


MEETING REPORT



Report of the 5th European expert meeting on rotavirus vaccination (EEROVAC)

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ABSTRACT

The Fifth European Expert Meeting on Rotavirus Vaccination was convened in Utrecht, The Netherlands, in March 2017. The 2-day meeting included invited lectures as well as original oral and poster presentations and brought together experts from 21 countries. Summary findings of the meeting include: Rotavirus vaccination programmes in Europe have resulted in reductions of 60–90% in rotavirus outpatient visits and hospitalizations. Long term trends indicate this impact is sustained over the years. Herd effects, protecting unvaccinated children and neonates too young to be vaccinated have been observed in many European countries. Early evidence now also suggests that rotavirus vaccination may be instrumental in the prevention of celiac disease. Special attention should be given to preterm infants, who may age out of the vaccination window before hospital discharge and to HIV infected children who are at increased risk of severe rotavirus AGE. There is a small but increased risk of IS following rotavirus vaccination and parents should therefore be informed about possible signs and symptoms of IS. New insights in rotavirus genetic susceptibility and interactions with microbiome may open opportunities for interventions to improve protection by vaccination, in particular in LMIC. The development of several novel rotavirus vaccines discussed at the meeting is also promising in this respect.

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Introduction

The Fifth European Expert Meeting on Rotavirus Vaccination was convened in Utrecht, The Netherlands, in March 2017. The 2-day meeting chaired by Dr. Patricia Bruijning-Verhagen (University Medical Center Utrecht, the Netherlands) brought together 110 experts from 21 countries.

The meeting marked a decennium of experience with rotavirus vaccination in Europe. National rotavirus vaccination programmes have now been implemented in twelve European countries and several more offer programmes at provincial level. The currently licensed live-attenuated oral vaccines in Europe include RV1 (RotarixTM, GlaxoSmithKline Vaccines, Wavre, Belgium), a single-strain (G1P[8]) human vaccine given as two doses and RV5 (RotaTeq[®], Merck and Co. Inc., Whitehouse Station, NJ, USA), a pentavalent (G1, G2, G3, G4, and P [8]) human-bovine (WC3) reassortant rotavirus vaccine given as three doses. During the meeting, experience with rotavirus universal mass vaccination (UMV) in Europe, remaining barriers and challenges, recent scientific insights and novel rotavirus vaccine developments were discussed. Sessions included invited lectures as well as original oral and poster presentations. The meeting opened with a keynote lecture by Dr. Federico Martinon-Torres.

The unexpected benefits of rotavirus vaccine

During his presentation, Dr. Martinon-Torres (University of Santiago de Compostela, Spain) outlined how rotavirus vaccines have been shown to be very effective in decreasing the gastrointestinal burden of the disease and related mortality in infants worldwide, as well as induce a significant herd effect, protecting unvaccinated individuals, when introduced into routine immunization programs. In addition, an unexpected positive impact on rotavirus extra intestinal manifestations has been suggested: a reduction in seizure incidence and seizure-related hospitalization in vaccinated children.^{1,2} Dr. Martinon-Torres speculated about the impact rotavirus vaccines may have on other, additional rotavirus clinical phenotypes outside the gut, including autoimmune diseases such as celiac disease or diabetes, where rotavirus might act as a trigger in otherwise susceptible children. He also suggested the potential of non-specific heterologous effects induced by live-attenuated rotavirus vaccines, similar to those found for BCG or oral polio vaccines. Such effects could generate broader clinical protection based on cross-protective immunity and immune training of the innate system. He concluded that rotavirus vaccines are teaching us that rotavirus infection is broader than just an enteral disease, but the real impact of rotavirus vaccines on

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these other rotavirus clinical phenotypes is yet to be known and deserves further assessment.³

Impact of rotavirus UMV; recent implementations

United Kingdom

Dr. Robin Marlow (University of Bristol, UK) discussed the early impact of rotavirus UMV in the United Kingdom, where RV1 was implemented in July 2013. Vaccine uptake was high immediately with first year coverage rates of 91.5% for one and 86.0% for two doses, rising to 94.6%/90.0% in 2016.⁴ During the first rotavirus season post-implementation (2014), a dramatic fall in total laboratory rotavirus detections was observed and numbers continued going down in 2015 and 2016.⁴ In < 1 year olds, the number of laboratory confirmed rotavirus infections declined by 77% (68–84%).⁵ A significant herd effect was found in all age groups on rotavirus specific and all cause AGE. Although the largest reductions were seen in 1 year olds (RR 0.64; 95CI: 54–82), the greatest numerical effect was seen for cases in the elderly ≥ 65 year of age. Due to the high coverage rate and observed herd effect, analysis for the first two years after rotavirus UMV introduction estimated that, for children under five years old, there had been a £12.2m reduction in direct healthcare costs per year and rotavirus UMV was highly cost-effective.⁶

Germany

Prof. Hans-Iko Huppertz (Hess-Kinderklinik, Bremen, Germany) summarized the implementation process of rotavirus UMV (RV1 and RV5) in Germany and presented data on rotavirus hospitalization rates. Rotavirus vaccination has been available in Germany on the private market since 2006, and was recommended for UMV by the Standing Committee on Vaccination (STIKO) in August 2013.⁷ Before UMV introduction, the rotavirus vaccine coverage had gradually increased from 19.7% in 2009 to 32.8% in 2012, with large differences across federal states. A contemporary significant decrease in number of rotavirus diarrhea cases was observed (61,574 in 2009 and 39,056 in 2012, respectively). Following the national recommendation, the vaccination coverage increased to 66.7% in 2015. In general, vaccine hesitancy has been more common in the western part of Germany, resulting in lower vaccination coverage rates (60.1%) compared to former Eastern states (76.8%).⁸ Rotavirus is a notifiable disease in Germany. Rotavirus surveillance data from the Robert Koch Institute showed a 45% decrease in rotavirus hospitalizations in children < 1 year of age in 2015 compared to pre-UMV 2013.⁹

Norway

Dr. Elmira Flem (Norwegian Institute of Public Health, Norway) presented an overview of the early results of routine RV1 immunization since October 2014. By December 2016, rotavirus vaccine coverage reached 98% for two doses¹⁰ with 92% vaccinated within the recommended upper age limits. The Norwegian Enhanced Pediatric Immunization Surveillance Network observed a 86% decrease in rotavirus confirmed and a

35% decrease in all-cause AGE hospital contacts in children <5 years in 2016 compared to 2014–2015. Proportionate reductions in AGE hospital cases were largest for vaccinated cohorts (i.e. <2 years, 81%). However, reductions were observed in all under five cohorts suggesting herd protection.

Latvia and Estonia

Dr. Dace Zavadzka (Riga Stradins University, Latvia) discussed the rotavirus national immunization programmes in both countries. In Latvia, rotavirus vaccine (RV1 and RV5) was available on the private market since 2007 and introduced in the National Immunization Programme in 2010. However, full reimbursement from the State Budget started only in January 2015 after a period of partial (50%) reimbursement between 2012 and 2015. Vaccine coverage was <5% before 2012, and increased to 87% in 2016. From 2012 onwards, there is a steady decline in rotavirus AGE with strongest reductions after 2015. Between 2015 and 2016, the incidence decreased from 150.5 to 76.3/100,000 person years (PY) in the pediatric general population.

In Estonia rotavirus vaccination (RV1 and RV5) was introduced in the National Immunization Programme in July 2014. Vaccine coverage one year post-implementation is moderate 66% (2015). Nonetheless, rotavirus incidence was decreased by 73.2/100,000 PY in 2015 and by 30.2/100,000 PY in 2016.

Israel

Dr. Khitam Muhsen (Tel-Aviv University, Israel) presented data from Israel where rotavirus had been available on the private market since 2007 and UMV was introduced in December 2010. Current vaccine coverage is 80% for three doses of RV5. Introduction of rotavirus UMV was followed by significant and sustained reductions of 80–88% in rotavirus hospitalization rates and of 30% in all cause AGE between 2011–2015 in children <5 year of age.¹¹ Rotavirus clinic visits were also reduced by 59%.^{12,13} RV5 vaccine effectiveness (VE) against rotavirus hospitalizations was estimated at 86% in children aged 6–23 months. Of note, among the subpopulation of Bedouin children, a lower vaccine coverage and lower VE estimate was found, both contributing to an overall smaller rotavirus vaccine impact compared to Jewish children.

Long-term impact of universal rotavirus vaccination

Four countries presented data on long-term trends in rotavirus epidemiology covering at least eight post-implementation years.

Belgium

Rotavirus vaccination (RV1 and RV5) has been recommended since October 2006 with partial reimbursed since November 2006.¹⁴ Dr. Sabbe (Scientific Institute of Public Health, Belgium) emphasized that despite the required co-payment by parents of €12,- per dose, vaccine uptake is high (87%). Both sentinel laboratory surveillance data and national hospital

administrative data confirm a substantial and sustained reduction in rotavirus AGE following widespread vaccine use. Most notably, in children below 2 years of age a mean and consistent reduction of 81% in rotavirus hospitalizations was observed post-vaccination and a 47% reduction in all-cause AGE. The number of laboratory rotavirus detections has decreased by 75% in this age group. Surveillance data demonstrate emergence of a biannual pattern in recent years, where rotavirus activity was increased in 2013 and 2015, but remained well below pre-vaccination levels.

Austria

In Austria, publicly funded UMV was implemented in July 2007. Owing to nationwide annual contracts there were alternating periods of RV5 or RV1 use between 2007 and 2012 and RV1 was used thereafter. Vaccine coverage is estimated at 72–87%.¹⁵ Dr. Martina Prelog (University Hospital Würzburg, Germany) presented data on rotavirus hospitalization rates during the pre- (2002 to June 2007) and post-vaccination period (July 2007 to 2012); a decrease of 89% was observed across all age-groups (0–18 years), including neonates of <42 days not yet protected by vaccination, suggesting herd protection.^{16,17} Of note, 6% of rotavirus hospitalizations occurred in vaccinated children. Incomplete rotavirus vaccination appeared a risk factor for vaccine failure (OR 5.7; 95%CI: 4.2–7.8). This highlights the importance of complete vaccination.

Finland

Data from Finland were presented by Dr. Maria Hemming-Harlo (University of Tampere, Finland). RV5 was introduced for routine vaccination in 2009. Vaccination coverage increased quickly and has remained at approximately 90%. The proportion of outpatient visits and AGE hospitalizations due to rotavirus in children decreased from 52% to 13% in 2012–2014. Dr. Hemming noted that norovirus is now the leading cause of AGE (34%) in Finish hospitals. Relative reductions in rotavirus hospitalizations and outpatient visits were 76% and 81%, respectively between 2009–2011 and were sustained at 90% between 2012–2014.¹⁸ The rotavirus age distribution has shifted towards older children with peak incidence currently at 4–7 years of age. Genotyping of rotaviruses demonstrates a higher diversity in children post-vaccination without any obvious predominant strain.

United States

Dr. Daniel Payne (US Centers Disease Control and Prevention (CDC), United States) presented data from the US where universal RV5 vaccination was implemented in 2006. RV1 became available in 2008 and both vaccines have been used since. Surveillance networks and field studies showed consistent and dramatic decreases in all measures of surveillance during the post-rotavirus vaccine era and vaccine effectiveness continues to be good (on average 80% across various rotavirus genotypes and post-vaccine years between 2008–2013). Rotavirus hospitalization rates are below the expected rate given

the measured vaccine coverage demonstrating a certain level of herd-protection. Preliminary results showed that this might have led to >27,000 extra averted hospitalizations over 9 post-licensure years. The US has seen a change in dominant rotavirus genotypes over the past years (G3P[8] in year 2009–2011 and G12P[8] in 2012–2015). This shift in genotypes is, however, not associated with changes in rotavirus hospitalization rates.

Global introductions, impact and remaining barriers

In 2016, 81 countries had introduced rotavirus UMV programmes. GAVI alliance supported rotavirus vaccine introductions in 38 developing countries between 2006 and 2015. Dr. Umesh Parashar (US Center for Disease Control and Prevention (CDC), United States) presented results on rotavirus vaccination impact in several of these countries. Most importantly, RV vaccine introduction has led to up to 50–80% reductions in RV hospitalizations in vaccinated infants,^{19,20} and a sustained mortality decline in Brazil and Mexico.²¹ However, rotavirus vaccine implementation in Eastern Europe and Asia lags behind. Several barriers are present, including the vaccine costs and the limited perception of rotavirus disease burden by family, public health authorities and physicians.²²

Policy issues

Several barriers to rotavirus UMV were discussed during this session. This included vaccination policy issues related to specific medical risk groups and barriers to the introduction of mass vaccination and possible alternatives.

From Yes to No in France

Dr. Pierre Pothier (University of Burgundy, France) discussed the current situation in France, where rotavirus vaccines are not included in the national immunization programme, nor reimbursed. In 2015, a previously issued rotavirus vaccine recommendation by the High Council for Public Health was withdrawn in response to a report from the Pharmacovigilance Committee. The high number of reported cases of intussusception (IS) following rotavirus vaccination, including two infant deaths, was considered worrying. The report had a significant impact in the media. Today's vaccine coverage is below 5%. The French observations have not been supported by data from other countries where rotavirus vaccines are being used, and a thorough evaluation of the events has been hampered by insufficient documentation. No re-evaluation of the decision on rotavirus vaccination is planned thus far.

Netherlands; selective or universal vaccination

The Netherlands has no rotavirus UMV programme (coverage < 1%). Yet, Dutch surveillance data suggest a transition from annual to biannual rotavirus epidemics since 2013, and an estimated reduction of rotavirus disease burden of approximately 50%. The reason for this transition is unclear, but may be explained, in part, by the UMV implementation in neighboring countries possibly reducing rotavirus circulation. Dr.

Bruijning-Verhagen presented an updated cost-effectiveness and risk-benefit analysis, based on recent epidemiological data. In this low-endemic setting, targeted rotavirus vaccination of medical risk groups, such as preterms, still appeared cost-effective and cost-saving, but UMV was only cost-effective at substantially reduced vaccine costs. The vaccination risk-benefit ratio was more favorable for medical risk group compared to healthy infants. Targeted vaccination could reduce fatal rotavirus cases by nearly 90%. Dr. Carlo Giaquinto (University of Padua, Italy) suggested that the high-risk approach might be an acceptable alternative for the French.

Vaccine administration in NICU settings

Dr. Caroline Quach (University of Montreal, Canada) discussed the difficulties around vaccinating preterm infants within the recommended age limits for rotavirus vaccination. In the United States and Canada, 23%–44% of the preterm infants exceed the upper age limit (104 days) for vaccination during their Neonatal Intensive Care Unit (NICU) admission.²³ Vaccination within the NICU is debatable due to a theoretical risk of transmission by live vaccine virus shed in stool. Dr. Quach presented data from US and Canadian studies, where preterm infants received rotavirus vaccine while on the NICU. No evidence for symptomatic transmission to ward mates was found under normal infection control measures (gowns and gloves). Rotavirus vaccine was generally well tolerated, but one study found an association between rotavirus vaccine administration and risk of central-line associated bloodstream infections.²⁴ Dr. Quach concluded that in the absence of UMV associated herd protection, vaccination in NICU settings could be a favorable strategy, while in a UMV setting with high coverage and thus herd protection, the added value of vaccinating in the NICU requires further confirmation.

Vaccination of special populations

This presentation on rotavirus vaccination of HIV infected, or otherwise immunocompromised children was given by Dr. Carlo Gianquinto (University of Padova, Italy). Studies in low- and middle-income countries (LMIC) have shown that rotavirus AGE is more common and more severe in HIV-infected than in uninfected children. Universal administration of either RV1 or RV5 vaccines has been effectively implemented in several HIV-high prevalent African countries. In South-Africa, this was associated with a 65% reduction in all-cause diarrheal hospitalizations in the 2010–2015 period in both HIV-infected and uninfected children.²⁵ Following earlier, smaller studies of rotavirus vaccination among HIV infected children, results from a large randomized controlled trial conducted in HIV exposed and HIV infected children in South-Africa recently demonstrated safety and immunogenicity of RV5 in both populations.²⁶ Dr. Gianquinto emphasized this is an important and reassuring confirmation that vaccination of HIV infected and exposed populations should be promoted.

Severe Combined Immunodeficiency (SCID) remains the only strict contraindication for rotavirus vaccination because of potential vaccine strain associated severe diarrhea.^{27,28} No safety data are available for other B and/or T cell immunodeficiency syndromes, but rotavirus vaccination is contraindicated

if already diagnosed at the time of immunization. Children with selective IgA deficiency may, asymptotically, have prolonged excretion of rotavirus vaccine strain, but this is not considered a contraindication.

Update on licensed rotavirus vaccines

Dr. Bernd Benninghoff (GSK Vaccines, Belgium) and Dr. Timo Vesikari (University of Tampere, Finland) summarized efficacy, effectiveness and impact data from high income settings for RV1 and RV5, respectively. In large Phase III trials, both vaccines demonstrated excellent efficacy against severe rotavirus AGE up to 95%. Post-licensure vaccine effectiveness estimates against rotavirus hospitalization range from 70% to more than 90%. Dr. Benninghoff discussed the impact of universal infant vaccination with RV1 using the Belgian experience for illustration. A sustained and continued decline in rotavirus hospitalizations and nosocomial infections in young children up to nine years post-implementation has now been confirmed. While the large Phase III safety trials did not find and increased risk of IS for either vaccine, following widespread use a small but increased risk of IS became evident mainly after the first dose. Dr. Benninghoff emphasized that parents should be systematically informed of the risk of IS and advised to seek medical care immediately should symptoms of IS occur.²⁹

Dr. Vesikari discussed results on long-term RV5 vaccine efficacy from The Finish Extension Study (FES) study, originating from the Rotavirus Efficacy Safety Trial (REST) conducted between 2001 and 2003.³⁰ Serotype-specific efficacy against rotavirus hospitalizations and emergency department visits up to 3-years post-vaccination was 82% (G2) to 95% (G1).³¹ Studies on the long-term impact of RV5 found that new genotypes appear following widespread rotavirus vaccination. Dr. Vesikari emphasized that RV5 retains its effectiveness against severe rotavirus AGE even with the “new” rotavirus genotypes, and therefore the strain replacement does not affect vaccine impact.

Vaccine Safety: Intussusception

During this session, rotavirus vaccine related IS was discussed by Dr. Doris Oberle (Paul-Erlich-Institute (PEI), Germany), Dr Umesh Parashar and Dr. Julie Bines (University of Melbourne, Australia). Population-based studies from Australia showed a relative risk for both vaccines in the first 7 days following dose one of 6.8 (95%CI 2.4 to 19.0] for RV1 and 9.9 (95%CI 3.7-26.4) for RV5. A smaller risk was identified 1–7 days following the second dose of both vaccines.³² Data from the US showed a relative lower risk of IS during day one and two post-vaccination, compared to day three to six after the first dose for both RV1 (daily reporting risks (DRRs): 7.5; 95%CI: 2.3 to 24.6) and RV5 (DRRs: 3.75; 95%CI: 1.90 to 7.39).³³ Overall, the risk of IS post dose one, estimated from the presented studies conducted in Australia, US and Europe varied between 1.04 and 5 additional cases per 100.000 first doses.^{32,34-37} In Germany, IS cases notified to pharmacovigilance because of a possible link with vaccination required partial bowel resection in 15.2% of cases. An ongoing matched case-control study by the German Federal Institute for Vaccines and Biomedicines evaluates IS risk factors in children below one year of age. Preliminary results are

expected end of 2017. IS and its association with rotavirus vaccination continues to be monitored.

Despite the small excess risk of IS in infants following vaccination, the benefit risk ratio strongly favors vaccination in both developed and developing countries.^{38,39} For example, in the US the number of averted rotavirus outpatient clinic visits and hospitalizations is 273,000 and 53,444, respectively. Per vaccine induced IS case, 28–134 rotavirus related deaths are averted and 3603–17,118 emergency visits.³⁶

Rotavirus; New insights

Dr. Ulrich Desselberger (University of Cambridge, UK), Dr. Lennart Svensson (University of Linköping and Karolinska Institute, Sweden), Dr. Vanessa Harris (Amsterdam Institute for Global Health and Development, The Netherlands) and Dr. Timo Vesikari presented new rotavirus insights from four different perspectives: rotavirus immune response (IR), interactions between rotavirus (vaccine) and the intestinal microbiome, genetic susceptibility to rotavirus strains and rotavirus' role in the development of chronic diseases.

Dr. Desselberger set out in detail the innate and acquired immune response to natural rotavirus infection and to RV5 and RV1. In particular, the search for adequate correlates of vaccine protection continues. The degree of neutralizing (NT) antibody synthesis (40–50%) elicited by rotavirus vaccination is below the protective levels against severe rotavirus disease (80–90%). This suggests that the correlates of protection are complex, consisting of type-specific and cross-NT VP7- and VP4-specific antibodies and non-NT, VP6-specific antibodies, acting by 'intracellular NT' after transcytosis.⁴⁰

Growing body of evidence indicates that composition of the intestinal microbiome is correlated with rotavirus vaccine response.^{41,42} Dr. Harris explained how these differences in intestinal microbes may contribute to the decreased efficacy of rotavirus vaccine found in resource-poor settings based on results of a matched case-control study conducted in Ghana. The intestinal microbiome composition and diversity between Ghanaian rotavirus vaccine seroconverters and nonseroconverters was significantly different. The responders' microbiota were more similar to those of Dutch infants, used as an external comparator.⁴³ These data can serve as a springboard for testing numerous mechanistic explanations of the relationship between the intestinal microbiome and rotavirus vaccine immunogenicity.

It is increasingly recognized that rotavirus vaccine effectiveness is dependent on the genetic susceptibility to rotavirus infection. Dr. Svensson explained how genetically determined expression of H type 1 (secretor status) and Lewis antigens in the gut mucosa is essential for rotavirus susceptibility in a genotype-dependent manner. Rotavirus P[8] infections are only detected among Lewis and secretor-positive children, while P[6] strains predominantly infect Lewis-negative children irrespective of their secretor status.^{44,45} The modest efficacy of P[8]-based vaccines in Africa could be due to host innate genetic resistance to infections with P[8] strains.⁴⁶ Preliminary RV1 and RV5 vaccine data from Nicaragua show that no children with the Lewis a phenotype seroconverted (IgA 4-fold increase) ($n = 14$; GMT pre 88; post 97) after the first dose as compared to 26% in children with Lewis b ($n = 175$; GMT pre 83; post

138) or 32% in children with the Lewis-negative ($n = 47$; GMT pre 75; post 124). He stated that a P[6] component in the existing vaccine formulations should be considered.

Rotavirus infection has been proposed to trigger type 1 diabetes (DM1) and celiac disease by molecular mimicry in genetically susceptible children.^{47–50} Dr. Vesikari presented results from the FES study, following former participants of the RV5 phase III trial. In 2015, a questionnaire was sent asking whether the child developed DM1 or celiac disease. Results showed that the prevalence of celiac disease was significantly lower in the RV5 vaccinated children compared to placebo recipients (0.60% versus 1.11%; $p = 0.027$). No association was found between DM1 and RV5 in over 10-year follow-up (1.04% vs 0.97%; $p = 0.810$). This is important first evidence of rotavirus vaccination beneficial effects in the prevention of chronic diseases.

New rotavirus vaccines

The need for new rotavirus vaccines is especially strong in LMIC where performance of the currently licensed rotavirus vaccines lacks behind compared to high income countries.⁵¹ Several new vaccine developments were presented during this meeting.

The RV3-BB vaccine is based on the asymptomatic human neonatal rotavirus strain RV3 (G3P[6]). Dr. Julie Bines (University of Melbourne, Australia) described the unique characteristics of this strain and how this provides an ideal opportunity to target a birth dose rotavirus vaccine strategy. The P[6] genotype may offer additional benefits in regions, such as Africa, where the Lewis-negative phenotype is more common. A Phase IIa trial in New Zealand showed a robust immune response with a 3-dose neonatal or infant RV3-BB schedule. A Phase IIb trial of the efficacy, safety and immunogenicity of oral RV3-BB rotavirus vaccine, administered as a neonatal schedule with a birth dose (age 0–5 days), 8–10 and 14–16 week doses or an infant schedule of 8–10, 14–16 and 18–20 week doses, was recently conducted in primary care centers and hospitals in Yogyakarta and Central Java provinces, Indonesia.

Dr. Michelle Groome (University of the Witwatersrand, South Africa) presented results from a recently completed randomized, double-blind, placebo-controlled trial on the safety and immunogenicity of a parenteral P2-VP8-P[8] subunit rotavirus vaccine conducted in South Africa. Results showed that the vaccine was well tolerated in both healthy toddlers ≥ 2 and < 3 years (single injection) and in term infants ≥ 6 and < 8 weeks (three injections four weeks apart) without identifiable safety concerns. The vaccine was immunogenic in infants and significant fewer infants vaccinated with P2-VP8-P[8] shed rotavirus compared to the placebo recipients. Currently a multi-center study in South Africa is conducted to evaluate safety and immunogenicity of a trivalent P2-VP8-P[4/6/8] vaccine in adults, toddlers and infants.

Dr. Baoming Jiang (US Centers for Disease Control and Prevention, United States) presented the progress towards the development of the inactivated rotavirus vaccine (IRV) with a CDC-9 strain (G1P[8]). In animal models, monovalent IRV can induce strong IgA and IgG, and cross neutralizing antibody

responses in serum, as well as mucosal immunity and induced solid protection against infection and diarrhea.⁵²⁻⁵⁴ Currently, first-in-human phase I clinical trials are planned.

Dr. Vesna Blazevic (University of Tampere, Finland) presented results from the recently developed non-live subunit norovirus and rotavirus combination vaccine consisting of GL3 and GII.4 norovirus-like particles (VLPs) and polymeric rotavirus VP6. Mice studies have shown high immunogenicity and protection from heterologous rotavirus infection. In addition, rotavirus VP6 oligomeric structural assemblies (VP6T and VP6S) act as adjuvants and delivery vehicles for norovirus VLPs in vivo. This dual role of VP6 as adjuvant and subunit rotavirus vaccine makes the VP6 a promising vaccine candidate for prevention of childhood AGE.

Summary

In conclusion, rotavirus vaccination programmes in Europe have resulted in reductions of 60–90% in rotavirus outpatient visits and hospitalizations. Long term trends indicate this impact is sustained over the years. Herd effects, protecting unvaccinated children and neonates too young to be vaccinated have been observed in many European countries. Early evidence now also suggests that rotavirus vaccination may be instrumental in the prevention of celiac disease. Special attention should be given to preterm infants, who may age out of the vaccination window before hospital discharge and to HIV infected children who are at increased risk of severe rotavirus AGE. There is a small but increased risk of IS following rotavirus vaccination and parents should therefore be informed about possible signs and symptoms of IS. New insights in rotavirus genetic susceptibility and interactions with microbiome may open opportunities for interventions to improve protection by vaccination, in particular in LMIC. The development of several novel rotavirus vaccines discussed at the meeting is also promising in this respect.

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No potential conflicts of interest were disclosed.

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References

- Pardo-Seco J, Cebej-López M, Martín-Torres N, Salas A, Gómez-Rial J, Rodríguez-Tenreiro C, Martín-Sánchez JM, Martín-Torres F. Impact of Rotavirus Vaccination on Childhood Hospitalization for Seizures. *Pediatr Infect Dis J*. 2015;34(7):769-73. doi:10.1097/INF.0000000000000723.
- Payne DC, Baggs J, Zerr DM, Klein NP, Yih K, Glanz J, Curns AT, Weintraub E, Parashar UD. Protective association between rotavirus vaccination and childhood seizures in the year following vaccination in US children. *Clin Infect Dis*. 2014;58(2):173-7. doi:10.1093/cid/cit671.
- Rivero-Calle I, Gomez-Rial J, Martinon-Torres F. Systemic features of rotavirus infection. *J Infect*. 2016;72 Suppl:S98-S105. doi:10.1016/j.jinf.2016.04.029.
- England PH. Health Protection Report: infection reports. 2016;10(32).
- Atchison CJ, Stowe J, Andrews N, Collins S, Allen DJ, Nawaz S, Brown D, Ramsay ME, Ladhani SN. Rapid declines in age group-specific rotavirus infection and acute gastroenteritis among vaccinated and unvaccinated individuals within 1 year of rotavirus vaccine introduction in England and Wales. *J Infect Dis*. 2016;213(2):243-9. doi:10.1093/infdis/jiv398.
- Thomas SL, Walker JL, Fenty J, Atkins KE, Elliot AJ, Hughes HE, Stowe J, Ladhani S, Andrews NJ. Impact of the national rotavirus vaccination programme on acute gastroenteritis in England and associated costs averted. *Vaccine*. 2017;35(4):680-86. doi:10.1016/j.vaccine.2016.11.057.
- Koch J, Wiese-Posselt M, Remschmidt C, Wichmann O, Bertelsmann H, Garbe E, Hengel H, Meerpohl JJ, Mas Marques A, Oppermann H. et al. Background paper to the recommendation for routine rotavirus vaccination of infants in Germany. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2013;56(7):957-84. doi:10.1007/s00103-013-1777-3.
- Impfquoten der Rotavirus-, Masern-, HPV- und Influenza-Impfung in Deutschland, in *Epidemiol Bulletin*, 5 January 2017;1:1-12.
- SurvStat@RKI.
- Valcarcel Salamanca B, Hagerup-Jenssen ME, Flem E. Uptake and timeliness of rotavirus vaccination in Norway: the first year post-introduction. *Vaccine*. 2016;34(39):4684-9. doi:10.1016/j.vaccine.2016.08.017.
- Givon-Lavi N, Ben-Shimol S, Cohen R, Greenberg D, Dagan R. Rapid impact of rotavirus vaccine introduction to the National Immunization plan in southern Israel: comparison between 2 distinct populations. *Vaccine*. 2015;33(16):1934-40. doi:10.1016/j.vaccine.2015.02.062.
- Muhsen K, Kassem E, Rubenstein U, Goren S, Ephros M, Cohen D, Shulman LM. Incidence of rotavirus gastroenteritis hospitalizations and genotypes, before and five years after introducing universal immunization in Israel. *Vaccine*. 2016;34(48):5916-22. doi:10.1016/j.vaccine.2016.10.021.
- Muhsen K, Rubenstein U, Kassem E, Goren S, Schachter Y, Kremer A, Shulman LM, Ephros M, Cohen D. A significant and consistent reduction in rotavirus gastroenteritis hospitalization of children under 5 years of age, following the introduction of universal rotavirus immunization in Israel. *Hum Vaccin Immunother*. 2015;11(10):2475-82. doi:10.1080/21645515.2015.1056951.
- Braeckman T, Theeten H, Lernout T, Hens N, Roelants M, Hoppenbrouwers K, Van Damme P. Rotavirus vaccination coverage and adherence to recommended age among infants in Flanders (Belgium) in 2012. *Euro Surveill*. 2014;19(20). doi:10.2807/1560-7917.ES2014.19.20.20806.
- Paulke-Korinek M, Rendi-Wagner P, Kundi M, Kronik R, Kollaritsch H. Universal mass vaccination against rotavirus gastroenteritis: impact on hospitalization rates in austrian children. *Pediatr Infect Dis J*. 2010;29(4):319-23.
- Prelog M, Gorth P, Zwazl I, Kleines M, Streng A, Zlomy M, Heinz-Erian P, Wiedermann U. Universal mass vaccination against rotavirus: indirect effects on rotavirus infections in neonates and unvaccinated young infants not eligible for vaccination. *J Infect Dis*. 2016;214(4):546-55. doi:10.1093/infdis/jiw186.
- Zlomy M, Kofler S, Orth D, Würzner R, Heinz-Erian P, Streng A, Prelog M. The impact of Rotavirus mass vaccination on hospitalization rates, nosocomial Rotavirus gastroenteritis and secondary blood stream infections. *BMC Infect Dis*. 2013;13:112. doi:10.1186/1471-2334-13-112.
- Hemming-Harlow M, Markkula J, Huhti L, Salminen M, Vesikari T. Decrease of rotavirus gastroenteritis to a low level without resurgence

- for five years after universal rotateq vaccination in Finland. *Pediatr Infect Dis J*. 2016;35(12):1304-08. doi:10.1097/INF.0000000000001305.
19. de Palma O, Cruz L, Ramos H, de Baires A, Villatoro N, Pastor D, de Oliveira LH, Kerin T, Bowen M, Gentsch J, et al. Effectiveness of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study. *BMJ*. 2010;340:c2825. doi:10.1136/bmj.c2825.
 20. Yen C, Armero Guardado JA, Alberto P, Rodriguez Araujo DS, Mena C, Cuellar E, Nolasco JB, De Oliveira LH, Pastor D, Tate JE, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. *Pediatr Infect Dis J*. 2011;30(Suppl 1):S6-S10. doi:10.1097/INF.0b013e3181fe05.
 21. Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, Esparza-Aguilar M, Johnson B, Gomez-Altamirano CM, Parashar U, Patel M. Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. *N Engl J Med*. 2010;362(4):299-305. doi:10.1056/NEJMoa0905211.
 22. Lo Vecchio A, Liguoro I, Dias JA, Berkley JA, Boey C, Cohen MB, Cruchet S, Salazar-Lindo E, Podder S, Sandhu B, et al. Rotavirus immunization: Global coverage and local barriers for implementation. *Vaccine*. 2017;35(12):1637-44. doi:10.1016/j.vaccine.2017.01.082.
 23. Stumpf KA, Thompson T, Sanchez PJ. Rotavirus vaccination of very low birth weight infants at discharge from the NICU. *Pediatrics*. 2013;132(3):e662-5. doi:10.1542/peds.2013-0291.
 24. Dahan M, O'Donnell S, Hebert J, Gonzales M, Lee B, Chandran AU, Woolsey S, Escoredo S, Chinnery H, Quach C. CLABSI risk factors in the NICU: potential for prevention: a PICNIC study. *Infect Control Hosp Epidemiol*. 2016;37(12):1446-52. doi:10.1017/ice.2016.203.
 25. Groome MJ, Zell ER, Solomon F, Nzenze S, Parashar UD, Izu A, Madhi SA. Temporal association of rotavirus vaccine introduction and reduction in all-cause childhood diarrheal hospitalizations in South Africa. *Clin Infect Dis*. 2016;62 Suppl 2:S188-95. doi:10.1093/cid/civ1204.
 26. Levin MJ, et al. Safety and immunogenicity of a live attenuated pentavalent rotavirus vaccine in HIV-exposed infants with or without HIV infection in Africa. *AIDS*. 2017;31(1):49-59. doi:10.1097/QAD.0000000000001258.
 27. Morillo-Gutierrez B, Worth A, Valappil M, Gaspar HB, Gennery AR. Chronic infection with rotavirus vaccine strains in UK children with severe combined immunodeficiency. *Pediatr Infect Dis J*. 2015;34(9):1040-1. doi:10.1097/INF.0000000000000788.
 28. Patel NC, Hertel PM, Estes MK, de la Morena M, Petru AM, Noroski LM, Revell PA, Hanson IC, Paul ME, Rosenblatt HM, et al. Vaccine-acquired rotavirus in infants with severe combined immunodeficiency. *N Engl J Med*. 2010;362(4):314-9. doi:10.1056/NEJMoa0904485.
 29. Bines JE, Kohl KS, Forster J, Zanardi LR, Davis RL, Hansen J, Murphy TM, Music S, Niu M, Varricchio F, et al. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. *Vaccine*. 2004;22(5-6):569-74. doi:10.1016/j.vaccine.2003.09.016.
 30. Vesikari T, Itzler R, Matson DO, Santosham M, Christie CD, Coia M, Cook JR, Koch G, Heaton P. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354(1):23-33. doi:10.1056/NEJMoa052664.
 31. Vesikari T, Karvonen A, Ferrante SA, Ciarlet M. Efficacy of the pentavalent rotavirus vaccine, RotaTeq(R), in Finnish infants up to 3 years of age: the Finnish Extension Study. *Eur J Pediatr*. 2010;169(11):1379-86. doi:10.1007/s00431-010-1242-3.
 32. Carlin JB, Macartney KK, Lee KJ, Quinn HE, Buttery J, Lopert R, Bines J, McIntyre PB. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program. *Clin Infect Dis*. 2013;57(10):1427-34. doi:10.1093/cid/cit520.
 33. Haber P, Patel M, Pan Y, Baggs J, Haber M, Museru O, Yue X, Lewis P, Destefano F, Parashar UD. Intussusception after rotavirus vaccines reported to US VAERS, 2006-2012. *Pediatrics*. 2013;131(6):1042-9. doi:10.1542/peds.2012-2554.
 34. Pérez-Vilar S, Diez-Domingo J, Puig-Barberà J, Gil-Prieto R, Romio S. Intussusception following rotavirus vaccination in the Valencia Region, Spain. *Hum Vaccin Immunother*. 2015;11(7):1848-52. doi:10.1080/21645515.2015.1049787.
 35. Tate JE, Yen C, Steiner CA, Cortese MM, Parashar UD. Intussusception Rates Before and After the Introduction of Rotavirus Vaccine. *Pediatrics*. 2016;138(3). doi:10.1542/peds.2016-1082.
 36. Yih WK, Lieu TA, Kulldorff M, Martin D, McMahill-Walraven CN, Platt R, Selvam N, Selvan M, Lee GM, Nguyen M. Intussusception risk after rotavirus vaccination in U.S. Infants. *N Engl J Med*. 2014;370(6):503-12. doi:10.1056/NEJMoa1303164.
 37. Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. *Vaccine*. 2016;34(32):3684-9. doi:10.1016/j.vaccine.2016.04.050.
 38. Dey A, Wang H, Menzies R, Macartney K. Changes in hospitalisations for acute gastroenteritis in Australia after the national rotavirus vaccination program. *Med J Aust*. 2012;197(8):453-7. doi:10.5694/mja12.10062.
 39. Jayasinghe S, Macartney K. Estimating rotavirus gastroenteritis hospitalisations by using hospital episode statistics before and after the introduction of rotavirus vaccine in Australia. *Vaccine*. 2013;31(6):967-72. doi:10.1016/j.vaccine.2012.11.099.
 40. Desselberger U, Huppertz HI. Immune responses to rotavirus infection and vaccination and associated correlates of protection. *J Infect Dis*. 2011;203(2):188-95. doi:10.1093/infdis/jiq031.
 41. Oh JZ, Ravindran R, Chassaing B, Carvalho FA, Maddur MS, Bower M, Hakimpour P, Gill KP, Nakaya HI, Yarovinsky F, et al. TLR5-mediated sensing of gut microbiota is necessary for antibody responses to seasonal influenza vaccination. *Immunity*. 2014;41(3):478-92. doi:10.1016/j.immuni.2014.08.009.
 42. Zhang B, Chassaing B, Shi Z, Uchiyama R, Zhang Z, Denning TL, Crawford SE, Pruijssers AJ, Iskarpatyoti JA, Estes MK, et al. Viral infection. Prevention and cure of rotavirus infection via TLR5/NLRC4-mediated production of IL-22 and IL-18. *Science*. 2014;346(6211):861-5. doi:10.1126/science.1256999.
 43. Harris VC, Armah G, Fuentes S, Korpela KE, Parashar U, Victor JC, Tate J, de Weerth C, Giaquinto C, Wiersinga WJ, et al. Significant correlation between the infant gut microbiome and rotavirus vaccine response in Rural Ghana. *J Infect Dis*. 2017;215(1):34-41. doi:10.1093/infdis/jiw518.
 44. Kambhampati A, Payne DC, Costantini V, Lopman BA. Host genetic susceptibility to enteric viruses: a systematic review and metaanalysis. *Clin Infect Dis*. 2016;62(1):11-18. doi:10.1093/cid/civ873.
 45. Nordgren J, Sharma S, Bucardo F, Nasir W, Günaydın G, Ouermi D, Nitiema LW, Becker-Dreps S, Simporé J, Hammarström L, et al. Both Lewis and secretor status mediate susceptibility to rotavirus infections in a rotavirus genotype-dependent manner. *Clin Infect Dis*. 2014;59(11):1567-73. doi:10.1093/cid/ciu633.
 46. Günaydın G, Nordgren J, Sharma S, Hammarström L. Association of elevated rotavirus-specific antibody titers with HBGA secretor status in Swedish individuals: the FUT2 gene as a putative susceptibility determinant for infection. *Virus Res*. 2016;211:64-8. doi:10.1016/j.virusres.2015.10.005.
 47. Dolcino M, Zanoni G, Bason C, Tinazzi E, Boccola E, Valletta E, Contreas G, Lunardi C, Puccetti A. A subset of anti-rotavirus antibodies directed against the viral protein VP7 predicts the onset of celiac disease and induces typical features of the disease in the intestinal epithelial cell line T84. *Immunol Res*. 2013;56(2-3):465-76. doi:10.1007/s12026-013-8420-0.
 48. Honeyman MC, Stone NL, Harrison LC. T-cell epitopes in type 1 diabetes autoantigen tyrosine phosphatase IA-2: potential for mimicry with rotavirus and other environmental agents. *Mol Med*. 1998;4(4):231-9.
 49. Troncone R, Auricchio S. Rotavirus and celiac disease: clues to the pathogenesis and perspectives on prevention. *J Pediatr Gastroenterol Nutr*. 2007;44(5):527-8. doi:10.1097/MPG.0b013e31804ca0ec.
 50. Zanoni G, Navone R, Lunardi C, Tridente G, Bason C, Sivori S, Beri R, Dolcino M, Valletta E, Corrocher R, et al. In celiac disease, a subset of autoantibodies against transglutaminase binds toll-like receptor 4 and induces activation of monocytes. *PLoS Med*. 2006;3(9):e358. doi:10.1371/journal.pmed.0030358.

51. Jiang V, Jiang B, Tate J, Parashar UD, Patel MM. Performance of rotavirus vaccines in developed and developing countries. *Hum Vaccin*. 2010;6(7):532-42. doi:10.4161/hv.6.7.11278.
52. Jiang B, Wang Y, Glass RI. Does a monovalent inactivated human rotavirus vaccine induce heterotypic immunity? Evidence from animal studies. *Hum Vaccin Immunother*. 2013;9(8):1634-7. doi:10.4161/hv.24958.
53. Wang Y, Azevedo M, Saif LJ, Gentsch JR, Glass RI, Jiang B. Inactivated rotavirus vaccine induces protective immunity in gnotobiotic piglets. *Vaccine*. 2010;28(33):5432-6. doi:10.1016/j.vaccine.2010.06.006.
54. Wang Y, Vlasova A, Velasquez DE, Saif LJ, Kandasamy S, Kochba E, Levin Y, Jiang B. Skin vaccination against rotavirus using microneedles: proof of concept in gnotobiotic piglets. *PLoS One*. 2016;11(11):e0166038. doi:10.1371/journal.pone.0166038.