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Intussusception among Norwegian children: What to expect after introduction of rotavirus vaccination?

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ABSTRACT

Background: To reduce the risk of vaccine-associated intussusception, rotavirus vaccination in Norway was implemented under strict age limits (the first dose given by 12 weeks of age and the second dose by 16 weeks of age) in 2014. We estimated the incidence of intussusception in children <2 years old before vaccine introduction and the number of vaccine-associated cases under current and extended age limits for vaccine administration in Norway.

Methods: To estimate the baseline incidence, we validated all diagnoses in children <2 years old registered in the national hospital registry during the pre-vaccine period of 2008–2013. Using national vaccine coverage data and international estimates of intussusception risk after rotavirus vaccination, we calculated the numbers of expected vaccine-associated intussusception cases to compare with the estimated numbers of averted rotavirus cases. Uncertainty was accounted for by several scenario analyses using current and extended age limits for vaccine administration.

Results: The pre-vaccine incidence of intussusception was 26.7 (95% CI 23.1–30.6) cases/year per 100,000 children <2 years old and 37.1 (95% CI 31.2–43.8) cases/year per 100,000 children <1 year old. In the 2016 birth cohort (approx. 60,000) vaccinated under the current age limits, 1.3 (95% CI 0.7–2.0) vaccine-associated intussusception cases were expected to occur. If age limits were extended to 16 weeks for the first vaccine dose and 24 weeks for the second dose, leading to more children vaccinated at an older age, 2.2 (95% CI 1.2–3.5) excess cases would be expected in the same cohort. Simultaneously, an estimated 1768 rotavirus hospitalizations/year in children <5 years old would be averted under current age limits, with 98 additional rotavirus hospitalizations averted under extended age limits.

Conclusions: Administering rotavirus vaccines beyond current age limits in Norway would lead to a marginal increase in the number of intussusception cases, which would be offset by the benefits of vaccination.

1. Introduction

Intussusception is the most common cause of bowel obstruction in infants and young children; without treatment it can disrupt the bowel's vascular supply and cause ischemia, perforation, and ultimately death. The background incidence of intussusception varies largely by country. Overall, many industrialized countries report a baseline incidence of under 60 cases per 100,000 person-years among children <1 year of age, with a peak incidence around 5–7 months of age [1–5]. Currently licensed rotavirus vaccines are associated with a small risk of intussusception of 1–5 cases per 100,000 vaccinees [1,6–8]. The vaccine-attributable risk seems to be highest in the first week following the first dose [9]. A previous rotavirus vaccine, Rotashield®, was withdrawn from the market due to a higher risk of intussusception (approximately 10 cases per 100,000 vaccinees) [10–12]; the risk was highest in infants who received their first dose after 3 months of age. Because the vaccine-attributable risk of intussusception seems to be age-dependent, the first dose of rotavirus vaccine is recommended in Europe between 6 and 12 weeks of age, with a full schedule (2 doses for Rotarix® and 3 doses for RotaTeq®) completed by 6 months of age [13].

Universal rotavirus vaccination programs are currently implemented only in one third of European countries [14]. Vaccine safety concerns have been considered a barrier to the introduction [15]. For example, French health authorities withdrew their vaccine recommendations in 2015 after two intussusception deaths temporally related to rotavirus vaccination [16]. Rotarix® and

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RotaTeq®, have been available for purchase on the Norwegian market since 2006 and 2010, respectively, with a minimal uptake prior to introduction in the national program. In 2014, Norway introduced rotavirus vaccination in the national immunization program using Rotarix® (GSK, Belgium). To minimize the risk of intussusception, Norway adopted strict age limits for vaccine administration despite a probability of negatively affecting vaccine uptake. The first dose is recommended at 6 weeks of age with a maximum age limit of 12 weeks, and the second dose is recommended at 12 weeks with a maximum limit of 16 weeks. An interval of at least 28 days is advised between doses. Norway rapidly achieved high national coverage and excellent adherence to the recommended vaccine schedule during the first year of introduction [17]. The national coverage for rotavirus vaccine was 91% for one dose among children aged 12 weeks and 86% for two doses among children aged 16 weeks in December 2017; 88% were vaccinated within the recommended age limits. However, the rotavirus vaccine coverage is still below the routine coverage of 96% for other pediatric vaccines in Norway.

The World Health Organization recommends post-licensure surveillance to detect rare adverse events, including intussusception, in countries with routine rotavirus vaccination [18]. Country-specific incidence estimates of intussusception are a prerequisite for detecting safety signals post-licensure. We estimated the baseline incidence of intussusception among children <2 years of age in Norway before vaccine introduction, and the expected numbers of vaccine-associated intussusception cases post-vaccination, under current and extended age limits for vaccine administration. We also performed a benefit–risk analysis by comparing the numbers of expected vaccine-associated intussusception cases with the estimated numbers of averted rotavirus cases in the post-vaccine birth cohorts.

2. Patients and methods

2.1. Pre-vaccine incidence of intussusception

We used data from the Norwegian Patient Registry, which contains information about nearly all hospitalizations in public and private hospitals in Norway [19]. We extracted data on hospital contacts with 10th Revision of the International Classification of Diseases (ICD-10) code K56.1 for intussusception in children <2 years of age occurring from January 1999 to December 2017. Data reported before 2008 did not contain the individual personal identification number, whereas data reported from 2008 onwards were person-identifiable, allowing us to link the registry data to patients' medical records to validate the intussusception diagnoses. Information extracted from medical records included admission dates, symptoms, treatments, and outcomes. Medical chart review and data extraction were conducted using a standardized form by three study investigators (physicians) from the Norwegian Institute of Public Health (NIPH) with support from a local pediatrician at each hospital. Two NIPH investigators reviewed each record to reduce observer bias. In case of doubt, the medical record was discussed until consensus was reached.

We classified intussusception cases for the period 2008–2013 as definite, probable, and possible using the Brighton Collaboration Clinical Case Definition [20]. To calculate the incidence among children <2 years of age, we included only the first episode of definite (confirmed by surgery, air or liquid-contrast enema, or ultrasound) intussusception occurring in each child during the study period. The annual numbers of children <2 years of age provided by Statistics Norway was used as denominator, assuming a constant birth-rate throughout the year [21]. We used a Poisson regression model fitted to weekly data on reported intussusception cases using a restricted cubic spline with 6 degrees of freedom to model the non-linear age association and predict the weekly intussusception rates before vaccine introduction.

2.2. Vaccine-associated intussusception

The size of the Norwegian birth cohort (approx. 60,000) does not allow a sufficient statistical power to estimate the country-specific risk of vaccine-associated intussusception after rotavirus vaccination. We therefore applied pooled estimates of intussusception risk for the monovalent rotavirus vaccine obtained in a meta-analysis for industrialized settings (relative risk 2.35 (95% CI 1.45–3.80) during days 1–21 after dose one, and 1.77 (95% CI 1.29–2.43) during days 1–21 after dose two) [8]. Using the predicted baseline incidence of intussusception, the weekly numbers of vaccinated children by age in weeks in 2016 and population data estimates from Statistics Norway for the period 2016–2019 [21], we estimated the mean number of vaccine-associated intussusception cases occurring in each birth cohort during 2016–2019 vaccinated under the current age limits. The Norwegian Immunization Registry SYSVAK provided data on age at rotavirus vaccination among children vaccinated in 2016 [22].

2.3. Scenarios

Furthermore, we estimated the mean number of intussusception cases that would occur if current age limits were extended to 16 weeks of age for the first dose and 24 weeks for the second dose. We used several scenarios to test the impact of different assumptions about the vaccine uptake and distribution of age at vaccination under extended age limits. The main scenario assumed that extended age limits would increase the coverage for one dose to 96% (based on the highest proportion of Norwegian children vaccinated with other routine vaccines at 2 years of age) and 91% for two doses (based on the difference between current coverage for one and two rotavirus doses). Currently, 95% of Norwegian children receive the first rotavirus dose within 3–4 weeks of the lowest recommended age limit of 6 weeks. If age limits were extended, we expect that the age distribution of vaccinated children would largely remain left-skewed but a shift to the right may occur with some children being vaccinated later compared to the present situation. Hence, in the main scenario, we assumed that age at vaccination would be uniformly distributed over the time window allowed for each dose, suggesting that equal proportions of children will be immunized each week. Because the baseline incidence of intussusception in Norway increases by age with a peak incidence at 6–7 months (Fig. 2), this scenario is considered to be least favorable with regard to the vaccine program. In addition we evaluated four other scenarios: (1) extending age restrictions under a uniform distribution of age at vaccination but without increasing the current coverage; (2) increasing the coverage under the current age restrictions with the same distribution of vaccination age as at present; (3) increasing the vaccine-associated intussusception risk to the upper bound of the confidence interval for the RR estimates; and (4) decreasing the vaccine-associated intussusception risk to the lower bound of the confidence interval. The confidence intervals for our intussusception estimates were generated by simulating 1000 datasets from the estimated error associated with our regression models and risk ratios, making estimates for each of the 1000 datasets, and then taking the 2.5th, 50th, and 97.5th percentiles.

2.4. Rotavirus episodes averted

Lastly, we compared the number of vaccine-associated intussusception cases with the number of rotavirus-related outcomes

that would be averted by vaccination under both extended and current age limits. Rotavirus-related outcomes (hospital and primary care contacts, homecare episodes and deaths) were estimated by using a previously published dynamic rotavirus transmission model [23,24] fitted to the Norwegian data. The model was updated with 2015–2017 birth cohort data and projections from Statistics Norway [21].

2.5. Statistical analyses and ethics

Analyses were performed using Stata version 13 (StataCorp., College Station, TX) and R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the Regional Committee for Medical and Health Research Ethics.

3. Results

3.1. Pre-vaccine incidence and epidemiology of intussusception

A total of 1512 admissions (annual mean 80, range 42–134) with the intussusception code in children <2 years of age were registered in Norway during 1999–2017. Overall during the 19-year study period, there was a decrease in the annual number of cases, with 134 in 1999 and 42 in 2017 (Fig. 1).

Of 447 intussusception-coded admissions registered during 2008–2013, 431 (96%) were linked to medical records. Linkage was not possible due to missing personal identifiers in 14 cases and missing medical records in two patients. The 431 admissions represented 274 disease episodes in 267 children <2 years of age (157 admissions were duplicate records of patients transferred between hospitals or readmitted in connection with the same episode). Seven intussusception episodes were excluded because they were the second or third episode in the same patient during the study period. Of 267 cases included in the analysis, 195 were defined as intussusception level 1 (definite) according to the Brighton Collaboration Clinical Case Definition, whereas 18 were level 2 (probable) and four were level 3 (possible). In 50 cases (18.7%), the intussusception diagnosis was ruled out during admission or the Brighton criteria were not met.

Over the 6-year study period from 2008 to 2013, the mean incidence of definite intussusception among children <2 years of age was 26.7 (95% CI 23.1–30.6) cases/year per 100,000 among children <2 years and 37.1 (95% CI 31.2–43.8) cases/year per 100,000 among children <1 year of age (Table 1).

The median age of patients <2 years of age with definite intussusception was 9.3 (IQR: 5.6–15.1) months (40.3 weeks) with a peak at 6–7 months (26–30 weeks) of age (Fig. 2). Children aged <12 months accounted for 69% of cases, and only four were <2 months old.

3.2. Vaccine-associated intussusception cases after rotavirus introduction

Under current age restrictions for rotavirus vaccination in Norway, 1.1 (95% CI 0.5–2.1) vaccine-associated intussusception cases per 100,000 vaccinees are expected to occur in the 2016 birth cohort after the first dose, and 1.3 (95% CI 0.5–2.4) cases per 100,000 are expected to occur after the second dose. This corresponds to a combined estimate of 1.3 (95% CI 0.7–2.0) intussusception cases in the entire cohort (Table 2). Simultaneously, rotavirus immunization program would avert a mean of 8534 rotavirus-related primary care consultations and 1768 hospitalizations (inpatient and outpatient contacts) in the same cohort during their first five years of life (Table 2), corresponding to 1360 rotavirus hospitalizations being averted for each intussusception hospitalization.

If the age limits for vaccine administration were extended to 16 weeks of age for the first dose and 24 weeks for the second dose with a uniform distribution of age at vaccination, 2.2 (95% CI 1.2–3.5) vaccine-associated intussusception cases are estimated to occur in the 2016 cohort, resulting in less than one additional vaccine-associated intussusception case compared to the present situation (Table 2). Considering an increase in vaccine coverage under this scenario, rotavirus immunization program would avert an additional 598 rotavirus primary care visits and 98 rotavirus hospitalizations in the same cohort (Table 2). Additional scenario analyses demonstrated that the estimates of vaccine-associated intussusception cases after rotavirus vaccination were more sensitive to the increase in the age at vaccination compared with an

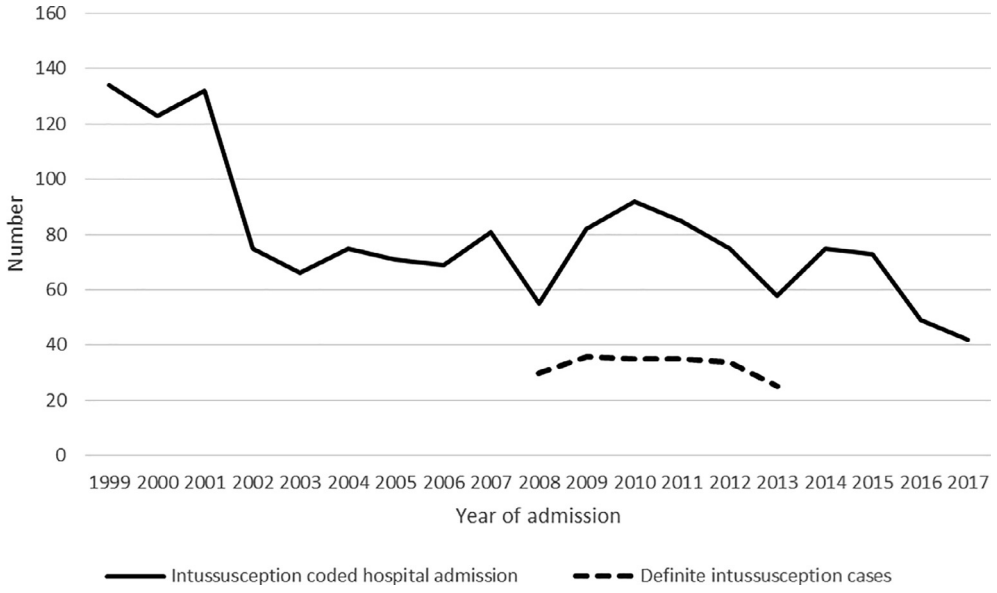

Fig. 1. Number of intussusception-coded hospital admissions (1999–2017) and definite intussusception cases (2008–2013) by year among Norwegian children <2 years of age.

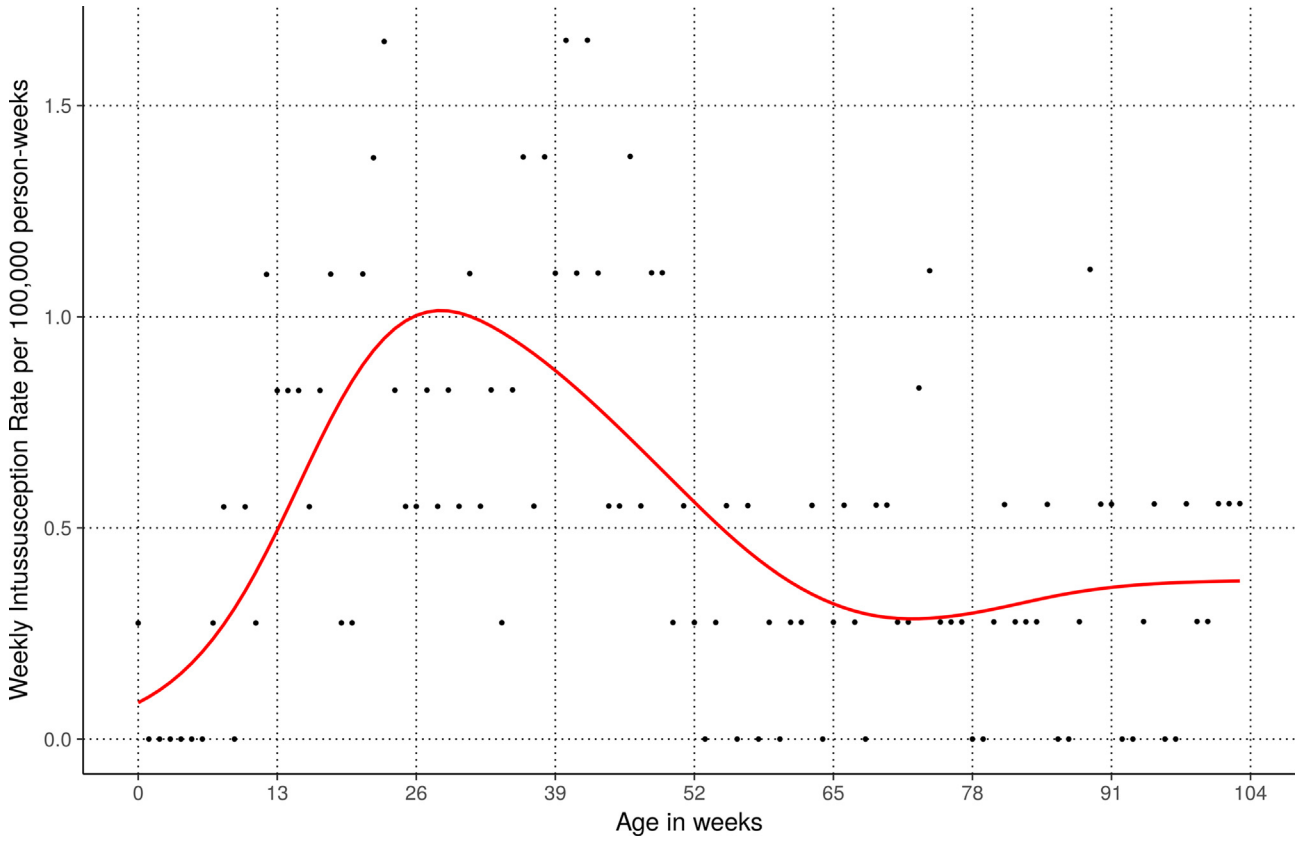

Fig. 2. Observed and predicted weekly intussusception rates per 100,000 person-weeks for definite cases <2 years of age hospitalized in Norway, 2008–2013.

Table 1
Pre-vaccine incidence of definite intussusception in hospitalized children <2 years of age in Norway, 2008–2013.

Year	No. cases <2 y	Incidence per 100,000 infants <2 y	95% confidence interval	No. cases <1 y	Incidence per 100,000 infants <1 y	95% confidence interval
2008	30	25.4	17.1–36.2	22	37.5	23.5–56.8
2009	36	30.0	21.0–41.5	26	42.9	28.0–62.8
2010	35	28.3	19.7–39.4	22	35.4	22.2–53.7
2011	35	28.1	19.6–39.1	26	42.2	27.6–61.8
2012	34	27.7	19.2–38.6	25	41.3	26.8–61.0
2013	25	20.5	13.3–30.3	14	23.1	12.7–38.8
Total	195			135		

increased vaccination coverage (Table 3). Nevertheless, in all our scenario analyses, only a marginal increase in the numbers of vaccine-associated intussusception cases was observed.

4. Discussion

This study confirms that childhood intussusception is a rare disease, with an estimated pre-vaccine rate of 27 cases annually per 100,000 children <2 years of age in Norway. Following introduction of rotavirus vaccination under the current age limits, between 1.2 and 1.3 vaccine-associated cases of intussusception were estimated to occur annually during 2016–2019. These estimates are based on the calculation of intussusception risk obtained in other industrialised settings outside Norway and represent a marginal increase compared with the pre-vaccine levels. The increase in intussusception would be offset by the number of rotavirus cases averted by vaccination. If age limits were extended and more children were vaccinated at an older age, roughly one additional intussusception case would occur annually in the vaccinated cohort, which would also be offset by the benefits of the vaccination program. Our scenario analysis demonstrated that the age at rotavirus vaccination is the key determinant in defining the expected number of vaccine-associated intussusception cases. However, we believe that despite extended age limits, most Norwegian infants will still be vaccinated closer to the lowest recommended age given a high compliance with existing recommendations, thereby minimizing the number of vaccine-associated intussusception cases.

A risk-benefit analysis from England reported that vaccination would prevent 375 rotavirus hospitalizations for each additional intussusception admission caused by the vaccine [25]. A study in the United States estimated the prevention of 1093 rotavirus admissions for each additional intussusception admission [26], closer to our estimate of 1360 averted rotavirus hospitalizations per excess intussusception case under the current age restrictions. In France, it was reported that for every intussusception hospitalization and every intussusception death caused by vaccination, 1624 rotavirus hospitalizations and 743 deaths were prevented by vaccination, respectively [27]. The recommended dosing schedule for Rotashield® in the United States resulted in many infants being vaccinated between three and seven months of age, a peak period for naturally occurring intussusception. Restricting vaccination to

Table 2
Estimated annual risks and benefits of the rotavirus vaccination in Norway under current and extended age limits for vaccine administration.

Current age restrictions and 91% coverage for first dose						
Birth cohort	Annual average vaccine-attributable intussusception cases (95% CI)	Annual average avoided rotavirus episodes in children < 5 y (95% CI)				
		Homecare episodes	Primary care visits	Inpatient hospital contacts	Outpatient hospital contacts	Deaths
2016	1.26 (0.71–1.96)	30,525 (30,515–30,534)	8,534 (8,525–8,543)	1,128 (1,123–1,133)	640 (638–641)	0.48 (0.45–0.51)
2017	1.24 (0.68–2.00)	19,184 (19,153–19,214)	6,034 (6,024–6,044)	903 (899–907)	512 (511–514)	0.41 (0.38–0.44)
2018	1.18 (0.65–1.97)	32,500 (32,490–32,509)	9,117 (9,108–9,125)	1,188 (1,183–1,194)	674 (672–676)	0.49 (0.46–0.52)
2019	1.19 (0.69–1.98)	18,520 (18,442–18,599)	7,104 (7,088–7,121)	979 (975–983)	555 (554–557)	0.42 (0.39–0.45)
Extended age restrictions and 96% coverage for first dose						
Birth cohort	Annual average vaccine-attributable intussusception cases (95% CI)	Annual average avoided rotavirus episodes in children <5 y (95% CI)				
		Homecare episodes	Primary care visits	Inpatient hospital contacts	Outpatient hospital contacts	Deaths
2016	2.17 (1.19–3.50)	32,929 (32,920–32,938)	9,132 (9,123–9,140)	1,191 (1,186–1,196)	675 (674–677)	0.50 (0.47–0.54)
2017	2.19 (1.20–3.57)	21,511 (21,479–21,542)	6,687 (6,677–6,698)	981 (977–985)	556 (555–558)	0.44 (0.41–0.47)
2018	2.06 (1.15–3.34)	30,525 (30,509–30,541)	8,806 (8,797–8,815)	1,162 (1,157–1,167)	659 (657–661)	0.48 (0.45–0.51)
2019	2.22 (1.23–3.42)	22,463 (22,399–22,528)	7,910 (7,896–7,925)	1,064 (1,059–1,069)	603 (602–605)	0.46 (0.43–0.49)

Table 3
Estimated number of vaccine-associated intussusception cases in the 2016 cohort, under different scenarios.

Scenario	No. (95% CI)
Current situation	1.26 (0.71–1.96)
Extended age restrictions with increased vaccine coverage and uniform distribution of age at vaccination	2.17 (1.19–3.50)
Extended age restrictions, current vaccine coverage and uniform distribution of age at vaccination	2.09 (1.16–3.30)
Current age restrictions, increased coverage and current distribution of age at vaccination	1.31 (0.70–2.09)
Upper bound of 95% CI of intussusception risk*, current age restrictions, current vaccination coverage and current distribution of age at vaccination	2.43 (1.53–3.72)
Lower bound of 95% CI of intussusception risk**, current age restrictions, current vaccination coverage and current distribution of age at vaccination	0.45 (0.09–0.93)

* Increasing RR to the higher confidence limit for the risk estimates (3.80 for dose 1 and 2.43 for dose 2).
** Lowering RR to the lower confidence limit for the risk estimates (1.45 for dose 1 and 1.29 for dose 2).

those younger than 3 months old would probably have reduced the risk [28]. Several studies suggest that adherence to upper age limits for vaccine administration may reduce the likelihood of vaccine-related intussusception. Data from Australia demonstrated a weaker association between Rotarix® and intussusception when cases of vaccination at an age beyond the upper limits (24 weeks) were excluded [29]. Estimates from Singapore showed that the risk of intussusception would be the lowest if both first and second vaccine dose were given at under three months of age [30]. Whether the risk of vaccine-associated intussusception relative to the baseline rates increases with age is not fully understood. Limited previous data have demonstrated no such effect modification by age [31], which is in line with a previous assessment of intussusception associated with Rotashield® [10].

It has been questioned whether rotavirus vaccines may trigger intussusception to occur earlier in some children with no overall long-term increase in the incidence [29]. This assumption is supported by Simonsen et al., who found no evidence of an increased rate of intussusception admissions during the Rotashield® period, but observed an increase in admissions at 2–4 months of age that was offset by a decrease among older infants during the Rotashield® period compared to the previous data period [32]. Several other studies also suggest that rotavirus vaccine does not increase the overall risk of intussusception [33–35].

The baseline incidence rates of intussusception were lower in our study than in neighboring Denmark (85 cases per 100,000 person-years among children <5 years of age) in 2000 [36], though we studied another age group (children <2 years of age). However, there has been a decreasing trend in both countries, and the difference may be partly explained by the different study periods. Earlier European studies conducted during 1995–2005 reported higher incidence rates [37]. In Finland, however, during the pre-vaccine years of 1999–2005, the mean incidence (12 cases per 100,000 person-years in children <1 year of age) was even lower than our rate (1). Our estimate of 37 cases per 100,000 children <1 year of age is nevertheless comparable to reports from Switzerland (4), the United Kingdom (2), the Netherlands [4], Australia [38] and the United States (5). A multi-country study from Latin America reported an incidence of definite intussusception ranging from 2 per 100,000 person-years in Brazil to 62 in Argentina for children <2 years of age, and from 4 per 100,000 person-years in Brazil to 105 cases in Argentina for children <1 year of age [39]. A literature review from 2014 reported a mean intussusception incidence of 74 per 100,000 (range: 9–328) infant years across studies from all regions of the world [40]. Differences in the reported rates may be true differences in the background rate of intussusception in the population or related to variations in health care utilization patterns, diagnostic and reporting practices. Study populations also differed substantially including only definite cases [1,2,38], probable cases [4,8] or all cases coded as intussusception in the hospital discharge database [5,36]. Several studies excluded cases with underlying pathology such as Meckel's diverticulum and other possible lead points [38,41]. We found a decrease in the rates of intussusception-coded hospital admissions from 1999 to 2017,

which is consistent with results from Denmark, the UK, and Ireland [2,36]. Coding and reporting differences might explain some of the decrease, however the reason for the observed decrease is unknown. Studies in other countries have found stable or increasing trends [5,41].

Children <12 months old in our study accounted for 69% of all cases aged <2 years of age, in line with data from Australia and Denmark [36,38]. Our model shows a peak in intussusception immediately after the sixth month of life, which is comparable to the peak incidence at 5–7 months of age noted in other studies [2,4,36,40,41]. Notably, this peak is well above the upper age limit for the second dose of rotavirus vaccination in Norway. Few of the patients were in the age group targeted by vaccination, only 6% were between 6 and 12 weeks of age which are the current age limits for the first dose in Norway.

Similar to reports from other high-income countries [41], zero mortality from intussusception was recorded in this study. However, children may die before reaching the hospital, without their death being registered in the medical record, leading to an underestimation of the true mortality.

The strength of this study is the use of data from a nationwide, population-based patient registry with personal identifier allowing us to validate the intussusception diagnoses through a review of the medical records. Because of the organization of the Norwegian healthcare system, nearly all hospital contacts are captured in the registry. We were able to identify all hospital contacts linked to one episode of intussusception and avoid counting all encounters as unique cases. If we used registry-based data alone without linking to medical records, the incidence could have been overestimated by almost one-third because 27% of the patients with intussusception-coded admissions did not meet the Brighton Collaboration criteria for definite intussusception [42]. Furthermore, using real-life data about weekly numbers of rotavirus vaccinations and the age at vaccination from a population-based vaccination registry enabled us to better estimate the number of vaccine-associated intussusception cases [22].

Even though we used comprehensive registry data, data validity should be considered. Because non-specific ICD codes are widely used by clinicians, the intussusception rates derived from hospital-based data may be underestimated. A study from the US demonstrated that intussusception rates derived on the basis of hospital discharge statistics alone underestimate the true incidence, whereas a study from Australia did not identify any additional intussusception cases during a search for associated conditions that may have been miscoded [38,43]. Moreover, we were unable to directly measure the vaccine-associated intussusception risk in Norway, which may have impacted our findings as the estimates of vaccine-associated risk were derived from countries with broader age limits for vaccine administration than Norway. This could possibly overestimate the numbers of expected cases post-vaccination. Lastly, the intussuception risk was estimated only during the three weeks after vaccination, and thus no possible compensatory reduction in the risk later in infancy was accounted for.

The benefits of rotavirus vaccination and risk of intussusception are not directly comparable. When estimating averted rotavirus cases, we did not take into consideration the expected herd protection, which may increase the benefits of vaccine program. Before vaccine introduction, rotavirus was estimated to cause one death every second year among Norwegian children <5 years of age [44], whereas no intussusception deaths were identified in our data. However, we did not further compare in detail the clinical severity and complications of rotavirus disease and intussusception. Besides, an adverse event caused by an intervention such as vaccination may be perceived more negatively than the condition caused by a failure to intervene.

5. Conclusion

Defining the acceptable risk for a vaccination program and how to manage and mitigate such risk remains a challenge. Childhood intussusception is rare in Norway, and administering rotavirus vaccines beyond the current strict age limits was estimated to result in a marginal increase in the number of vaccine-associated intussusception cases. The exact intussusception risk in Norway is yet to be determined, and because it is unclear whether an increased intussusception risk after vaccination implies an increase in the overall childhood risk, it is important to continue monitoring intussusception trends after vaccine introduction.

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Declaration of Competing Interest

All authors have indicated they have no potential conflicts of interest to disclose.

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