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National Study of Off-label Proton Pump Inhibitor Use Among New Zealand Infants in the First Year of Life (2005–2012)

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ABSTRACT

Objectives: Off-label prescribing of proton pump inhibitors (PPIs) to infants to treat symptoms attributed to gastroesophageal reflux disease (GERD) is widely reported, despite evidence that PPIs are no more effective than placebo in relieving those symptoms. To initiate discussion about appropriate prescribing of these drugs for infants, we describe the characteristics of PPI use among infants in New Zealand.

Methods: In this population-based study we used routinely collected dispensing data to identify all children born between 2005 and 2012 who were dispensed a government-subsidized PPI (omeprazole, lansoprazole, pantoprazole) before their first birthday. Unique patient identifiers were used to link administrative datasets containing patient-level demographic, dispensing, and health information.

Results: In total, 22,643 children were dispensed a study PPI before their first birthday. The prevalence of infant PPI use as a proportion of all live births increased from 2.4% for children born in 2005 to 5.2% for children born in 2012. Overall, 71.6% of infants were dispensed a PPI by 3 months of age, and 8.7% received a PPI within the first month of life. Before PPI initiation, only 7.0% of infants had a hospital-based diagnosis of GERD (with or without esophagitis), and 4.7% of infants had a hospital-based diagnosis of one or more known or suspected GERD risk factors.

Conclusions: Off-label prescribing of PPIs to New Zealand infants was relatively common and increased over the study period. The appropriateness of PPI treatment should be questioned, as the majority of infants who received these drugs were not diagnosed with severe GERD.

Key Words: infants, off-label prescribing, proton pump inhibitors

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What Is Known

- Proton pump inhibitors are prescribed off-label to infants to treat symptoms attributed to gastroesophageal reflux disease; however, there are no reliable population-based estimates of use available.
- Industry-sponsored randomized controlled trials have failed to demonstrate that proton pump inhibitors are more effective than placebo in reducing the symptoms of presumed gastroesophageal reflux disease in infants.
- Previous studies conducted in the USA, Belgium, and New Zealand have observed increases in proton pump inhibitor use among infants over time; however, these studies relied upon unrepresentative samples of infants, or data that were unable to be linked to individual patients.

What Is New

- This is the first nationwide population-based study using individually linked patient-level administrative data to investigate proton pump inhibitor use during the first year of life.
- The prevalence of proton pump inhibitor use among New Zealand infants is much higher than previously published estimates.

Until 2011, no proton pump inhibitors (PPIs) were approved for use in children younger than 1 year (infants) for the treatment of symptoms attributed to gastroesophageal reflux disease (GERD) (1). Published guidelines urge physicians to exercise caution before prescribing PPIs off-label to infants (2,3), advising that gastric acid–suppressing medicines are not recommended for otherwise healthy infants with uncomplicated gastroesophageal reflux.

Nevertheless, several studies have not only documented that PPIs (including omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) are being prescribed off-label to infants, but that the use of PPIs among infants has increased dramatically over time (2,4–9). Barron et al (4), analyzed 4 private health insurance plans in the United States from 1999 to 2004, finding that 0.2% of enrolled infants were prescribed a PPI (omeprazole or lansoprazole), with an estimated 7.5-fold increase in the number of PPI dispensing claims over the study period. Chen et al (5), reported on data obtained from a United States database of retail pharmacy outlets that is used to generate national-level projections of prescription claims. Analyses of this database suggested that the

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TABLE 1. Demographic characteristics of children in New Zealand born between 2005 and 2012 who were dispensed at least 1 course of proton pump inhibitor (omeprazole, lansoprazole, pantoprazole) treatment during the first year of life, by year of birth

Year of birth Patients	2005 n = 1408	2006 n = 2024	2007 n = 2667	2008 n = 3085	2009 n = 3223	2010 n = 3557	2011 n = 3522	2012 n = 3157	2005–2012 n = 22,643
Female, n (%)	601 (42.7)	893 (44.1)	1128 (42.3)	1324 (42.9)	1445 (44.8)	1554 (43.7)	1512 (42.9)	1385 (43.9)	9842 (43.5)
Ethnicity (prioritized)*, n (%)									
Māori	82 (5.8)	145 (7.2)	187 (7.0)	251 (8.1)	274 (8.5)	338 (9.5)	344 (9.8)	303 (9.6)	1924 (8.0)
Pacific	33 (2.3)	38 (1.9)	60 (2.2)	63 (2.0)	87 (2.7)	94 (2.6)	98 (2.8)	81 (2.6)	554 (2.4)
Asian	61 (4.3)	86 (4.2)	135 (5.1)	136 (4.4)	136 (4.2)	193 (5.4)	222 (6.3)	277 (8.8)	1246 (5.5)
Other	16 (1.1)	24 (1.2)	33 (1.2)	44 (1.4)	52 (1.6)	67 (1.9)	69 (2.0)	64 (2.0)	369 (1.6)
European	1204 (85.5)	1711 (84.5)	2232 (83.7)	2581 (83.7)	2671 (82.9)	2859 (80.4)	2787 (79.1)	2425 (76.8)	18,470 (81.6)
Missing	12 (0.9)	20 (1.0)	20 (0.7)	10 (0.3)	3 (0.1)	6 (0.2)	2 (0.1)	7 (0.2)	80 (0.4)
Socioeconomic quintile (area-level)†, n (%)									
5 (Most deprived areas)	121 (8.6)	162 (8.0)	250 (9.4)	294 (9.5)	349 (10.8)	409 (11.5)	422 (12.0)	443 (14.0)	2450 (10.8)
4	232 (16.5)	334 (16.5)	479 (18.0)	549 (17.8)	658 (20.4)	798 (22.4)	780 (22.1)	728 (23.1)	4558 (20.1)
3	283 (20.1)	470 (23.2)	499 (18.7)	643 (20.8)	696 (21.6)	778 (21.9)	781 (22.2)	683 (21.6)	4833 (21.3)
2	337 (23.9)	464 (22.9)	600 (22.5)	700 (22.7)	716 (22.2)	713 (20.0)	718 (20.4)	623 (19.7)	4871 (21.5)
1 (most privileged areas)	425 (30.2)	591 (29.2)	830 (31.1)	889 (28.8)	796 (24.7)	843 (23.7)	815 (23.1)	669 (21.2)	5858 (25.9)
Missing	10 (0.7)	3 (0.1)	9 (0.3)	10 (0.3)	8 (0.2)	16 (0.4)	6 (0.2)	11 (0.3)	73 (0.3)

*Statistics New Zealand level 1 prioritized ethnicity classification based on self-reported ethnic identification(s) according to the following order: Māori, Pacific, Asian, Other, European, Missing.
†New Zealand Index of Deprivation based on 2006 Census data.

number of claims for new PPI dispensings for infants increased 11-fold between 2002 and 2009. Likewise, Illueca et al (6), in an analysis of a large database of United States hospital discharge information, found that between 2004 and 2008 there was more than a doubling in the proportion of children younger than 1 year who received a PPI while in hospital. Also in the United States, Slaughter et al (7), observed that the use of PPIs among infants admitted to neonatal intensive care units peaked at 12.2% in 2010, before declining to 7.9% in 2013. In Europe, De Bruyne et al (8), observed that the volume of Belgian pediatricians' PPI reimbursement claims, as measured in defined daily doses, increased 30-fold from 1997 to 2009. In New Zealand, the Best Practice Advisory Center reported that the annual number of omeprazole prescriptions for infants increased nationally from 4650 in 2006 to 8231 in 2010 (2). Meanwhile, from 2005 to 2010 Hudson et al (9), observed almost a 4-fold increase in omeprazole use among infants enrolled in a primary health organization in the Canterbury region. In 2005, 4% of enrolled infants had been prescribed omeprazole, increasing to 15% of enrolled infants in 2010.

Given the evidence that PPIs are being prescribed off-label to infants, it is worrying that a number of industry-sponsored randomized controlled trials have failed to demonstrate that PPIs (including omeprazole, lansoprazole, pantoprazole, and esomeprazole) are more effective than placebo in relieving symptoms, such as excessive crying, irritability, and back arching, that are commonly attributed to GERD and gastroesophageal reflux in infants (5,10).

Although previous studies have demonstrated increases in the use of PPIs among infants over time, many of these studies did not use population-based samples, or relied on aggregated prescription or sales data. In order to address these methodological shortcomings, and to help initiate a conversation about the rational use of PPIs in infants, we conducted a national, population-based study to describe the characteristics and PPI use patterns for all infants in New Zealand born between 2005 and 2012 who were dispensed at least 1 government-subsidized PPI (omeprazole, lansoprazole, pantoprazole) during their first year of life, using linkable databases of patient-level administrative information.

Ethical Approval and Funding

Ethical approval for the present study was received from the Southern Health and Disability Ethics Committee (14/STH/2). Funding was provided by the New Zealand Pharmacovigilance Center and Medsafe (New Zealand's medicines and medical devices regulatory agency), and a Strategic Research Grant from the Department of Preventive and Social Medicine, University of Otago.

RESULTS

The Ministry identified 22,661 National Health Index (NHI) identifiers from the Pharmaceutical Collection with a recorded date of birth between January 1, 2005 and December 31, 2012, and at least one recorded dispensing of a study PPI within the first year of life. After receiving the datasets, we identified 18 ''patients'' during the data cleaning process with implausible linkages (eg, drugs dispensed before being born). These ''patients'' and all of their associated data were excluded from the study, resulting in a cohort of 22,643 infants.

METHODS

Methods are available online as Supplemental Digital Content 1 (*http://links.lww.com/MPG/A975*).

Demographic Characteristics

Table 1 shows the demographic characteristics of the cohort, by birth year. The sex distribution was consistent over the study period, with a smaller proportion of girls (overall 43.5%) than boys dispensed a PPI. In contrast, the ethnic distribution over the study period varied: the proportion of Māori (the indigenous peoples of New Zealand) infants increased by two-thirds (2005 5.8%, 2012 9.6%), whereas the proportion of infants of Asian ethnicities doubled (2005 4.3%, 2012 8.8%). The proportion of infants of Pacific ethnicities remained stable at between 2% and 3% of the cohort by birth year, whereas there was a proportional 10% decrease

TABLE 2. Proton pump inhibitor (omeprazole, lansoprazole, pantoprazole) use, and selected pharmacological treatments and hospital-based diagnoses before proton pump inhibitor initiation, for children in New Zealand born between 2005 and 2012 who were dispensed at least 1 course of proton pump inhibitor treatment during the first year of life, by year of birth

Year of birth	2005	2006	2007	2008	2009	2010	2011	2012	2005–2012
Patients	n = 1408	n = 2024	n = 2667	n = 3085	n = 3223	n = 3557	n = 3522	n = 3157	n = 22,643
Patients as percentage of national births*, n (%)	57,745 (2.4)	59,193 (3.4)	64,044 (4.2)	64,343 (4.8)	62,543 (5.2)	63,897 (5.6)	61,403 (5.7)	61,178 (5.2)	494,346 (4.6)
Total dispensed courses of PPI treatments, n	6319	10,035	13,292	15,281	14,973	16,280	16,221	13,670	106,071
PPI prescribers†, n (%)	1121 (10.2)	1441 (12.6)	1817 (15.3)	2070 (17.0)	2244 (18.0)	2531 (20.0)	2527 (18.7)	2296 (16.5)	5721 (28.1)
Age at PPI initiation, n (%)									
0–3 mo	794 (56.4)	1356 (67.0)	1858 (69.7)	2214 (71.8)	2327 (72.2)	2611 (73.4)	2701 (76.7)	2356 (74.6)	16,217 (71.6)
4–6 mo	382 (27.1)	439 (21.7)	537 (20.1)	585 (19.0)	581 (18.0)	642 (18.0)	536 (15.2)	526 (16.7)	4228 (18.7)
7–9 mo	173 (12.3)	170 (8.4)	189 (7.1)	219 (7.1)	228 (7.1)	231 (6.5)	213 (6.0)	208 (6.6)	1631 (7.2)
10–12 mo	59 (4.2)	59 (2.9)	83 (3.1)	67 (2.2)	87 (2.7)	73 (2.1)	72 (2.0)	67 (2.1)	567 (2.5)
Total days of PPI use by age at initiation, mean (SD)									
0–3 mo	126.7 (97.9)	125.3 (96.0)	129.8 (98.5)	124.1 (94.2)	109.8 (91.3)	109.7 (91.4)	107.8 (92.3)	107.1 (90.1)	115.4 (93.7)
4–6 mo	103.7 (69.1)	103.5 (69.3)	95.3 (68.3)	89.4 (68.1)	86.7 (66.2)	81.9 (65.4)	80.1 (67.1)	83.1 (69.6)	89.4 (68.2)
7–9 mo	77.7 (38.7)	67.5 (41.0)	67.3 (40.4)	64.0 (39.7)	59.2 (38.9)	57.0 (37.9)	59.5 (38.0)	63.0 (41.1)	63.8 (39.8)
10–12 mo	32.5 (17.3)	27.5 (17.2)	23.5 (14.7)	25.9 (15.8)	23.2 (14.0)	26.3 (16.5)	25.3 (16.7)	21.8 (13.8)	25.5 (15.9)
Antireflux treatments dispensed before PPI initiation, n (%)									
Alginate	543 (38.6)	720 (35.6)	993 (37.2)	1047 (33.9)	1113 (34.5)	1200 (33.7)	1137 (32.3)	1036 (32.8)	7789 (34.4)
H_2 receptor antagonist	411 (29.2)	548 (27.1)	593 (22.2)	668 (21.7)	709 (22.0)	687 (19.3)	527 (15.0)	421 (13.3)	4564 (20.2)
Prokinetic	13 (0.9)	7 (0.3)	1 (<0.1)	4 (0.1)	7 (0.2)	5 (0.1)	7 (0.2)	10 (0.3)	54 (0.2)
Antacid	4 (0.3)	6 (0.3)	2 (0.1)	5 (0.2)	8 (0.2)	4 (0.1)	7 (0.2)	14 (0.4)	43 (0.2)
Hospital-based diagnoses before PPI initiation, n (%)									
GERD‡ w/esophagitis	6 (0.4)	7 (0.3)	12 (0.4)	7 (0.2)	9 (0.3)	16 (0.4)	7 (0.2)	9 (0.3)	73 (0.3)
GERD w/o esophagitis	133 (9.4)	140 (6.9)	144 (5.4)	188 (6.1)	213 (6.6)	240 (6.7)	235 (6.7)	229 (7.3)	1522 (6.7)
≥1 GERD risk factor§	73 (5.2)	90 (4.4)	101 (3.8)	126 (4.1)	144 (4.5)	169 (4.8)	176 (5.0)	180 (5.7)	1059 (4.7)
≥1 Severe illness‖	194 (13.8)	255 (12.6)	330 (12.4)	361 (11.7)	360 (11.2)	451 (12.7)	427 (12.1)	479 (15.2)	2857 (12.6)
≥1 hospital admission for any diagnosis (excluding birth event)	453 (32.2)	575 (28.4)	772 (28.9)	991 (32.1)	1037 (32.2)	1209 (34.0)	1196 (34.0)	1084 (34.3)	7317 (32.3)
Premature (<37 wk)¶	170 (12.2)	269 (13.4)	325 (12.4)	389 (12.9)	367 (11.5)	495 (14.1)	409 (11.7)	417 (13.5)	2841 (12.7)

GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor; SD = standard deviation.

*Percentages calculated using Statistics New Zealand live birth counts per year in the denominator.

†Denominator: the number of doctors who held a current practicing certificate issued by the Medical Council of New Zealand at 30 June of each relevant year.

‡Gastroesophageal reflux disease.

§Recorded diagnosis of at least 1 of the following: esophageal anomalies (including achalasia of cardia, Barrett esophagus, erosion, hiatus hernia and congenital malformations), neurological impairment (including cerebral palsy, epilepsy, kernicterus, congenital malformations, and other disturbances of cerebral status), developmental delay (including motor function and physiology), chronic respiratory disease (including bronchopulmonary dysplasia), cystic fibrosis, congenital hypotonia, and Down syndrome.

‖Recorded diagnosis of any of the preceding diagnoses, or of congenital malformation of the heart, lungs, upper alimentary tract or dentofacial area, cardiac or respiratory disorders originating during the perinatal period, chromosomal abnormalities, metabolic disturbance, compromised immunity, cancer, or muscle tone disorders.

¶Number of children in the cohort with missing data for gestational age, by year of birth: 2005 n = 18, 2006 n = 19, 2007 n = 36, 2008 n = 61, 2009 n = 30, 2010 n = 37, 2011 n = 37, 2012 n = 70, 2005–2012 n = 308.

in infants of European ethnicities (2005 85.5%, 2012 76.8%). Compared with data from the 2006 Census, the ethnic distribution of the cohort was not reflective of the wider New Zealand population (11). There were substantial under-representations of infants of Māori (cohort 8.0%, Census 14.6%), Pacific (cohort 2.4%, Census 6.9%), and Asian (cohort 5.5%, Census 9.2%) ethnicities. Similarly, the socioeconomic distribution of the cohort differed from the underlying population with only 10.8% of the cohort living in the least privileged areas (quintile 5) and 25.9% living in the most privileged areas (quintile 1).

Proton Pump Inhibitor Use

By birth year, the number of children in the cohort as a percentage of national live births increased from 2.4% in 2005 to 5.2% in 2012 (Table 2). These national figures mask a large degree of regional variation by District Health Board (DHB), as shown in Figure 1. Of note, 3.5% of infants from Canterbury DHB (the largest DHB by population in the South Island) who were born in 2005 were dispensed a PPI, increasing to 10.2% for those born in 2009, before reverting to baseline levels (3.7%) for children born in 2012.

Table 2 also shows that a total of 106,071 courses of PPI treatment were dispensed to the 22,643 cohort members. Virtually all (99.9%) of the dispensed treatments were for omeprazole; lansoprazole accounted for 60 dispensings overall (14 patients), whereas pantoprazole was dispensed once. Comparing children born in 2005 with those born in 2012, there was a doubling in the number of patients dispensed a PPI and the total number of PPI dispensings dispensed to the cohort. There were also substantial increases in the number and proportion of prescribers who wrote a PPI prescription for an infant (overall 28.1% of registered medical practitioners).

There was a marked shift over the study period in the distribution of the patients' age at PPI initiation (Table 2). The proportion of the cohort who started treatment within the first 3 months of life increased by almost one-third, from 56.4% for children born in 2005, to 74.6% in 2012. There was also a doubling in the proportion, that started treatment within the first month of life, from 4.5% in 2005 to 9.4% in 2012. In the first week of life, 29 infants were dispensed a PPI, with the youngest children 4 days old at treatment initiation (n = 3).

Of the 106,071 courses of PPI treatment dispensed to the cohort, 89,182 (84.1%) were recorded with a ''days supply'' field of

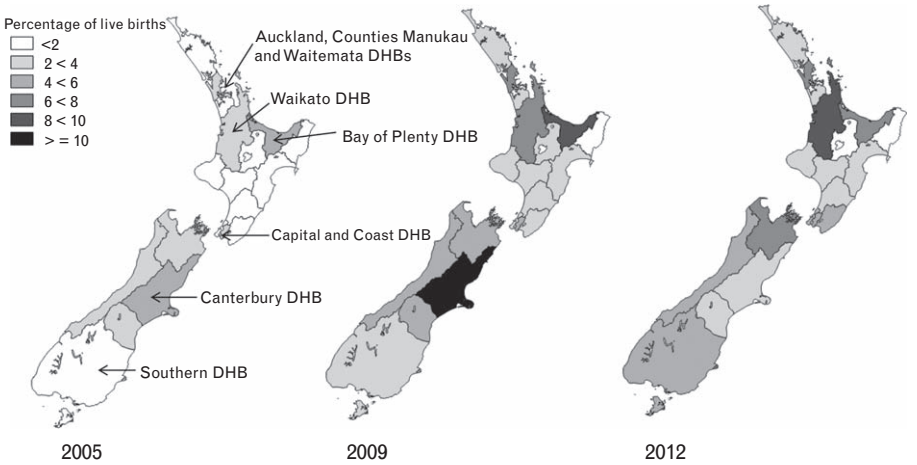

FIGURE 1. Infants in New Zealand who were dispensed a proton pump inhibitor (omeprazole, lansoprazole, pantoprazole) as a percentage of live births, by District Health Board (2005, 2009, 2012). Labels indicate District Health Boards with cities with a population of at least 100,000 residents.

zero. After applying the imputation rules described in Supplemental Digital Content 2, Figure, *http://links.lww.com/MPG/A976*, we found a pattern of decreasing total mean days of PPI use in the first year of life, by age group at initiation (Table 2). The largest percentage decrease (32.9%) was observed for children who were first dispensed a PPI aged 10 to 12 months old. Decreases of 15.5% (0–3 months), 19.9% (4–6 months), and 18.9% (7–9 months) were observed for the other age groups.

Other Dispensed Drugs Commonly Used to Treat Symptoms Attributed to Gastroesophageal Reflux Disease

Overall, and by year of birth, approximately one-third of infants were dispensed an alginate before PPI initiation (99.8% of these dispensings were for sodium alginate) (Table 2). The proportion of infants who were dispensed a histamine receptor antagonist (99.9% of these dispensings were for ranitidine) before PPI initiation decreased over the study period by more than half (2005 29.2%, 2012 13.3%). Prokinetics (domperidone, metoclopramide) and antacids (simethicone, calcium carbonate, magnesium hydroxide) were not widely dispensed before PPI initiation (0.2% of the cohort for each drug class).

Hospital-based Diagnoses Before Proton Pump Inhibitor Initiation

Table 2 shows that during the study period only 0.3% of the cohort had a hospital-based diagnosis of GERD with esophagitis, whereas 6.7% of the cohort was diagnosed with GERD without esophagitis (7.0% of the cohort [n = 1587] was diagnosed with either or both conditions). Overall, only 4.7% of the cohort had been diagnosed with 1 or more known or suspected GERD risk factors before PPI initiation. Table 3 shows the prevalence among the cohort of these risk factors. Overall, no individual diagnosis exceeded 2% of the cohort, although 12.7% of the cohort was born prematurely. No children in the cohort had been diagnosed with achalasia of cardia, Barrett esophagus, or esophageal erosion. Over the study period, approximately one-third of the cohort had a hospital admission for any diagnosis between birth and cohort entry (Table 2). There was also a relatively low prevalence (12.6%) of ''severe illness'' diagnoses before PPI initiation (Table 2). Overall, there were no substantial increases in the proportion of the cohort diagnosed before PPI initiation with GERD, individual GERD risk factors, severe illness, or prematurity.

DISCUSSION

The present study described the characteristics and PPI use patterns of a national cohort of infants in New Zealand born between 2005 and 2012 who were dispensed omeprazole, lansoprazole, or pantoprazole during the first year of life. Overall, 4.6% of infants were dispensed a PPI before their first birthday, with the proportion more than doubling over the study period, from 2.4% of national live births for children born in 2005, to 5.2% in 2012. Over the study period both the age at PPI initiation and the mean total number of days of PPI use (by age at initiation) decreased. Only small proportions of the cohort had a hospital-based diagnosis for

TABLE 3. Prevalence of known or suspected gastroesophageal reflux disease risk factors diagnosed in hospital before proton pump inhibitor (omeprazole, lansoprazole, pantoprazole) initiation, for children in New Zealand born between 2005 and 2012 who were dispensed at least 1 course of proton pump inhibitor treatment during the first year of life

Risk factor	n*	(%)†
Brain malformations	117	(0.5)
Cerebral palsy	15	(<0.1)
Congenital hiatal hernia	2	(<0.1)
Congenital hypotonia	104	(0.5)
Congenital lung disease	254	(1.1)
Congenital malformations of the esophagus	70	(0.3)
Cystic fibrosis	21	(<0.1)
Developmental delay	430	(1.9)
Down syndrome	64	(0.3)
Epilepsy	61	(0.3)
Neurological impairment	114	(0.5)
Premature (<37 wk gestation)	2841	(12.7)‡

*Total count for each health condition (some patients will have had >1 condition diagnosed).

†Percentage calculated using the whole cohort (n = 22,643 patients) as the denominator, unless otherwise indicated.

‡Percentage calculated using the number of children in the cohort for whom gestational age data were available (n = 22,335).

GERD (with or without esophagitis), known or suspected GERD risk factors, or other serious illness. Finally, 28.1% of registered medical practitioners had prescribed a PPI to an infant.

Compared to published studies, the prevalence of PPI use among New Zealand infants is high. In the United States, Barron et al (4), reported an overall prevalence of 0.2% for infants enrolled in 4 health insurance plans, whereas Illueca et al (6) estimated an overall prevalence among hospitalized children of 0.13% for newborns (<1 month), and 2.65% for infants (1–12 months). Although Slaughter et al (7), recently observed a prevalence of 7.9%, their study was restricted to patients admitted to neonatal intensive care units. The 2-fold increases we observed for both the number of patients dispensed PPI treatment and the volume of dispensed PPI treatments were less than the increases in PPI use (7.5-, 11-, or 30-fold) reported in overseas studies (4,5,8). The smaller relative increase in dispensed PPI treatments found in the present investigation (which is based on data from 2005 onwards) compared to the previous studies (all of which used reimbursement claims data from the late 1990s and early 2000s) may reflect the different stages in the drugs' product lifecycle that were assessed by the studies. In New Zealand, omeprazole prescribing was restricted from market introduction in 1990 until December 1996, while the drug was being monitored as part of the Intensive Medicines Monitoring Program, a national prescription event monitoring system (12). During this period, treatment with omeprazole had to be initiated by a specialist (eg, gastroenterologist), was only available for specific diagnoses and regular endoscopies were recommended during long-term courses of treatment (personal communication with Janelle Ashton, Intensive Medicines Monitoring Program Data Manager). These requirements served to restrict omeprazole use to the most severely affected patients, with only 22,050 patients (of all ages) prescribed omeprazole during the monitoring period. By 2005 PPIs had, however, been available without prescribing restriction for 8 years, and may have achieved a level of market ''maturity.'' In contrast, the study in Belgium by De Bruyne et al (8), covered a period (1997–2009) when there were several regulatory decisions concerning PPIs, including the lifting of prescribing restrictions in 2003, which the authors demonstrated had an immediate effect on the number of defined daily dose reimbursement claims made by pediatricians. Similarly, covering the period 1999 to 2004, Barron et al (4), referred to a formulary change from omeprazole to lansoprazole that was implemented in 2003 by several of the insurance plans that were included in the study, with a corresponding increase in both the number of claims, and the proportion of children, who were prescribed lansoprazole. These 2 studies captured periods of PPI use that, although induced by policy changes, included a market ''introduction'' stage when rapid growth would be expected, as opposed to the present study, which has assessed PPI use during a more stable ''maturity'' stage. The increases we observed are most similar to those reported by Illueca et al (6), who may have captured a period of market maturity in the United States during their study period (2004–2008).

Our findings complement and extend earlier New Zealand research on PPI use in infants. Best Practice Advisory Center had previously reported an almost 2-fold increase in the annual number of prescriptions for omeprazole between 2006 and 2010 (2). We were able to explore national patterns of PPI use over a longer period, and were able to examine the number of courses of PPI treatment that were actually dispensed to infants (rather than simply prescribed), and the numbers, proportions, and characteristics of infants to whom PPIs were dispensed. The study by Hudson et al (9), reported on omeprazole prescribing for infants enrolled in a Primary Health Organization covering the Christchurch area of the Canterbury DHB region, finding that 15% of enrolled infants had been prescribed a PPI in 2010. In contrast, we found that 9.5% of infants in the overall Canterbury DHB region were dispensed a PPI in the same year. This difference in proportions may be explained by differences in the study population—Christchurch is the second largest city by population in New Zealand, whereas the Canterbury DHB region is predominately rural; infant prescribing practices may differ between urban and rural doctors. Of note, when the high level of infant PPI prescribing was recognized in Christchurch, an academic detailing intervention was implemented in 2011, which saw prescribing levels quickly drop to baseline levels (13).

As far as we are aware, this is the first nationwide study to describe the patient characteristics and PPI use patterns of infants during the first year of life using linkable, patient-level data in a country with universal healthcare coverage. Our cohort of infant PPI users will have included virtually all children eligible for inclusion in the study because a patient's unique National Health Index identifier, our record linkage key, is a mandatory reporting field for reimbursement claims from community pharmacists. Hence a reliable data source was the basis for the numbers and proportions of infants who were dispensed PPIs. An additional strength of the present study is that the patient-level drug data related to dispensings, not prescriptions. Although it is impossible to know whether the drugs were administered to the infants as prescribed, because dispensing data are closer to the point of patient use than prescription data, a more accurate picture of use is possible.

The present study has some limitations, chief among them being the large proportion of PPI dispensings where the ''days supply'' field was recorded as zero. In these situations we imputed ''days supply'' values based on the patient's pattern of PPI dispensing dates, quantity of medicine dispensed, and New Zealand guidelines for maximum dispensed supplies of compounded PPI preparations (15 days) and pharmaceuticals in general (90 days). Although this may have affected the accuracy of our duration of use estimates, the general pattern we observed over the study period of declining duration of use according to age at PPI initiation would not be affected by the imputation method chosen. In addition, we did not have data for PPIs administered in hospital or bought over-the-counter (OTC). This may have resulted in observation gaps, which would have resulted in an underestimation of duration of use. It is, however, unlikely that access to OTC sales data would substantially alter the findings as OTC PPI sales were restricted to customers 18 years and older during the study period. We were unable to calculate the daily PPI doses that were dispensed to the patients, as we lacked information on the child's weight at the time of each dispensing, and, for the majority of dispensings, ''dose,'' and ''frequency'' data, because these fields are not mandatory for reimbursement. Finally, we were unable to fully assess whether PPIs were being appropriately prescribed to the children in the cohort, because we only had data on hospital discharge diagnoses and lacked detailed clinical information on the indications for PPI treatment.

New Zealand prescribers have enthusiastically adopted the use of PPIs for infant patients, and the prevalence of use among New Zealand infants appears to be much higher than published, non–population-based estimates from the United States. Local guidelines (2) recommend that ''omeprazole should only be considered in cases of severe infantile reflux esophagitis or if GERD is causing complications such as failure to thrive'' (p. 34). It is therefore concerning that we observed that only a small proportion of children in the cohort had been diagnosed with GERD before starting a PPI, and that the prevalences of known or suspected GERD risk factors, or other severe illness, were also low. Although none of the study PPIs are approved for use in children younger than 1 year, there may be some infants who would benefit from their administration; however, the use of these drugs among otherwise healthy children should be questioned by caregivers and clinicians. In order to reduce the clinically inappropriate overtreatment of healthy infants with PPIs, further investigation of the underlying

potential drivers of overtreatment is warranted, including caregiver-initiated demand, pharmaceutical reimbursement policies, and a culture of defensive medicine.

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