Uptake and timeliness of rotavirus vaccination in Norway: The first year post-introduction

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Abstract

Background: To minimise vaccine-associated risk of intussusception following rotavirus vaccination, Norway adopted very strict age limits for initiating and completing the vaccine series at the time rotavirus vaccination was included in the national immunisation programme, October 2014. Although Norway has a high coverage for routine childhood vaccines, these stringent age limits could negatively affect rotavirus coverage. We documented the status and impact of rotavirus vaccination on other infant vaccines during the first year after its introduction.

Methods: We used individual vaccination data from the national immunisation register to calculate coverage for rotavirus and other vaccines and examine adherence with the recommended schedules. We identified factors associated with completing the full rotavirus series by performing multiple logistic regression analyses. We also evaluated potential changes in uptake and timeliness of other routine vaccines after the introduction of rotavirus vaccine using the Kaplan-Meier method.

Results: The national coverage for rotavirus vaccine achieved a year after the introduction was 89% for one dose and 82% for two doses, respectively. Among fully rotavirus-vaccinated children, 98% received both doses within the upper age limit and 90% received both doses according to the recommended schedule. The child’s age at the initiation of rotavirus series and being vaccinated with diphtheria, tetanus, pertussis, polio and Haemophilus influenzae type b (DTaP/IPV/Hib) and pneumococcal vaccines were the strongest predictors of completing the full rotavirus series. No major changes in uptake and timeliness of other paediatric vaccines were observed after introduction of rotavirus vaccine.

Conclusions: Norway achieved a high national coverage and excellent adherence with the strict age limits for rotavirus vaccine administration during the first year of introduction, indicating robustness of the national immunisation programme. Rotavirus vaccination did not impact coverage or timeliness of other infant vaccines.

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1. Introduction

In October 2014, the two-dose oral Rotarix® vaccine (GlaxoSmithKline Biologicals, Rixensart, Belgium) was introduced in the Norwegian immunisation programme. Current European guidelines from 2014 recommend initiating rotavirus vaccination between 6 and 8 weeks of age and completing the entire series by 24 weeks of age due to age-specific vaccine-associated risk of intussusception following vaccination [1,2]. The previous version of these guidelines recommended the first rotavirus dose to be given between 6 and 12 weeks of age and completing the entire vaccine series by the age of 27 weeks [3]. The World Health Organization recommends an upper age limit of 15 weeks for the first rotavirus dose and a maximum age of 36 weeks to complete the full series [4]. The upper age limits for vaccination are recommended because of a risk of intussusception following rotavirus vaccination [5–7]. The baseline annual incidence of intussusception in Norway before rotavirus vaccine introduction was estimated at 3.7 (95% CI 3.3–4.2) cases per 10,000 children <2 years of age [8]. To minimise vaccine-associated risk of intussusception, Norway was the first among all industrialised countries to adopt the strictest age limits for initiating and completing the vaccine series. Thus, the initiation of rotavirus vaccination is recommended at 6 weeks of age with the second dose given at 12 weeks of age. The Norwegian absolute upper age limit for the first dose is 12 weeks (84 days) and for the second dose is 16 weeks (112 days). An interval of at least 4 weeks (28 days) is recommended between the two doses.

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At the time rotavirus vaccination was introduced in October 2014, Norway had a consistently high uptake for other childhood vaccines included in the national immunisation programme (e.g. ≥93% for the third dose of diphtheria, tetanus, pertussis, polio and Haemophilus influenzae type b vaccine (DTaP/IPV/Hib) at 2 years of age). However, a recent study found that at least one routine vaccination was slightly delayed in 45% of Norwegian children aged ≤2 years [9]. The stringent age cut-offs for rotavirus vaccine administration could negatively affect its uptake, but delayed rotavirus vaccination could affect vaccine safety and potentially jeopardize sustainability of the entire immunisation programme. Thus, a timely assessment of both vaccine coverage and adherence with the recommended age limits is crucial to ensure the adequate implementation, performance and safety of a newly introduced immunisation programme.

The aim of this study was to document the status and impact—on other vaccines—of rotavirus vaccination in Norway during the first year after its inclusion in the national immunisation programme, and to identify predictive factors for completion of the two-dose vaccination course.

2. Materials and methods

2.1. Data source and study population

We obtained data from the Norwegian Immunisation Register (SYSVAK), a national, electronic immunisation register which uses population census data as a denominator to estimate vaccine coverage [10]. Reporting to SYSVAK is mandatory for all programme vaccines and is based on a unique personal identification number assigned to all legal residents in Norway. Immunisation providers report the following data to SYSVAK: personal identification number, birth date, sex, administration date for each vaccine dose, vaccine-specific code (a reporting code assigned by the register to differentiate between various vaccines), name and municipality of the immunisation provider, and reporting date. Nearly all providers (99%) report data electronically in real time by transferring information to SYSVAK through a secure link. The remaining 1% report by using paper forms; these data are entered manually. The completeness of reported data is high, as 98% of the annual birth cohorts (n ~ 60,000) are registered in SYSVAK.

For this study, we used two cohorts of children: a pre-rotavirus vaccine cohort and a post-rotavirus vaccine cohort. The pre-rotavirus vaccine cohort consisted of all children born from 1 September 2009 through 31 August 2014 or during five years before the introduction of rotavirus vaccine. The post-rotavirus vaccine cohort includes children born from 1 September 2014 through 31 August 2015; the first annual cohort eligible to receive rotavirus vaccine within the national programme. For the post-rotavirus vaccine cohort, data extraction and evaluation was done on a weekly basis during January–December 2015 to ensure that the each member of the cohort was age-eligible for vaccination. Immunisation status and time of vaccination for each child were first evaluated when the child had reached 16 weeks of age and re-evaluated on a weekly basis until the end of study period.

If multiple vaccinations targeting the same diseases were recorded on the same date, only one vaccination was included in the analysis. If more than two rotavirus doses were recorded for the same child, information about only the first two doses was included in the analysis. This is because multiple reporting to SYSVAK is possible even though the national programme offers only a two-dose rotavirus vaccine. We calculated age at vaccination for all received doses and intervals between doses using the birth date and administration dates for each dose.

2.2. Coverage, timeliness and completeness of rotavirus vaccination

Rotavirus vaccine coverage was calculated from January 2015 to December 2015 using the post-rotavirus vaccine cohort. We calculated the general coverage for rotavirus vaccination by using the total number of children who had received the vaccine as the numerator and the number of children born in Norway during the study period as the denominator. Both the numerator and the denominator included only children who were 16 weeks and older at the time of each data extraction because 16 weeks is the maximum recommended age for a two-dose rotavirus vaccine course in Norway [8]. We examined timeliness of rotavirus vaccination by calculating a time-dependent coverage. The latter was calculated by restricting the numerator to children who received dose one by age 12 weeks and dose two by 16 weeks of age. We assessed adherence with the recommended schedule by restricting the numerator to children who received dose one between 6 and 12 weeks of age and dose two by age 16 weeks, including an interval of at least 4 weeks between the doses. The proportions of children vaccinated before reaching the lower age limit of 6 weeks or outside the upper age limit of 16 weeks were also calculated.

We evaluated differences in the rotavirus vaccine coverage by sex and geographic regions using a chi-square test. For the latter, data were divided into five regions: Northern, Central, Western, Southern and Eastern. In addition, we assessed the relationship between completeness of rotavirus schedule and a set of predictor variables. Rotavirus vaccination status was defined as partially vaccinated if only one rotavirus dose was administrated or fully vaccinated if two rotavirus doses were administrated. The set of predictor variables included age at administration for rotavirus dose one, sex, geographical region, having received at least one dose of DTaP/IPV/Hib, pneumococcal or hepatitis B vaccines, and having received one dose of Bacillus Calmette-Guerin (BCG) vaccine. Socio-economic characteristics such as parental educational status or household income are not available in the immunisation register. To explore the association between rotavirus vaccination status and each of these predictor variables, we first performed a univariate logistic regression analysis; Odds Ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated. Variables found to be associated in the univariate models at the threshold of p < 0.1 were entered into multiple logistic regression models through a forward stepwise selection process and retained if their inclusion produced a significant likelihood ratio test result (p < 0.05) as compared to the previous model. ORs and their 95% CIs were calculated for the final adjusted model. Statistical significance for the multiple logistic regression model was determined by setting a conservative Bonferroni corrected threshold of p < 0.05/M, where M denotes the number of explanatory variables included in the final adjusted model.

2.3. Comparison between rotavirus vaccine and other programme vaccines

We assessed uptake for other childhood programme vaccines such as the BCG and hepatitis B vaccines, which Norway offers to children whose parents originate from areas with high endemicity of tuberculosis or hepatitis B virus infection. Simultaneously with the introduction of rotavirus vaccine, timing of BCG vaccination was moved from birth to 6 weeks of age per modified national recommendations. In addition, we calculated coverage of dose one for DTaP/IPV/Hib vaccine and dose one of pneumococcal vaccine and compared coverage for these vaccines with a two-dose coverage for rotavirus vaccine. Both DTaP/IPV/Hib and pneumococcal vaccines should be administered concomitantly with the second rotavirus dose before age 16 weeks in the Norwegian programme. Coverage for these vaccines was calculated by using the same
post-rotavirus vaccine cohort of children and the same method as described above for rotavirus vaccine.

2.4. Impact of rotavirus vaccine introduction on other infant vaccines

We examined differences in uptake and timeliness of other paediatric vaccines between the pre- and post-rotavirus vaccine periods. For pre-rotavirus vaccine period, data were divided into five birth cohorts; each cohort included children born during 1 September–31 August annually. Immunisation data were used for all children with information on the birth date and dates of vaccination. We ensured that all children included in the analysis were age-eligible for vaccination by evaluating immunisation data for children who were 16 weeks of age or older by the end of each study period (i.e. 31 August). If a child was not vaccinated by the end of the study period, the child was considered as right-censored. For each vaccine included in the study, timeliness and coverage at any given age were estimated by the Kaplan–Meier (KM) method using age at vaccine administration as the time scale [11]. The KM method estimates the survival function, \( KMS(t) \), for each age interval, \( t \), as the proportion of children unvaccinated at the end of the age interval divided by those unvaccinated at the beginning of the age interval. The immunisation coverage at any given time is calculated by the inverse of survival function, \( 1 – KMS(t) \) [12].

All analyses were performed using the statistical software STATA, version SE13 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Coverage, timeliness and completeness of rotavirus vaccination

From January 2015 to December 2015, rotavirus vaccine coverage in Norway increased from 77% to 89% for one dose and from 65% to 82% for two doses. We observed no differences by sex for either one or two doses. However, there were significant differences in the coverage by geographical regions for both dose

<table>
<thead>
<tr>
<th>OR</th>
<th>[95% CI]</th>
<th>p-val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (ref)</td>
<td>0.95</td>
<td>0.89</td>
</tr>
<tr>
<td>Female</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Age at vaccine administration</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Not vaccinated (ref)</td>
<td>60.48</td>
<td>48.82</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>49.76</td>
<td>34.74</td>
</tr>
<tr>
<td>DTP</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Not vaccinated (ref)</td>
<td>1.08</td>
<td>1.00</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>1.35</td>
<td>1.12</td>
</tr>
<tr>
<td>BCG</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Not vaccinated (ref)</td>
<td>0.84</td>
<td>0.78</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>0.58</td>
<td>0.49</td>
</tr>
<tr>
<td>HEP</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Not vaccinated (ref)</td>
<td>15.80</td>
<td>13.92</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>3.77</td>
<td>2.77</td>
</tr>
<tr>
<td>PNE</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Not vaccinated (ref)</td>
<td>0.76</td>
<td>0.70</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>0.78</td>
<td>0.70</td>
</tr>
</tbody>
</table>

OR: Odd ratios and 95% confidence intervals for OR’s; p-val: p-values obtained from logistic regression models.

Variables included in the final multiple logistic regression models; Ref: reference group used in the logistic regression model. Bold indicates significant association between rotavirus vaccine status and explanatory variables in the multiple logistic regression model using a Bonferroni corrected threshold of \( p < 0.05/M \), where \( M = 6 \), number of variables included in the final multiple logistic regression model. DTP: diphtheria, tetanus, pertussis, inactivated polio, haemophilus influenzae type b vaccine; PNE: pneumococcal vaccine; BCG: Bacillus Calmette-Guerin vaccine.
3.2. Comparison between rotavirus vaccine and other programme vaccines

3.2.1. DTaP/IPV/Hib and pneumococcal vaccines

During the first year of rotavirus vaccine introduction, coverage for dose one of DTaP/IPV/Hib vaccine among children also eligible for rotavirus vaccination was higher (95%) than rotavirus coverage for dose two (82%). Of 47,419 children vaccinated with both vaccines during this period, 92% were immunised concomitantly. Differences in coverage between rotavirus vaccine and DTaP/IPV/Hib vaccines varied across Norway with the largest difference (16%) found in the Southern part of Norway and the smallest (12%) in Eastern Norway. The difference in coverage between these two vaccines reduced over time. The proportion of children vaccinated with two rotavirus doses among those receiving one dose of DTaP/IPV/Hib vaccine increased from 77% in January 2015 to 86% in October 2015, suggesting an improved performance of the immunisation programme over time. Coverage of pneumococcal vaccine during the first year of rotavirus vaccine was very similar to DTaP/IPV/Hib vaccine.

3.2.2. BCG and hepatitis B vaccines

By December 2015, 11,087 (20%) children born from 1 September 2014 to 31 August 2015 and eligible for rotavirus vaccination were BCG immunised. Among these children, 93% also received at least one rotavirus dose and 50% received both vaccines concomitantly with the mean age at vaccination of 6.8 weeks (median: 6.7; IQR: 6.3–7.3). Among the same cohort of children, 12,642 received one dose of hepatitis B vaccine, 11,385 received two doses and 5269 received three doses. Of the children that received at least one dose of hepatitis B vaccine, 91% received also one rotavirus dose and 80% received two rotavirus doses.

3.3. Impact of rotavirus vaccine introduction on other infant vaccines

We compared coverage and timeliness of other infant vaccines during the pre- and post-rotavirus periods and observed no differences between the two periods (Fig. 1). The mean age at vaccination was 13.5 weeks for the DTaP/IPV/Hib vaccine and pneumococcal vaccines during both study periods; 90% of children were vaccinated with these vaccines before age 16 weeks during both pre- and post-rotavirus periods.

The proportion of children vaccinated with the BCG vaccine was also similar during the pre-rotavirus period (19%) to the proportion estimated during the first year after the introduction of rotavirus vaccine (20%). There was a change in the age at BCG vaccination during the post-rotavirus period, with one half of all children receiving the vaccine by 6.7 weeks of age compared to the same proportion being vaccinated by 1.7 weeks of age during the pre-rotavirus period. This change is likely a result of modifying the recommended age for BCG vaccination from birth to 6 weeks, which was introduced in Norway simultaneously with rotavirus vaccination.

4. Discussion

A year after the inclusion of rotavirus vaccine in the national immunisation programme, Norway achieved a highly satisfactory

![Fig. 1. Cumulative vaccination coverage (inverse Kaplan-Meier curves) with DTP: diphtheria, tetanus, pertussis, inactivated polio, haemophilus influenzae type b vaccine; PNE: pneumococcal vaccine; BCG: Bacillus Calmette-Guerin vaccine during pre-rotavirus vaccine and post-rotavirus vaccine periods, Norway.](image)
coverage compared to other industrialised countries [13–15]. From January 2015 to December 2015, rotavirus vaccine coverage was 77–89% for dose one and 65–82% for dose two. Adherence with the national recommendations for the rotavirus vaccination schedule was also very high for each of the two doses; 98% of children received both doses within the upper age limits, and 90% were immunised per national recommendations. Such high adherence with the rigid age limits for a newly introduced vaccine is indeed impressive. To our knowledge, Norway is the only industrialised country at present that adopted such strict age limits in the national programme in order to reduce vaccine-associated risk of intussusception. Such risk mitigation strategy has not been pursued elsewhere due to feasibility issues and concerns about reaching a high coverage. Since rotavirus vaccine introduction in 2014, no signal of increased intussusception incidence has been identified. However, a detailed assessment of the post-introduction incidence of intussusception over a longer period is required to fully evaluate the benefits of a strict administration schedule.

Completing rotavirus vaccine series is critical to increase vaccine effectiveness and provide full protection against rotavirus disease. In Norway, a high completeness of vaccine series was obtained throughout the first introduction year: 92% of children who received one rotavirus dose also received dose two. Because of the strict age limits established in the Norwegian programme, children who were delayed with dose one, were less likely to complete the full vaccine series.

Despite rapidly achieved high coverage for rotavirus vaccine, it was still 13% lower at the end of the first introduction year compared with coverage for other childhood vaccines such as the DTap/IPV/Hib and pneumococcal vaccines. A similar phenomenon was reported from other countries that introduced rotavirus vaccination [16]. The strict age recommendations for rotavirus vaccination are a likely explanation for a lower rotavirus coverage compared with other routine immunisations. Other explanations are lower community acceptance, vaccine hesitancy, and safety concerns about a newly introduced vaccine [17,18]. Differences in coverage between rotavirus and other programme vaccines varied across the country with the largest difference found in the Southern part. Because organisation and delivery of immunisation services in Norway is a local responsibility, regional differences in coverage could be explained by different implementation routines in various regions and delays in reporting of immunisation data [10].

Previous studies have shown an improvement in the timeliness of other paediatric vaccines after the introduction of rotavirus vaccine in the national immunisation programme [19,20]. However, a year of rotavirus vaccine use in Norway did not seem to influence timeliness of the DTap/IPV/Hib, pneumococcal or hepatitis B vaccines. We found a shift in the age at vaccination with the BCG vaccine after introduction of rotavirus vaccine, which is likely due to the modified national BCG recommendations. The inclusion of rotavirus vaccine also did not influence the coverage of other paediatric vaccines during the first post-introduction year, demonstrating that uptake of other vaccines was not jeopardized by the introduction of a new oral vaccine with strict age limits for administration. Interestingly, we found that children vaccinated against hepatitis B virus infection were less likely to complete the full rotavirus series. As hepatitis B vaccination is currently offered only to children with immigrant parents, it is possible that socioeconomic and cultural determinants in this population affect immunisation rates, in particular for newly introduced vaccines.

The strength of our study is the use of individual immunisation data from a national population-based register, which is the most robust source for estimating population-based vaccine coverage. The Norwegian immunisation register is among the most developed electronic immunisation registries in Europe [10]. The validity and completeness of data are ensured through mandatory reporting of all programme vaccines and an extensive quality assurance programme. Despite using highly robust immunisation data, coverage for rotavirus and other vaccines in our study may have been underestimated. Miscoding of newly introduced vaccines can occur, especially at the start of introduction, if a reporting code for a new vaccine is missing in the medical records’ system used by immunisation providers or if providers are not aware of a new vaccine. Underreporting is also possible because vaccinations are reported using a personal identification number, and some infants may not be assigned such numbers at the time when they were eligible to receive the first rotavirus dose. In this case, vaccination is reported using a temporary personal identification number but unless reported data are updated by the provider after the permanent personal identification is assigned, there will be a mismatch between the provider’s system and the register. This may reduce our estimates of rotavirus vaccine coverage, especially for two doses, because when only one dose is reported, a child would be included in the coverage estimates for one dose but not in the estimates for two doses even though he or she may have received two doses.

5. Conclusion

This study provides the first insight into the performance of rotavirus vaccination programme since its introduction in Norway. High vaccine coverage together with a highly satisfactory adherence with the strict age recommendations was achieved during the first year of introduction, indicating feasibility of such vaccination strategy and robustness of the Norwegian immunisation programme. Introduction of rotavirus vaccination did not affect coverage or timeliness of other infant vaccines.

Conflict of interest

The authors declare that they have no competing interests.

Author’s contributions

BVS conducted data analysis and drafted the manuscript. MEHJ provided data for analysis and helped to draft the manuscript. EF conceived and designed the study and drafted the manuscript. All authors read and approved the final manuscript.

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