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EAP STATEMENT

Rotavirus vaccination for all children or subgroups only? Comment of the European Academy of Paediatrics (EAP) and the European Society for Paediatric Infectious Diseases (ESPID) recommendation group for rotavirus vaccination

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Abstract

Rotavirus gastroenteritis affects all children. Studies indicate that by the age of 5 years, almost all children have developed rotavirus antibodies. It has been estimated that in Europe, approximately 6550 children each year die as a result of rotavirus infection. Most of this mortality does not affect children from identifiable risk groups, but previously healthy infants. There is no accountable evidence on increased severity of rotavirus infection in specific risk groups, including children previously born preterm or immunocompromised children. Universal immunization in areas that have successfully achieved large coverage has greatly improved the health of children, reducing infection rates, hospitalization, and costs. Vaccination of infants with presumed high risk may be beneficial for the vaccinated individuals, and such a strategy may also be cost-effective in certain settings. Identifying all high-risk infants within the first few weeks of life is rather difficult especially in countries without primary care pediatricians and goes along with additional costs.

Conclusion: Rotavirus vaccines should be recommended as a universal approach for all children and not be restricted to subgroups with assumed increased risk. Targeted vaccination could be considered as an option in countries with limited financial resources.

Keywords Rotavirus · Gastroenteritis · Diarrhea · Vaccine · Targeted vaccination

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Introduction

The European Academy of Paediatrics (EAP) and the European Society for Paediatric Infectious Diseases (ESPID) recommendation group for rotavirus vaccination comment here on the question whether rotavirus vaccination should be offered to all children in Europe or only to children considered at increased risk. This statement was developed after the Nederlandse Vereniging voor Kindergeneeskunde informed EAP that reimbursement for rotavirus vaccination shall be offered in the Netherlands from the summer of 2019 onwards only for children considered at high risk, such as premature and dysmature babies and babies with congenital defects.

Rotavirus gastroenteritis affects all children [1]. Population studies indicate that by the age of 5 years, almost all children have developed rotavirus antibodies, which indicate they have been in contact with the infectious agent [2]. Although mortality is highest among children in low and low-medium income countries, it has been estimated that also in the European Region, approximately 6550 children had died each year as a result of rotavirus infection in the pre-vaccine era [3]. Of importance, most of this mortality does not affect children from identifiable risk groups but previously healthy infants and children who usually die as a consequence of severe and fast progressing dehydration.

Current recommendation and efficacy of rotavirus vaccination

After the licensure of the current live oral rotavirus vaccines in 2006, a joint ESPID/ESPGHAN working group was formed to provide guidance on the use of rotavirus vaccine in Europe. The unanimous recommendation based on firm evidence was that rotavirus vaccination should be offered to all children in all European countries [4]. Similar conclusions were subsequently drawn by other international authoritative institutions and agencies [5–7]. There is no accountable evidence on increased severity of rotavirus infection in specific risk groups, including children previously born preterm or immunocompromised children. Rotavirus infection generally causes more severe disease than other etiologies of acute gastroenteritis independently of its target age [8, 9]. A recent study explored differences in demographic and other risks between children with severe and less severe diarrhea in low-income countries and found no risk predictors for severe diarrhea, suggesting that no specific risk groups can be defined that are prone to developing a particularly severe disease course [10].

Epidemiological evidence confirms the major role of rotavirus as a potentially dangerous agent to all children. Universal immunization in areas that have successfully achieved large coverage has greatly improved the health of children, reducing infection rates, hospitalization, and costs [6, 11–16]. In European countries with successful rotavirus vaccination programs, such as Belgium and Finland, the long-term reduction in severe RV cases has been 85 to 90%, respectively [17, 18]. According to the Global Rotavirus Surveillance Network the European Region has documented the largest decrease in rotavirus-related gastroenteritis incidence after vaccine introduction, with a mean reduction of 53% [19].

Targeted rotavirus vaccination

Vaccination of children with presumed high risk may be beneficial for the vaccinated individuals, and such a strategy may also be cost-effective in certain settings [20]. According to a recent cost-benefit and risk-efficacy analysis performed in the Netherlands (a country with low RV-related mortality) [21], a targeted vaccination strategy was proposed as providing the most favorable risk-benefit ratio and as nearly eliminating rotavirus-related mortality. Although the model took several parameters into account, including health-care costs, nosocomial infections, risk of intussusception, and herd immunity, these results are substantially related to the intrinsic vaccine cost. A universal vaccination strategy would prevent additional hospitalizations and fatal cases, but it would become cost-saving only if direct vaccine costs are reduced to about € 30, per child or less [21]. This price level is probably possible to achieve through centralized purchasing.

Another model calculation recently demonstrated a favorable cost-effectiveness profile of universal rotavirus vaccination in South Korea (also a country with low RV-related mortality) [22]. The two cost-effective analyses differ in some input parameters including mortality estimation or intervention main outcome: quality-adjusted life years in the Netherlands and disability-adjusted life years averted in South Korea. However, when compared to the South Korean model, the Dutch analysis reported a lower estimated vaccination coverage and higher costs for vaccination program start-up or for the management of complications (e.g., intussusception), and that might have impacted on final results favoring targeted vaccination [21, 22].

Universal rotavirus vaccination

There are several arguments supporting universal vaccination as preferred strategy to decrease the high disease burden

among young children. The limitation of vaccination to at-risk groups would require identification and specific pathways for preterm and low birth weight babies and for congenital abnormalities. This can be difficult to achieve in countries without primary care pediatricians and goes along with additional costs that were not included in the analysis mentioned above. Furthermore, feasibility of the desirable rotavirus immunization early in life (ideally starting at the age of 6–8 weeks) [6] in selected risk groups is limited, since many of the concerned children are difficult to identify with certainty within the first few weeks of life. This includes infants undergoing intestinal surgery, receiving artificial nutrition, and acquiring or being diagnosed with conditions such as immunodeficiencies. All those patients would benefit from RV immunization or herd immunity later in their lives. In addition, siblings of at-risk children may contract and transmit RV infection, suggesting at least a cocooning strategy by immunizing also the siblings of infants at risk. Moreover, with a targeted immunization strategy, borderline cases of the high-risk indication will possibly be missed.

In a recent survey, the global coverage and barriers toward universal immunization against rotavirus were reported [23]. Belgium, Luxemburg, and Austria started universal immunization programs in 2007, followed by Finland in 2009. These programs have been highly successful in preventing severe rotavirus disease and reduction of rotavirus circulation [12, 13, 15]. Other European countries that introduced universal programs include Germany, the UK, Norway, Greece, Estonia, and Latvia and, in 2019, Italy, Sweden, and Lithuania (Fig. 1). Globally, currently in about 90 countries, rotavirus vaccination has been offered to all children [23]. An exception is Croatia, which in 2011 introduced rotavirus vaccination for selected at-risk categories including preterm babies (gestational age < 33 weeks), neonates with congenital heart defects or inborn metabolic diseases, and infants with chronic liver or kidney diseases or with severe neurological morbidity [24]. To the best of our knowledge, data about the efficacy and cost-effectiveness of this selective vaccination strategy has not been published. In addition, discrepancies in the "at-risk categories" identified by the Dutch and Croatian policies highlight the need of a more accurate target group definition, in order to set up appropriate targeted vaccination strategies.

Additional long-term beneficial effects of rotavirus vaccination

In more than 10 years after the introduction of rotavirus vaccination in several countries, additional indirect and extra-intestinal effects of widespread rotavirus vaccination have emerged.

Due to the molecular mimicry between rotavirus proteins and gluten (among other peptides), rotavirus has been postulated to trigger the onset of celiac diseases as well as of type 1 diabetes mellitus. In this respect, prevention of wild-type rotavirus infection might have an impact on autoimmune diseases. According to a recent survey performed on the population having participated in the Rotavirus (vaccine) Efficacy and Safety Trial (REST) more than 10 years after vaccination, the prevalence of celiac disease was almost halved in rotavirus vaccine recipients compared to the placebo group [25]. Similarly, the incidence of type 1 diabetes mellitus significantly decreased after the introduction of rotavirus vaccination in Australia, and the risk of type 1 diabetes decreased by more than 30% in US children who had completed rotavirus vaccination [26, 27].

A further observation is a 20% reduction of childhood seizures after full course of rotavirus vaccination and an up to 50% reduction of hospitalization rates for seizures even in areas with moderate vaccination coverage [28, 29]. These data support the hypothesis that children may benefit from rotavirus vaccination also later in their lives.

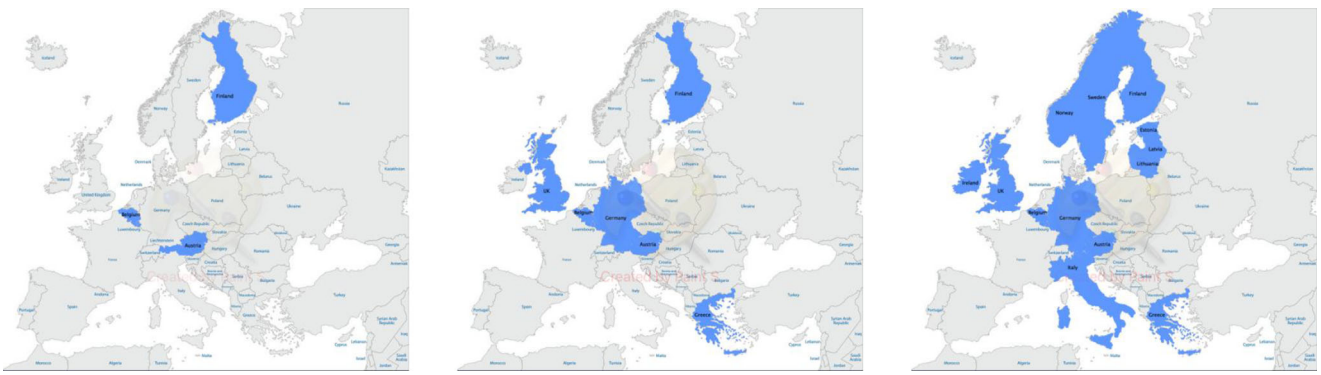

Fig. 1 Implementation of universal rotavirus vaccination in European countries in the years 2009, 2013 and 2019. Graphs derived from vectorstock.com

Conclusion

In conclusion, based on current evidence, inclusion of rotavirus vaccines in national immunization programs should be recommended as a universal approach for all children and not be restricted to subgroups of children with assumed increased risk. Targeted vaccination could be considered as an option in poor countries with limited financial resources. In high-income countries, prevention of severe rotavirus disease should not be an issue limited to cost-benefit consideration but a medical and social issue. It is a question of equity and inequity, and the benefit of rotavirus vaccination should be made available to all children.

Authors' contributions

- **Hans Jürgen Dornbusch**: Study conception, design, and drafting the article
- **Timo Vesikari**: Added significant content to the manuscript
- **Alfredo Guarino**: Added significant content to the manuscript
- **Andrea Lo Vecchio**: Added significant content to the manuscript
- **Adamos Hadjipanayis:** Study conception and reviewed the manuscript
- **Berthold Koletzko**: Study conception, design, and drafting the article

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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