EXCELLENCE IN PEDIATRICS INSTITUTE

Improving Child Health Globally

MEETING REPORT

ROTAVIRUS VACCINATIONS. WHAT SHOULD CHANGE?

Policy Focus Group Meeting on Rotavirus Vaccination

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Initiative History, Purpose and Work Within the EU Coalition on Vaccination

Since 2015 the Excellence in Pediatrics Institute (EIP) has worked with European and global partners to help overcome the many remaining barriers to vaccination uptake. By connecting and working with colleagues across Adolescent Medicine, General Practice, Pharmacy and Nursing, and uniting behind the **EU Commission's Coalition on Vaccination**, EIP's goals is to promote a LifeCourse approach to vaccines.

Most notably, EIP believes that the following barriers remain: 1) **Policy discrepancies** - Heterogeneous national vaccination policies. Differences in approach, prioritisation and decision making processes. 2) **Overarching barriers** - Lack of policies to increase vaccines confidence, counteract misinformation, increase awareness and mobilise medical communities, and 3) **Failure to adopt a LifeCourse approach** - Prevention Policies not adapted to demographic changes and an increasingly ageing population. Disease prevention in all stages of life is not yet a priority.

As part of EIP's work within the **EU Coalition on Vaccination**, 8 Stakeholder Working Groups, as well as a joint EU Commission and WHO plenary briefing, took place at 11th EIP Annual Conference in Copenhagen in December 2019. During the Working Groups, speakers were asked to share their opinions on ways to increase vaccination uptake in both general public and healthcare

professionals, on the current state and progress made in increasing vaccination coverage rates in different countries and to mention the obstacles faced in the process of doing so.

One of the Expert Working Groups was tasked to look at **Rotavirus Vaccinations**. The Working Groups discussions are set within the context of the increasing importance of Rotavirus vaccination as severe gastroenteritis can cause significant direct costs, indirect costs and societal impacts associated with infection. However, despite the clear evidence of implementing rotavirus vaccinations, not all countries have implemented a common strategy to address this issue.

The Working Group gathered pediatricians and infectious disease experts from many countries across Europe to share their knowledge and expertise from their own countries trying to outline a common point of view and implement a universal vaccination strategy, with a focus on overcoming the obstacle of perceived cost-effectiveness of implementation in countries across Europe.

The following report summarises the invited expert's briefings, discussions, and proposed action plans that were debated during the proceedings of the **Policy Focus Group focused Rotavirus Vaccinations and What should change to increase uptake across Europe.**

EVALUATING THE LATER EVIDENCE

Working Group Briefing

Prof Timo Vesikari, Professor Emeritus of Virology and Paediatrics and Director of Vaccine Research Center in Finland, started the Working Group by pointing out that although Finland was one of the first countries that implemented vaccination against rotavirus, they didn't find any serotype-specific or associated protection. With this in mind, Prof Vesikari suggested that all our rotavirus vaccines follow the same pattern, function and mechanism, which is genotype independent protection. Consequently, Prof Vesikari can't find any important differences between the two vaccines that are available[1] [2].

Prof Vesikari then continued with a historic reference to Germany and the UK working together to promote rotavirus vaccination across Europe which actually worked, as an application of the domino theory. However, he acknowledged that each country is a separate case and no country can be easily influenced because it carries its own ideas and beliefs.
During Prof Vesikari's briefing, he made it very clear that we cannot eliminate rotavirus from the circulation and that we can only protect against severe rotavirus disease[3]. That is because there will always be a reservoir of the virus in the elderly and some outbreaks at schools due to susceptible children. Prof Vesikari then examined rotavirus vaccination policy in Finland commenting on low hospitalization rates, very high coverage rates, high effectiveness and a good vaccine 4-9 years after the implementation of the program[4].

Prof Vesikari then went on to mention a significant reduction, by one third, in celiac disease with the rotavirus vaccination, which counts as an additional argument in favor of the vaccination[5]. He concluded that all children should enjoy the benefits of this vaccine and that maybe in the future a parenteral vaccine could be manufactured to bypass the gut but, until then, we will have to continue with the oral vaccine for many years to come.

During the Working Group discussion that followed the briefing Prof Vesikari underlined the importance of the domino theory as a universal human reaction to a certain extent and he did not link that to the rotavirus specifically. He also stated that he is against health economics and, **despite the fact that the hospitalization care costs too much, the main reason he is pro-rotavirus vaccination is medical with regard to not letting children fall ill.**

[1] Vesikari T. et al., Efficacy of Rotarix in Europe against RV gastroenteritis by genotype, Lancet 2007;370:1757–63

[2] Vesikari T. et al., Lack of G-type-specific efficacy of RotaTeq, Eur J Pediatr 2010;169(11):1379-86

[3] Standaert et al., Medium to long-term Impact of rotavirus vaccination on hospital care in Belgium: a 7-year follow-up of the rotavirus Belgium impact study (RotaBIS), Infect Dis Ther 2016;5:31–44.

[4] Markkula J et al., RV genotype diversity in Finland after Rotateq vaccinations, Infect Dis (Lond) 2017 Jan 9:1-8. doi: 10.1080/23744235.2016.1275773.

[5] Hemming-Harlo M., M-L Lähdeaho, M. Mäki & T. Vesikari 2019. Rotavirus Vaccination Does Not Increase Type 1 Diabetes And May Decrease Celiac Disease In Children and Adolescents. The Pediatric Infectious Disease Journal 38:5.

EXAMINING THE COST EFFECTIVENESS OF UNIVERSAL ROTAVIRUS VACCINATIONS

Working Group Briefing

Following on from Prof Vesikari's comprehensive evaluation of the latest evidence, the Working Group invited Prof Vytautas Usonis, Professor of Paediatrics at Clinic of Paediatrics, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University in Lithuania to examine the cost effectiveness of implementing a universal rotavirus vaccination policy.

During the opening section of his briefing, Prof Usonis fully agreed with Prof Vesikari on the wellness of children being the most important issue rather than a cost-effectiveness analyses. Prof Usonis then outlined the significant burden of rotavirus gastroenteritis in terms of cost and in the society. Reviews and studies from all over the world come to the conclusion that the costs are extremely high when it comes to rotavirus disease for the community, both in industrialized and in developing countries[6]. Apart from the direct costs, we must also consider the indirect cost of such diseases such as outpatient office visits, home care and lost work hours[7].

Prof Usonis suggested that just trying to measure the cost-effectiveness of rotavirus vaccination in different countries is, more often than not, an impossible task because of the huge disparities of vaccination prices, prices of healthcare provided, official data disposed and so on. **That brings us again to the conclusion that each country is a different and separate case. When the same working methodology applied in one setting is then applied to a different setting, it is highly likely that we get misleading results back[8].**

Prof Usonis concluded his briefing by proposing that estimating cost-effectiveness should be made considering at least two different groups: industrialized and developing countries. In the discussion that ended this section of the Working Group, it was stated that today's health economics should not only focus on today but on the future as well and that we have to probably think of vaccination as an investment for the years to come[9].

Vaccination would prevent 2.4 million rotavirus deaths and 182 million disability-adjusted life-years (DALYs) in 64 of the 72 GAVI-eligible countries introducing vaccines from 2007 through 2025[10]. By applying the baseline scenario with an initial vaccine price of $7 per dose for a 2-dose vaccine, with a gradual decrease beginning in 2012 and stabilizing at $1.25 per dose by 2017, vaccination was very cost-effective in all GAVI-eligible countries.

PERCEIVED LOW PUBLIC HEALTH PRIORITY

Working Group Briefing

Prof Roman Prymula, Professor of Preventive Medicine at School of Medicine, Charles University in Prague, Czech Republic was then invited to brief the Working Group on the perceived low public health priority of protecting against rotavirus when compared to other diseases. Prof Prymula started his briefing by pointing out that the rotavirus vaccine is a very significant tool in our arsenal in order to decrease the burden of rotavirus disease in society. However, despite the huge potential to protect, the current outlook is not currently so optimistic, in terms of coverage, in Europe compared to other regions, such as Australia and North and South America. Even when we apply ECDC or WHO recommendations, the coverage still remains quite low and the disease burden hasn't dropped. Every year, rotavirus accounts for 231 deaths, >87,000 hospitalizations and almost 700,000 outpatient visits [11]. Some may claim that full reimbursement of the vaccines must be issued but this is not the case either because, as Prof Prymula went on to explain, we still have very low coverage rates in regions where the vaccination is totally supported and reimbursed.

Prof Prymula then presented a recent study requiring data from 80 countries with only 49 presenting their share of information. It was found that in several countries there is a limited budget for vaccination and immunization and that in some of them politicians along with physicians get to decide which

[6] Tucker A et al., Cost-effectiveness Analysis of a rotavirus Immunization Program for the United States, JAMA, 1998. 279(17): p. 1371-6

[7] Lee et al., Nonmedical costs associated with rotavirus disease requiring hospitalization, Pediatr Infect Dis J 2005;24: 984–988

[8] Vesikari T. et al., European Society for Paediatric Infectious Diseases Consensus Recommendations for Rotavirus Vaccination in Europe Update 2014, The Pediatric Infectious Disease Journal, 2015. 34(6): p. 635–643.

[9] Rheingans et al., Economics of rotavirus gastroenteritis and vaccination in Europe. What makes sense?, PIDJ, 2006. 25 Suppl 1: p. 48-55

[10] Atherly et al., Rotavirus Vaccination: Cost-effectiveness and impact on child mortality in developing countries, J Infect Dis, 2009. 200 Suppl 1: p. S28-38

[11] Soriano-Gabarro et al., Burden of rotavirus disease in European Union Countries, Pediatr Infect Dis J 2006;25: S7–S11

vaccine will be implemented and which will not[12] [13]. So, the rotavirus burden is often considered not as important, and gastroenteritis not so significant, as other threats and that's why it is still currently excluded from vaccination programs in many countries.

Prof Prymula concluded that he agreed with the fact that each country should be addressed individually and that differences in populations, communities, cultures, priorities, policies exist and are significant. Before closing his briefing, **Prof Prymula highlighted the adversities that the healthcare professionals have to face when trying to convince parliaments to adopt vaccinations and often trying to convince parents is not much easier as a significant part of young parents view many vaccines with skepticism[14].**

UNIVERSAL VACCINATIONS OR THE VACCINATION OF HIGH-RISK GROUPS?

Working Group Briefing

Prof Irena Bralic, an associate Professor of Pediatrics, University of Split, School of Medicine, Croatia was then tasked with providing the Working Group with a summary of the arguments for either following a Universal Vaccinations approach, or alternatively one focused on the Vaccination of High-Risk Groups.

Prof Irena Bralic started by reminding everyone that rotavirus is the most common cause of severe acute gastroenteritis according to the WHO[15]. Both monovalent and pentavalent vaccines are particularly effective against rotavirus in children below 5 years of age[16] [17]. Prof Bralic also stated that most international organizations recommend universal rotavirus vaccination, but in Croatia, only high-risk groups of children receive the vaccine.

Rotavirus vaccines can be safely administered in infants living in households with immune-compromised individuals. Monovalent and pentavalent vaccines however should not be administered to individuals with SCID, to immuno-compromised infants, infants that receive high doses of corticosteroids and to infants with primary and acquired immunodeficiencies[18]. Still, implementing universal vaccination in Croatia seems to be a complex public health, clinical and epidemiological matter and also in terms of cost-effectiveness. In a meta-analysis of 20 studies it was found that the highest NRI (nosocomial rotavirus infection) incidence rate was found in children less than 2 years old[19] [20].

During the discussion Prof Bralic made very clear that she is against the selective approach and that all children should receive what's best for their health. **Consequently, the best approach is the universal rotavirus vaccination. Last but not least, common problems in everyday practice like insignificant problems mentioned by the parents that lead to avoid immunization need to be factored into a successful universal immunisation approach.**

COUNTRY UPDATES

Spain

Dr Francisco Gimenez-Sanchez updated the Working Group regarding the Spanish Association of Pediatrics recommendation that rotavirus vaccinations are provided for children and this has been the case for the past 12 years. However the vaccine was only reimbursed for preterm babies resulting in an average uptake of 60%. Most of the parents in Spain still pay for the vaccines and that is something that will hopefully change in the future. **Pressure is accumulated from the parents towards the government because on one hand all pediatricians suggest that their children should get the vaccine and on the other hand the effects of gastroenteritis in a small baby can be very stressful.**

Hungary

Dr Zsofia Meszner then updated the Working Group on the current situation in Hungary in relation to rotavirus prevention. Most children with gastroenteritis do not get diagnosed with rotavirus unless they are hospitalized where all the tests are made, which is only the tip of the iceberg. So, in Hungary there

[12] Poelaert et al., Vaccine Volume 36 Issue 17, 19 April 2018, Pages 2243-2253

[13] Vecchio et al. : Vaccine. 2017 Mar 14; 35(12): 1637–1644.

[14] Napolitano et al., Rotavirus Infection and vaccination: Knowledge, Beliefs and Behaviors among parents in Italy, Int J Environ Res Public Health. May 2019; 16(10): 1807, published online 2019 May 21 doi: 10.3390/ijeprh16101807

[15] Parashar UD et al. Emerg Infect Dis 2003;9:565; http://view-hub.org.

[16] CORTESE et al PEDIATRICS Volume 132, Number 1, July 2013

[17] European Centre for Disease Prevention and Control. ECDC Expert opinion on rotavirus vaccination in infancy.Stockholm: ECDC; 2017

[18] Steele A et. Al. Pediat Infect Diseas Jour. 2011;30(2):125-30.

[19] Gleizes O, et al. Pediat Infe Dis J. 2006;25(1 Suppl.):S12-S21

[20] Bruijning-Verhagen P, et al. Pediatrics. 2012;129(4):e1011-e9

are approximately 70,000 cases per year and one third of that is attributed to rotavirus while intensive care units take up around a couple of hundred cases yearly, especially in the winter months. Most parents, while knowing what diarrhea is, they haven't a clue about rotavirus gastroenteritis. **Dr Zsofia Meszner then went on to explain that currently there is quite a high cost for the vaccine and the parents have to pay the full price for it in Hungary. However, even with this self-funding constraint 33.2% of the eligible children were vaccinated in 2018 in Hungary.**

Belgium

Prof Marc Van Ranst, Professor, Department Chair of the Department of Microbiology, Immunology and Transplantation, Head of the Laboratory of Clinical and Epidemiological Virology, Rega Institute for Medical Research in Belgium, stated that rotavirus vaccination worked remarkably well. Prof Van Ranst then went on to explain that **uptake in Belgium went above 90% very rapidly despite the fact that it was only partially reimbursed, when introduced back in 2007**. Infection cases and hospitalization rates dramatically dropped since the implementation of the vaccination and **rotavirus season has shifted as well towards the spring months**. Prof Van Ranst suggested that this success was down to the remarkable readiness of the Minister of Health, vaccine companies and pediatrics associations as these were the key reasons why the vaccination was so impressively well perceived by the parents.

United Kingdom

Mr Malcolm Taylor, General Secretary Coalition for Life-Course Immunisation (CLCI), UK started by pointing out that cost-effectiveness analyses gains more and more ground when it comes to health policies evaluation and implementation on one hand and that healthcare professionals should make good use of social media and other means available in order to enhance the parents' and patient's push towards the politicians on the other. In the case of the UK, not everyone agreed with the cost-effectiveness concept set aside and the need to come back the next time and try to convince the parliaments about the necessity of the vaccination program was illustrated. Direct costs, indirect costs (both individual and public health perspective) and societal impact must be taken into consideration. Mr Taylor then suggested what vaccines can do in terms of improved education, the fact that they are beneficial across the whole family rather than just the recipient and their contribution to national economic
wellbeing, all of which are sincerely underestimated.

INTERVENTIONS AND COMMENTS

Dr Zsofia Meszner spoke to the Working Group regarding the mechanism responsible for seeing less diabetes type one and less celiac disease associated with the rotavirus vaccination. Although **Prof Timo Vesikari** responded that the mechanism is not fully understood yet and that knowledge is still accumulating in this area.

Dr Mihai Craiu, who is a Professor of Pediatrics, Carol Davila University of Medicine in Bucharest, Romania pointed out that more and more parents are digitally connected almost all the time and a weak government may fall against that huge pressure from the other side. He suggested that we should keep things simple and address the problem as "diarrhea" and not as "rotavirus vaccination".

Dr Valtyr Thors, lead for paediatric infectious diseases at the Children's Hospital in Reykjavik and adjunct lecturer at the University of Iceland, then commented that when he came back to his country, rotavirus was not thought of as a big problem at all, but there was no data to support that. So he and his team conducted a 2-year research and prospective study and they also made a questionnaire for the public. The data from this latest study, once completed, will then be sent immediately to the policy makers and Dr Thors, believes the uptake will be extremely high in Iceland.

Prof Simon Kroll, Professor of Paediatrics and Molecular Infectious Diseases, Imperial College and St. Mary's Hospital, member of the Uk Health Protection Agency Meningococcus Forum in the UK, spoke about the impact of vaccination not only on the recipient but across the whole family as well. Prof Kroll expressed some doubts whether the vaccination needs to be universal and mandatory or if it is better and more benefi- cial to be voluntary instead.

Prof Anna Odone, associate professor of public health – Director of the School of Public health, vita-salute San Raffaele University in Milan, Italy then spoke to the Working Group regarding mandatory vaccination in Italy. Currently Rotavirus vaccines are not mandatory and Prof Odone commented that having some vaccines that are just recommended and others that are mandatory creates more problems than it solves because parents wonder if some vaccines are less or more important than others, and this creates confusion.

Prof Odone then asked the Working Group whether epidemiological data can justify compulsion around rotavirus vaccination and **Prof Timo Vesikari** responded that he advocated that it should be voluntary. **Prof Vesikari** then compared the importance of coverage rate between rotavirus and measles.

Dr Irene Rivero-Calle, Consultant in Pediatrics and Pediatric infectious diseases, University Clinical Hospital of Santiago de Compostela in Spain then spoke about the surveillance of rotavirus burden across the globe made by WHO. At the moment there are 61 countries, 131 sentinel sites reporting to this network and this provides information on vaccine coverage, on seasonality and it gives direct information on impact on severe cases. Also it allows cost effectiveness studies and to optimize vaccination schedules and also it addresses questions on the performance of the vaccine, the uptakes and it can be reassuring on the safety of the vaccine. These post commercialization studies also give lots of information. **Dr Rivero-Calle** suggests that globally it can promote decision making to new vaccine introduction, including rotavirus vaccines.

CONCLUSIONS

The Working Group was dedicated to rotavirus vaccination, its current uptake rates around Europe, and where barriers to uptake still remain. It was concluded that the vaccine is a very significant tool in our arsenal in order to decrease the burden of rotavirus disease in society, where rotavirus is the most common cause of severe acute gastroenteritis. In particular the Working Group has raised the following areas that need to be explored in more detail with necessary actions taken in 2020-21 to achieve, they include:

- **Apart from the direct costs, we must also consider the indirect cost of such diseases, such as: outpatient office visits, home care and lost work hours.** Direct costs, indirect costs (both individual and public health perspective) and societal impact must be taken into consideration by policymakers

- **Rotavirus vaccines can be safely administered in infants living in households with immune-compromised individuals, but all children should receive what's best for their health.** Consequently, the best approach is the universal rotavirus vaccination.

- **The rotavirus vaccine is beneficial across the whole family** rather than just the recipient and their contribution to national economic well being is sincerely underestimated.
- **Having some vaccines that are just recommended and others that are mandatory creates more problems than it solves** because parents wonder if some vaccines are less or more important than others. This creates confusion.

SUGGESTED ACTION PLAN FOR 2020/2021

Target 1
Improving Public Awareness of the Burden of the Disease and the Need for Universal Rotavirus Vaccinations that are State Funded.

Need: There is a need to make the public aware that rotavirus vaccines can protect children, immunocompromised and wider society from the most common cause of severe acute gastroenteritis. Despite the fact that Rotavirus-associated medical and emergency room visits and hospitalizations are significant across Europe, there is significant lack of public awareness while the health authorities frequently fail to recognise the need for rotavirus vaccination.

Proposed Actions - An HCP led campaign to the general public. An awareness campaign highlighting the expanded spectrum of rotavirus disease in Europe and the effective role universal vaccinations can play aiming to change public perception.

Target 2
Developing Improved Surveillance and Reporting Tools for Incidents of Rotavirus, Along with a More Harmonised Evaluation Methodology across Europe

Need: Improved surveillance and reporting tools are needed to collect evidence on the true disease burden, circulation of rotavirus genotypes and the cost–effectiveness. Also, there's a need to adopt a harmonised economic evaluation methodology to make the process more comparable and transparent across European countries

Proposed Actions - A dedicated Expert-led European Working Group convened for countries who want to join together and implement the next wave of rotavirus vaccination programmes.