Finland introduces rotavirus vaccine into the national vaccination programme in September 2009

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Supported by an economic evaluation, rotavirus vaccine is introduced into the national immunisation schedule in Finland. The vaccination programme has been estimated to be reasonably cost-effective. Given at the age of two, three and five months, the vaccine is expected to prevent annually in Finland among children under the age of five years approximately 2,000 rotavirus diarrhoea episodes needing hospitalisation, and over 10,000 outpatient visits. The impact of the programme will be evaluated in 2011 by repeating the economic analysis and carefully monitoring adverse events.

Rotavirus causes epidemics every year during the months of winter and spring in northern Europe. Especially in young children, the infection manifests as acute gastroenteritis with high fever, vomiting and watery diarrhoea, with 10-20 stools per day, lasting for a total of three to eight days. The first rotavirus infection in a person is usually symptomatic, and can easily lead to severe dehydration. The typical clinical picture is usually observed in children between the ages of six months and two years. Almost all children are infected with rotavirus, either with symptoms or asymptomatic, before they are five years old. Rotavirus infection is easily transmitted, since a lot of virus is excreted in stools during diarrhoeal bouts.

As in Europe in general, serotypes G1 and G4 have been the dominant serotypes causing annual rotavirus diarrhoea epidemics during 1980s and 1990s in Finland [1,2]. In recent years, serotype G9 has gained importance and was the most common serotype found in 2005. Among the total 125 isolates serotyped from the Helsinki metropolitan area during the epidemic season in 2006-7, the G1P[8] was dominant (57%) followed by G9P[8] (29%). The G4P[8] serotype was found in only four isolates [3].

Presently there are two live rotavirus vaccines on the market, which differ in their antigenic composition and protective principle [3]. The RotaTeq vaccine is a live reassortant vaccine derived from human and bovine rotaviruses. For sufficient protection, three doses are needed. Rotarix is a live attenuated vaccine based on human rotaviruses (RIX4414). For sufficient protection, two doses are needed. The vaccine preparations contain different rotavirus serotypes: RotaTeq is composed of serotypes G1, G2, G3, G4 and P[8] and Rotarix of G1P[8].

In clinical trials, vaccine efficacy of either vaccine against severe rotavirus diarrhoea that requires rehydration therapy was over 90 %, and against any rotavirus diarrhoea 60–70 % (3). Although no formal comparative efficacy analysis was performed, there is no scientific reason to believe that the protective efficacy of these two vaccines would be significantly different that could guide the choice of one vaccine over the other. Based on the trial outcome, the risk profiles of the two vaccines are also fairly similar.

In Finland, a new vaccine can be introduced to the national immunisation programme if it fulfils four key criteria. There needs to be a public health disease burden that is to be prevented, the vaccine needs to be safe and able to reduce the disease burden, it should not have any significant adverse events on the population level, and finally, the intervention should be reasonably cost-effective to justify the expense from the state budget [4].

Evaluation of the cost-effectiveness of rotavirus vaccination

In order to understand the burden of disease caused by rotavirus, we estimated the proportion of healthcare resource use attributable to rotavirus. We regressed [5,6] the weekly laboratory reports of gastrointestinal pathogens on the weekly infectious and non-infectious intestinal disease episodes (constructed from the hospital outpatient visits and inpatient hospitalisations) and weekly primary healthcare visits according to a model. According to this estimation of the burden of disease, approximately 11,100 children under five years of age annually need health care services due to rotavirus in Finland [7]. We estimated that rotavirus gastroenteritis annually leads to 2,400 episodes needing hospitalisation, 3,700 hospital outpatient visits and 9,000 visits to healthcare centres.

To investigate the potential cost-effectiveness of the vaccination programme, a cohort model was constructed to compare the costs and outcomes of the two rotavirus vaccines to a scenario without intervention [8]. A hypothetical birth cohort was followed over the first five years of life. The analysis was conducted from the perspectives of the health care provider and of society.

It was estimated that a rotavirus vaccination programme in Finland could prevent annually approximately 2,000 rotavirus diarrhoea episodes requiring hospitalisation and over 10,000 outpatient visits among children under the age of five years. The estimated annual costs to the healthcare provider of rotavirus infection among children under five years were EUR 4.2 million without vaccination. The cost per quality-adjusted life year (QALY) gained from the perspective of the healthcare provider was EUR 25,218 for Rotarix (assuming EUR 39.5 per dose) and EUR 45,199 for Rotateq (assuming EUR 29.5 per dose). In the

probabilistic sensitivity analysis (healthcare payer perspective), the 95% confidence intervals for cost per QALY gained ranged from EUR 20,370 to EUR 30,498 for Rotarix and from EUR 38,177 to EUR 48,506 for Rotateq.

The Finnish National Institute of Health and Welfare (THL) and National Advisory Boards of Vaccination and Infectious Diseases who reviewed the analysis in 2007 agreed that the parameter values were based on good quality national data and that the assumptions chosen were conservative enough to give relevant guidance for national decision making [4]. Based on this analysis, the rotavirus vaccination programme appeared to be not cost-saving but reasonably cost-effective, especially if nosocomial infections and home-treated rotavirus cases were included. Thus, rotavirus vaccine was recommended to be included into the national programme – a recommendation which the Ministry of Social Affairs and Health as well as the Ministry of Finances agreed to in 2008.

Choosing the vaccine to be used

In Finland, the procurement of vaccines for the national programme is centralised. In the competitive bidding done in 2008, the only decisive factor was the price. The offer of RotaTeq manufactured by Sanofi Pasteur MSD was cheaper; at this price the programme was cost-saving. Finland has now agreed to include RotaTeq into the national programme for two years after which a new tender will be launched. Today, given the present price of Rotateq, the rotavirus vaccine programme is estimated to be cost saving both from the societal and health care provider perspective. Also, it is to be expected that the vaccine provides indirect protection to the society as a whole when transmission of rotavirus is reduced [9].

In Finland, the three doses of the vaccine will be given at the ages of two, three, and five months thus increasing by one the visits to a well-baby clinic for vaccination (the one at two months of age). As a precaution, the first dose is recommended to be given before the age of 12 weeks, but not earlier than six weeks. Also, the child should not be older than 26 weeks (i.e. 6.5 months) when the third dose is given. These age limits approved by the European Medicines Agency (EMEA) are somewhat stricter than those recommended by the United States Food and Drug Administration (FDA), which has recently raised the upper limit of the third dose to the age of eight months. In addition, the Strategic Advisory Group of Experts (SAGE) and the Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organization (WHO) have suggested that these limits be raised even more in resource-poor countries where the rotavirus disease burden is very high, and where it is important for rotavirus vaccine coverage to be as high as possible. In such countries the recommended upper limit is 15 weeks for the first dose and 36 weeks for the third dose [10].

Safety of the RotaTeq vaccine

The clinical safety of RotaTeq was proven in trials involving approximately 70,000 children in 12 countries. One third of these were Finnish children (11). By spring 2009, the manufacturer had sold approximately 22 million doses of RotaTeq. In those countries where the vaccine was introduced into the national programme (i.e. Australia, Austria, Luxemburg, and the United States), it has proved to be safe. In the US, the reported incidence of intussusception (1/25–50,000 first doses) did not differ from that expected, i.e. from the observed incidence before starting the vaccinations [12]. Cases of intussusception were reported somewhat more often after the first than after the second or third doses. Another cause for concern has been Kawasaki disease. During the clinical trials the suspicion of an increased incidence of Kawasaki disease arose, although the difference between the vaccines and controls was not significant. After the introduction of the vaccine and careful monitoring, there has been no evidence that would point to an increased risk of Kawasaki disease among those vaccinated [12]. The most common expected adverse events are mild and transient gastrointestinal and respiratory symptoms [11]. After the first dose, less than 9 % of the vaccinees excrete the vaccine virus into stools. This is even more rare after receiving the second or third dose.

Monitoring the impact of rotavirus vaccination

Rotavirus vaccinations will be started in September 2009 in all the well-baby clinics in Finland, which cover approximately 99% of the Finnish cohort of newborns. For the time being, Finland does not have an operational vaccine registry. Thus, vaccine coverage, which traditionally has been high in the country, i.e. above 90% for most vaccines used in the national programme [13], will be monitored using the administrative method combined with periodic surveys of the vaccination status of a randomly chosen sample of 1,000 children. Adverse events associated with rotavirus vaccination will be monitored through the existing passive surveillance system, i.e. health care personnel will notify of any suspect case of adverse events following immunisation (AEFI) to THL. In addition, certain clinical manifestations like intussusception and Kawasaki disease will be actively monitored as part of the VAESCO project, a project for harmonising vaccine safety in Europe (www.vaesco.net). A systematic monitoring of the effectiveness of the rotavirus vaccination programme is planned for the year 2011 repeating the collection of morbidity and mortality data as done for the economic evaluation [7,8]. In addition, isolated rotavirus vaccine strains will be sero- and genotyped to understand the possible impact of vaccination on new reassortments and shifts in the proportions of the prevailing serotypes [2].

Details on the rotavirus vaccines used, vaccinating, adverse event monitoring and frequently asked questions can be found at the THL website both in Finnish and Swedish language (www.thl.fi).

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