a survey carried out by the VENICE Project in 2007, only three countries (Austria, Belgium, and Luxembourg) decided to introduce the rotavirus vaccine into the childhood vaccination schedule, while three countries (France, Germany, and Spain) decided against the start of universal rotavirus vaccination. None of the other EU MS took a decision at that time. In 2011 (VENICE Project survey) only four countries declared to have completed (Finland, Ireland, Luxembourg) or have an ongoing (Norway) health technology assessment (HTA) process for supporting the decision. At the present, five more countries (Estonia, Finland, Germany, Norway, and the United Kingdom) introduced rotavirus vaccination in the routine schedule and three (Czech Republic, Greece, and Poland) recommended the vaccine, which is not included in the national programme. More recently the High Council of Public Health in France recommended the introduction of rotavirus vaccination, subject to a favourable pricing policy. Lack of cost-effectiveness evaluation (including HTA), competing priorities with other vaccines, and fear for increasing intussusception cases in vaccinated children are the main obstacles to expand rotavirus vaccine recommendation in the EU.

UK experience in introduction of universal RVimmunization

Adam Finn
Professor of Paediatrics
University of Bristol, UK

Following cost evaluation and tendering, the UK introduced a 2 dose schedule of monovalent attenuated human rotavirus vaccine (Rotarix) to the universal primary schedule in July 2013. Acceptance and uptake rates have been high across the country alongside the other infant schedule vaccines. Active surveillance for acute gastroenteritis (AGE) has been undertaken in the Emergency Department at Bristol Royal Hospital for Children since 2 winters prior to the vaccine introduction. Children presenting with >2 loose stools and/or >1 episode of vomiting in the previous 24 hours have stool virology analysis by quantitative PCR, severity assessment (Vesikari) and outcome recorded. In the first winter season after vaccine was started 6 months earlier there were 42-47% fewer attendances with AGE ($p<0.001$) and 38-58% fewer AGE admissions. This represents 300-358 fewer bed occupancy days. In 1 year olds young enough to have been immunised there was a 94% fall in RV positive cases but there was also a 67-70% drop among children too old to have been offered the vaccine. This experience in Bristol reflects national surveillance data from Public Health England.

This apparent early direct and indirect impact of immunisation exceeds expectations. Reports of a lower-than-expected RV epidemic last season in the Netherlands and other unimmunised areas suggests that at least some of observed fall may have occurred in the absence of immunisation. Nevertheless the high acceptance rate of the vaccine and the apparent impact on hospital attendances and admissions at the peak of the winter rise in acute illness are very encouraging.

Germany - The road to STIKO recommendation and afterwards

Hans-Iko Huppertz
Prof.-Hess-Kinderklinik, Bremen, Germany

In 2006 the German Academy of Pediatrics and Adolescent Medicine (DAKJ) recommended general introduction of rotavirus vaccination (RVV) for all infants based on the available scientific evidence (1). In 2008 the German state of Saxony (6% of the German population) introduced mass vaccination for all infants free of cost. At a coverage of 58% cases of RV acute gastroenteritis were halved. In 2011, the German vaccination committee (STIKO) at the federal health institute (RKI) had implemented national RV surveillance and assessed RVV as useful, but not cost effective without reduction of vaccine cost by 65%. An increasing number of parents, pediatricians and insurance companies voted for RVV, reaching a coverage of RVV of 33% of all infants in 2012. Based on an excellent review of existing evidence (2), in August 2013 STIKO recommended general introduction of RVV, but it lasted till spring 2014 when this recommendation could be realized in all parts of the federal republic. In 2014 about 2/3 of the birth cohort received RVV with remarkable regional differences, being lowest in Western affluent urban areas. Recently additional recommendations were published in a joint statement for the vaccination of premature born children still hospitalized at the age of 6-12 weeks when the first dose of RVV is applied: vaccination was recommended for all children with a gestational age of ≥32 weeks (3).

1. http://dakj.de/media/stellungnahmen/infektionskrankheiten-impffragen/2006-empfehlung-rotavirusimpfung.pdf
2. Koch J et al: Background paper to the recommendation for routine rotavirus vaccination of infants in Germany. Bundesgesundheitsbl 2013;56:957-984
3. http://dakj.de/media/stellungnahmen/infektionskrankheiten-impffragen/2014-rotavirus-impfung-neugenorene.pdf

How France reversed its position on rotavirus vaccination

Pierre Pothier
National Reference Center on enteric viruses, CHU Dijon, France.

The rotavirus vaccines Rotarix and RotaTeq received European marketing authorization in 2006; they have been marketed in France since then but are not reimbursed. Three committees must give their opinion on such issues. First, the High Council for Public Health (HCSP) recommends (or not) the vaccine, then the Health Authority (HAS) determines the level of reimbursement, and finally, the Economic Committee for Health Products (CEPS) negotiates the prices of reimbursable vaccines with producers.

Following discussions in HCSP committee meetings since 2006, the vaccines were finally approved in December 2013 after two negative opinions: In December 2006, a first working-group requested postponement of the recommendation and reevaluation of the vaccination after two years. These two years were to allow time to improve the prescription of Oral Rehydration Solutions, to set up a network of surveillance for acute intestinal intussusceptions and for the virological surveillance of circulating strains. A new working-group then re-evaluated the efficacy of and tolerance to vaccination and analyzed its cost-effectiveness. A draft opinion (April 2010) supported the recommendation, but the presence of porcine circovirus in the vaccine and some acute invaginations following vaccination (published in May 2010) reversed the decision. At the last meeting in May 2010, the working-group did not recommend vaccination. Three years later, in 2013, another new working-group recommended vaccination against rotavirus.

After recommendation, reimbursement? Unfortunately for rotavirus vaccination the “Commission on Transparency” of the HAS just given a negative opinion for reimbursement of the vaccination.

SESSION II: CURRENT RV VACCINES

Post-marketing experience in industrialised countries with Rotateq®

Laurence Nicolas Spony1, Cécile Eymin2
1 Medical affairs, Sanofi Pasteur MSD, Lyon, France
2 Franchise development, Sanofi Pasteur MSD, Lyon, France

RotaTeq® is a pentavalent, live , rotavirus vaccine combining five human-bovine reassortant rotavirus strains (G1, G2, G3, G4, and P1[8]) in a liquid formulation for oral administration. Since European license in 2006, about 136 million doses have been distributed worldwide as of the end of 2014. In clinical trials, RotaTeq® has demonstrated high efficacy against rotavirus gastroenteritis[RVGE] due to the genotypes G1-G4 and G9, the five most common rotaviruses virus strains circulating in Europe. Efficacy was 98%-100% against severe RVGE and 72%- 90% against RVGE of any severity. The high efficacy of the pentavalent rotavirus vaccine in disease protection was confirmed in routine practice. In the United-States, effectiveness of 3 doses was 84-100% against RVGE hospitalisations and emergency visits. Sustained high effectiveness in preventing RVGE hospitalisations and emergency visits has been also demonstrated up to the fifth year of life with no evident waning of immunity, confirming 3-year clinical protection with RotaTeq®'s.

In Europe, RotaTeq® has been exclusively used in the Finnish national immunisation programme (NIP) since 2009 with a high vaccine coverage rate (>90%). During the 3-year prospective surveillance, the vaccine effectiveness against hospitalised RVGE for fully vaccinated children was 92.1% [95% CI : 50.0 to 98.7] among children eligible for the NIP. In France (Brest area), RotaTeq® was used in a population of 201 premature children (born before 37 weeks of gestation) under 3 years old with a vaccination coverage rate for a complete vaccination schedule equal to 41.9%. RVGE hospitalisations were reduced by a factor of 2.6 [95%CI,1.3 to 5.2] during the first two seasons and by 11 [95%CI,3.5 to 34.8] during the third season. Effectiveness of RotaTeq® against a range of rotavirus strains (homotypic and heterotypic) has been confirmed , including the rotavirus strain G12P[8]. Unexpected benefits of rotavirus vaccination programmes have been described suggesting indirect protection and a decrease of childhood seizures.

Apart for a small increased risk of intussusception mainly the first week after 1st dose documented for both rotavirus vaccines, RotaTeq® is well tolerated and the benefits of rotavirus vaccination programs have been consistently demonstrated worldwide.

Observing rotavirus vaccines deployment worldwide: lessons learned

Christian Agboton, Bernd Benninghoff
GSK Vaccines, Wavre, Belgium

Rotarix™ is the most used rotavirus (RV) vaccine with more than 250 million doses sold since its launch in 2004. These 10 years offered the unique opportunity to observe the vaccine being implemented in countries all over the world – as of January 2015, 74 countries have implemented RV vaccination in their national immunization programmes, and a little less than 60 are using Rotarix™.1

In countries where the coverage reached a high level rapidly, the impact has been very fast, as observed recently in the UK.2 Furthermore, in most countries an indirect protection in very young (less than 2 months) and older age groups (>1 y of age) was observed;3 a significant decrease of the circulation of rotaviruses during the colder months of the year was observed. Actually, the impact went beyond RV gastroenteritis, as Rotarix™ was able to decrease all-cause diarrheal deaths in countries such as Mexico, Brazil or Panama- by 20%-40%; depending on the age group considered.4 ,5 ,6

The questions of how a single G1P[8] strain vaccine could possibly be effective in preventing diseases due to 5 commonly circulating strain was raised many times. And if there was some effectiveness, would it be at the expense of a strain selection? And how would this 2 dose vaccine compare to the 5 strains 3 dose vaccine? We know now, that Rotarix™ did demonstrate effectiveness on fully heterotypic strains (e.g. G2P[4]) and did not alter the natural variability in strains predominance from year to year.7,8 ,9 ,10,11 Moreover, studies showed that the two globally available vaccines were equally effective, with the added benefit of one dose less for Rotarix™.12, 13,14 Interestingly, the fact that only 2 doses are necessary to complete the vaccine course translated into a better compliance and completeness as compared to the 3 dose RV vaccine.15,16

In economic terms, the introduction of RV vaccines has generally been considered cost-effective. However, only recently were we able to fully comprehend the widespread impact of the vaccine. As expected, hospitalizations decreased, but an unexpected effect was the increase in Quality of Care. 17 Models have shown that hospitals benefit from the freed beds and are more able to cope with other seasonal diseases.

Last but not least, the temporary increase risk of intussusception after dosing with both vaccines was analyzed using a systematic meta-analysis of the published literature.[paper accepted for publication] Data convincingly showed a class effect, as both vaccines displayed similar risk (relative risk of 5.4 after Dose 1 and 1.8 after Dose 2). Taking into account the added value of RV vaccines, all analyses concluded that the benefit/risk ratio of RV vaccines remains largely positive.18

The potential of RV vaccines is still mounting, as both industrialized and developing countries are introducing RV vaccination at an increasing pace. In 10 years from now, it is expected that rotavirus vaccines would have saved 2.4 million lives and half a billion dollars in direct medical costs19 a significant contribution to the WHO Millennium Development Goal to reduce child mortality.

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2. Successful start to rotavirus vaccination programme - News stories - GOV.UK. https://www.gov.uk/government/news/successful-start-to-rotavirus-vaccination-programme. Accessed August 21, 2014.
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ABSTRACTS

Rotavirus vaccine impacts and effectiveness in the US

Daniel C. Payne
Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Surveillance systems to assess the impacts and effectiveness of rotavirus vaccines in US children have been operational since before 2006, when rotavirus vaccines were licensed and approved for universal vaccination. In 2013, 73% of US children eligible to have received vaccine had been fully vaccinated with either RotaTeq® (Merck and Co.) or Rotarix® (GlaxoSmithKline Biologicals) rotavirus vaccines. Throughout this period of time, the US Centers for Disease Control and Prevention has actively tracked rotavirus epidemiologic trends in US children, the impact of rotavirus vaccines upon healthcare costs and pediatric hospitalizations, the field effectiveness of both rotavirus vaccines in concurrent, routine use, unexpected benefits from rotavirus vaccination, and rotavirus genotypic trends over time.

This presentation will review this portfolio of US rotavirus vaccine assessments, and will introduce for the first time preliminary results from the largest and most recent post-licensure US vaccine effectiveness study. This presentation of 2011-2013 US data includes vaccine effectiveness results that are stratified by vaccine dose, clinical setting, age (up to 7 years old), ethnicity, gestational duration, and by predominant, circulating rotavirus strains (including G12, P[8]) for both licensed vaccines.

Vaccine effectiveness in Europe

Tessa Braeckman
Research assistant
Centre for the Evaluation of Vaccination
VAXINFECTIO
Faculty of Medicine and Health Sciences
Belgium, University Antwerp

After extensive documentation of the efficacy and safety profile, two live oral vaccines against rotavirus (RV) have been approved and licensed in Europe in 2006. Currently, the RV vaccination status among the European countries is very dissimilar as there are many differences in national recommendations, implementation and reimbursement modalities.This patchwork setting of different policies concerning the introduction of RV vaccination into the infant immunization schedule results in highly variable coverage estimates between and even within the countries. Despite this situation, several countries have accomplished to demonstrate the vaccine effectiveness (VE) of those RV vaccines in a real life situation, as requested by the regulatory authorities (EMA). Effectiveness results of Austria, Belgium, Finland, France (Brest region), Germany, Portugal, Israel and Spain highlight the good performance of the vaccines in preventing both outpatient visits due to RV GE (range of VE of at least one dose of any RV vaccine: 78.0-91.5%) and more severe cases, requiring hospitalization (range of VE of at least one dose of any RV vaccine: 83.0-95.6%). There has been no significant difference between age-groups, and there even was significant benefit for older children who have not been eligible for vaccination. These results suggest that herd or indirect protection attribute to the good performance of the vaccination programmes. More data is needed for the post-marketing evaluation of strain-specific protection in Europe, to closely monitor G2P[4]-prevalence. This field confirmation of the efficacy results, in high and middle income setting, should encourage other countries to adopt universal mass RV vaccination.

European Society for Paediatric Infectious Diseases Consensus. Recommendations for Rotavirus Vaccination in Europe. Update 2014

Timo Vesikari (1), Pierre Van Damme (2), Carlo Giaquinto (3), Ron Dagan (4), Alfredo Guarino (5), Hania Szajewska (6), Vytautas Usonis (7)

1Vaccine Research Centre, University of Tampere Medical School, Tampere, Finland
2Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
3Department of Paediatrics, University of Padova, Padova, Italy
4Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of Negev, Beer Sheva, Israel
5Departments of Paediatrics, University Federico II, Naples, Italy
6The Medical University of Warsaw, Department of Paediatrics, Poland
7Centre of Paediatrics, Vilnius University, Vilnius, Lithuania

Since the first evidence-based recommendations for rotavirus (RV) vaccination in Europe (2008) several countries in Europe and more globally have adopted universal rotavirus vaccination. This has generated a wealth of post-introduction effectiveness data.

The pre-licensure safety trials of Rotarix™ and RotaTeq®, each in populations of over 60.000 infants, did not reveal risk of intussusception (IS). However, post-vaccination surveillance in several countries, particularly Australia and Mexico, has established that a risk of IS for both vaccines after the first dose might be between 1:50.000 and 1:80.000. While it may be argued that the risk is acceptable vis-à-vis the great benefits of rotavirus vaccination, this argument alone may not suffice, and every effort should be made to reduce the risk of IS. Considerable evidence, including post-vaccination surveillance data from Germany, suggests that the risk of IS can be reduced by early administration of the first dose of oral RV vaccine. The previous ESPID/ESPGHAN recommendations held that the first dose of oral RV vaccine should be given between 6 and 12 weeks of age; this recommendation is still sustained but with an emphasis towards preferably between 6 to 8 weeks of age. At the time of the earlier recommendations experience of RV vaccination in premature infants and other special target groups was limited. It is now recommended with greater confidence than before that prematurely born infants should be vaccinated according to their calendar age. It is now strongly recommended that all HIV-infected/HIV-exposed infants be vaccinated with RV vaccine; while infants with known severe combined immunodeficiency should not receive RV vaccine.

SESSION III: EFFECT OF ROTAVIRUS VACCINATION

Rotavirus serotypes before and after rotavirus vaccination in Europe

Franco Maria Ruggeri
Istituto Superiore di Sanità, Rome, Italy

The European Rotavirus Network EuroRotaNet was established in 2007, and has conducted rotavirus strain surveillance in Europe for 8 consecutive years, collecting basic patient information and performing molecular strain characterization on more than 60,000 cases in 17 countries. The network adopts shared protocols for rotavirus typing, validated through annual ring tests, and gathers data in a comprehensive central database to ensure uniform analysis of epidemiological and virological data.

During the past years, an increasing number of European countries have included mass vaccination against rotavirus in their national or regional vaccine programs, and EuroRotaNet has now a chance to investigate the possible effects of vaccine-induced immune pressure on positive and negative selection of different genotypes of rotavirus co-circulating through the population.

During the whole period, 6 G and P genotype combinations (G1,3,4,9,12-P[8] AND G2P[4]), out of almost 50 identified in total, showed a prevalence of more than 1% and altogether accounted for 91% of all strains genotyped. G1 rotavirus represented almost 50% of all strains throughout Europe, but less common G and/or P types were occasionally spreading in different years or countries. Differences were noted both in the genotype distribution among countries and among patients with different ages, suggesting partial natural cross-protection between some genotypes, particularly G2P[4].

Despite some variation in the relative genotype prevalence before and after vaccine introduction, no significant evidence of selection of breakthrough strains has emerged in EuroRotaNet countries. Conversely, a large reduction in the number of admitted rotavirus cases appeared evident in countries using rotavirus vaccines.

Long term shedding and formation of RotaTeq® double reassortants

Timo Vesikari
University of Tampere, Vaccine Research Center, Tampere, Finland

Rotavirus vaccine RotaTeq® was added into National Immunization Programme (NIP) of Finland in September 2009, and since then RotaTeq® has been used exclusively in the country. The vaccine coverage is over 95%, and the vaccine is given in three doses at ages 2, 3 and 5 months. RotaTeq® vaccine contains on a bovine G6P[5] backbone 5 reassortants, 4 of which express the human VP7 antigen G1, G2, G3 and G4, respectively. One reassortant expresses human VP4 P1A[8] and retains VP7 type G6 from the parental bovine strain WC3.

We studied the prevalence of asymptomatic shedding of RotaTeq® strains in vaccinated children hospitalized for respiratory tract infection (RTI) in a 2-year period. Asymptomatic shedding of RotaTeq® vaccine strains was detected in 17% (30 children) of 182 vaccinated children hospitalized for RTI and, of the strains, 93% had RotaTeq® G1 genotype. Prolonged shedding over 14 days from immunization was detected in 16 cases (53%) with the latest detection at the age of 8 months. In 709 children hospitalized for AGE, shedding of RotaTeq® strains was detected in 32 of 709 cases (5%). Of these cases, 26 shed vdG1P[5] or just the VP7 G1 or part of it or several vdVP4 proteins concomitantly with another GE virus in stools, but four had AGE symptoms possibly or probably associated with the vdG1P[8] double reassortant. (For more details please see abstract and poster Markkula J, Hemming M, Vesikari T. Shedding and clinical significance of RotaTeq® vaccine viruses).

We conclude that shedding of RotaTeq® G1 vaccine strains is common after vaccination and may be prolonged up to several months even in immunocompetent children. Prolonged shedding equals chronic infection in the gut. The clinical significance of such long-term intestinal infection is not known, but requires further attention and study.Vaccine-derived G1P[8] rotavirus has been detected in both symptomatic and asymptomatic children and may explain diarrheal symptoms in a small percentage of RotaTeq® recipients. VdG1P[8] is stable and may be transmitted to contacts in the environment.

Vaccination of pre-term infant

Patricia Bruijning-Verhagen
Pediatrician Epidemiologist
Assistant Professor, Julius Center for Health Sciences and Primary Care UMC Utrecht, Netherlands

Premature infants are at increased risk of severe rotavirus gastroenteritis. Due to frequent and prolonged hospitalization, they are also at increased risk of nosocomial rotavirus infections. Vaccination of these infants is therefore of highest priority. Vaccine efficacy, safety and tolerability was tested in premature infants during phase III trials, but there are remarkably little

post-implementation data on vaccine effectiveness among this high-risk group. Vaccine coverage among premature infants appears to be lower than average. This can be, at least partially, explained by reluctance to vaccinate infants during hospitalization with the life-attenuated rotavirus vaccines. As vaccine shedding occurs frequently during days to weeks following vaccination, benefits for the hospitalized premature infant and potential risks for ward mates should be carefully weighted and will be discussed during this presentation.

SESSION IV: ADVERSE EFFECTS

Intussusception experience from the US

Umesh D. Parashar
Centers for Disease Control and Prevention, Atlanta, USA

In 1999, the first rotavirus vaccine licensed in the United States was withdrawn 9 months after introduction due to an association with intussusception that was detected in post-licensure surveillance. This association prompted large clinical trials designed to ensure the safety of two current live oral rotavirus vaccines, RotaTeq and Rotarix, which have since been recommended for use worldwide. These clinical trials did not demonstrate an increased risk of intussusception with either of the two vaccines, but further post-licensure monitoring was recommended. In the United States, RotaTeq and Rotarix were recommended for routine use in 2006 and 2008, respectively. Following their introduction, several post-licensure studies have focused not only on the effectiveness and impact of these vaccines, but also on continued surveillance for intussusception. While initial studies did not demonstrate increased risk, recent evidence shows a small increased risk of intussusception following vaccination with both Rotarix and RotaTeq, in the order of 1-5 excess cases per 100,000 vaccinated infants. This level of risk is exceeded by the benefits of vaccination; consequently, continue use of rotavirus vaccines is recommended in the United States.

Intussusception experience from Japan

Toyoko Nakagomi, Miho Kaneko and Osamu Nakagomi
Department of Hygiene and Molecular Epidemiology
Graduate School of Biomedical Sciences
Nagasaki University, Nagasaki, Japan

Globally-licensed rotavirus vaccines carry a small risk of intussusception. However, it remains unclear whether the risk will increase in countries where the incidence of naturally-occurring intussusception is high. The incidence of intussusception in Japan is at the higher end of the global spectrum; 150-190 per 100,000 person-years among children age <1 year. The monovalent vaccine (RV1) and the pentavalent human-bovine reassortant vaccine (RV5) have been available in Japan since November, 2011 and July, 2012, respectively. As of September, 2014, 1,779,117 doses of RV1 and 1,073,719 doses of RV5 were dispatched for administration. During the period of 34 months for RV1 and 25 months for RV5, 59 and 43 cases of intussusception that satisfied the level 1 of the Brighton criteria were reported for RV1 and RV5, respectively. When the number of intussusception cases per 1 million doses occurring 0-6 days after the first dose of either RV1 or RV5 was compared between Japan and the USA, there were 6-7 times more cases reported in Japan. A self-controlled case-series analysis of the data made available to medical experts revealed a relative risk of 10.4 (95%CI: 3.0-36) for RV1 and 16.1 (1.7-150) for RV5, under the assumptions that the risk period for intussusception was between 3-7 days post vaccination and the control periods were 0-2 and 21-41 days for RV1, and 0-2 and 21-55 days for RV5. In conclusion, the risk of intussusception exists for both vaccines, but whether the level of relative risk is higher in Japan requires a larger sample size.

Intussusception experience from Europe

Doris Oberle
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel Federal Institute for Vaccines and Biomedicines Paul-Ehrlich, Langen, Germany

Published postmarketing surveillance studies associate the second generation rotavirus (RV) vaccines (Rotarix, GSK, and RotaTeq, Sanofi Pasteur MSD) that were both centrally authorized by the European Medicines Agency (EMA) in 2006 with intussusception (IS).

Individual case safety reports (ICSR) of IS following administration of RV vaccines from European countries received by the German Federal Institute for Vaccines and Biomedicines were analyzed. Besides addressing the frequency of IS reporting in Europe in general, a more detailed analysis will be presented for Germany.

SESSION V: BEST COMMUNICATIONS – SHORT ORAL PRESENTATIONS

The impact of rotavirus vaccination on outpatient pediatric emergency room visits and hospitalization in southern Israel in children <5 years

Ron Dagan
Pediatric Infectious Disease Unit, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Rotavirus vaccine was licensed in Israel in 2007, and in 2011 the pentavalent vaccine (RV5) was introduced to the national program, at 2, 4 and 6 m. This prospective population-based study assessed the impact of vaccination on Emergency room outpatient visits and hospitalizations in children < 5 in southern Israel. This study was conducted in the only hospital in a region with a cohort of 15,000 births (~50% Jewish and ~50% Bedouin children), enabling incidence calculation. The period was 2006-2013, with a continuous daily surveillance on all visits. Two years after introduction of RV5, Rotavirus gastroenteritis (RVGE) hospitalization was reduced in children <5 by 74% and 61% in Jewish and Bedouin children, respectively. The respective all-cause GE reduction was 37% and 24%, all values being statistically significant. The attached table shows the relative impact of RVGE on hospitalization compared to that of non-RVGE gastroenteritis, alveolar pneumonia, and lower respiratory infections (LRIs). Although PCV7 was introduced in mid-2009 and PCV13 at the end of 2010, the data clearly show that the highest reduction in hospitalization occurred in RVGE compared to the other endpoints (reducing RVGE burden from 5.0% of overall hospitalization to 1.8% in children <2 years (with an attributable reduction of 600 cases/100,000.

Conclusion: RV5 had a significant impact on emergency room visits and hospitalization for diarrhea. Our data support that in the immediate post RV5 and PCV implementation, the impact of rotavirus vaccine surpasses that of PCVs.

Table1. Rates per 1,000 and incidence rate ratios (IRRs) of RVGE, non-RVGE GE, alveolar pneumonia and LRI among hospitalized children <2 years old in southern Israel, April 2006 – March 2013

		Pre RV5	Transmission Period	1st post rotavirus introduction	2nd post rotavirus introduction	IRR (95% CI)*
		Apr 06-Mar 08	Apr 08-Mar 11	Apr 11-Mar 12	Apr 12-Mar 13	
Rates	RVGE	8.8	10.6	4.3	2.9	0.34 (0.27-0.42)
	Alveolar pneumonia	14.9	16.0	9.5	9.5	0.64 (0.56-0.73)
	LRI	59.4	58.6	48.5	41.6	0.71 (0.67-0.75)
	Non-RVGE GE	36.7	29.0	25.9	27.2	0.74 (0.69-0.81)
	All visits**	175.5	164.9	147.8	160.5	0.93 (0.90-0.96)
Proportions of all hospitalizations	RVGE	5.0%	6.5%	2.9%	1.8%	0.37 (0.30-0.45)
	Alveolar pneumonia	8.5%	9.7%	6.5%	5.9%	0.70 (0.62-0.79)
	LRI	33.8%	35.5%	32.8%	25.9%	0.77 (0.73-0.81)
	Non-RVGE GE	20.9%	17.6%	17.6%	16.9%	0.81 (0.75-0.87)

* IRR (95% CI) is calculated for comparison of the 4th and the 1st periods
** IRR (95% CI) is calculated for the rate of PER outpatients and hospitalized children of the entire region population

Rotavirus genotypes and the indigenous children of Brazilian Midwest in the vaccine era, 2008 to 2012

Adriana Luchs(1), Audrey Cilli(1), Simone G Morillo(1), Cibele D Ribero(1), Rita de Cassia C Carmona(1), Maria do Carmo S T Timenetsky(1), (1)Enteric Disease Laboratory, Adolfo Lutz Institute, Sao Paulo, Brazil

Background and aims: World group A rotavirus (RVA) surveillance data provides useful estimates of the disease burden, however, indigenous population might require special consideration. The aim of this study was to describe the results of G- and P-types from Brazilian native children ≤3 years. Furthermore, selected strains have been analyzed for the VP7, VP6, VP4 and NSP4 encoding genes in order to gain insight into genetic variability of Brazilian strains.
Methods: A total of 149 samples, collected during 2008-2012, were tested for RVA using ELISA and PAGE, following by RT-PCR and sequencing.
Results: RVA infection was detected in 8.7% of samples (13/149). Genotype G2P[4] was detected in 2008 and 2010, G8P[6] in 2009, and G3P[8] in 2011. The phylogenetic analysis of the VP7 and VP4 genes grouped the Brazilian G2P[4] and G3P[8] strains within the lineages currently circulating in humans worldwide. However, the phylogenetic analysis of the VP6 and NSP4 from the Brazilian G2P[4] strains, and the VP7 and NSP4 from the Brazilian G3P[8] strains suggest a distant common ancestor with different animal strains (bovine, caprine and porcine).
Conclusions: The epidemiological and genetic information obtained in the present study is expected to provide an updated understanding of RVA genotypes circulating in the native infant population, and to formulate policies for the use of RVA vaccines in indigenous Brazilian people. Moreover, these results highlight the great diversity of human RVA strains circulating in Brazil, and an in-depth surveillance of human and animal RVA will lead to a better understanding of the complex dynamics of RVA evolution.

Bed occupancy for rotavirus gastroenteritis before and after the implementation of the vaccination program with Rotateq® in Finland

Susanne Hartwig(1), Matti Uhari(2), Marjo Renko(2), Maria Hemming(3), Timo Vesikari(3), (1)Sanofi Pasteur MSD, France, (2)University of Oulu, Finland, (3)University of Tampere Medical School, Finland

Background and aims: In Finland the immunization program with Rotateq® was introduced in 2009 with coverage rates >90%. Vaccination-impact studies have demonstrated that the burden of acute rotavirus gastroenteritis RVGE has been reduced significantly since, less is known about the benefit on hospital overcrowding.
Methods: Retrospectively collected hospital discharge data were used to calculate the number of bed-days for RVGE and all cause AGE before and after the introduction of the immunization program. The results were extrapolated to the whole country, estimating the annual number of prevented bed days.
Results: An important decrease in the number of beds-days for RVGE and all cause AGE was observed in the post-vaccination compared to the pre-vaccination period.

Period	Years	Tampere		Oulu	
		RV AGE	All cause AGE	RV AGE	All cause AGE
Pre-vaccination period	2001-2006	193.6*	781.0	219.4	1038.4
Post-vaccination period	2009-2012	28.0	393.7	46.7	316.3
% reduction [95%CI]	post-vacc. period vs. pre-vacc. period	**86 [66-94]**	**50 [29-65]**	**79 [49-92]**	**70 [58-79]**

*mean number bed-days for RVGE per RV season

Estimation of the national annual number of prevented bed days after the introduction of the national RV program.

		Children < 16 years
Number of prevented bed days	RV AGE	1,880 (1769;1992)
(95% confidence interval)	All AGE	6,219 (5956;6483)

Conclusions: This study demonstrated that universal RV vaccination is associated with a clear decrease in the number of bed days and occupancy rates for RV AGE and all cause AGE, allowing a better management of other winter epidemics as bronchiolitis or influenza.

Measuring the quality of life lost due to rotavirus gastroenteritis in children and their families in the UK

Robin Marlow(1), Caroline Trotter(2), Adam Finn(1), (1)University of Bristol,UK, (2)University of Cambridge, UK

Aims: Although safe and effective, Rotavirus vaccines (RV) demand significant investment of healthcare resource. In countries with low mortality due to rotavirus, a key component to demonstrating cost-effectiveness is quantifying the Quality of Life (QoL) lost due to rotavirus acute gastroenteritis (RVAGE). UK RV cost-effectiveness calculations used estimates from Canadian primary-care of 5.8 Quality Adjusted Life Years (QALY) lost per thousand family units.
Methods: Children under six years old presenting with gastroenteritis to Bristol Children's Hospital Emergency Department were recruited with their families. Children's QoL was assessed using Health Utilities Index 2 (HUI2) with visual analogue scale(VAS) at presentation. The effect of the child's illness on the QoL of up to two adult caregivers was assessed using EQ-5D-5L. Stools were tested for viral causes of gastroenteritis. Families completed a daily symptom diary to assess time to recovery and within-family transmission.
Results: 127 families consented to take part, 79(61%) had rotavirus as the cause of illness. At attendance, mean paediatric QoL with RVAGE was 74%(HUI2) and 42%(VAS). Primary / secondary caregiver's QoL was 68%/80% (EQ5D) or 70%/79% (VAS). The mean number of QALYs lost due to RVAGE was 3.1-3.5 per thousand children and 7.7-8.7 per thousand family units. In 29% of RVAGE families at least one other member developed a secondary case of gastroenteritis. For working parents, 63% missed a median of 2.3 days' work(IQR 1.4-3.6).
Conclusions: QoL loss associated with RVAGE presenting to Paediatric Emergency departments is significantly higher than estimates used in UK cost-effectiveness calculations.

Rotavirus disease revisited: snapshot prior to vaccine introduction in Norway

Tone Bruun (1), Kirsti Vainio(1), Terese Bekkevold(1), Astrid Rojahn(2), Gunnar Størvold(2), Kirsti Jakobsen(2), Kirsti Egge Haugstad(2), Ketil Størdal(3), Anita Kanestrøm(3), Anette Lunde(3), Henrik Døllner(4), Lars Høsøien Skanke(4), Svein Arne Nordbø(4), Magnhild Owesen Eidem(4), Ann Marit Gilje(5), Elisebet Haarr(5), Heidi Christin Sivertsen (5), Moustafa Gibory(1), Susanne Gjeruldsen Dudman(1), Elmira Flem(1), (1) The Norwegian Institute of Public Health, Oslo, Norway, (2) Oslo University Hospital Ullevål, Oslo, Norway, (3)Østfold Hospital, Fredrikstad, Norway, (4) St. Olavs University Hospital, Trondheim, Norway, (5)Stavanger University Hospital, Stavanger, Norway

Background: Only a limited number of the European countries have done so (Austria, Belgium, Finland, Germany, United Kingdom, Estonia and Luxembourg). However Norway has introduced routine rotavirus immunization for all infants born from September 1, 2014 with 2 doses administered at 6 and 12 weeks of age. We established a national surveillance platform to monitor the impact of the vaccination program.
Methods: Active surveillance for acute gastroenteritis (AGE) in children <5 years old is established since January 2014 at four hospitals with a combined catchment population of 31% of Norway. National data on AGE-associated hospitalizations and primary care visits are systematically reviewed. The vaccine uptake is monitored by the national electronic immunization registry.
Results: Prior to vaccine introduction during 2009-2013, 220 388 primary care visits and 8 890 hospitalizations (22% coded as rotavirus-specific) associated with AGE occurred in Norwegian children <5 y. During 2014, 354 children hospitalized with AGE were enrolled in the active surveillance and 263 (74%) had ELISA results available. Rotavirus was detected in 63% of all samples. Among RV cases, 77% were classified as severe per the Vesikari severity scale. Children aged 6-24 months accounted for 64% of all confirmed RV cases. By January 27, 10 679 children received at least one dose and 5 553 received 2 doses of vaccine indicating high uptake.
Conclusions: Rotavirus remains to be the most important cause of severe gastroenteritis in children in Norway. The early vaccine uptake seems to hold future promise to reduce the burden of disease substantially. The established surveillance platform will be essential for future monitoring of the impact of RV vaccination.

Epidemiology of group a rotaviruses in Brazil, 1996-2013: impact of universal vaccination with the monovalent vaccine

Filipe Anibal Carvalho-Costaa, Rosane Maria Santos de Assisa, Alexandre Madi Fialhoa, Irene Trigueiros Araújoa, Marcelle Figueira Marques da Silvaa, Mariela Martínez Gómeza, Juliana da Silva Ribeiro Andradea, Tatiana Lundgren Rosea, Aline Araújo Nobrec, Eduardo de Mello Volotãoa, Mauricio L. Barretod, Jose Paulo Gagliardi Leite.
Laboratory of Comparative and Environmental Virology, Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro, Brazil, Program for Scientific Computing, Fiocruz, Rio de Janeiro, Brazil, Institute of Collective Health, Federal University of Bahia, Salvador, Bahia, Brazil.

Background and aims: Assess group A rotavirus (RVA) epidemiology, the temporal and regional trends in diarrheal diseases (DD) related mortality in Brazil.
Methods: Epidemiological aspects of DD in Brazil, particularly RVA-associated DD are described, focusing on changes observed after the introduction of the monovalent (Rotarix®, RV1) RVA vaccine, in March 2006. We assessed the prevalence of RVA-infection in children with DD and changes in genotype distribution, RV1 coverage, geographical and temporal trends in DD-related mortality in Brazil. Large-scale laboratory-based RVA surveillance with wide geographical coverage was performed from 1996 to 2013 and for that purpose, 20,419 patients in 22 Brazilian states were enrolled. Diarrhea-related mortality secondary data from all Brazilian regions were analyzed.
Results: RVA-positivity was reduced in the 4-11 months age bracket (33.3% in 1996-2005, 16% in 2006-2013; $p<0.001$) and in the 13-24 months group (28.2% to 22.2%; $p<0.001$). RVA genotypes fluctuated, G2P[4] peaking in a 10-year interval in 1996 and 2006. RV1 coverage has increased, being lower in Northern and Northeastern Brazil, where DD-specific and DD-proportional mortality are higher. From 1996 to 2011, DD-specific and DD-proportional mortality rates have been substantially reduced throughout Brazil, remaining unchanged the regional differences.
Conclusions: DD mortality and RVA-associated DD present a changing epidemiological profile in Brazil, marked by important regional differences. The RV1 vaccine can be considered as one among other socioeconomic measures implemented in the last two decades, with the goal of reducing child mortality and, specifically, DD-related mortality in Brazil.
Funding: IOC-Fiocruz; CNPq; Faperj; Capes, CGLAB/SVS/M of H.

Intussusception following rotavirus vaccination in the Valencia region, Spain

Silvia Pérez-Vilar (1), Javier Diez-Domingo (2), Joan Puig-Barberà(2), Hector S. Izurieta (3), Ruth Gil-Prieto(4), Silvana A. Romio(5), (1)Vaccine Research. FISABIO-Public Health, Valencia, Spain. Medical Informatics. Erasmus University Medical Center, Rotterdam, The Netherlands, (2)Vaccine Research. FISABIO-Public Health, Valencia, Spain, (3)EPI consultant, World Health Organization, Geneva, Switzerland, (4)Department of Preventive Medicine and Public Health & Immunology and Microbiology. Rey Juan Carlos University, Madrid, Spain and (5)Medical Informatics. Erasmus University Medical Center, Rotterdam, The Netherlands. Department of Statistics and Quantitative methods, University Milano-Bicocca

Background: Studies have shown high background rates of intussusception in Spain, thus, its association with rotavirus vaccination could cause concern. Our aim was to investigate this association in the Valencia Region, Spain.
Methods: Hospital-based retrospective observational study, using a self-controlled cases series (SCCS) design, including also an assessment of the positive predictive value (PPV) of the diagnosis code for intussusception (ICD-9-CM code 560.0). Potential cases among infants aged 6-42 weeks during 2007-2011 were identified from the Spanish hospital discharge database. A review of hospitalization and primary care medical records of all cases was performed using Brighton Collaboration´s case definition for intussusception. First confirmed episodes were analysed.
Results: A total of 151 potential cases were identified. Three intussusception cases occurred within days 1-7 following first dose of rotavirus vaccine resulting in a crude incidence rate ratio (IRR) point estimate of 9.0, CI 95%(0.9-86.5), and in an age-adjusted estimate of 4.7, CI 95%(0.3-74.1) within this risk window. The PPV of hospitalized intussusception cases was 93% (95% CI: 87%-96%).

Conclusions: We found an elevated intussusception incidence rate point estimate during the first week following administration of the first dose of rotavirus vaccines. Our findings were not statistically significant, maybe because of limited study power, despite having analysed almost all the population of a whole region. The high PPV found in our study has opened the door for implementation of larger studies without performing medical record review. Thus, we plan to continue the study for additional years, and invite participation from other regions.

SESSION VI: ROTAVIRUS VACCINE RESEARCH

Rotavac: The indian neonatal rotavirus vaccine

Roger I. Glass, Nita Bhandari, Harry Greenberg, Krishna Ella, John Boslego for the Indian Neonatal Rotavirus Program. CDC; Dept. of Biotechnology, India; Society for Applied Studies; Stanford University; Bharat BiotechLtd; PATH.

India has the most estimated deaths from rotavirus, ~80,000/year, and depends primarily on childhood vaccines that it manufactures itself. In 1985, investigators at the All India Institute of Medical Sciences (AIMMS) made the seminal observation that neonates were becoming infected with rotavirus in the newborn unit but did not develop the characteristic symptoms of diarrhea. A series of in-depth investigations identified the strain to be an unusual natural human-bovine reassortant, serotype G9P10, that induced a strong immune response in the infants and protected them against severe rotavirus diarrhea upon reinfection. The strain was developed as a candidate vaccine by an Indian manufacturer, Bharat Biotech, and proceeded through clinical trials. The pivotal phase 3 trials in 6800 infants conducted by the Society for Applied Studies in India found 3 doses of the vaccine to be safe, immunogenic and effective in diminishing the incidence and severity of rotavirus diarrhea in those infants who had been immunized. Levels of efficacy of 57% were achieved in the first year post- immunization and unlike other currently licensed vaccines, this efficacy was sustained for the second year of exposure. The vaccine has been licensed in India in 2014 and was launched in January, 2015. The program was the results of team science, supported initially through the Indo-US Vaccine Action Program, a bilateral collaboration between the Department of Biotechnology of India (DBT) and the US National Institutes of Health. The early research was conducted by investigators at CDC, AIIMS, and Stanford University and subsequent support was provided by DBT, the Gates Foundation with project management from PATH. The vaccine is being launched in the public market for ~$1/dose and future evaluation of the effectiveness and safety of this vaccine in the field is anticipated in the next 2 years. The vaccine should offer a low cost yet effective alternative to increase vaccine supply while supporting the global program for rotavirus immunization.

Non-live whole rotavirus vaccine

Baoming Jiang
Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, USA

Ongoing efforts to address the lower efficacy of currently licensed live oral rotavirus vaccines in developing countries have not produced any real improvements. This efficacy issue, together with lingering concerns about intussusception, porcine circovirus contamination, and the need for a separate supply chain with large volume cold storage, appear to dampen the interest in introducing these life-saving vaccines in some countries. To overcome these concerns, we have been developing a second generation whole inactivated rotavirus vaccine (IRV) CDC-9 strain suitable for intramuscular (IM) or intradermal (ID) administration. We have demonstrated strong immunogenicity and protective efficacy of our IRV adjuvanted with alum and administered IM in mice and gnotobiotic piglets. We have further observed comparable titers of IgG, IgA, and cross-reactive neutralizing activity in sera of piglets that received three doses of IM or ID vaccine.

This ID IRV immunization regimens protected piglets from oral challenge with a virulent human Wa strain, as evidenced by the reduction or the lack of rotavirus antigen shedding in stool and by lower mean diarrhea scores when compared with placebo-vaccinated piglets. In addition, I will describe the rationale for developing our monovalent human IRV and provide the evidence of this IRV for inducing cross-reactive immunity against homotypic and heterotypic human rotavirus strains. Our findings of robust immunogenicity and protection of a monovalent IRV delivered IM or ID in animals have helped establish the proof of concept for parenteral immunization and thus hold promise for a low cost and more effective vaccine against various circulating rotavirus strains among children in all settings. Studies to advance this candidate vaccine are in progress and will be discussed.

Non-live VP8* based vaccine

Xi Jiang
Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

The success of the two current rotavirus (RV) vaccines (Rotarix and RotaTeq) and a number of other candidates under development suggest that the live attenuated reassortant approach is a good strategy for vaccine development against RVs. The recent discovery of human RV recognizing the polymorphic histo-blood group antigens (HBGAs) in a strain-specific manner provided strong supports on the effectiveness of the two vaccines in many parts of the world. However, the two vaccines also encountered problems of low efficacy for children in developing countries and remote areas. Effort for further improvement of these vaccines is needed. In addition, the recent finding of potential species barriers of many RVs between human and animal after the discovery of HBGAs as receptors for RVs also raises questions on future strategy in development of RV vaccines using the live attenuation approaches. This presentation will discuss these questions based on our new understanding on HBGAs as RV receptors, focusing on future improvement of RV vaccines, including the importance of G vs. [P] types for broad protection, selection of parental strains for reassortants between human and animal hosts, and selection of natural attenuated strains as vaccines against RVs. The finding of strain-specific recognition of HBGAs by RVs also has led to new hypotheses and novel approaches for further improvement of the current vaccines, which will also be discussed. Finally, our group has developed a recombinant VP8* based-RV vaccine candidate using the P particles of norovirus as the carrier to present the VP8* antigens that is highly immunogenic, with authentic HBGA binding property, and highly efficient with low cost for production of the vaccine, which also will be discussed.

Non-live VP6 vaccine

Vesna Blazevic
Head of Laboratory, Vaccine Research Center, University of Tampere Medical School, Finland

Live oral rotavirus (RV) vaccines are part of the routine childhood immunizations in many countries. However, alternative non-live RV vaccines are being evaluated. RV inner-capsid VP6 protein is the most conserved, abundant and highly immunogenic RV protein. Recombinant VP6 has been considered as a non-live subunit protein vaccine candidate against RV infection and disease. Although VP6 does not induce classical RV neutralizing antibodies it induces IgA antibodies which inhibit RV replication by intracellular neutralization. Interestingly, RV-specific serum IgA levels have been used as a correlate with protection against severe clinical disease and live RV vaccine induced efficacy. Our laboratory has developed a combined non-live RV and norovirus (NoV) vaccine candidate consisting of baculovirus produced polymeric human RV VP6 protein and NoV virus-like particles (VLPs). Preclinical immunogenicity studies in mice have shown

strong type-specific and cross-reactive VP6-specific antibody and T cell responses. Challenge studies with murine RV strain EDIMwt in immunized mice showed protection against heterologous RV infection. The protection correlated with VP6-specific serum IgA but not IgG antibodies. In addition, VP6 exerted in vivo adjuvant effect on NoV-specific antibody responses sparing the NoV VLP antigen dose and broadening the responses. Altogether, our results show that VP6 induces protective immunity against RV infection and acts as a potent adjuvant for NoV-specific responses and therefore strongly support the use of RV VP6 protein as a subunit non-live RV vaccine candidate.

SESSION VII: ROTAVIRUS RESEARCH

Role of the intestinal microbiota in the uptake of rotavirus vaccines

Vanessa C. Harris
Amsterdam Institute for Global Health and Development and Department of Global Health and Center for Experimental and Molecular Medicine, Division of Infectious Diseases, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Ninety-five percent of rotavirus deaths occur in Africa and Asia where rotavirus vaccines have low efficacy. To test the hypothesis that the differential presence of immune-stimulating intestinal microbes influences RVV efficacy, we conducted a nested, case-control study comparing the intestinal microbiota composition between 10 Pakistani rotavirus vaccine-responders, 56 non- responders, and 10 healthy Dutch infants.Rotavirus vaccine-responders showed a higher diversity and abundance of Clostridium-cluster XIVa and Proteobacteria, particularly bacteria related to Escherichia coli, than rotavirus vaccine non-responders. Remarkably, Proteobacteria levels were also significantly higher in Dutch infants that respond well to rotavirus vaccine. We speculate that a high abundance of Proteobacteria or their cell envelope components augments immune responses to rotavirus vaccine in poor settings.

Interferon and rotavirus

John T. Patton, Allison F. Dennis and Marco Morelli
Laboratory of Infectious Diseases, NIAID, NIH, Bethesda, USA

The segmented genome of rotavirus allows the generation of new virus strains through reassortment. However, the vast majority of human rotaviruses have either of two genotype constellations: G1/3/4/9/12-P[8]-I1-R1-C1-M1-A1-N1-T1-E1-H1 or G2-P[4]-I2-R2-C2-M2-A2-N2-T2-E2-H2. Thus, human rotaviruses are under selective pressures that favor maintenance of certain genotype constellations, despite their opportunity to reassort with genetically distinct human and animal rotaviruses. The nature of the barriers that limit reassortment is not understood, but may include rotavirus adaptation giving rise to viral proteins that are species-specific in their function. One such protein may be the nonstructural protein NSP1, a putative viral E3 ubiquitin ligase with a conserved N-terminal RING domain and a highly variable C-terminal domain. NSP1 proteins of most human (genotype A1/A2) and many porcine (A1/A8) rotaviruses block the function of β-Tr-CP, a cellular protein critical to NF-κB activation and interferon (IFN) expression. In contrast, most other animal rotaviruses prevent IFN expression by inducing the degradation of IFN regulatory factors (e.g., IRF3, IRF7). Together, these and additional findings indicate that the NSP1 proteins of human/porcine rotaviruses have activities that are distinct from the NSP1 proteins of most animal rotaviruses. Hence, the emergence of human reassortant rotaviruses expressing animal NSP1 proteins as significant causes of human disease seems improbable, since such reassortants would lack NSP1 activities normally associated with human rotaviruses. However, given that the porcine A8 NSP1 functions similarly to human A1 and A2 NSP1 proteins, continued emergence of the A8 genotype among circulating human rotaviruses could be predicted.

The humoral basis of heterotypic immunity to rotaviruses in people

H. Greenberg1, M. Sanyal1, N. Nair1,2, N. Feng1, LScalfone1, W. Robinson1, B. Jiang3, X. He1
1Stanford University School of Medicine, Stanford, CA; 2Division of Immune Monitoring & Biomarker Development, Aduro Biotech, Berkeley, CA and 3Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, GA

A variety of studies have shown that a single natural RV infection or a monotypic RV vaccination will induce heterotypic immunity against diarrheal disease, especially severe disease. This heterotypic immunity is critical to the successful Rotarix vaccine, which contains only a single strain of attenuated G1P8 human RV. The goal of this study was to elucidate the mechanism responsible for heterotypic humoral immunity to RVs in humans by analyzing steady-state RV- specific intestinal B cells. Intestinal RV specific B cells were isolated from gastric resections using Cy5 conjugated CDC9 (G1, P[8]) TLPs. Intestinal IgA+ antibody secreting cells were single cell sorted and subjected to paired heavy and light chain antibody gene sequencing. A rooted evolutionary tree representing the RV-specific antibody repertoire was generated from each subject by clustering these sequences. Subsequently, selected mAbs were -synthesized expressed and characterized for their binding specificity and neutralizing activity against homotypic and hererotypic RV strains in vitro and in vivo. We observed that the majority of antibodies are directed against VP4 (VP8* specifically) with many fewer against VP7 or VP6. Approximately 20% of these antibodies displayed RV neutralizing activity and half of these neutralized RVs with diverse serotypes. These results indicate that humans can circumvent the serotypic diversity of circulating RV strains by expressing individual VP4 and/or VP7 epitope-specific Ig molecules that mediate heterotypic as well as homotypic neutralization. Characterization of the targets of these recombinant mAbs at the protein, serotypic and structural levels and determination of the extent to which they arise following primary RV infection of young children will provide the basis for designing more effective future vaccines.

POSTERS EXHIBITS

1. Frequency and characteristics of rotavirus infections in The Basque Country

Javier Arístegui(1), Elisa Garrote(2), Ana Partidas(3), Noelia López(4) and María San-Martín(4), (1) Head of Pediatrics Infectology Unit. Hospital de Basurto, (2)Pediatrics Infectology Unit. Hospital de Basurto, (3)Pediatrics Service. Hospital de Basurto, (4)Medical Department. Sanofi Pasteur MSD

Background and aims: There is few information on the epidemiology of rotavirus (RV) acute gastroenteritis (AGE) managed at primary care in Spain . This study aimed to assess the frequency and characteristics of RVAGE in young children in primary care and Emergency Room (ER) in the Basque Country.
Methods: Epidemiological, prospective study carried out in pediatrics consultations and a hospital ER in the Basque Country between December-2013 and April-2014. All children <3 years with AGE attended by investigators were registered and tested for RV. Patient data were collected for all children recruited until AGE resolution.
Results: 37.7% (203/538) of all AGE cases registered were positive for RV (RV+). Incidence rate of RVAGE during the 5-months study period was 1.67 cases/100 children <3 years (CI95%, 1.46-1.91), with a peak of 3.58 (CI95%, 2.91-4.37) in January. Mean age of patients was 15.6 (±8.75) months. Symptoms different from diarrhea were significantly more frequent in RV+ vs RV- cases: fever in 63.9% vs 45.1% and vomiting in 61.2% vs 44.3%, respectively. Dehydration was also significantly more frequent among RV+ cases (14.6% vs 3.7%). RV+ cases required more frequently hospital treatment (7.5% vs 1.4%), hospital admission (5.8% vs. 1.0%) and visits to the ER (41.7% vs 15.7%), compared to RV- cases.
Conclusions: RV infections are responsible for a significant proportion of AGE cases managed at primary care and ER level. RV cases seems to be related to a higher presence of symptoms, severity and health care resource consumption that non RV AGE.

2. Impact on children and parents of rotavirus infections in The Basque Country

Javier Arístegui(1), Elisa Garrote(2), Ana Partidas(3), Noelia López(4) and María San-Martín(4), (1) Head of Pediatrics Infectology Unit. Hospital de Basurto, (2)Pediatrics Infectology Unit. Hospital de Basurto, (3)Pediatrics Service. Hospital de Basurto, (4)Medical Department. Sanofi Pasteur MSD

Background and aims: Rotavirus (RV) is associated more frequently to severe symptoms compared to AGE due to other causes. This higher severity of RVAGE may have an impact in the affected children and their parents.
Methods: Prospective study carried out in pediatrics consultations and a hospital ER in the Basque Country between December-2013 and April-2014. Children<3 years with AGE were selected and tested for RV. Data on child's behavior and parents quality of life (QoL) were collected for all children recruited until AGE resolution.
Results: 211 children <3 years with AGE were included in the study. 49.3% tested positive for RV (RV+). Mean age of patients was 15.6 (±8.75) months. Significant differences were observed in child's behavior between RV+ and RV- cases: crying more (70.2% vs 49.0%), more tired (78.8% vs 53.3%) and less playful (69.9% vs 46.2%) than usual. Parents of children with RVAGE were significantly more worried about symptoms than non-RV cases' parents (median of 7 vs 6 on a 10-points scale) and suffered from more sleep disturbance (95.2% vs 81.9%). Work time was more frequently affected in parents of children RV+ (39.8% vs 14.3%), leading to a loss of income in some cases. Mean added costs for parents of children with AGE were significantly higher in RV+ cases (52.3±50.7€ vs 26.3±18.6€).
Conclusions: RVAGE managed at primary care and ER has a more adverse impact in children and parents in terms of QoL and costs than non-RV AGE.

3. In vivo adjuvant effect of rotavirus VP6 on norovirus-specific antibody responses

Maria Malm(1), Timo Vesikari(1), Vesna Blazevic(1), (1) Vaccine Research Center, University of Tampere

Background: We have developed combined rotavirus (RV) VP6 + norovirus (NoV) virus-like particle (VLP) based vaccine candidate against the two leading causes of acute viral gastroenteritis. Both components, produced by baculovirus-insect cell expression system were shown to induce strong type-specific and cross-reactive immune responses. As oligomeric VP6 protein is highly immunogenic, we investigated whether it has an adjuvant effect on NoV-specific immune responses.
Methods: BALB/c mice were immunized twice (at day 0 and day 21) intramuscularly with a suboptimal dose (0.3 μg) of NoV GII-4 or GI-3 VLPs either alone or in a combination with 10 or 30 μg doses of recombinant VP6. An ELISA assay was used to measure NoV-specific serum IgG titer and cross-reactive antibodies. Blocking assay using human saliva or synthetic histo-blood group antigens was employed to test for blocking antibodies against NoV VLPs.
Results: Suboptimal dose of the GI-3 and GII-4 VLPs alone did not induce detectable NoV-specific antibodies. When co-administered with the rVP6, the suboptimal dose of the VLPs induced considerable serum IgG titers and cross-reactive antibodies against NoV VLP genotypes not included in the vaccine composition. Most importantly, NoV-specific blocking antibodies, a surrogate for neutralization antibodies, were generated.
Conclusions: Our results show that RV VP6 protein has an in vivo adjuvant effect on NoV-specific antibody responses. Although the exact mechanism/s is yet to be identified preliminary results indicate that VP6 stimulates strong Th2 type cytokine IL-4 production. Finally, these results support the use of VP6 protein as a part of the RV-NoV combined vaccine.

4. Effectiveness of rotavirus vaccines, licensed but not funded, against rotavirus hospitalizations in the Valencia region, Spain

Silvia Pérez-Vilar(1), Javier Díez-Domingo(1), Mónica López-Lacort(1), Sergio Martínez-Úbeda(1) and Miguel Ángel Martínez Beneito(2), (1)Vaccine Research. FISABIO-Public Health, (2) Health Inequalities, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de laComunitat Valenciana, FISABIO-Public Health, Valencia, Spain. Ciber de Epidemiología y Salud Pública-CIBERESP, Instituto de Salud Carlos III, Madrid, Spain

Background: Although rotavirus vaccines have been licensed in Spain for over 8 years, they are not funded by its public health systems. The analysis of their effectiveness in the Valencia Region could better inform decisions about potential inclusion in the official immunization schedule.
Objective: Assess the effectiveness of Rotarix® (RV1) and RotaTeq® (RV5) against rotavirus hospitalizations.
Methods: We conducted a retrospective cohort study using the region's health care databases, among resident children aged <3 years covered by the National Health System, during January 2007-June 2012. We compared two cohorts of vaccinated children: the first included children who received at least one dose of a rotavirus vaccine, and the second included children who were not vaccinated with rotavirus vaccines but received at least one dose of a pneumococcal vaccine, another licensed but non-funded vaccine. The main outcome was rotavirus hospitalization, either laboratory-confirmed (confirmed) or codified as rotavirus (probable). Rotavirus vaccine effectiveness (RVE) was assessed using Cox proportional hazards models. The analyses were performed by vaccine brand.
Results: The study included 78,281 rotavirus and 96,643 pneumococcal vaccinees. Adjusted RVE against probable or confirmed rotavirus hospitalizations was 86% (95% CI: 78-91%) and 88% (95% CI: 81-92%) for a complete series of RV1 and RV5 respectively.
Conclusions: Both rotavirus vaccines were over 85% effective against rotavirus hospitalization among young children. The high effectiveness shown argues in favor of their inclusion in the official schedule. Additional information on rotavirus vaccine safety, duration of protection, and benefit-risk will also be needed to inform such deliberations.

5. Comparing hospitalisation caused by rotavirus infection in the very young children pre- and post-vaccination using a belgian follow-up study

Bernd Benninghoff(1), Danielle Strens(2), Xiao Li(3) and Marc Raes(4), (1) Health Economics Department, GSK Vaccines, Wavre, Belgium, (2) Realidad, Grimbergen, Belgium, (3) Health Economics Department, GSK Vaccines, Wavre, Belgium, (4) Department of Pediatrics, Jessa Ziekenhuis, Hasselt, Belgium

Background and aims: Rotavirus vaccination was introduced in Belgium end 2006 with a high uptake (>85%) maintained over years. Consequently, a sustained 75% reduction in rotavirus-related hospitalisations is observed in children <5-year-old (5y). We investigated how infants prior to age of vaccination, <2-month-old (2m), remain at risk of infection because being susceptible.
Methods: Rotavirus test results were collected retrospectively from 11 hospitals across the country in children <5y. If the test was performed 48 hours after being hospitalised, it was considered as a nosocomial infection. We compared data of post-vaccination period (2007-2012) for nosocomial and for overall rotavirus disease relative to pre-vaccination period (2005-2006) for two age-groups, <2m and >2m.
Results: Pre-vaccination, the number of positive tests in hospitalised infants <2m was on average 81/year, 52% were nosocomial. For the children>2m, the number of events was 695/year with only 15% being nosocomial. A linear decrease in positive tests after vaccine introduction was observed for the >2m age-group in both nosocomial and overall rotavirus disease. For the <2m age-group, a reduction was observed but without a clear gradual annual decrease.

Conclusion: Assuming no change in catchment area for those 11 hospitals, infants <2m remain at increased risk for rotavirus infection that is partially explained by nosocomial infection. It is worth considering specific preventative intervention methods to reduce this specific risk.

Table 1: Remaining hospitalisation caused by rotavirus per year and per agegroup relative to the average pre-vaccination period (2005-2006)

		Average cases of 2005 & 2006	Relative remaining vs. pre-vaccine period					
			2007	2008	2009	2010	2011	2012
<2 months old	Nosocomial	42	0.69	0.38	0.21	0.33	0.47	0.33
	Overall	81	0.75	0.49	0.43	0.43	0.64	0.51
>2 months old	Nosocomial	106	0.40	0.36	0.29	0.19	0.16	0.07
	Overall	685	0.31	0.37	0.35	0.25	0.23	0.11

6. A review of Rotarix™ 10 years after its introduction: delivering the promise of protection against rotavirus diarrhoea

C. Agboton(1), P. Pereira(1) and B. Benninghoff(1), (1)Medical Affairs, GSK Vaccines, Wavre, Belgium

Rotavirus is the most frequent cause of severe acute gastroenteritis among young children - both in developing and developed countries. Rotarix™ (GSK, Belgium) - a live attenuated human G1P[8] strain oral vaccine – was launched in July 2004 in Mexico; it opened a new era as this was the first viral vaccine to be initially introduced by a pharmaceutical company in a less-developed country.

Rotarix™ was made possible thanks to the introduction of techniques allowing the propagation of human rotavirus in cell culture. Rationale of the Rotarix™ clinical development was based on mimicking the natural infection without triggering the disease; knowing that the two first infections due to rotavirus are the most severe. With more than 100,000 participants, Rotarix™ is the most comprehensive vaccine development done at GSK Vaccines.

Ten years after its launch, the impact of Rotarix™ has been profound, as it managed to get rotavirus epidemics under control in most countries where it has been introduced. In particular, Rotarix™ helped reducing the number of diarrhoeal deaths in developing countries, and contributed to decrease health resources use in developed ones. Some events unknown at launch were identified, such as the discovery of an adventitious virus and the transitory increase of intussusception after dosing. However, these events did not alter the safety profile of Rotarix™, based on robust safety data suggesting a favourable risk/benefit ratio. Rotarix™ is now licensed in more than 130 countries, and used in 58 of the 75 countries that have introduced rotavirus vaccination in their immunisation calendars.

7. Impact of rotavirus vaccination on childhood seizures hospitalization

J. Pardo-Seco(1), M. Cebey-Lopez(1), N. Martinon-Torres(2), A. Salas(3), J. Gomez-Rial (4), C. Rodríguez-Tenreiro(4), J.M. Martinon-Sánchez(5) and Federico Martinon-Torres(5) (1)Affiliation: Genetics Vaccines Infections and Pediatrics Research Group (GENVIP), Healthcare Research Institute of Santiago de Compostela, Santiago de Compostela, Spain, (2)Affiliation: Genetics Vaccines Infections and Pediatrics Research Group (GENVIP), Healthcare Research Institute of Santiago de Compostela, Santiago de Compostela, Spain. Pediatric Infectious Disease and Vaccines Unit, Area Asistencial Integrada de Pediatría; Hospital Clínico Universitario de Santiago de Compostela; Santiago de Compostela, La Coruña, Spain, (3)Affiliation: Genetics Vaccines Infections and Pediatrics Research Group (GENVIP), Healthcare Research Institute of Santiago de Compostela, Santiago de Compostela, Spain. 3Unidade de Xenética, Departamento de Anatomía Patolóxica e Ciencias Forenses, and Instituto de Ciencias Forenses, Grupo de Medicina Xenómica (GMX), Facultad de Medicina, Universidad de Santiago de Compostela,Santiago de Compostela, Galicia, Spain, (4)Affiliation: Genetics Vaccines Infections and Pediatrics Research Group (GENVIP), Healthcare Research Institute of Santiago de Compostela, Santiago de Compostela, Spain, (5)Affiliation: Genetics Vaccines Infections and Pediatrics Research Group (GENVIP), Healthcare Research Institute of Santiago de Compostela, Santiago de Compostela, Spain. Pediatric Infectious Disease and Vaccines Unit, Area Asistencial Integrada de Pediatría; Hospital Clínico Universitario de Santiago de Compostela; Santiago de Compostela, La Coruña, Spain

Background and aims: Rotavirus vaccine might reduce the risk of hospitalization due to childhood seizures. We aimed to assess variations in the incidence of hospitalizations for childhood seizures among children < 5 years of age before and after rotavirus vaccine introduction.
Methods: Annual hospitalization rates for any kind of childhood seizures (CS), before and after rotavirus vaccine (RV) introduction, were calculated by using the official surveillance system for hospital data.
Results: Our study cohort totaled 6,149 children <5 years admitted to the hospital between 2003 and 2013 with any kind of CS (780.3*+779.0*+333.2*+345*ICD-9-CM code). The annual hospitalization rates for any kind of CS in children <5 years were correlated with RV coverage (Pearson's correlation r=-0.673, P=0.033) and rotavirus acute gastroenteritis admission rates (Spearman's correlation ρ=0.506, P=0.001), with decrease rates ranging from 16.2% (95% CI=8.3-23.5%) in 2007 to 34.0% (27.3–40.1%) in 2010, as compared to the median rate of the pre-vaccination period (2003 to 2006). Similarly, for convulsions (780.3*ICD-9-CM code) the decrease seen in children <5 years was significantly correlated with the increase in rotavirus vaccine coverage (r=-0.747, P=0.013) and rotavirus acute gastroenteritis admission rates (ρ=0.543, P<.001), with decrease rates ranging from 18.7% (9.6-26.8%) in 2007 to 42.5% (35.3-48.9%) in 2012. Significant results were also obtained for infants <12 months and infants 1-2 years.
Conclusions: Our results show that RV may have a significant impact in the decrease in seizure-related hospitalizations in childhood. This additional benefit of rotavirus vaccination seems more marked in the youngest infants.

8. Shedding and clinical significance of RotaTeq® vaccine viruses

Maria Hemming(1), Timo Vesikari(1), (1)Vaccine Research Center, University of Tampere, Finland

Introduction: Rotavirus vaccine RotaTeq® was added into National Immunization Programme (NIP) of Finland in September 2009, and since then RotaTeq® has been used exclusively in the country. The vaccine coverage is over 95%, and it is given in three doses at the ages 2, 3 and 5 months. RotaTeq® contains 5 reassortant rotaviruses on a bovine G6P[5] backbone, 4 of which express the human VP7 antigen G1, G2, G3 and G4. One reassortant expresses human VP4 P1A[8] and retains VP7 type G6 from the bovine parental strain WC3. High vaccine coverage and exclusive use of RotaTeq® has provided an optimal setting for follow-up on the impact and shedding of rotavirus vaccine strains.

Materials and methods: After universal mass vaccination, two prospective studies on the etiology of AGE in children have been conducted in 2009-2011 and 2012-2014. The prevalence of asymptomatic shedding of RotaTeq® strains was studied in vaccinated children hospitalized for respiratory tract infection (RTI) between 2009 and 2011. In both studies, stool samples were studied for the presence of rotaviruses and several other gastroenteritis agents by RT-PCR and further sequencing of rotavirus VP7, VP4 and VP6 to study the origin of the virus (vaccine-derived (vd) or wild-type (wt)). If VP7/VP4/VP6 sequence had similarity with RotaTeq® strain, the samples were studied for the presence of rotavirus antigen by ELISA, and if positive, they were propagated in MA104 cells to study the viability and stability of detected rotavirus.
Results: Asymptomatic shedding of RotaTeq® vaccine strains was detected in 17% (30 children) of 182 vaccinated children hospitalized for RTI and of these, 93% were detected with RotaTeq® G1 genotype. Majority of children shed either vdG1P[8] combination or vdG1 alone in their stools, but also other combinations such as vdG1P[5], vdG1+P[5]+P[8], vdG1+wtP[8] and vdG6P[8] were detected. None of these children were ELISA positive. The shedding was observed in 50% of children between 1st and 2nd vaccine dose, in 27% between 2nd and 3rd dose and in 5% of children after the 3rd immunization. Prolonged shedding (over 14 days from immunization) was detected in 53% (16 cases) with the latest detection at the age of 8 months. In children hospitalized for AGE, shedding of RotaTeq® strains has been detected in 5% (32 of 709 cases). Of these cases, 26 have shed vdG1P[5] or just the VP7 G1 part of it separately or detected with several vdVP4 proteins and detected concomitantly with other GE pathogen in stools. In addition, we detected 5 cases of vdG1P[8] and one case of vdG6P[8]. Of vdG1P[8] cases, one was observed in previously healthy unvaccinated 7-year-old girl and in only one case another GE pathogen was detected concomitantly in stools. The vdG1P[8] was found as only GE pathogen in 4 cases, in both vaccinated and unvaccinated children. After positive ELISA result, the vdG1P[8] was further propagated in MA104 cells upon 5 passages and the virus remained stable as a double reassortant and identical to the original isolates.
Conclusion: Shedding of RotaTeq® G1 vaccine strains is relatively common short after vaccination and might be prolonged up to several months even in immunocompetent children. Vaccine-derived G1P[8] rotavirus has been detected in symptomatic and asymptomatic children, and the clinical significance seems to be related to the number or viral copies (ELISA positivity) in stools. Formation of vdG1P[8] may explain diarrheal symptoms in a small percentage of RotaTeq® recipients, it appears stable and might be transmitted to contacts in environment.

9. Infants rotavirus vaccine coverage in the area of Aragon in Spain

M.I. Lostal Gracia(1), F.de Juan Martín(2), M.Méndez Díaz (3), N.García Sánchez(4), F.Bielsa Rodrigo(5), A. Poncel Falcó(6), (1)Primary Care Pediatrician. Actur Oeste Heath Centre(Spain), (2)Pediatrician Advisory Committe on Vaccines of Aragón, (3)Vaccination Programme General Management of Public Health Aragón Government, (4)Primary Care Pediatrician Delicias Sur Health Centre (Spain) Advisory Committe on Vaccines of the Spanish Association of Paediatrics, (5)Primare Care Physician Funcional responsable for OMI- AP Center for Integrated Corporated Projects Management of Aragon Health Service, (6)Bachelor in Computer Sciences Center for Integrated Corporated Projects Management of Aragon Health Service

Background: Uptake of rotavirus vaccine is unknown in Spain. The aim of this study is to assess the rotavirus vaccine coverage in Aragon using the Population Data Base.
Methods: Database:Computer Medical History (OMI-AP). Population: vaccinated children in the Healthcare Service of Aragon during years 2011, 2012, 2013. Data: number of doses, date of birth and administration date.
Results: Rotavirus vaccine coverage was 18%, 26% and 27% in 2011, 2012 and 2013, respectively. Regions (2013): Zaragoza 30%, Huesca 23%, Teruel 12% (table 1). First dose administration average age is 10.5 weeks (table 2). Number of doses per child: 3, (72.6%), 2 (15.7%), 1(11.5%).

Conclusions: Infants begin rotavirus vaccine at 10.5 weeks, although the advice is starting earlier. Most children fulfill the rotavirus immunization schedule. There was a slight trend to increase the uptake between 2011 and 2012, that stopped in 2013. The vaccine coverage remains too low compared with DTPa first dose coverage (97,9%) .There are inequalities among different areas in our region.
In collaboration with SPMSD

Table 1.Rotavirus vaccine coverage in Aragon: 2011, 2012 and 2013

	2011	2012	2013	TOTAL
ZARAGOZA	22,00%	30,00%	30,00%	**27,00%**
HUESCA	10,00%	18,00%	23,00%	**16,00%**
TERUEL	4,00%	13,00%	12,00%	**9,50%**
OVERALL	**18,00%**	**26,00%**	**27,00%**	**23,50%**

Table 2. Rotavirus vaccination in Aragon (Spain). Starting average age in weeks

RIQ	N	mean	SD	CI 95%	median	
ZARAGOZA	**6.934**	**10.5**	**9.3**	**(10.3 – 10.8)**	**9.1**	**(8.7 – 10.3)**
ZARAGOZA 1	2.258	9.9	5.6	(9.7 – 10.2)	9	(8.7 – 9.8)
ZARAGOZA 2	2.548	11.3 *	12.8	(10.8 – 11.8)	9.3	(8.8 – 12.6)
ZARAGOZA 3	1.798	10.3	7.6	(10.0 – 10.7)	9	(8.7 – 10)
CALATAYUD	330	10.1	4.4	(9.6 – 10.5)	9	(8.7 – 9.8)
HUESCA	**938**	**10.4**	**4.5**	**(10.1 – 10.7)**	**9.1**	**(8.8 – 10.4)**
TERUEL	**370**	**10.3**	**2.8**	**(10.1 – 10.6)**	**9.4**	**(8.8 – 10.7)**
OVERALL	**8.242**	**10.5**	**8.7**	**(10.3 – 10.7)**	**9.1**	**(8.7 – 10.4)**

SD: Standar
IC 95%: Confidence Interval 95%
RIQ: Interquartilic range

Table 3. Infants Rotavirus vaccination in Aragon (Spain). Number of doses received

	Nº dose/child				
	1	2	3	4	Total
ZARAGOZA	**788 (11.4%)**	**1.091 (15.7%)**	**5.043 (72.7%)**	**12 (0.2%)**	**6.934 (100%)**
ZARAGOZA 1	165 (7.3%)	227 (10.1%)	1.861 (82.4%)*	5 (0.2%)	2.258 (100%)
ZARAGOZA 2	343 (13.5%)	490 (19.2%)	1.711 (67.1%)	4 (0.2%)	2.548 (100%)
ZARAGOZA 3	232 (12.9%)	321 (17.8%)	1.242 (69.1%)	3 (0.2%)	1.798 (100%)
CALATAYUD	48 (14.5%)	53 (16.1%)	229 (69.4%)	0 (0.0%)	330 (100%)
HUESCA	**114 (12.2%)**	**144 (15.3%)**	**677 (72.2%)**	**3 (0.3%)**	**938** (100%)
TERUEL	**46 (12.4%)**	**64 (17.3%)**	**260 (70.3%)**	**0 (0.0%)**	**370** (100%)
OVERALL	**948 (11.5%)**	**1.299 (15.7%)**	**5.980 (72.6%)**	**15 (0.2%)**	**8.242** (100%)

10. May be salivary Rotavirus-IgA a more reliable correlate of protection than serum IgA for rotavirus vaccines?

J. Gómez-Rial, C. Talavero-Gonzalez, Lucia Vilanova Trillo, Irene Rivero, M. Gomez-Carballa A, Cebey-Lopez, A. Salas, C. Rodríguez-Tenreiro, L. Redondo Collazo, C.Curros Novo, J.M. Martinon-Sánchez and Federico Martinon-Torres
1 Translational Pediatrics and Infectious Diseases, Pediatrics Department, Hospital Clínico Universitario de Santiago de Compostela
2 Genetics, Vaccines, Infections and Pediatrics Research Group (GENVIP), Healthcare Research Institute of Santiago, Santiago de Compostela, SpainTranslational Pediatrics and Infectious Diseases section
3 Unidade de Xenética, Departamento de Anatomía Patolóxica e Ciencias Forenses, and Instituto de Ciencias Forenses, Grupo de Medicina Xenómica (GMX), Facultad de Medicina, Universidad de Santiago de Compostela,Santiago de Compostela, Galicia, Spain

Introduction: RV-IgA levels constitute the best available correlate of protection for rotavirus vaccine efficacy trials. However serum IgA levels may not adequately reflect intestinal immunity and sometimes serum conversion rates exceed actual protection rates. In order to identify new correlates of protection that better reflect intestinal immunity, we have hypothesized that salivary IgA could be an adequate candidate.

Methods and materials: We conducted a prospective comparative study of the serum versus saliva humoral response to rotavirus in vaccinated and infected children. Total RV-IgA levels were measured in serum and saliva samples of 123 rotavirus vaccinated patients (baseline and 40±3 days after 3rd vaccine dose) and 10 infected patients (at recruitment during acute phase and at convalescence - i.e. at least 3 months after recovery) by the ELISA method described by Ward (1989) with slight modifications. To control eventual interference of maternal RV-IgA antibodies in breast milk with the saliva samples, three groups were established within vaccinated patients according to the feeding mode by the time of sampling: only Bottle-feeding; only Breast-feeding; and Mixed (breast-feeding at1stsample and bottle-feeding at 2nd sample).

Results: Total RV-IgA values are expressed as Median (± SD) OD450nm in the table below:

		SERUM				SALIVA			
	Feeding	1st sample	2nd sample *	*p*	Conversion Rate	1st sample	2nd sample **	*p*	Conversion Rate
VACCINATED	*Bottle-Bottle (n= 60)*	0,154 ± 0,17	1,303 ± 0,86	*<0,001*	> 3-fold	0,160 ± 0,21	0,314 ± 0,42	*<0,001*	2-fold
	Breast-Breast (n= 40)	0,074 ± 0,14	1,023 ± 0,89	*<0,001*	> 3-fold	0,221 ± 0,31	0,338 ± 0,59	*0,01709*	NA
	Mixed (n= 23)	0,09 ± 0,098	1,286 ± 0,78	*<0,001*	> 3-fold	0,248 ± 0,78	0,219 ± 0,38	*0,49*	NA
INFECTED	*n= 10*	0,297 ± 0,26	1,118 ± 0,86	*<0,001*	> 3-fold	0,187 ± 1,15	0,565 ± 1,84	*<0,001*	> 3-fold

*Serum 2nd sample OD values in only Breast feeding are lower than only Bottle feeding (*p<0,01*)
**Saliva 2nd sample OD values in Mixed feeding are lower than in only Bottle feeding (*p=0,019*). Comparison with only Breast feeding is not possible due to interference of maternal antibodies in the sample
Saliva 2nd sample OD values of infected patients are higher than all vaccinated patients groups, while serum 2nd sample OD values are not significantly different between infected and vaccinated patients.

Conclusions:
1. There is no correlation in IgA values between serum samples and saliva samples.
2. Breast milk interferes with rotavirus vaccine response at saliva IgA levels. Analysis of post-vaccination samples in bottle-feeding group compared to Mixed group showed an interference of maternal RV-IgA antibodies present in breast milk with the oral vaccine response.
3. For these reasons we speculate that total salivary RV-IgA levels might be a better correlate of protection than serum values and a more reliable representation of intestinal immunity.

MEETING NOTES

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Aimed at

Healthcare professionals with a particular interest in the field on rotavirus.

Venue Place

School of Medicine
Rúa de San Francisco, s/n
15782 Santiago de Compostela, Spain

Opening registration desk during the course

Monday 23rd March: from 17:00 p.m. to 08:00 p.m.
Tuesday 24th March: from 08:30 a.m. to 06:30 p.m.
Wednesday 25th March: from 08:30 a.m. to 12:30 p.m.

Registration Fees

Early registration (before 1st December 2014)
Resident/Student: 75 € Participant: 150 €
Later registration (after 1st December 2014)
Resident/Student: 100 € Participant: 200 €
March 16th, 2015. After this date, the registration must be done at the registration desk in the School of Medicine.

Further Information

www.eerovac.org

Technical Secretariat

cyex CONGRESOS

Contact person: Ms. Iria Barcia
C/Ferrol, 2 - Edificio Cyex - Urbanización La Barcia
15897 Santiago de Compostela (A Coruña) - Spain
Tel.: 981 555 720 - Email: iriabarcia@cyex.es

