

# Epidemiology of intussusception in New Zealand pre-rotavirus vaccination

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## ABSTRACT

**AIMS:** To describe the epidemiology of intussusception in New Zealand children aged 0–36 months prior to the introduction of routine rotavirus vaccination.

**METHODS:** ICD-10 coding data from the New Zealand National Minimum Data Set (NMDS) was used to identify all cases of intussusception in children aged 0–36 months between January 1998 and December 2013. These data were linked with birth data from the New Zealand census. Population incidence rates of intussusception were calculated, and demographic characteristics described.

**RESULTS:** Over the 16-year study period, there were 794 cases of intussusception. The majority (56%) occurred in the first year of life (age adjusted incidence rate 56.1/100,000 child-years, 95% confidence interval (CI) 41.7–71.2). Intussusception occurred more frequently in males (36.4/100,000 (95% CI 24.6–48.2) versus 19.5/100,000 (95% CI 10.8–28.1,  $p<0.001$ )). There was no difference in intussusception incidence between ethnic groups, although cases occurred at a younger age in Māori and Pacific infants compared to Asian and other ethnicities (Pacific median 7.5 months (interquartile range 5.9–11.6), Māori 7.8 months (IQR 5.5–12.3), European 9.2 months (IQR 5.8–15.8), Other Ethnicity 10.2 months (IQR 8.2–12.3), Asian 10.5 months (IQR 7.0–17.1)). There was a weak seasonal trend with incidence troughs in January and July, and corresponding peaks in March and September.

There was wide variation in presentation rates across District Health Board (DHB) regions, with a national average of 18.0/100,000 child-years (95% CI 9.7–26.3). Most patients were admitted on a single occasion to a single hospital for treatment (81%).

**CONCLUSIONS:** This study updates background incidence rates of intussusception prior to the introduction of a national rotavirus vaccination programme in July 2014. It identifies a trend of earlier intussusception in Māori and Pacific infants; the relationship between earlier intussusception and the risk of vaccine-associated events is unknown.

Intussusception occurs when one segment of the intestine invaginates into the adjacent distal segment,<sup>1</sup> with the initiating event subclinical infection and gut adenopathy. Untreated intussusception disrupts the bowel's vascular supply and can cause ischaemia, perforation and ultimately death. Intussusception is a relatively rare event, with a worldwide incidence of 74 per 100,000 (range 9–328) in children aged less than one year of age.<sup>2</sup>

Rotavirus is a significant cause of infant gastroenteritis worldwide both in developed and developing countries. Annual estimates of rotavirus associated deaths in children under five range from 200,000 to 450,000,

most of which occur in the developing world.<sup>3</sup> Rotavirus is also a significant cause of morbidity, responsible for 2.4 million hospitalisations worldwide each year.<sup>4</sup> In New Zealand it is estimated that rotavirus is responsible for the hospitalisation of one in 43 children by the age of five.<sup>5</sup>

In 1999 an oral human-rhesus rotavirus quadrivalent vaccine (RotaShield, Wyeth-Lederle) was introduced to the US infant schedule, but withdrawn later that year after reports of an association with intussusception (a risk of approximately one case in 5,000–10,000 vaccinees).<sup>6</sup>

Two second-generation vaccines against rotavirus are available in New

Zealand: RotaTeq (Merck Sharp Dohme), a pentavalent human-bovine reassortment vaccine, containing viral protein types G1–4 and P8; and Rotarix (Glaxo Smith Klein), a human monovalent G1 vaccine. No increased risk of intussusception was detected in the large phase III pre-licensure clinical trials of Rotarix and RotaTeq despite this being a specifically monitored adverse event.<sup>7</sup>

Prior to 2014, only Rotarix was marketed for private sale in New Zealand and covered <10% of the annual birth cohort.<sup>8</sup> From July 2014, New Zealand included RotaTeq in the National Immunisation Schedule (NIS) at six weeks, three months and five months of age.

Introduction of these vaccines has been remarkably successful in both high and middle-income countries. Brazilian and Mexican studies have shown significant declines in diarrhoeal mortality post-vaccine introduction.<sup>9</sup> Studies from high-income countries have identified a 74–90 percent decline in rotavirus gastroenteritis hospitalisations in children under two, and a 29–50 percent decline in ‘all-cause’ acute gastroenteritis hospitalisations for children under five.<sup>10</sup> Recent studies have demonstrated post-vaccination reductions in hospitalisations for ‘all-cause’ seizures in children under five, most likely attributable to decreased rotavirus associated febrile illnesses.<sup>11,12</sup>

However, post-licensure studies of both RotaTeq and Rotarix in a number of countries including Australia have demonstrated small increases in intussusception attributable to the vaccines, particularly following the first dose.<sup>13</sup> Recent Australian data estimated the excess risk attributable to rotavirus vaccination to be 5.6 additional cases of intussusception per 100,000 vaccinated infants.<sup>7</sup> It is not clear whether populations with a high background risk of intussusception have a proportionally elevated risk of vaccine associated intussusception.<sup>2</sup>

Given this complex relationship, it is important for countries including New Zealand to monitor intussusception rates before and after establishment of rotavirus vaccination programmes.

A previous New Zealand study<sup>14</sup> found no association between wild type rotavirus gastroenteritis hospitalisations at eight

sites and national intussusception rates over a two year period. However, these data are over a decade old. We undertook the current study, incorporating 16 years of data, to determine a contemporary intussusception rate prior to the national introduction of the RotaTeq vaccine to allow monitoring for vaccine-associated change in intussusception rates and to assess for evidence of changing intussusception rates over time.

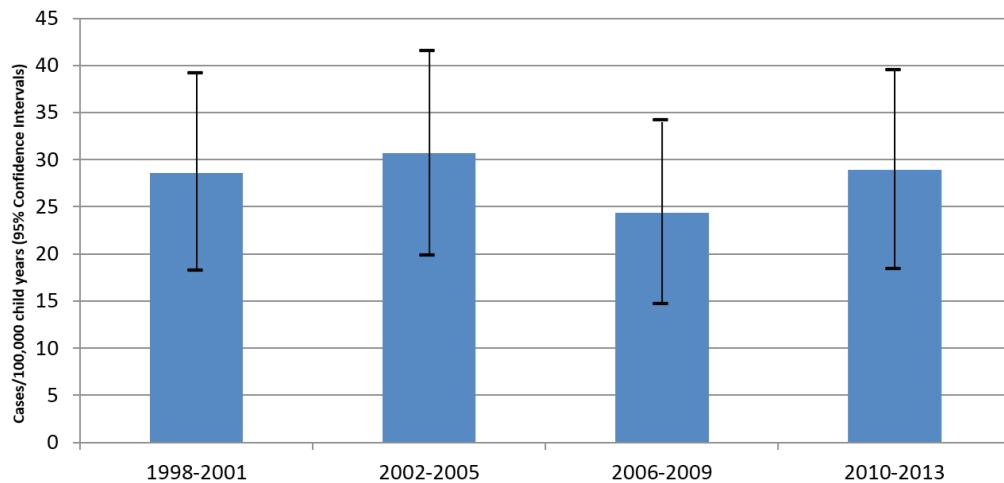
## Methods

Data for all public hospitals for the period January 1998 to December 2013, collected in the National Minimum Dataset (NMDS), were reviewed. Intussusception cases in children aged 0–36 months were identified by discharge code (ICD-10 AM code K561 or equivalent ICD-9 code).<sup>15</sup> Additional data on patient birth date, sex, ethnicity, and admitting hospital were also extracted. Within the NMDS, ethnicity is assigned using a standard priority system where Māori, Pacific Islander and Asian ethnicity is assigned preferentially (in the order stated).<sup>16</sup> NHI numbers (national health index number, a unique identifier), were not extracted, ensuring that patients remained anonymous.

Intussusception cases where the patient had the same birth date, sex and ethnicity, and which occurred within a one-week period were counted as a single episode.

Population birth rates by month of birth, sex, ethnicity and DHB region were obtained from Statistics New Zealand.<sup>17</sup> These data were used to calculate the ‘at risk’ population (children age 0–36 months) for each month of the study period. These population estimates did not take into account deaths, immigration, or emigration. New Zealand census allows individuals to identify themselves in more than one ethnic group, so total population numbers by ethnicity are higher. This slightly decreased ethnicity-specific incidence rates.

Intussusception incidence rates were estimated by combining monthly cases from the NMDS data set with monthly birth rates from Statistics New Zealand. As intussusception is a rare event, confidence intervals were calculated using standard poisson distribution methods. Significance tests were completed using standard nonpara-

**Figure 1:** Incidence of intussusception by year (New Zealand children 0–36 months, 1998–2013).

metric methods (Kruskal Wallis and Mann Whitney-U) with Bonferroni corrections when comparing multiple groups.

The study protocol was reviewed by the New Zealand Health and Disabilities Ethics Committee who determined ethical approval was not required because of the anonymous nature of the data.

## Results

Over the 16-year study period (January 1998–December 2013) 961 episodes were identified with an ICD9 or ICD10 code for intussusception in children aged 0–36 months. One hundred and sixty-seven (17%) of these episodes constituted re-presentations within a week. Thus we identified 794 patients with non-concurrent intussusception events, an average of 50 cases per year (range 39–62).

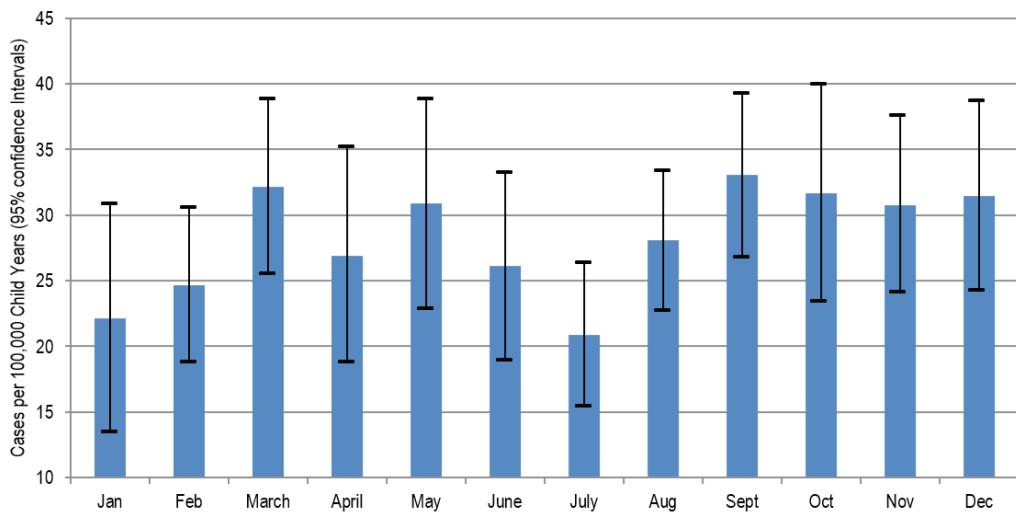
The incidence of intussusception (cases/100,000 child-years) varied from a low of 20.8/100,000 child-years in 2009, to a high of 37.3/100,000 child-years in 2002 (Figure 1). There was no increasing or decreasing trend over the study period (Kruskal Wallis,  $p=0.54$ ).

The data was initially analysed in two periods, the first corresponding to the time period of the previous New Zealand study<sup>14</sup> (Jan 1998–Jun 2003) and the second comprising all subsequent data (July 2003–Dec 2013). There was no significant difference in incidence between the two periods and for all subsequent analyses, the data were considered as a single group (Table 1).

Intussusception rates varied significantly by season, with troughs in January and July and corresponding peaks in March and

**Table 1:** Intussusception rates (cases/100,000 child-years) in New Zealand children 0–36 months, 1998–2013.

Period	Duration	Age Group	Cases	Population	Incidence	Confidence Intervals
Jan 1998–Jun 2003	5.5 years	<1 year	181	307,388	58.9	49.2–80.7
Jan 1998–Jun 2003	5.5 years	1–2 years	53	309,362	17.1	9.9–26.6
Jan 1998–Jun 2003	5.5 years	2–3 years	22	312,194	7.0	2.4–13.4
Jan 1998–Jun 2003	5.5 years	Total	256	928,944	27.6	19.4–41.0
Jul 2003–Dec 2013	9.5 years	<1 year	350	639,226	54.8	37.9–66.2
Jul 2003–Dec 2013	9.5 years	1–2 years	123	650,304	19.3	10.3–27.3
Jul 2003–Dec 2013	9.5 years	2–3 years	65	603,715	10.3	3.7–16.0
Jul 2003–Dec 2013	9.5 years	Total	538	1,893,245	28.2	16.8–37.2
Jan 1998–Dec 2013	16 years	<1 year	531	946,614	56.1	41.7–71.2
Jan 1998–Dec 2013	16 years	1–2 years	176	959,666	18.6	9.4–25.9
Jan 1998–Dec 2013	16 years	2–3 years	87	915,909	9.2	3.3–15.2
Jan 1998–Dec 2013	16 years	total	794	2,822,189	28.0	17.5–38.2

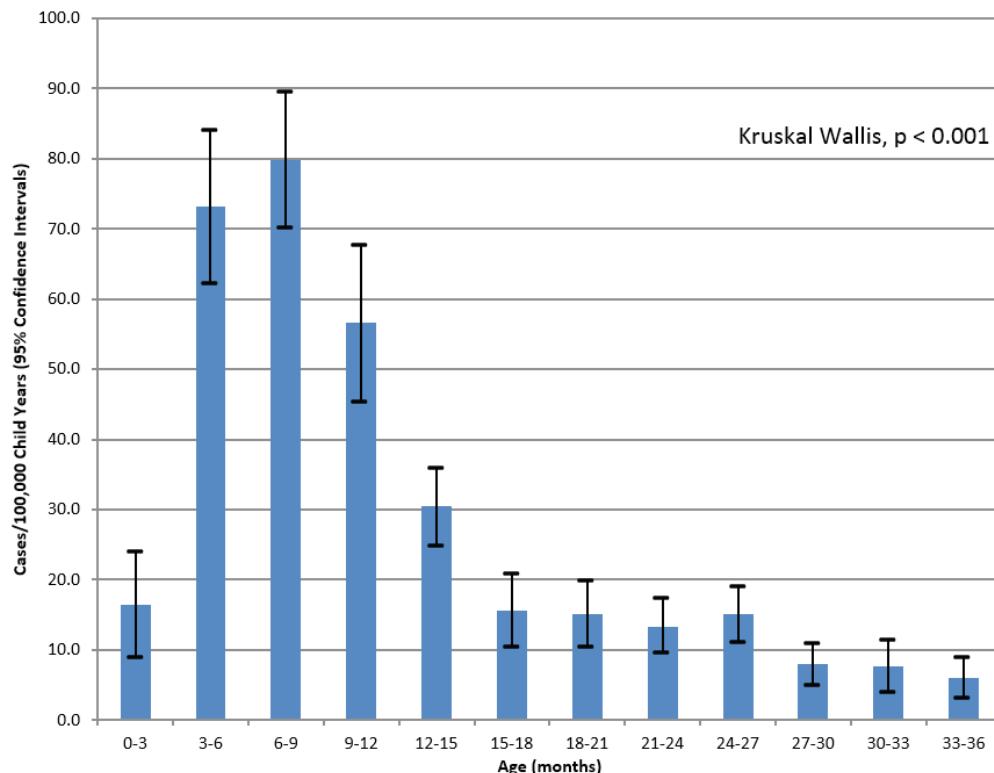
**Figure 2:** The effect of season on intussusception rates (New Zealand children 0–36 months, 1998–2013).

September (22.1/100,000 and 20.8/100,000 versus 32.1/100,000 and 33.0/100,000 child years, Kruskal Wallis,  $p<0.001$ , Figure 2).

Intussusception was commoner in younger children, with 531 (56%) cases occurring in infants aged 0–12 months. The youngest infant was ten days old. Median age was 8.95 months (IQR 5.80–14.53), with incidence peaking between six–nine months (79.8 cases/100,000 child-years), and falling

by 33–36 months of age (<6.0/100,000 child-years; Kruskal Wallis,  $p<0.001$ , Figure 3).

Intussusception was more common in males (male:female ratio 1.87). Male incidence was 36.4/100,000 child-years, while female incidence was 19.5/100,000 child-years, (Mann Whitney U,  $p<0.001$ ). There was no significant difference between males and females in the age at which intussusception occurred.

**Figure 3:** The effect of age on intussusception rates (New Zealand children 0–36 months, 1998–2013).

**Table 2:** The effect of ethnicity on intussusception rates (New Zealand children 0–36 months, 1998–2013).

Ethnicity	Incidence (cases/100,000 child-years)	95% Confidence Intervals
European	24.5	13.6–32.4
Māori	23.0	12.9–31.4
Pacific	22.1	14.8–34.2
Asian	26.7	16.6–36.9

There was no significant difference in intussusception rates between ethnic groups (Table 2).

New Zealand census allows more than one ethnic group, thereby increasing total population numbers and decreasing calculated intussusception rates.

However, the age at which intussusception occurred varied with ethnicity, occurring significantly earlier in Māori and Pacific infants than other ethnicities (Kruskal Wallis,  $p<0.03$ , Figure 4).

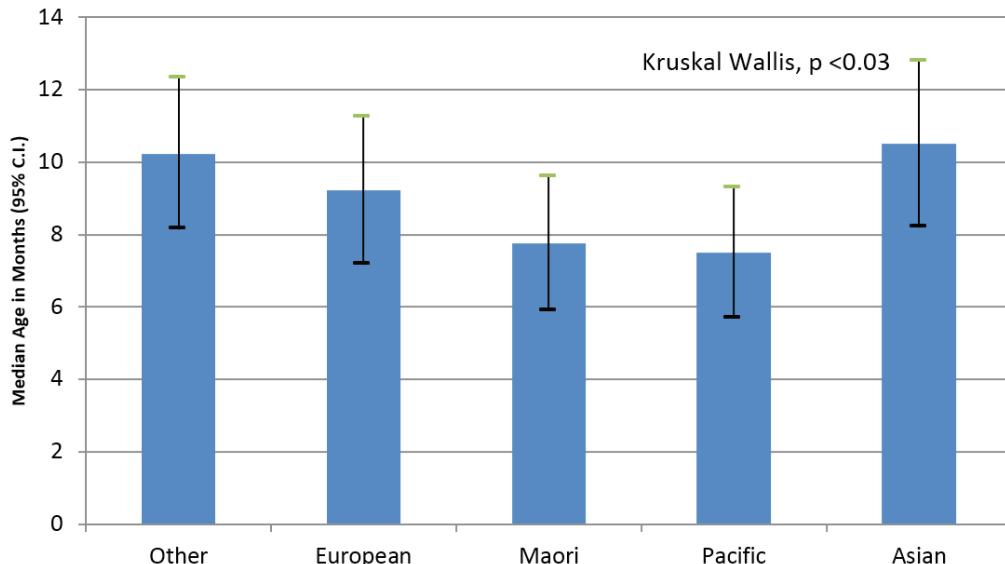
There was wide variation across District Health Board (DHB) regions, with rates reflecting primary care referral patterns. For example, Auckland DHB performs the majority of the region's paediatric surgery and had a markedly elevated rate of 49.0/100,000 while nearby, Waitemata DHB and Counties Manukau DHB had low rates of 7.1/100,000 and 7.2/100,000 respectively. There was no significant difference in incidence between the North and South Islands.

Most patients were admitted on a single occasion to a single hospital for treatment (81%). However, a significant minority (16.6%) required transfer to another hospital and a few patients (3.7%) required readmission to the same hospital within the same week.

## Discussion

Over the last 16 years, the incidence of intussusception in those aged between 0–36 months has remained constant in New Zealand, with an average rate of 28 cases/100,000 child-years. These data will be critical for ongoing monitoring of intussusception rates, following the recent introduction of a rotavirus vaccine into the New Zealand national immunisation schedule.

The current study calculated an incidence rate of 56.1/100,000 years in children <1 year from January 1998 to December 2013. The earlier New Zealand study<sup>14</sup> reported

**Figure 4:** Age of intussusception by ethnicity (New Zealand children age 0–36 months, 1998–2013).

a rate of 65/100,000 child-years and identified 21 more cases over the period January 1998 to June 2006. The extra cases may have resulted from their concomitant use of surgical and radiological databases in addition to NMDS data. Alternatively, their methodology for defining non-concurrent episodes may have varied from ours. Nonetheless, their incidence rate was statistically indistinguishable from ours for the same period ( $\text{Chi}^2=0.64$ ).

As with other international datasets we found intussusception incidence peaked in the first year of life. Our incidence rate of 56.1/100,000 child-years in infants <1 year is in the lower/mid range of international comparisons (Bangladesh 9/100,000 child-years, North America 33/100,000 child-years, England 66/100,000 child-years, Australia 101/100,000 child-years, Vietnam 302/100,000 child-years and South Korea 328/100,000 child-years).<sup>2</sup>

The reasons for this regional variation are poorly understood. Some variation is undoubtedly attributable to differences in data quality and diagnostic criteria. However, other factors such as genetic influences, dietary factors and precipitant infectious diseases (particularly gastroenteritis) have been suggested.<sup>18</sup> Regardless of underlying mechanism, the existence of regional differences emphasises the need for local data to monitor for vaccine-associated adverse events. Our study has clearly established this data for New Zealand.

Infection is hypothesised to precipitate intussusception; aggregated lymphoid tissue in the gut wall (Peyer's Patches) hypertrophies following infection and may subsequently function as a 'lead point'. Recent episodes of viral<sup>19</sup> or bacterial<sup>20</sup> gastroenteritis have been consistently linked to intussusception. Several studies have found adenovirus at higher rates in the faeces of children with intussusception than in controls.<sup>21,22</sup> Others report a temporal association between recent respiratory tract infection and intussusception.<sup>23</sup> No studies have identified an association between rotavirus gastroenteritis and intussusception,<sup>22,24</sup> including an earlier New Zealand study.<sup>14</sup>

Previous authors have investigated the association between intussusception and

the spring and autumn epidemics of viral gastroenteritis typical of temperate countries.<sup>25</sup> In contrast with earlier studies, two recent large literature reviews did not identify seasonal patterns.<sup>2,23</sup> Although contributing studies were separated according to geographic origin, and the data for Oceania showed a winter trough, it did not reach statistical significance.<sup>2</sup> Our study found summer and winter troughs and corresponding spring and autumn peaks.

The absence of strong seasonal patterns argues against rotavirus as a significant precipitant of intussusception<sup>23</sup>, although the presence of multiple viral agents may obscure a rotavirus-associated seasonal effect. The relative potency of different viral precipitants remains to be elucidated.<sup>22</sup>

The current New Zealand vaccination schedule recommends completion of rotavirus vaccinations prior to peak age of intussusception occurrence. There is preliminary evidence to support this strategy; a recent Australian study found a weaker association between rotavirus vaccination and intussusception when patients vaccinated after recommended age limits were excluded from their data.<sup>7</sup>

Existing data do not clarify whether vaccination associated intussusceptions represent an overall increase in incidence or an earlier age of onset among those in whom intussusception would have occurred later in infancy, regardless of vaccine exposure.

The possibility that vaccination does not increase cumulative incidence is supported by a large Rotarix pre-licensure trial which found a significantly lower risk of intussusception in recipients of the vaccine compared with recipients of placebo after one year of follow-up (relative risk 0.28; 95%CI, 0.1–0.81).<sup>26</sup> These findings suggest that the short-term increase in intussusception risk after rotavirus vaccination may be offset by a decrease in the longer-term risk of intussusception during the first year of life.

We found that intussusception incidence peaked in infants aged six months, with a median age of 8.95 months. Our data are very similar to the international literature,<sup>2,23</sup> with peak incidence older than the recommended age for completion of rotavirus vaccination.

We found no ethnic difference in intussusception rates. This finding contrasts with the earlier New Zealand study which identified a lower incidence among Māori compared to other ethnic groups.<sup>14</sup> Ethnic differences have been identified in other settings, with lower rates noted in indigenous versus non-indigenous children in Australia,<sup>27</sup> Bedouin Arab versus Jewish children in Israel<sup>28</sup> and white versus black/hispanic children in the US.<sup>29</sup>

We did identify a difference in median age of occurrence, with earlier intussusception in Pacific and Māori children compared to those of Asian or other ethnic origin. This association has not been reported previously and could be associated with the variable burden of infectious diseases, with Pacific and Māori children more likely to be admitted to hospital with gastroenteritis or respiratory infections.<sup>30</sup> An alternative factor could be infant weight, as Pacific and Māori infants are typically heavier than other ethnic groups.<sup>31</sup> It is uncertain whether earlier intussusception in Māori and Pacific infants increases their risk of vaccine associated events.

Timeliness of vaccine delivery remains problematic for New Zealand infants. A recent study found 23% of six week infants received the first vaccination of their primary series more than four weeks late, with 27% of three-month infants receiving their second vaccination more than six weeks late.<sup>32</sup> Unpublished data suggest that Māori infants are more likely than other ethnicities to receive their primary series late.<sup>33</sup> It remains to be clarified whether this delay extends to rotavirus vaccinations, and how the delay affects intussusception risk.

Vaccination associated intussusception is a rare event. Extrapolating Australian rates, and assuming a birth cohort of 60,000 and a vaccination rate of 95% (MoH HealthTarget), New Zealand might expect three extra intussusception cases per year. Given year-to-year variability as well as New Zealand's small immunisation cohort, it would take a number of years to detect this small increase in intussusception cases. However, the ethnic differences in timing of intussusception

combined with later immunisation delivery in Māori, occurring closer to the peak incidence of intussusception, make a compelling case for continued intussusception surveillance in New Zealand.

Intussusception symptoms include the baby having intermittent crying/screaming episodes, curling up or pulling the knees to the chest, vomiting +/- passing bloody, pink or red coloured jelly-like stools; this information is provided in several forums for parents as part of vaccination (<http://www.immune.org.nz/vaccines/rotate-q%C2%AE>, <http://www.kidshealth.org.nz/intussusception>).

Our study has a number of shortcomings. The data is anonymous, making it impossible to audit case notes to ascertain diagnostic accuracy or management details. We do not have length of stay nor outcome data.

Our study relies on retrospective coding data rather than prospectively identified cases. Coding data compiles data from large patient populations over significant time periods. It also has recognised weaknesses, including variable coding practices between institutions, changes in coding practice over time and simple coding errors. Hospitals are required to load discharge data into the NMDS within 21 days of the month of discharge, so our data are likely to be complete up to December 2013.

A Canadian study examining the reliability of ICD-9 and ICD-10 coding data in identifying intussusception calculated a sensitivity of 89.3%, and a specificity of >99.9%.<sup>34</sup> This study implies that ICD coding data miss intussusception cases and thus under-estimate the background incidence rate. Comparing an under-estimate of incidence with prospectively collected data would over-estimate the risk of vaccine associated adverse events.

Conversely, some study infants may have received Rotarix privately. If so, comparing our data with prospectively collected data would under-estimate vaccine risk. As our data were blinded and rotavirus vaccination was not systematically recorded prior to 2014, we were unable to assess this possibility.

## Conclusion

The benefits of rotavirus vaccines vary between populations and similarly the disadvantages need to be balanced. In high-income countries such as Australia and New Zealand, most intussusception cases are diagnosed early and treated by enema with good outcomes.

In settings of high rotavirus mortality, particularly those with low background rates of intussusception, risk-benefit analyses overwhelmingly favour vaccination. In settings where rotavirus mortality is uncommon, and the background rates of intussusception are relatively high such as Australia, the benefits may be less dramatic. Nonetheless, recent Australian

work supports vaccination, estimating >6500 fewer gastroenteritis hospitalisations compared to 14 additional intussusception cases annually.<sup>7</sup> Rotavirus hospitalization rates are higher in New Zealand than Australia<sup>35</sup> and intussusception rates are lower and thus the relative benefits of vaccination are likely to be greater.

It remains important for New Zealand to monitor the impact of rotavirus vaccination, specifically any increase in intussusception. It is particularly important to assess the impact on Māori and Pacific infants in whom intussusception occurs at an earlier age. By describing pre-vaccination epidemiology, our study will inform ongoing analyses of the rotavirus vaccine programme.

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Nil.

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