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ROTAVIRUS VACCINATION

– a health technology assessment

Summary

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For further information please contact:
National Board of Health
Danish Centre of Health Technology Assessment (DACEHTA)
Axel Heides Gade 1
DK-2300 Copenhagen
Denmark
Phone: +45 72 22 74 00

E-mail: dacehta@sst.dk
Home page: www.dacehta.dk

The English summary can be downloaded at www.dacehta.dk

What is Health Technology Assessment?

Health Technology Assessment (HTA) contributes to decision making in the health care sector. A HTA collects and assess existing knowledge about a given health technology. A health technology is defined broadly as procedures and methods for prevention, diagnostics, treatment, care and rehabilitation including devices and medicine. An example could be a new method to treat patients. Focus is on healthcare, patient, organisational and economical aspects. New research can be conducted if the number of sufficient studies is limited to elucidate one or more of these aspects.

The HTA results in a report that can contribute to better planning, quality enhancement and prioritizing in the health care sector. The target group is decision-makers in the health political field. The primary users are therefore administrations and politicians and other decision-makers in the health political field. The HTA contributes to decisions within administration as well as political management as to which services should be offered in the health care sector and how they should be organized.

Health technology assessment is defined as:

HTA is a comprehensive systematic assessment of the prerequisites and consequences of applying a health technology

HTA is a research-based, application-oriented assessment of relevant existing knowledge about problem areas applying a technology within the field of health and illness.

The project is funded by a HTA-fund that was terminated in 2007. The purpose of the fund was to spread out knowledge and use of HTA locally. The funded HTA-reports are prepared in collaboration with an external interdisciplinary project group. The project group systematically reviews the existing literature, contributes with data collection and produces the chapters and conclusions of the report. The project management is placed at the National Board of Health who is also responsible for the editing of the final report. The report has been submitted to an external reference group and is also externally peer-reviewed.

Find more information about HTA at www.sst.dk/mtv under HTA toolbox:
“Handbook of Methods for Health Technology Assessment”
“Health Technology Assessment – Why? What? When? How?”

Summary

Introduction

Rotavirus gastroenteritis is the most common cause of acute dehydrating diarrhoea among children younger than 5 years and globally the most important cause of severe diarrhoea in this age group. Most children acquire rotavirus infection before they turn 2 years of age. The severity varies from complete absence of symptoms to severe disease including hospitalization with the need for intravenous fluids. The illness usually lasts about 1 week.

Rotavirus is highly infectious, and if one child is infected child in a daycare centre, the rest of the children bare easily infected as well. Traditional means of preventing transmission such as thorough handwashing are not sufficient to avoid transmission of rotavirus, and applying alcohol rub sanitizers to the hands has no effect. Symptoms appear arround 2 days after infection. The person is not infectious during that period. When illness appears, the person excretes large quantities of the virus in the faeces and vomit, and this creates difficulty in avoiding transmitting the virus to other people.

Studies have shown that between 31,200 and 52,000 children are infected with rotavirus annually in Denmark depending on the year and the method of calculation. This results in about 6500 to 31,000 consultations with general practitioners and about 1200 hospital admissions. These estimates are in accordance with the estimates in Norway and Sweden. The hospitalized children are usually well in about 1 week if they get are rehydrated with appropriate and electrolytes. Children in Denmark therefore very seldomly die from the diarrhoea caused by rotavirus gastroenteritis. Each year about 500,000 to 600,000 children die from rotavirus infection, mostly in low- and middle-income countries, because of lack of access to early and correct treatment with fluids and electrolytes. Before rotavirus vaccination was implemented, rotavirus caused an estimated 114 million cases of diarrhoea, 24 million consultations with a physician and 2.4 million hospital admissions globally, including 700,000 consultations with a physician and 87,000 hospital admissions annually in European Union countries. In addition, rotavirus infection results in other forms of socioeconomic burden to society, such as lost production if parents have to stay home from work to take care of a sick child or if the parents get infected. Rotavirus gastroenteritis can also cause severe diarrhoea among adults.

Rotavirus vaccination can prevent rotavirus infection. Denmark has approved two rotavirus vaccines: Rotarix® from GlaxoSmithKline Pharma A/S and RotaTeq® from Sanofi Pasteur MSD ApS. Both vaccines are among the most thoroughly tested of all vaccines and are considered very effective and safe. Both vaccines are available as drops and are administered orally, with two doses for Rotarix and three for RotaTeq.

In 2007, the World Health Organization (WHO) recommended rotavirus vaccination in the WHO European Region and elsewhere. Rotavirus vaccination has now been added to the childhood vaccination programmes in Austria, Belgium, Finland and Luxembourg. Other countries such as France and Spain have decided not to implement this vaccination, and such countries as Norway and Sweden are still considering. In Denmark, the Health and Prevention Committee of the Folketing (parliament) requested an assessment of this issue. The Vaccination Committee of the Danish Health and Medicines Authority is a scientific committee that advises the Authority on the use of vaccination to prevent infectious diseases. The Committee has requested that

a health technology assessment report be prepared that outlines the advantages and disadvantages of implementing vaccination against rotavirus as part of Denmark's childhood vaccination programme. Health technology assessment documents and assesses the existing knowledge in a field of health technology, focusing on the aspects related to health technology, the perspectives of citizens and patients, organization and economics. An assessment of health technology results in a report that contributes to improving priority-setting and planning related to health.

Purpose

The purpose of this report is contribute to a decision-making basis that outlines the advantages and disadvantages of implementing vaccination against rotavirus in Denmark's childhood vaccination programme.

The report attempts to answer the following questions related to assessing health technology in the four categories of technology, perspectives of citizens and patients, organization and economics.

Technology

- What evidence indicates that implementing vaccination against rotavirus gastroenteritis in Denmark's childhood vaccination programme would improve health? This includes investigating the effect on the frequency and severity of rotavirus infection and the overall morbidity.
- What side effects are associated with vaccination against rotavirus?
- How does rotavirus vaccine interact with the other vaccines in Denmark's childhood vaccination programme?

Perspectives of citizens and patients

- What are the attitudes and patterns of behaviour of parents in Denmark in relation to vaccinating children?
- What are the attitudes and patterns of behaviour of parents in Denmark in relation to adding vaccination against rotavirus to Denmark's childhood vaccination programme?

Organization

- Which other European countries have experience in adding vaccination against rotavirus to their childhood vaccination programmes? What organizational experience did this provide?
- What are the organizational opportunities and barriers related to adding vaccination against rotavirus to Denmark's childhood vaccination programme?

Economics

- How cost-effective are the vaccines in relation to a narrow health system perspective and to a broader socioeconomic perspective for society as a whole, including the loss of production because of sick leave?
- How would adding vaccination against rotavirus affect the operating costs of the health system?

Target group

The target group for this health technology assessment is mainly the Vaccination Committee of the Danish Health and Medicines Authority, which advises the Authority. Other target groups include the Authority's Division of Hospital Services and Emergency Management, the Health and Prevention Committee of the Folketing (parliament) and the Ministry of Health. Other stakeholders are Danish Regions, the manufacturers and distributors of vaccines, representatives of patients, researchers and the general public.

Scope

This health technology assessment focuses on assessing the effectiveness of the two approved vaccines against rotavirus in Denmark. Several other vaccine candidates are underway, but these are probably far from being approved for marketing, and there is little literature available on their efficacy. This assessment therefore does not cover these alternatives.

Risk stratification is not part of the questions asked and is therefore not included in the systematic review of the literature. Chapter 2 on rotavirus covers this topic briefly.

Methods

The literature was systematically reviewed to investigate the questions within all four categories. The annex details the specific search strategies for each of the four categories. The aspects related to the perspectives of citizens and patients were bolstered with focus group interviews, and the analysis of organization includes information from key informants. The economic analysis includes assessment based on registry data and on an economic model used in a health technology assessment report published in Norway.

The analysis solely includes studies of sufficiently high quality based on critical assessment of the literature.

The annex contains evidence tables describing the studies included. These use the Levels of Evidence and Grades of Recommendation of the Oxford Centre for Evidence-Based Medicine, which solely grade the level of evidence based on the design of the study. In addition, the quality of the relevant literature for each question has been graded overall. The evidence has been consistently graded in the chapters based on the assessment of quantitative studies. The following levels of evidence are used: high, moderate and low. The decision on which level is used in the individual conclusions includes assessment of the studies that support the conclusion, including the study design, the quality of the studies and the significance of the studies for clinical practice. The individual chapters and the annex describe in detail the methods used, including the grading of the evidence.

Technology

The main finding of the literature search of secondary literature is a thorough and very complete meta-analysis published in the *Cochrane Database of Systematic Reviews*. This is very useful in answering all three questions in this category, but mainly questions 1 and 2.

High quality evidence indicates that both vaccines are very effective in preventing both mild and severe rotavirus gastroenteritis. Further, high quality evidence indicates that both vaccines prevent the need for consulting physicians and hospitalization in controlled trials. Thus, high quality evidence indicates that both RotaTeq and Rotarix substantially reduce the frequency and severity of rotavirus gastroenteritis. Moderate quality evidence indicates that both vaccines prevent hospitalization and result in reduced morbidity under routine conditions (effectiveness), even if all the recommended doses are not taken. Further, moderate quality evidence indicates that these positive effects exceed the possible negative effects of the vaccine.

Based on the available evidence, the conclusion is that both rotavirus vaccines are generally safe, and the incidence of intussusception is only 1 case per 65,000 children vaccinated. A previously marketed vaccine against rotavirus, Rotashield, was withdrawn due to increased incidence of intussusception among vaccinated infants. Intussusception is a disease among young children that arises by an upper segment of the intestine invaginating into the adjoining intestinal lumen, causing bowel obstruction. This produces abdominal pain and bleeding and can lead to compromised blood supply to the intestine with risk of necrosis of the bowel wall, which is a potential life threatening situation in the most severe cases. Further, high quality evidence indicates that the vaccines generally have no side effects, since fever and vomiting occur at the same frequency as with placebo. Thus, the people who are vaccinated do not have more side effects than the controls, who receive a product without vaccine.

High quality evidence indicates that the rotavirus vaccines do not significantly interact with the other vaccines administered in Denmark's childhood vaccination programme. This means that both Rotarix and RotaTeq may be administered simultaneously with the other vaccines in the childhood vaccination programme without producing additional side effects or reducing the effectiveness in preventing gastroenteritis. Further, high quality evidence indicates that rotavirus vaccines do not influence the antibody response against the other vaccines. Studies are lacking that investigate the nonspecific effects of the rotavirus vaccines, including how they influence the effectiveness of other vaccinations: that is, whether rotavirus vaccination positively or negatively affects other diseases than rotavirus infection.

Perspectives of citizens and patients

The literature included in the systematic review on the perspectives of citizens and patients did not contain any studies of the attitudes and behaviour patterns of parents in Denmark in relation to vaccinating children or more specific attitudes towards vaccination against rotavirus. The attitudes of parents in Denmark were therefore investigated by gathering new data in a Danish context through focus group interviews.

The focus group interviews were based on two qualitative focus group discussions with a total of 18 parents of at least one child 0–2 years old living in Denmark.

The survey showed that the parents surveyed have positive attitudes towards vaccinating children. The parents strongly trust the Danish Health and Medicines Authority and the composition of the current childhood vaccination programme. Vaccinating children is also an obvious measure for most parents, who believe that the childhood vaccination programme primarily vaccinates against severe diseases.

Parents do not worry very much about the side effects of vaccinating children but recognize that health professionals have considerable knowledge about vaccination. Some parents are more concerned about the combined effects of administering many vaccines at one time. Further, many mention a need for setting limits. Several parents think that the limits are changing and that there therefore are limits on how many and which vaccinations children should have as part of the childhood vaccination programme.

The parents are divided on their attitudes towards adding vaccination against rotavirus to the childhood vaccination programme: both their attitudes towards the severity of the effects of rotavirus infection and their willingness to participate in such a vaccination on behalf of their children. One group is positive and would like their children to be vaccinated. They consider rotavirus gastroenteritis to be severe enough and therefore relevant to combat. The other group does not consider the disease very severe and therefore is not as positive about adding vaccination against rotavirus to the childhood vaccination programme. The parents discussed extensively setting limits in relation to vaccination against rotavirus.

In addition, many parents consider rotavirus infection to be a very infectious disease, and some therefore support vaccination. The parents do not know the effectiveness of the vaccine against gastroenteritis generally, and the public authorities consider it very important to ensure that parents do not incorrectly think that vaccinating against rotavirus will protect their child against acute gastroenteritis in a broader sense.

The parents are positive towards administering the vaccine orally. The overall organizational conclusion among parents is that the vaccine should optimally be implemented in the existing structures for general practitioner consultations and the childhood vaccination programme. A few parents emphasized the possibility of solely offering the vaccine to selected (vulnerable) groups of children instead of offering it to all children. Most of the mothers surveyed do not see the benefit of adding the vaccination during the woman's consultation with the general practitioner at 8 weeks after birth, since they consider this as a time when they can consult the general practitioner and focus on themselves.

The parents' self-rated probability of participating in vaccination against rotavirus as part of a future childhood vaccination programme was divided. Slightly more than half the parents would seek the vaccination; slightly less than half said that they would decline or were undecided. None of the parents would vaccinate their children if they had to pay for it themselves.

The decisive argument for declining the vaccination is not considering rotavirus gastroenteritis to be severe enough. Nevertheless, the parents have difficulty in deciding whether the vaccination should become part of the childhood vaccination programme. Many therefore urge the public authorities to assess whether rotavirus infection is severe enough to include this vaccination in the childhood vaccination programme.

The literature in this area does not provide much support for the results of the focus group interviews. The main reason, however, is the quantity and type of literature. There is little literature within this topic and very few studies that specifically focus on vaccination against rotavirus. Further, the design of most of the studies found does not fit into the hierarchy of evidence.

Overall, parents' discussions about setting limits, the severity of the disease and the purpose of vaccinating children are the most important findings to consider in the continued decision-making process related to potentially implementing vaccination against rotavirus. Given the other findings in the focus group interviews, adding vaccination against a disease of moderate severity to the childhood vaccination programme may clearly have ethical implications. If parents do not consider the disease to be severe enough, the population's attitudes towards the childhood vaccination programme and its aims might change. Thus, the participation in the programme risks being reduced. This should also be considered in relation to the fact that the argument for parents who say they would participate in the vaccination against rotavirus is that they trust the assessment of the Danish Health and Medicines Authority that the disease for which vaccination is proposed is important and severe enough to add it to the childhood vaccination programme. Decision-makers should therefore consider the implications of adding vaccinations to the childhood vaccination programme based on the importance from a societal perspective instead of based on narrow health system calculations, and especially being explicit about which reasons are crucial in this decision. According to the Danish Health and Medicines Authority, the severity criterion has previously been important in determining which vaccinations to include in the childhood vaccination programme. The question is which considerations will be emphasized in the priority-setting of the future.

Organization

It is concluded that the two-dose vaccine has a clear advantage in implementation, since the childhood vaccination programme needs to add one less dose than with a three-dose vaccine, but planning must take place to include either vaccine, since rotavirus vaccination is subject to public procurement tendering in accordance with European Union rules.

Adding this vaccine has been relatively easy in Finland and Norway, since the existing childhood vaccination programme includes consultations that already fit the approved administration schedules for the vaccines.

In Denmark, there are four theoretical options for adding rotavirus vaccination to the childhood vaccination programme.

- Option 1: maintain the current childhood vaccination programme and administer two doses of rotavirus vaccine at 3 and 5 months of age, respectively. This option is the simplest way to adjust the programme but is only relevant in practice if a two-dose vaccination is added.
- Option 2: move the current standard examination of children at 5 weeks of age to 6 weeks of age, thus administering the first dose at 6 weeks of age, the second dose at 3 months of age and the possible third dose at 5 months. Option 2 would be equivalent to the practice recommended to be implemented in Norway. Consultations in Denmark's childhood vaccination programme are often delayed more than 1 week, but option 2 would theoretically mean a 1-week delay in the only systematic medical examination of infants currently taking place in Denmark, and there may be concern about how moving this might affect the general participation in vaccination.
- Option 3: off-label use of rotavirus vaccine at the 5-week examination: that is, administering the first dose at 5 weeks of age, the second dose at 3 months of age and a possible third dose at 5 months of age. Option 3 avoids moving or adding consultations in the childhood vaccination programme. Nevertheless, no large clini-

cal study supports initiating rotavirus vaccination before 6 weeks of age, and it is therefore not indicated.

- Option 4: begin rotavirus vaccination at the mother's postpartum examination: that is, administering the first dose at 8–9 weeks of age, the second dose at 3 months of age and a possible third dose at 5 months of age. Administering the first dose at 8–9 weeks of age is in accordance with most childhood vaccination programmes against rotavirus. Option 4 would result in one extra consultation in the childhood vaccination programme, and there is therefore concern about the participation in the entire vaccination programme. The parents say that they will follow the recommendations of the Danish Health and Medicines Authority but think that the postpartum examination of the mother should not be linked to a childhood vaccination.

Implementing a catch-up programme to vaccinate all children in the target group at the same time that the vaccination is added to the routine programme is difficult, but adding a two-dose vaccination is easier than adding a three-dose vaccination. Administering the first dose of the vaccine against rotavirus infection early in the childhood vaccination programme is also easier: that is, option 2 at 6 weeks of age or option 3 at 5 weeks of age.

An average general practitioner would have to schedule about 10 extra consultations per year compared with current practice if vaccination against rotavirus infection is implemented in Denmark. The Organisation of General Practitioners in Denmark has not dismissed these options but does not consider rotavirus vaccination to be a priority.

If rotavirus vaccination is implemented, this should be followed up with guidance for parents, which should be able to take place in the usual manner as a combination of mass media and specifically targeted information. In addition, health personnel in general practice would need to be trained in how to administer the vaccine, in effectiveness and safety and in the importance of complying with the relatively narrow time intervals. Further, a decision needs to be taken on whether any catch-up programme should be recommended, and this is not recommended in several countries.

Finally, the monitoring of rotavirus vaccination should be prepared before adding this vaccination. Statens Serum Institut (National Institute for Health Data and Disease Control) can manage the monitoring, which specifically for rotavirus vaccine is recommended to include surveillance of the vaccination participation rate, incidence of rotavirus infection, circulating genotypes of rotavirus and more intensively monitoring the safety of rotavirus vaccination (with a special focus on intussusception).

Economics

Based on assumptions on the expected trends and transmission of rotavirus related to a cohort of children in the first 5 years of life, the costs and benefits were modelled in relation to vaccinating children against rotavirus versus not vaccinating them. The model is based on a similar model prepared by the Norwegian Knowledge Centre for the Health Services.

The cost–effectiveness analysis included information on the incidence of rotavirus infection in Denmark, the quality of life of children infected with rotavirus in Denmark, medicine prices in Denmark and other factors. The analysis showed that the cost per quality-adjusted life-year gained is about DKK 371,000 for vaccination with

Rotarix and DKK 532,000 for vaccination with RotaTeq based on a narrow health-sector perspective. In contrast, a broader societal perspective that includes the value of parents' reduced absence from work because of vaccination shows that vaccination with either vaccine adds positive economic value (the benefits exceed the costs).

Sensitivity analysis of the results shows that a 50 % discount in the price of the vaccine would approximately halve the cost per quality-adjusted life-year gained. Based on the broader societal perspective, the sensitivity analysis shows that the calculated positive socioeconomic benefit of adding rotavirus vaccination remains positive as long as parents' actual current sick leave resulting from children's infection with rotavirus is at least half of the number used in the modelling of economic costs and benefits.

Finally, the analysis of operating costs for the health system shows that the annual cost of adding vaccination against rotavirus to the childhood vaccination programme would be DKK 46 million for vaccination with Rotarix and DKK 62 million for vaccination with RotaTeq based on the pharmacies' purchase prices. If the discount for a collective purchase of vaccine for all of Denmark were 25 %, the annual costs would be DKK 36 million for Rotarix and DKK 49 million for RotaTeq.

As indicated in the description of the methods used in the economic analysis, these results are uncertain. One reason is that the model used simplifies reality, and another reason is that many of the parameters used are not known precisely but are estimated based on existing data and studies.

The most important weaknesses of the modelling include the following.

- Any community (herd) immunity resulting from vaccination is not included. Since vaccines inherently strongly influence the frequency of infections, ignoring any additional effect in the form of community immunity is not considered to be able to change the overall result decisively.
- The model assumes that rotavirus infection provides full immunity, but children may be reinfected. Nevertheless, the existing data do not enable initial infection to be differentiated from reinfection.
- The parents and not the children themselves rate the children's health-related quality of life in rotavirus infection. The people who are ill normally rate their own health-related quality of life to obtain credible estimates. Nevertheless, studies of this could not be obtained. Similarly, it can be discussed whether quality-adjusted life-years as a measure of effect adequately describes how vaccination affects children's health, since the calculation of quality-adjusted life-years is inherently based on assumptions and simplifications. However, the literature frequently uses quality-adjusted life-years as a measure of effects in the economic analysis of vaccination.
- The risk of parents acquiring rotavirus infection from their children is not included. Vaccination would also reduce the risk of infection among family members older than 5 years. Even though this risk is estimated to be minimal, including this would further increase the societal benefits of vaccination and thus reduce the total cost.
- The analysis does not consider that rotavirus infection may affect the health and the length of hospitalization of other children who are already hospitalized. Including these factors is considered to reduce the total costs of vaccination and treating rotavirus infection, but no useable studies focusing on this were found. Note that children who have acquired rotavirus infection in hospital and become ill after discharge are included.

- The analysis does not consider that the effectiveness of the vaccine may change over time. The studies on which the effectiveness of vaccination is estimated measure the efficacy during 1–2 years. Some studies show a slight decline in the efficacy from the first to the second year, but for RotaTeq the trend in the measured efficacy has not been investigated. Including this could have resulted in slightly higher costs and thereby a slightly higher incremental cost–effectiveness ratio. The efficacy is not included, since the trend over time for both vaccines during the first 5 years of life is not known precisely.
- The analysis is based on estimates of efficacy (under controlled conditions) and not effectiveness (under routine conditions), but one may argue that effectiveness data provide a more realistic sense of the effect of the vaccine in accordance with Drummond et al. (*Methods for the economic evaluation of health care programmes*, Oxford University Press, 2005). The sensitivity analysis shows, however, that this does not decisively change the overall result, since an estimated lower effectiveness of the vaccines on the number of hospital admissions under routine conditions (estimated to be 85 %) only results in a slight increase in the incremental cost–effectiveness ratio. Further, it is necessary to be aware that the grade of evidence in studies of effectiveness is low and that the results may be influenced by other factors than the vaccine, such as random variation in the incidence rate.
- Many minor costs of vaccination have been ignored. This applies to the increased cost of gathering data in connection with the possible monitoring of the effectiveness of the vaccination. Similarly, the costs of informing the families of children about the vaccination against rotavirus have been ignored. In contrast, the costs of parents' transport, extra use of diapers and special care for children with rotavirus infection have been ignored, and including these factors would reduce the total socioeconomic costs of vaccination to society.

Note that these problems and limitations are common to most of the economic analyses of vaccination against rotavirus infection in the literature. Nevertheless, the assessment is that the conclusion of the economic analysis would not differ decisively if the model included the limitations mentioned.

Overall assessment

The chapter on overall assessment summarizes the field briefly and the most important results of the report. Further, the results are assessed and the results from the four categories are weighed against one another. The chapter ends with a summary.

Most children in Denmark acquire gastroenteritis before they become 5 years old, and rotavirus is often the cause. Children typically have fever and vomit and/or have diarrhoea. These children usually become healthy without intervention in 3–7 days. Some children, however, have deficiencies of fluids and electrolytes to the extent that they must be hospitalized and be treated with intravenous fluids.

About 85–90 % of the children in Denmark participate in the childhood vaccination programme and are vaccinated against several diseases. Denmark has two well-tested and approved vaccines against rotavirus. Both vaccines are administered orally and not by intradermal injection as are the other vaccines in the childhood vaccination programme.

WHO and scientific societies in Denmark and the rest of Europe have recommended that children be vaccinated against rotavirus. Several European countries have implemented vaccination against rotavirus in their childhood vaccination programmes.

Other European countries have decided not to add rotavirus vaccination to their childhood vaccination programmes, and others are still deciding.

The purpose of this health technology assessment is to contribute to a decision-making basis that outlines the costs and benefits of implementing vaccination against rotavirus in Denmark's childhood vaccination programme. This assessment outlines: 1) the effectiveness and side effects of vaccination against rotavirus; 2) parents' attitudes towards adding vaccination against rotavirus to the existing childhood vaccination programme; 3) the organizational opportunities to implement the vaccination; and 4) the economic effects for the health system and for society. The assessment included systematic literature review, focus group interviews, gathering information from key informants, analysis based on registry data and the results of a health technology assessment carried out in Norway.

Both vaccines have well-documented effectiveness based on high quality evidence, and vaccination can significantly reduce both the frequency and severity of rotavirus infection. Further, the registered side effects of both vaccines among vaccinated children are of the same type and frequency as those among children who received placebo. The clinical studies have shown great differences in the effectiveness of the vaccine in high-income countries and low-income countries. One reason is that the health systems differ considerably in these two groups of countries. This assessment has also therefore assessed the effectiveness during routine use in several of the high-income countries that have added this vaccination to their childhood vaccination programmes. The efficacy found in well-controlled clinical studies is slightly higher that the effectiveness found in routine use, probably mainly because that the entire population does not participate in vaccination in routine conditions. The effectiveness of the two available vaccines does not differ overall, and the effectiveness of the vaccination is estimated to be about 70 % for avoiding rotavirus infection, 90 % for avoiding a consultation with a physician and more than 95 % for avoiding hospitalization. Both vaccines are thus very effective and safe.

The quality of evidence from the studies that assess the efficacy in controlled trials is high, and the quality of evidence from the studies examining the effectiveness under routine conditions is moderate.

High quality evidence indicates that rotavirus vaccine has no substantial interaction with the vaccines that are part of Denmark's childhood vaccination programme. It would therefore be natural to time an added rotavirus vaccination so that it is administered together with some other vaccinations carried out by general practitioners. Implementation in the existing childhood vaccination programme is the preferred option among the parents participating in focus group interviews. This would also avoid one or more extra consultations with a general practitioner. Rotarix requires two doses and RotaTeq three doses to obtain full protection. The entire vaccination programme should be completed by the age of 6 months, since the risk of acquiring rotavirus infection increases considerably after this age. The vaccines have not been approved for administration before children are 6 weeks old, and vaccination begins at 2 months of age in most of the countries that have implemented rotavirus vaccination. The report presents several alternatives for adding vaccination against rotavirus to Denmark's childhood vaccination programme. Without changing the scheduled times in the existing childhood vaccination programme, the two-dose vaccine can be added at the existing consultations at 3 and 5 months of age. Implementing the three-dose vaccine would require moving the existing consultation at 5 weeks of age to 6 weeks of

age. The Organisation of General Practitioners in Denmark, however, does not see the benefit of moving the scheduling of the current vaccination programme. Another option is to administer the first dose at 8–9 weeks of age, when a postpartum follow-up examination of the mother is offered. The participants in the focus group interview did not support adding a vaccination in connection with the postpartum examination of the mother since they think that this consultation should focus on the mother's well-being and health and not on the child. A third option is to begin rotavirus vaccination one week earlier than recommended, administering the first dose at the existing standard consultation at 5 weeks of age. Nevertheless, no large clinical study supports the effectiveness of vaccination before 6 weeks of age. Based on the options assessed, implementing the two-dose vaccine (Rotarix) would be easier, since this can be administered at the existing consultations at 3 and 5 months of age. However, public procurement tendering in which both vaccine manufacturers would be able to bid would have to be followed in accordance with European Union rules before vaccination against rotavirus infection could be added to Denmark's childhood vaccination programme.

According to the Danish Health and Medicines Authority, the purpose of Denmark's childhood vaccination programme is to protect children from diseases that can result in either death or long-term harm. The Authority has previously maintained that Denmark should not implement vaccinations in the childhood vaccination programme merely because this is feasible. Rotavirus infection almost never results in death or long-term harm in such countries as Denmark, which has a well-developed health system. Further, the literature review shows that rotavirus vaccination is not associated with children's mortality.

Several of the interviewed parents said that limits need to be set about how many and which vaccinations their children should have, and several of the interviewed parents stated that the saturation limit is about to be reached if vaccination against acute gastroenteritis is implemented. It can therefore not be excluded that the otherwise very high trust in the composition of the current childhood vaccination programme expressed by the interviewed parents might change if vaccination against rotavirus were added to the childhood vaccination programme. This could indirectly affect the participation in the programme, which already has insufficient participation in the striving to eradicate such diseases as measles, for which a participation rate of 95% is considered necessary. Adding vaccination against rotavirus to Denmark's childhood vaccination programme would therefore require a strategy for informing both parents and general practitioners and other relevant health personnel that considers counteracting the low participation in the rest of the childhood vaccination programme. In addition, regularly monitoring the participation rates in the rest of the childhood vaccination programme would be important. This assessment used a qualitative method to investigate the perspectives of citizens and patients, and the parents interviewed are all from Greater Copenhagen. As a result, no conclusion can be drawn on how widespread these attitudes are. A quantitative survey with a random sample of parents from all of Denmark could contribute to determining this.

This assessment has not attempted to assess risk stratification with the aim of deciding whether special groups of children at higher risk should be vaccinated. Nevertheless, vaccination against rotavirus is especially effective and should be considered as a preventive option for children with a very high risk of severe effects of rotavirus infection, such as children with chronic disease or children with cancer.

Based on the literature review of the efficacy and effectiveness of the vaccines and the estimated incidence of rotavirus infection in Denmark in the section on technology, implementing rotavirus vaccination in Denmark's childhood vaccination programme would be expected to prevent about 30,000 cases of acute gastroenteritis, 9000 physician consultations and 1100 hospital admissions per year.

This report assesses the direct costs to the health system of implementing a vaccination programme. With an expected discount of 25 % for wholesale purchasing, the total cost of implementing Rotarix vaccination would be about DKK 36 million per year and DKK 49 million annually for RotaTeq. The difference results from RotaTeq requiring an extra physician consultation for the third dose, whereas Rotarix can be administered in two doses within the existing standard examinations by general practitioners. Although implementing the two-dose vaccine in the current childhood vaccination programme should be simplest and least expensive, public procurement tendering in accordance with European Union rules is assumed to change the prerequisites for the costs in the economic calculations considerably.

The cost to the health system of every quality-adjusted life-year saved would be about DKK 371,000 for Rotarix vaccination and about DKK 532,000 for RotaTeq vaccination. Thus, the economics from the narrow viewpoint of the health system shows that this vaccination has a relatively high price per quality-adjusted life-year compared with other health interventions.

Based on a broader societal perspective, however, which includes the value of reduced absenteeism if the children are vaccinated, the analysis shows that vaccination with either vaccine adds positive economic value.

Regularly monitoring the indirect economic effects would be important if rotavirus vaccination is implemented. WHO thus recommends monitoring the participation in the vaccination programme, the incidence of rotavirus infection, the circulating rotavirus genotypes and safety, especially focusing on intussusception, in connection with adding the vaccination. These monitoring measures are easy to implement in Denmark, which already has several well-established national systems that enable this part of the surveillance.

In conclusion, two very effective and safe vaccines have convincing preventive effectiveness in relation to morbidity measured by the number of cases of diarrhoea, physician consultations and hospital admissions. Implementing vaccination against rotavirus is a rational intervention based on a socioeconomic perspective that includes the societal value of parents' absence from work. In contrast, the cost of implementing vaccination against rotavirus would not be offset by a similar reduction in treatment costs, and the intervention would thus not save money within the narrow perspective of the health sector.

Implementing the two-dose vaccination in the current childhood vaccination programme would be the simplest and least expensive option, but public procurement tendering in accordance with European Union rules with the participation of both vaccine manufacturers would probably reduce the final cost of the vaccine considerably. Many of the parents who participated in the qualitative interviews as part of investigating the perspectives of citizens and patients said that they do not consider acute gastroenteritis to be severe enough to warrant implementing vaccination against rotavirus in Denmark's childhood vaccination programme and raised the issue of a possible satura-

tion point for vaccination. Based on this and based on the views expressed by the Danish Health and Medicines Authority on Denmark's childhood vaccination programme, discussing and clarifying the severity principle in the childhood vaccination programme will be decisive for deciding whether the childhood vaccination programme should include this vaccination. Nevertheless, the vaccines are clearly effective and safe and can be relatively easily be added to Denmark's childhood vaccination programme. The modelling shows that the vaccination has an overall socioeconomic benefit for society but a net cost to the health system.

www.dacehta.dk

National Board of Health
Axel Heides Gade 1
2300 København S
Tlf. 72 22 74 00

dacehta@sst.dk
www.dacehta.dk