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Rotavirus Infection in the Auckland Region Following the Implementation of Universal Infant Rotavirus Vaccination: Impact on Hospitalisations and Laboratory Implications

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Background

In July 2014, New Zealand introduced universal infant vaccination with Rotateq (Merk & Co.) administered as three doses at 6 weeks, 3 and 5 months of age. We sought to assess the impact of rotavirus vaccination on gastroenteritis hospitalizations in the greater Auckland region and analyze changes in rotavirus testing in the period around vaccine introduction.

Methods

Hospitalizations, laboratory testing rates and methods were compared between the pre-vaccine period (2009-2013), post vaccine period (January-December 2015), and year of vaccine introduction (2014).

Results

There was a 68% decline in rotavirus hospitalizations of children aged <5 years following vaccine introduction (from 258 per 100,000 to 83 per 100,000) and a 17% decline in all-cause gastroenteritis admissions (from 1815 per 100,000 to 1293 per 100,000). Reductions were also seen in pediatric groups too old to have received vaccine.

Despite these changes, rotavirus testing rates in our region remained static in the year after vaccine introduction compared with the two prior years, and following vaccine introduction we observed a high rate of false positives 19/58 (33%) in patients with reactive rotavirus tests.

Conclusions

Rotavirus vaccine has had a significant early impact on gastroenteritis hospitalizations for children in the Auckland region. However, continued rotavirus testing at pre-vaccine rates risks generating false positive results. Laboratories and clinicians should consider reviewing their testing algorithms prior to vaccine introduction.

KEYWORDS: Rotateq; New Zealand; false positives; rotavirus testing; roll out planning

INTRODUCTION

Over the last decade rotavirus vaccine has been introduced into the immunization schedules of over 80 countries worldwide, leading to 74-90% reductions in rotavirus (RV) hospitalizations, and 29-50% reductions in all-cause gastroenteritis admissions for children in both high and low income countries [1,2]. Direct and indirect vaccine effects have been seen in children and the wider community [3] as early as the first year following introduction of vaccine [4]. Additional unexpected benefits have included reductions in febrile and non-febrile seizure pediatric emergency department presentations [5, 6]. In New Zealand (NZ) RotaTeq (RV-5; Merck & Co, live oral attenuated rotavirus vaccine) was introduced to the infant national immunization schedule on 1st July 2014 as three doses administered at 6 weeks, 3 months and 5 months of age without catch-up and minimal previous private use [7]. New Zealand has a publicly financed healthcare system providing free hospital and outpatient care for residents. Where children require emergency admission, this is provided almost exclusively in public hospitals. Children <13 years old also receive free primary care including scheduled vaccines: in 2016, 94.1% of children at 1 year of age received vaccinations according to the national immunization schedule [8]. Prior to the introduction of rotavirus vaccine in NZ, yearly epidemics occurred with peaks in Winter/Spring (June-November). It was estimated 43% of all-cause gastroenteritis admissions in NZ were due to rotavirus infection and that 1 in 43 children were hospitalized for rotavirus by the age of five [9].

Despite many reports worldwide recording the success of rotavirus vaccine on reducing the burden of disease, there have been few that address how vaccine introduction may impact upon the provision and interpretation of rotavirus testing in diagnostic laboratories. Rotavirus testing following vaccine introduction presents challenges: there is a risk of generating false positive

results [10], and testing may not be targeting other important causes of disease in that patient group, such as norovirus, the predominant cause of GE after vaccine introduction [11]. Additionally, changes undertaken in testing algorithms by laboratories may impact on trends of rotavirus detection over time, which are an important component of vaccine surveillance [12]. Therefore it is important to understand how rotavirus testing rates, laboratory methods, and test reliability change in the period around vaccine introduction.

We undertook to assess the impact of rotavirus vaccination on gastroenteritis hospitalizations in the greater Auckland region since the advent of vaccination (January-December 2015). The greater Auckland region, population 1.4 million, accounts for one third of NZ's population [13]. Our secondary aim was to assess and discuss the impact of changes in laboratory testing over the study period.

MATERIALS AND METHODS

Hospitalization data

Hospitalization data were obtained from the health intelligence units of the Auckland region district health board (DHB) hospitals. Three DHBs provide healthcare for this region. Data for all ages were included in the study.

Hospitalizations were included if there was an admission date between 1st January 2009 and 31st December 2015 with a primary or secondary diagnosis that had an International Classification of Diseases, 10th Revision (ICD-10) of rotavirus gastroenteritis or all-cause gastroenteritis (AGE, ICD-10 codes; A00-A09). Hospitalization rates for the DHBs were calculated using annual population estimates for the Auckland region from Statistics NZ [20] and analyzed by year of age for those aged 0-4 and as a group for those ≥ 5 years old. For the pre-vaccine period, average annual rates were calculated using the mean of 2009-2013 hospitalizations and relevant

population estimates. Data were analyzed by comparing pre vaccine (Jan 2009-December 2013), year of vaccine introduction (January-December 2014) and post vaccine (January-December 2015) periods.

The estimated reduction in hospitalizations were calculated as the difference between mean and the highest and lowest number of hospitalizations in 2009-2013 and those in 2015.

Vaccine coverage

Vaccine coverage data were obtained from the NZ Ministry of Health [21].

Laboratory data

Laboratory data were obtained from the laboratory information systems of the Auckland region DHBs. Laboratories at these sites provide diagnostic testing for their respective hospitals and outpatient clinics. Samples submitted by primary care providers are tested elsewhere. Data were analyzed by proportion of samples positive for rotavirus over the study period, testing rate over time and stratified by age group.

Annual population estimates for the Auckland region, DHB and age group were used [13]. Comparisons were made between pre vaccine (January 2009-December 2013) the year of vaccine introduction (January-December 2014) and post-vaccine period (January-December 2015) and for annual changes over the study period.

Laboratory methods

Over the study period, laboratory rotavirus assays and testing algorithms varied by laboratory (Table 1 and results). Positive results presented are those initially reactive by rotavirus immunochromatography (ICT). Polymerase chain reaction (PCR) confirmatory results are also presented separately where these were performed: Counties Manukau District Health Board (CMDHB) had PCR confirmatory results available on positive rotavirus samples sent to the

national reference laboratory (the Institute of Environmental and Scientific Research, ESR) for rotavirus genotyping (January –December 2015), and Auckland District Health Board (ADHB) performed in-house PCR confirmation of reactive ICTs from September 2015.

Statistical analysis

Chi square was used to compare categoric variables. Relative risk and 95% confidence intervals were calculated to compare rates. Statistical significance was considered where *P* value <0.05.

Ethical approval

Ethical approval was sought and deemed not required for this study in view of anonymized data and audit function (HDEC NZ reference 16/CEN/55).

RESULTS

Vaccine coverage

From 1st July 2014, RV-5 was administered as 3 doses given orally to infants at 6 weeks, 3 and 5 months of age.

By 1st April 2015, 19% of infants <1 year of age in the Auckland region had received 3 doses of vaccine. Infant coverage increased rapidly to 78.3% by the end of 2015. From September to December 2015 the vaccinated cohort also included 20%-35% of one year olds who had received their vaccine in infancy.

Hospitalizations

Between January 2009-December 2015 there were 1,898 laboratory confirmed rotavirus hospitalizations and 54,021 AGE admissions (12,705 in those <5 years of age) resident in the Auckland region.

Annual winter peaks in rotavirus hospitalization occurred in the pre-vaccine period (2009-2013) with highest monthly incidence in Winter-Spring (June-October) (Figure 1).

Annual admission rates for children <5 years old were 205-315 per 100,000 over this period (Table, Supplemental Digital Content 1, http://links.lww.com/INF/C778). The highest rates of admission occurred in children <1 year of age (351-683 per 100,000) followed by those 1-2 years old (338-563 per 100,000) and then reduced with increasing age. Rotavirus hospitalizations for >5 year olds were uncommon.

Vaccine was introduced onto the immunization schedule in July 2014, and the annual rotavirus season was evident shortly afterwards with rates in <5 year olds comparable with the pre vaccine years. In 2015, consistent with an increasing cohort of vaccinated infants there was a delay in the seasonal onset of rotavirus activity and a significant reduction in rotavirus admissions. Peak hospitalizations were seen in early summer (December 2015). There was a substantial 74% (17-25 per 100,000 to 7 per 100,000, *P* <0.001) reduction in all-age rotavirus hospitalizations in 2015 compared with the pre-vaccination period. For individual age groups, the greatest reduction (77%, RR 0.23, *P* <0.001) was seen for infants less than a year of age, but statistically significant reductions were also seen for 1-2 (75%, RR 0.25, *P* <0.001) and 2-3 year olds (41%, RR 0.59, *P* 0.04).

There was no overall change in AGE admissions in 2015 compared with the pre-vaccine period, but a 17% (RR 0.83, *P* <0.001) reduction was seen for children aged <5 years old. Children 1-2 years old appeared to have the most benefit with a 24% (RR 0.76, *P* <0.001) reduction in this age group though less hospitalizations were also seen for those <1 year of age (RR 0.87, *P* <0.001) and those 2-3 years (RR 0.8, *P* <0.001), and 3-4 years old (RR 0.83, *P* 0.002). Notably, there was a 4% (RR 1.04, *P* <0.001) increase in all-cause gastroenteritis admissions for patients aged >5 in

2015 compared with the pre-vaccine period. The modest reduction in rotavirus hospitalizations for 2-3 year olds and in AGE hospitalizations for 2-4 year olds, groups too old to have received vaccine, is consistent with indirect vaccine effects.

We estimate that rotavirus vaccine prevented 316 (range 289-349) AGE admissions including 180 (142-219) laboratory confirmed rotavirus admissions for children under 5 years old in the Auckland region in 2015.

Laboratory Methods

All laboratories used ICT throughout the study period, although these differed between sites (Table 1.). At the beginning of the study period, testing was automatically performed on all samples submitted from children <3-5 years of age, whereas this changed at two sites over the study period. From 2012, Auckland District Health Board (ADHB) tested samples for rotavirus from children only on specific request. From June 2014, in the year of vaccine introduction CMDHB also ceased automatically performing rotavirus testing of samples submitted from children and performed testing only on request.

At ADHB restrictions were applied to testing of adults and duplicate samples in 2011-2012.

No changes in testing protocols occurred at Waitemata DHB (WDHB) during the study period.

In the post-vaccine period confirmatory testing was instituted at CMDHB by the use of a second ICT for reactive samples in August 2015, and at ADHB by the use of a rotavirus PCR from September 2015.

Laboratory data

Over the study period 12,671 rotavirus tests were performed in hospital laboratories in the Auckland region. During the pre-vaccine period the proportion of laboratory tests positive for

rotavirus varied between 11-19% for any given year (Table, Supplemental Digital Content 2, http://links.lww.com/INF/C779) and this proportion reduced to 7% in 2015 (*P* <0.001). Positivity rates differed by study site and over time. Rates were significantly lower over the study period at ADHB (11% positive) compared with both CMDHB (20% positive, *P* <0.001) and WDHB (25% positive, *P* <0.001).The average annual rotavirus positivity rate at ADHB increased to 14% (range 11-19%) in 2012-2014 from 11% (range 7-12%) in 2009-2011 (*P* <0.001) whereas it was unchanged at the other two sites over this period.

The number of rotavirus tests performed in our region reduced over the pre-vaccine period, and rates of testing were 23% (RR 0.77, 95% CI 0.72-0.82, *P* <0.001) lower in 2015 compared with the 2009-2013. These changes differed between age groups (Figure 2), and study sites: testing rates were 38% lower in infants (RR 0.62, *P* <0.001), and 31% lower in 1-2 year olds (RR 0.69, *P* <0.001) in 2013 compared with 2011. By study site, rates were 31% lower at ADHB (RR 0.69, 95% CI 0.63-0.75, *P* <0.001) in 2013 compared with 2011 and 35% lower at CMDHB (RR 0.65, 95% CI 0.6-0.69, *P* <0.001) in 2014 compared with 2013.

The declines in testing for 0-3 year olds, those at ADHB over the pre-vaccine period and CMDHB in the year of vaccine introduction, as well as the increase in positivity rate at ADHB are consistent with changes in laboratory testing protocols during this time (Table 1).

Despite the introduction of vaccine in 2014 and marked reductions in rotavirus hospitalizations in 2015, there was no significant reduction in the overall rotavirus testing between 2015 (104 per 100,000) compared with the 2013-2014 period (106 per 100,000 per year).

Trends were apparent by age group: whilst testing rates in 0-1 and 2-5 year olds in 2015 were unchanged compared with 2013-2014, 1-2 year olds were tested less frequently in 2015 (227 per 100,000) compared with 2013-2014 (290 per 100,000 per year, *P* 0.002) and there was an

increase in testing for those >5 years old (from 20 per 100,000 per year in 2013-2014 to 24 per 100,000 in 2015, *P* 0.01).

In 2015, 58 (53%) of the 109 positive rotavirus ICT tests in the Auckland region had confirmatory testing by PCR performed. Of these 19 (33%) were not confirmed as rotavirus positive by PCR.

DISCUSSION

We compared rotavirus and all-cause gastroenteritis hospitalizations in the Auckland region before and after the introduction of rotavirus vaccine.

The pre-vaccine mean annual rotavirus hospitalization rate of 258 per 100,000 per year in children aged <5 is consistent with prior NZ reports of rotavirus hospitalization rates ranging from 146-416 per 100,000 [9, 14, 15]. There was a substantial early impact of rotavirus vaccine in the region with a 68% reduction in rotavirus hospitalizations in those aged < 5 within 18 months of rotavirus vaccine introduction. This is in line with other high income countries including the US [12], UK [4], and Australia [16] and a recent NZ report [17].

A 17% decline in AGE admissions for children <5 years old, extension of protection to unvaccinated age groups, and a later seasonal peak of rotavirus activity were also seen following the introduction of vaccine in common with findings elsewhere[3,18].

Using laboratory data, we observed a significant reduction in rotavirus positivity rates between the pre vaccine (11.9-18.8%) and post-vaccine period (7.4%) in the Auckland region. These results are also consistent with those reported in Belgium [18] where annual positivity rates fell from 14% to 4% after vaccine introduction. We estimate that rotavirus vaccine prevented 316 (range 289-349) AGE admissions including 180 (142-219) laboratory confirmed rotavirus admissions for children under 5 years old in the Auckland region in 2015.

We sought to analyze the implications of vaccine introduction on diagnostic testing for rotavirus and found that diagnostic methods differed between sites over the study period. Laboratory algorithms changed over time, in particular there was a shift from routine reflex testing in children less than 5 years of age to performing tests only on request. It appears that these changes in algorithms were linked with a reduction in tests performed for children under two years of age, and may have led to an increase in the positivity rate of rotavirus tests [12]. We also saw a difference in test positivity rates between sites which could reflect differing laboratory algorithms, request patterns, or patient characteristics.

These changes in laboratory protocols occurred in the pre-vaccine period and year of vaccine introduction. In contrast, there was no change in the number of rotavirus tests requested in the year after vaccine introduction compared with the two prior years. This is notable given the changes in rotavirus epidemiology over this period. The modest reduction in AGE hospitalizations in 2015, with an increase in hospitalizations for those >5 years old offers a partial explanation: because agents of viral GE are clinically indistinguishable [19] trends in RV testing will reflect those performed for AGE. Consistent with this we observed less testing in 1-2 year olds, the group where vaccine had the most impact on AGE admissions, and more testing was seen in those >5 years old, who had more hospitalizations in the post vaccine period. The lack of impact of vaccine introduction on testing in infants and 2-4 year olds, who also had reduced AGE hospitalization rates in 2015 is intriguing, and may reflect other testing behaviors in these groups. Though we recognize that these changes may represent secular patterns, these findings are not unique: reductions in rotavirus testing of 28-36% in the US and 5-18% in Australia have been reported in the years following introduction of vaccine [20, 21], but these declines were smaller and delayed compared with those which occurred in rotavirus activity. It

is unclear whether changes in these reports were associated with changes in laboratory practice or clinician testing patterns over time.

If no alterations in rotavirus testing pattern occur with the introduction of vaccine then continued testing at pre-vaccine rates with a falling prevalence of disease may lead to an increased proportion of falsely positive results, regardless of the specificities of commercially available ICTs and EIAs [22, 23]. In Spain, Lopez-Lacourt *et al* estimated that 53% of rotavirus tests, when performed by ICT without PCR confirmation were likely to be false positive, due to out of season sampling and excessive testing in vaccinated children [10]. In the Auckland region, we found that a third of positive rotavirus tests which underwent confirmatory testing were falsely reactive. Whilst we recognize that confirmatory testing was performed for only a subset of patients, similar proportions of unconfirmed ICT and EIA results have also recently been reported from other NZ laboratories [17]. Concerns of generating falsely reactive results led two sites in our study to adopt confirmatory testing in the post-vaccine period.

Changes in rotavirus epidemiology are predictable based on the global experience of vaccine efficacy. We believe that in the face of the accompanying challenges to diagnostic testing, guidance should be provided at the vaccine planning stage to address the risks of over testing and generation of false positive results which may occur in the early post vaccine period. Laboratories may wish to reconsider their algorithms and consider confirmatory testing for positive tests in vaccinated groups [24] in preparation for vaccine introduction. However, it is important that clinicians are also engaged, by reviewing their testing patterns and limiting microbiologic investigation for children presenting with AGE to selected patients such as those with severe disease, immunocompromising conditions and in outbreak management [19,25]. As well as directly improving the accuracy of rotavirus testing these changes may also lead to cost

savings by avoiding unnecessary tests, and reduce inappropriate interventions resulting from erroneous results [26,27]. As pre-analytical decisions to test and laboratory testing algorithms will differ worldwide, a local assessment of practices is warranted.

It is important to note that any changes undertaken around the time of vaccine introduction can influence rotavirus activity trends and must be considered in laboratory based surveillance programs [12].

CONCLUSIONS

The introduction of rotavirus vaccination has had a significant early impact on gastroenteritis hospitalizations for children in the Auckland region in keeping with reports from other high-income countries. Despite this rotavirus testing rates remained at pre-vaccine levels, with consequent risks of false positive results. Laboratories and clinicians should consider reviewing their rotavirus testing algorithms in preparation for vaccine-related epidemiologic changes.

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FIGURE LEGENDS

Figure 1. Rotavirus hospitalizations by month and infant vaccine coverage Auckland region 2009-2015

Figure 2. Rotavirus testing rates by age group, Auckland region 2009-2015

Table 1. Rotavirus testing protocols at hospital laboratories in the Auckland region 2009-2015.

Laboratory site	**Method**	**Pre vaccine 2009-2013**	**Vaccine introduction 2014**	**Post vaccine 2015**
Auckland District Health Board	SAS Rota Test (SA Scientific, USA) ICT	All samples < 3yrs old until 2012 then only if requested. No duplicate requests within 30 days from 2011. Restricted testing of adults 2012.	No changes	PCR confirmation of ICT from September*. Parallel testing of ICT with rotavirus and norovirus PCR from November (trial)
Counties Manukau District Health Board	RIDA QUICK Rotavirus/Adenovirus Combi (R-Biopharm, Germany) ICT	All samples for children <5 years old and on request for others	June 2014 on request only	Introduction of confirmatory ICT **GastroVir-Strip** (Coris BioConcept, Belgium from August*
Waitemata District Health Board	CerTest Rotavirus + Adenovirus (CerTest BIOTEC, Spain) ICT	All samples for children <5yrs old and on request for others	No changes	No changes

* The initial results are presented in our data

Table 2. Hospitalisation by age group before and after the introduction of rotavirus vaccine, Auckland region, New Zealand, Jan 2009 to Dec 2015

	Before vaccination	**Vaccine introduction**		**Post vaccine**		
		Year 0		Year 1		
	2009-2013	2014		2015		
Patient age (years)	Mean annual rate* (range)	Rate	Relative risk (95% CI)	Rate	Relative risk (95% CI)	*P* value
Rotavirus coded hospitalisations						
<1	523 (351-683)	448	0.85 (0.64-1.12)	120	0.23 (0.14- 0.35)	<0.001
1	465 (338-363)	538	1.12 (0.85-1.47)	120	0.25 (0.15-0.39)	<0.001
2	189 (121-223)	228	1.20 (0.78-1.84)	111	0.59 (0.35-0.98)	0.04
3	73 (49-107)	122	1.66 (0.87-3.16)	39	0.53 (0.22-1.25)	0.15
4	39 (25-64)	39	1.00 (0.37-2.66)	24	0.63 (0.20-1.91)	0.4
All <5	**258 (205-315)**	**275**	**1.06 (0.9-1.26)**	**83**	**0.32 (0.25-0.41)**	**<0.001**
All ≥5	2 (2-3)	3	1.48 (0.92-2.37)	2	0.72 (0.41-1.26)	0.26
All ages	20 (17-25)	23	1.10 (0.94-1.29)	7	0.36 (0.28-0.45)	<0.001
All cause gastroenteritis hospitalisations						
<1	3768 (3186-4244)	4033	1.04 (0.99-1.09)	2907	0.87 (0.81-0.92)	<0.001
1	2940 (2522-3328)	3329	1.06 (1.01-1.27)	1809	0.76 (0.70-0.83)	<0.001
2	1231 (1212-1410)	1468	1.09 (1.00-1.17)	824	0.8 (0.70-0.90)	<0.001
3	669 (469-811)	795	1.09 (0.97-1.20)	475	0.83 (0.71-0.97)	0.002
4	456 (412-603)	593	1.13 (0.99-1.27)	431	0.97 (0.82-1.12)	0.2
All <5	**1815 (1659-2008)**	**2046**	**1.06 (1.03-1.09)**	**1293**	**0.83 (0.80-0.86)**	**<0.001**
All ≥5	428 (356-490)	504	1.08 (1.06-1.1)	464	1.04 (1.02-1.06)	<0.001

All ages	**527 (461-595)**	**614**	**1.08 (1.06-1.09)**	**523**	**1.0 (0.98-1.01)**	**0.6**

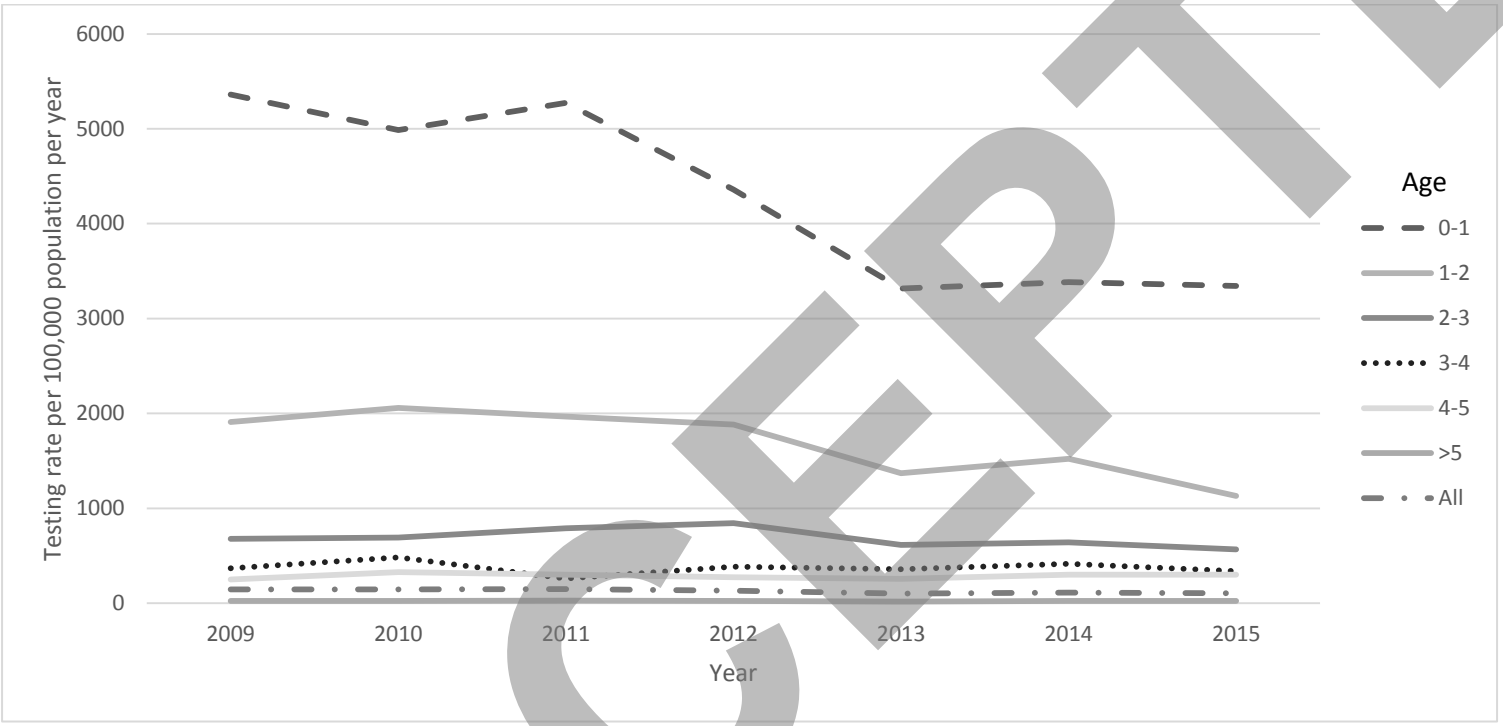
*Rates per 100,000 population per year by age group resident in Auckland region

Table 3. Rotavirus tests performed, positivity rate, and testing rate by District Health Board

DHB	ADHB			WDHB			CMDHB			Total Auckland region		
Year	Positive (%)	Tested	Rate*	Positive (%)	Tested	Rate	Positive (%)	Tested	Rate	Positive (%)	Tested	Rate
2009	122 (9.8)	1240	284	63 (31.8)	198	38	151 (23.1)	653	139	336 (16.1)	2091	146
2010	158 (12.1)	1310	300	141 (38.6)	365	69	88 (22.9)	385	82	387 (18.8)	2060	144
2011	89 (7.2)	1232	282	67 (16.4)	408	77	95 (20)	474	101	251 (11.9)	2114	148
2012	118 (10.8)	1088	249	132 (32.7)	404	77	80 (19.6)	408	87	330 (17.4)	1900	133
2013	115 (13.6)	846	194	57 (24.2)	236	45	64 (17.5)	365	77	236 (16.3)	1447	101
2014	183 (18.6)	986	226	85 (25.4)	335	64	58 (22.7)	256	54	326 (20.7)	1577	110
2015	60 (6.4)	942	214	15 (5.7)	265	50	34 (12.4)	275	58	109 (7.4)	1482	104
Total	**845 (11.1)**	**7644**	**250**	**560 (25.3)**	**2211**	**60**	**570 (20.2)**	**2816**	**85**	**1975 (15.6)**	**12671**	**126**

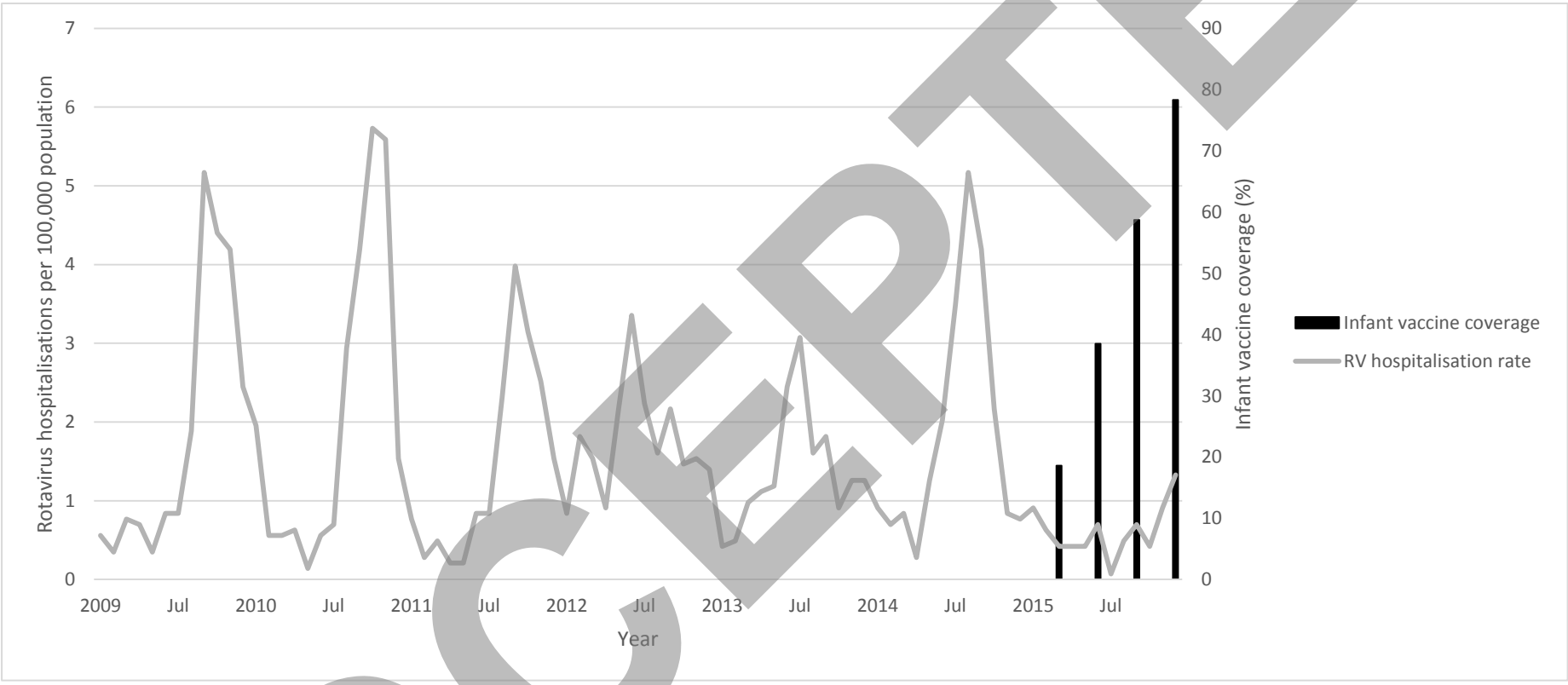
Rates of testing per 100,000 population per year calculated using population estimates for all ages separated by each District Health Board

Figure 2. Rotavirus testing rates by age group, Auckland region 2009-2015



Testing rates are by age group resident in Auckland region.

Figure 1. Rotavirus hospitalizations by month and infant vaccine coverage Auckland region 2009-2015



Hospitalization rates are per 100,000 population/ month for all age groups resident in Auckland region. Vaccine coverage is proportion of children <12 months who have received 3 dose regime.