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Australia's rotavirus immunisation program: Impact on acute gastroenteritis and intussusception hospitalisations over 13 years

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A B S T R A C T

Background: Australia was one of the first countries to include rotavirus vaccines in its National Immunisation Program, in 2007. We compared trends in acute gastroenteritis (AGE) and intussusception-coded hospitalisations over 13-year post-vaccine period against five-year pre-vaccine baseline.
Methods: In a descriptive before-after study, incidence of hospitalisations with ICD-code of rotavirus AGE (A08.0), other AGE (K52, A01–A09 excluding A08.0) or intussusception (K56.1) between 2002 and 2020 was calculated using population denominators by age and Indigenous status. We used 2002–2006 as pre-vaccine baseline and calculated Incidence Rate Ratios [IRRs] for 2008–2019 and 2020.
Findings: In children aged <5 years, mean annual hospitalisation rate/100,000 decreased by 85% for rotavirus-coded AGE, from 248.3 in 2002–2006 to 37.6 (IRR 0.15; 95% CI 0.15–0.16) in 2008–2019 (61.4% for Indigenous children, from 680.2 to 262.2), and 46% for other AGE, from 1274.5 to 689.1 (IRR 0.54; CI 0.54–0.55), decreasing further in 2020 to 6.3 (rotavirus-coded) and 445.0 (other AGE). Rates for rotavirus-coded and other AGE declined in 2008–2019 in those aged 5–<20 years (IRR 0.52; CI 0.49–0.56 and 0.86; CI 0.85–0.87, respectively), but increased in 20–<65 years (IRR 2.38; CI 2.01–2.83 and 1.15; CI 1.15–1.16) and ≥65 years (IRR 2.24; CI 1.91–2.62 and 1.24; CI 1.23–1.25). Average annual hospitalisation rate for intussusception in infants was similar in pre-vaccine and post-vaccine periods (IRR 0.97; CI 0.90–1.04).
Conclusion: Over a 13-year period post-rotavirus vaccine introduction we document major sustained declines in hospitalisations coded as rotavirus and other AGE in age groups <20 years, with no change in intussusception hospitalisation rates in infants. Despite small increases in AGE hospitalisations in adults, likely due to increased PCR testing, our findings are consistent with highly favourable risk benefit ratio at whole-of-population level in Australia.

1. Background

Rotavirus is a non-enveloped RNA virus that is the leading global cause of severe dehydrating diarrhoea in children aged <5 years [1]. The severity of rotavirus infection ranges from asymptomatic, to diarrhoeal illness managed in the community to severe dehydrating gastroenteritis which is life-threatening without prompt hospital-based care. Rotavirus deaths are rare in countries with good access to health services, but much more common in low and middle income countries. [2,3] Globally in 2016, rotavirus infection caused an estimated 128,000 deaths and 258 million episodes of diarrhoea among children aged <5 years [4]. By 2022, rotavirus vaccine had been introduced in 120 of 194 countries, with coverage for the last dose of a rotavirus vaccine course estimated to be 51% globally, ranging from 4% in the World Health Organization Western Pacific Region to 74% in the Americas Region [5].

In Australia, rotavirus vaccines were included on the fully funded National Immunisation Program (NIP) in July 2007. Prior to vaccine introduction, rotavirus caused approximately 10,000 hospitalisations in children aged <5 years each year in Australia [6]. In this age group around half of all hospitalisations due to acute gastroenteritis (AGE), a syndromic condition which can be due to a range of bacterial and viral pathogens, were coded as rotavirus. However, variable laboratory testing practices meant that the rotavirus-attributable hospitalisation rate was likely much higher [6]. Medically attended rotavirus infection, at either general practitioner or hospital emergency department level, was estimated to occur in 1 in 27 children (about 4%) by the age of 5 years [6]. Reported rotavirus-related mortality in the pre-vaccine period was very low [7].

Initially, five of the eight Australian states and territories (jurisdictions) used the Rotarix® vaccine administered orally at 2 and 4 months (Northern Territory, New South Wales, Australian Capital Territory, Tasmania and Western Australia) and three used the RotaTeq® vaccine

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administered orally at 2, 4, and 6 months (Victoria, South Australia, Queensland), with Western Australia switching to RotaTeq® from June 2009. From 1 July 2017, all eight jurisdictions used Rotarix®. Since inception of the program, catch-up vaccination has not been recommended: infants who do not receive their first dose by defined age limits (before turning 15 weeks of age for Rotarix® and before turning 13 weeks of age for RotaTeq®) are not recommended to commence a vaccine course. This recommendation was precautionary due to concerns about intussusception (a rare and usually idiopathic condition resulting in acute bowel obstruction peaking at around 9 months of age [8]) which was found to be associated with a withdrawn rotavirus vaccine (RotaShield) [9].

In Australian infants, coverage for a complete course of a rotavirus vaccine increased from 82.3% in 2008 [10], the first full year of rotavirus vaccination on the NIP, to 92.5% in 2020 [11]. Coverage was lower (87.6%) among Aboriginal and Torres Strait Islander (hereafter, respectfully, Indigenous) infants, who comprise approximately 4% of the Australian birth cohort [12], are at higher risk of hospitalisation due to severe gastroenteritis, and in whom delayed receipt of vaccines is more common [11]. Coverage of rotavirus vaccine is lower than other childhood vaccines on the NIP, due to the strict upper age cut-offs for administration [11].

Studies in the first five years following addition of rotavirus vaccine to the NIP reported reductions in hospital admissions of close to 70% for both rotavirus-coded and all-cause AGE [13–15]. Declines in rotavirus-coded and all-cause AGE have also been documented following rotavirus vaccination program implementation in international studies [4,16].

Review of the benefits and risks of the rotavirus vaccine program over the long term is important. First, age related shifts in the incidence of rotavirus may occur if infection in early childhood is averted, as observed in the first 5 years post-program in England [17], where median age of infection increased and biennial rather than annual peaks were observed, driven by unvaccinated older children. Second, studies in Australia and some other high-income settings after widespread introduction of the current rotavirus vaccines suggested a small, time-limited increase in the risk of intussusception in infants in the 1–3 weeks following vaccination [18–20], especially for first rotavirus vaccine doses. Conversely, studies in low- and middle-income countries and a systematic review and meta-analysis including data from 33 countries have not shown a risk [21–23]. In Australia, the absolute increase in intussusception was estimated to be 6 cases for every 100,000 infants vaccinated in the first three weeks after receiving the first or second dose of rotavirus vaccine, representing 14 excess cases per year [18]. A 2017 review found a high overall benefit for the Australian program, with rotavirus vaccines estimated to be cost-saving to society [24].

In this study, we used comprehensive data on coded hospitalisations at national level to examine long-term benefits and risks of the Australian rotavirus immunisation program, by analysis of data on all-age trends in hospitalisations and deaths coded as rotavirus and other causes of AGE and intussusception in young children during the 13 years following vaccine introduction compared with a 5-year pre-vaccine baseline period.

2. Methods

In this observational before-after study we used data from the following sources:

2.1. Hospitalisations

The Australian Institute of Health and Welfare (AIHW) captures clinical and demographic data of patients admitted to public and private hospitals in Australia in the National Hospital Morbidity Database. All hospital admissions with a primary and or additional diagnosis of rotavirus gastroenteritis (ICD-10-AM code A08.0), other AGE (K52 and A01 to A09, excluding A08.0) and intussusception (K56.1) between 1 January 2002 and 31 December 2020 were included. These codes align with those used in previous Australian and international studies [13,25,26]. Appendix A lists the International Statistical Classification of Diseases and Related Health Programs, 10th revision, Australian Modification [ICD-10-AM] codes that contribute to all-cause gastroenteritis.

The variables included in our analysis were age group; sex; Indigenous status (Indigenous people or non-Indigenous people, with individuals with unclear status included under in the non-Indigenous people category); state or territory of residence; length of stay in days; mode of separation; principal and additional diagnoses and month and year of admission. While we analysed data by principal and additional diagnoses, our focus was on principal diagnoses. We analysed data using hospital admission rather than discharge date to account for timing of onset given the seasonality of rotavirus disease. We suppressed small cell counts (1–4) as per conditions of release of hospitalisation data by the data custodian.

2.2. Mortality

Registries of Births, Deaths and Marriages in each state and territory collect data on deaths, collated by the Australian Coordinating Registry (ACR), and prior to 2006 by the Australian Bureau of Statistics (ABS). Deaths coded by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) with A08.0 (rotavirus) or K56.1 (intussusception) as the underlying or an associated cause of death between 1 January 2002 and 31 December 2020 were included. These data were categorised as finalised to 2017, revised for 2018 and preliminary for 2019 and 2020. The variables examined and categories used were identical to those for hospitalisations. We suppressed small cell counts (1–5) as per conditions of release of death data by the data custodian.

2.3. Population estimates

Resident population estimates were obtained from the ABS. Mid-year estimates were used as population denominators for calculation of annual incidence rates, including by population subgroups (age group, Indigenous status).

2.4. Statistical analysis

All statistical analyses for this study were performed in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC USA).

Descriptive statistics are presented for categorical data as counts and relative frequencies. Crude and age-specific annual hospitalisation rates per 100,000 population per year were calculated by dividing the number of cases by the relevant ABS mid-year population estimate for each year. Rates were further stratified by state or territory of residence, gender, Indigenous status, and age group.

Incidence rate ratios for all-cause AGE hospitalisations, rotavirus-coded AGE hospitalisations, other AGE (i.e. AGE hospitalisations not coded as rotavirus) and selected subcategories of other AGE (hospitalisations coded as adenoviral enteritis, norovirus, other viral enteritis or unspecified viral intestinal infection) were calculated for the post-vaccine (2008–2019) compared to pre-vaccine (2002–2006) period by age group. We assessed the pandemic year 2020 separately due to the comprehensive public health measures implemented to control SARS-CoV-2 transmission during the pandemic.

Long-term trends in intussusception-coded hospitalisations in children aged <2 years over the period 2002 to 2020 were analysed by age group and year. Since previous studies [18,27] had shown short-term risk following doses 1 and 2 in early infancy, we aimed to look at cumulative incidence to ascertain if an overall absolute risk existed over the first year of life, and also conducted cross-sectional analysis to two years to examine any differences between the first and second years of life. We examined the cumulative percentage of intussusception-coded hospitalisations in infants aged younger than 12 months by month of age in 3 birth cohorts: pre-vaccine (2002–2006); post-vaccine (2008–2019) and first pandemic year (2020). Incidence rate ratios were calculated for intussusception hospitalisations in the post-vaccine (2008–2019, broken down into early post-vaccine [2008–2013] and late post-vaccine period [2014–2019] where relevant) compared to pre-vaccine (2002–2006) period by age group.

For analysis of hospitalisation data by Indigenous status we only included data from the 4 jurisdictions where recording of Indigenous status was 80% or more complete over the whole study period (Queensland, Western Australia, South Australia and the Northern Territory) [28].

When appropriate, 95% confidence intervals and *p*-values were calculated. A p-value <0.05 was considered statistically significant.

2.5. Ethics Approval

The Sydney Children's Hospitals Network Human Research Ethics Committee provided an exemption for surveillance activities involving de-identified data conducted by the National Centre for Immunisation Research and Surveillance, under its funding agreement with the Australian Government Department of Health and Aged Care; as such, specific ethical approval was not required for this project.

3. Results

3.1. Rotavirus-coded AGE hospitalisations before and after vaccine introduction

Annual rotavirus-coded (using principal or additional diagnosis) AGE hospitalisation rates declined from 25.0 per 100,000 per year in 2006 to 5.7 per 100,000 per year in 2019 for all ages combined, from 346.1 per 100,000 per year to 41.4 per 100,000 per year for children aged <5 years, and from 543.7 to 72.3 for children aged <2 years (Fig. 1). The average annual rotavirus-coded (principal or additional diagnosis) hospitalisation rate declined between the pre-vaccine (2002–2006) and post-vaccine (2008–2019) periods by 71.9% for all ages combined, from 19.6 per 100,000 (95% CI 19.4–19.9) to 5.5 per 100,000 (95% CI 5.4–5.6), IRR 0.28 (95% CI 0.28–0.29) and by 81.8% for children aged <5 years, from 275.1 per 100,000 (95% CI 271.1–279.2) to 50.1 per 100,000 (95% CI 49.1–51.1), IRR 0.18 (95% CI 0.18–0.19).

All-age incidence of rotavirus-coded (principal or additional diagnosis) AGE hospitalisation by jurisdiction is shown in Appendix B. Differences in rates between jurisdictions should be interpreted with caution as incidence for the 2002–2006 pre-vaccine period varied widely, likely related to testing and diagnostic practices, despite similar incidence of all-cause AGE hospitalisation in all jurisdictions except the Northern Territory (data not shown). Despite widely differing baselines, it is apparent that the incidence of rotavirus-coded AGE hospitalisation was substantially lower in the post-vaccine period (2008–2019) in all jurisdictions, with all-age incidence ranging from 2.2 per 100,000 per year in Victoria to 36.7 per 100,000 per year in the Northern Territory. Peak incidence and fluctuations in incidence were greatest in the Northern Territory.

Pre-vaccine period rotavirus-coded AGE hospitalisation incidence in Indigenous children aged <5 years also varied widely, from 278.8 per 100,000 population per year in Queensland to 472.8 in Western Australia, 876.8 in South Australia and 1995.2 per 100,000 in the Northern Territory (Appendix C). The average annual incidence in the pre-vaccine period in Indigenous children aged <5 years across these four jurisdictions was 680.2 per 100,000, more than three times that in

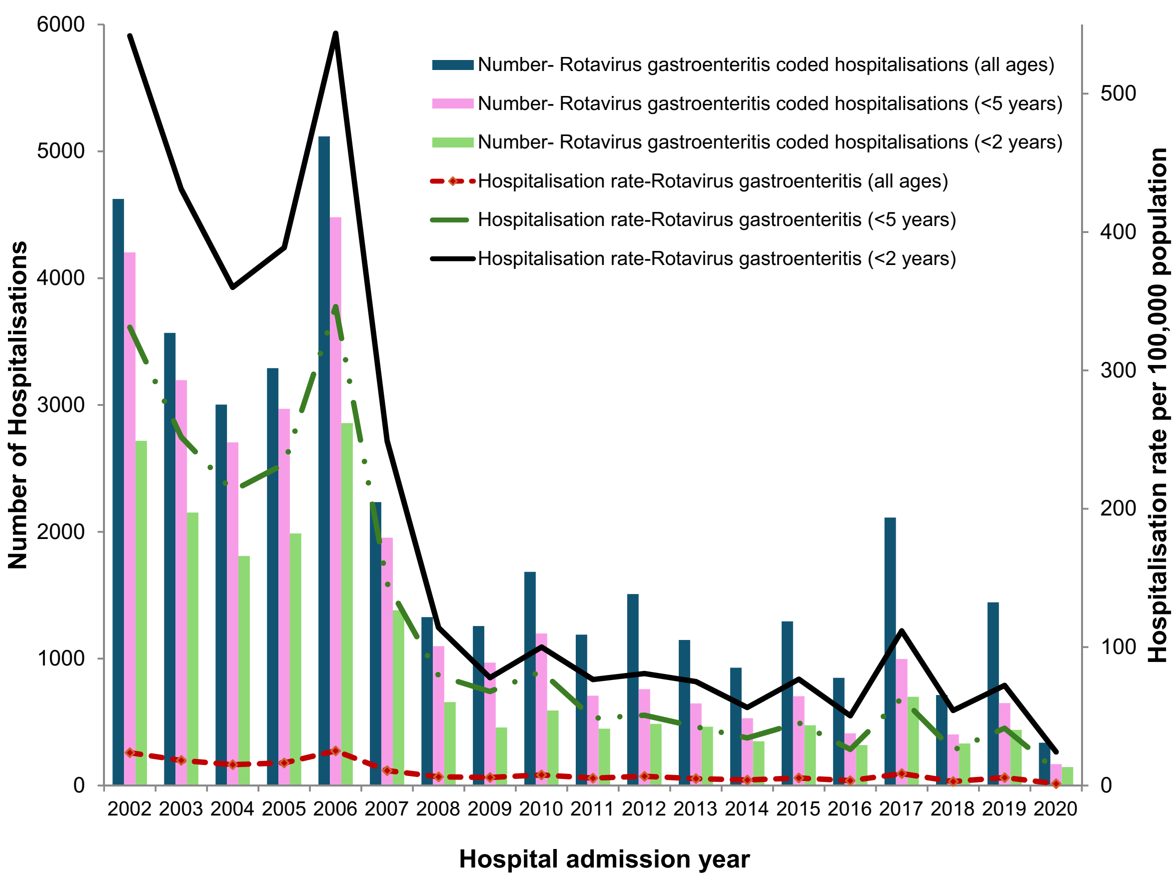

Fig. 1. Number and rate per 100,000 population of rotavirus-coded hospitalisations (all ages, <5 years and < 2 years)*, Australia, January 2002 to December 2020.

their non-Indigenous counterparts (IRR 3.32, 95% CI 3.14, 3.51). In the post-vaccine period (2008–2019), the rotavirus-coded AGE hospitalisation rate in Indigenous children aged <5 years in these four jurisdictions was 61.4% lower at 262.2 per 100,000 per year, but more than six times higher than in their non-Indigenous counterparts (IRR 6.72, 95% CI 6.33–7.14).

All cause AGE hospitalisations before and after vaccine introduction.

Hospitalisations coded with AGE as principal diagnosis (Table 1) or in any diagnosis field (Appendix D) were compared and showed important differences by age. While the all-cause AGE hospitalisation (any diagnosis field) incidence per 100,000 population per year in the period 2002–2006 was only 16.4% higher than the all-cause AGE (principal diagnosis only) rate in children aged <5 years (1773 and 1523, respectively) and 24.5% higher in the 5 to <20 years age group (264 and 212, respectively), it was 68.5% (460 and 273) and 125.1% (1506 and 669) higher in adults aged 20–<65 and ≥ 65 years respectively. Hence, we focussed our analyses focus solely on principal diagnosis.

Table 1 shows age-specific (<5, 5–<20, 20–<65 and ≥65 years) incidence of AGE hospitalisations (principal diagnosis only) coded as rotavirus or other selected categories of AGE, along with all-cause AGE and AGE not coded as rotavirus, with incidence rate ratios (IRRs) for the post-vaccine (2008–2019) compared to pre-vaccine (2002–2006) period. Among children <5 years of age, the average annual incidence per 100,000 of rotavirus-coded hospitalisation was 85% lower in 2008–2019 (37.6) than the pre-vaccine period (248.3), an IRR of 0.15 (95% CI 0.15–0.16). In 2020, the first year of the COVID-19 pandemic, the rotavirus-coded AGE hospitalisation rate in children aged <5 years significantly decreased six-fold to 6.3 (95% CI 5.1–7.6) per 100,000 population. Hospitalisation for AGE not coded as rotavirus also declined in this age group by 46%, from 1274.5 per 100,000 per year in the 2002–2006 period to 689.1 per 100,000 per year in the 2008–2019 period, with an IRR of 0.54 (95% CI 0.54–0.55), despite a 10-fold increase in hospitalisations coded as due to norovirus (IRR 10.6; 95% CI 8.5–13.3) and lesser, but significant, increases in hospitalisations coded as adenovirus or other viral enteritis. In 2020, the incidence of AGE hospitalisation not coded as rotavirus in children aged <5 years was at an all-time low of 445.0 per 100,000 population compared with 689.0 per 100,000 per year between 2008 and 2019.

In older children and adolescents aged between 5–<20 years, rotavirus-coded hospitalisation (principal diagnosis) declined by 47.2%, from a much lower incidence (than children aged <5 years) of 7.2 per 100,000 per year in 2002–2006 to 3.8 per 100,000 per year in 2008–2019 (IRR 0.5, 95% CI 0.5–0.6) and, like children aged <5 years, with lesser but significant decreases in AGE not coded as rotavirus (IRR 0.86, 95% CI 0.85–0.87) despite significant increases in hospitalisations coded as norovirus, adenovirus and other viral enteritis. In contrast, in adults aged 20–<65 years and ≥65 years there were significant increases from a very low baseline incidence of rotavirus-coded hospitalisation, with IRRs of 2.4 (95% CI 2.01–2.83) and 2.2 (95% CI 1.91–2.62) respectively for 2008–2019 compared to 2002–2006. Both adult age groups had small but significant increases in all-cause AGE (IRRs of 1.15 and 1.24, respectively), contributed to by steep increases in hospitalisations coded as norovirus, adenovirus and other viral enteritis, similar to those seen in younger age groups (Table 1).

4. Intussusception hospitalisations before and after vaccine introduction (any diagnosis field)

4.1. Ecological data analysis

Fig. 2 shows intussusception-coded hospitalisation rates in children aged <2 years, from January 2002 to December 2020. Overall, the intussusception-coded hospitalisation rates fluctuate across years with the lowest rate observed in 2020. The incidence of hospitalisation coded as intussusception among infants aged 1–<4 months of age was similar in the post-vaccine (2008–2019, 47.9 per 100,000 population per year) and pre-vaccine (2002–2006, 44.3 per 100,000 per year) periods, IRR

Table 1
Incidence of hospitalisations (principal diagnosis) for rotavirus and other causes of acute gastroenteritis by age group, Australia, 1 January 2002 to 31 December 2020.

	0–<5 years				5–<20 years				20–<65years				≥65 years			
	Pre-vaccine period	Post-vaccine period	Post-vaccine period	Incidence rate ratio (IRR)	Pre-vaccine period	Post-vaccine period	Post-vaccine period	Incidence rate ratio (IRR)	Pre-vaccine period	Post-vaccine period	Post-vaccine period	Incidence rate ratio (IRR)	Pre-vaccine period	Post-vaccine period	Post-vaccine period	Incidence rate ratio (IRR)
	2002 – 2006	2008 – 2019	2020	2008–2019 /2002–2006 (95% CI)	2002 – 2006	2008–2019	2020	2008–2019 /2002–2006 (95% CI)	2002–2006	2008–2019	2020	2008–2019 /2002–2006 (95% CI)	2002–2006	2008–2019	2020	2008–2019 /2002–2006 (95% CI)
	Rates	Rates	Rates	IRR	Rates	Rates	Rates	IRR	Rates	Rates	Rates	IRR	Rates	Rates	Rates	IRR
Rotavirus gastroenteritis (ICD-10-AM code A08.0)	248.3	37.6	6.3	0.15 (0.15–0.16)	7.2	3.8	0.5	0.52 (0.49–0.56)	0.2	0.6	0.2	2.38 (2.01–2.83)	1.3	3.0	1.2	2.24 (1.91–2.62)
Norovirus (ICD-10-AM code A08.1)	1.3	13.7	11.6	10.63 (8.53–13.25)	0.1	1.1	0.9	8.64 (5.88–12.70)	0.2	1.2	1.4	6.74 (5.56–8.16)	1.0	6.4	3.4	6.17 (5.18–7.35)
Adenoviral enteritis (ICD-10-AM code A08.2)	13.3	16.0	8.5	1.20 (1.11–1.30)	0.4	0.5	0.3	1.37 (1.06–1.78)	0.0	0.2	0.1	9.72 (5.46–17.30)	0.1	0.7	0.3	12.68 (5.99–26.84)
Other viral enteritis (ICD-10-AM code A08.3)	8.9	19.7	15.7	2.21 (2.02–2.41)	0.8	1.1	0.6	1.41 (1.18–1.69)	0.6	1.1	0.8	1.84 (1.64–2.06)	1.4	4.6	2.1	3.28 (2.81–3.82)
Viral intestinal infection, unspecified (ICD-10-AM code A08.4)	403.2	254.4	160.3	0.63 (0.62–0.64)	54.6	48.4	25.5	0.89 (0.87–0.91)	28.9	35.7	25.9	1.23 (1.21–1.25)	63.3	83.5	51.9	1.32 (1.29–1.35)
Acute gastroenteritis (ICD-10-AM code K52; A01 to A09 ***excluding*** A08.0)	1274.5	689.1	445.0	0.54 (0.54–0.55)	205.1	175.8	108.9	0.86 (0.85–0.87)	272.8	313.9	261.2	1.15 (1.14–1.16)	667.5	827.6	677.0	1.24 (1.23–1.25)
All cause acute gastroenteritis (ICD-10-AM code K52; A01 to A09 ***including*** A08.0)	1522.8	726.6	451.2	0.48 (0.47–0.48)	212.3	179.5	109.5	0.85 (0.84–0.86)	273.0	314.5	261.4	1.15 (1.15–1.16)	668.8	830.5	678.2	1.24 (1.23–1.25)

Note: Blue shaded boxes indicate pre-vaccine periods; green shaded boxes indicate statistically significant decrease in hospitalisation rates in the post-vaccine and pandemic period compared to the pre-vaccine period; grey shaded boxes indicate statistically significant increase in hospitalisation rates and IRRs in the post-vaccine and pandemic period compared to the pre-vaccine period and those not shaded are where rates are no different in the pre-vaccine and post-vaccine periods.

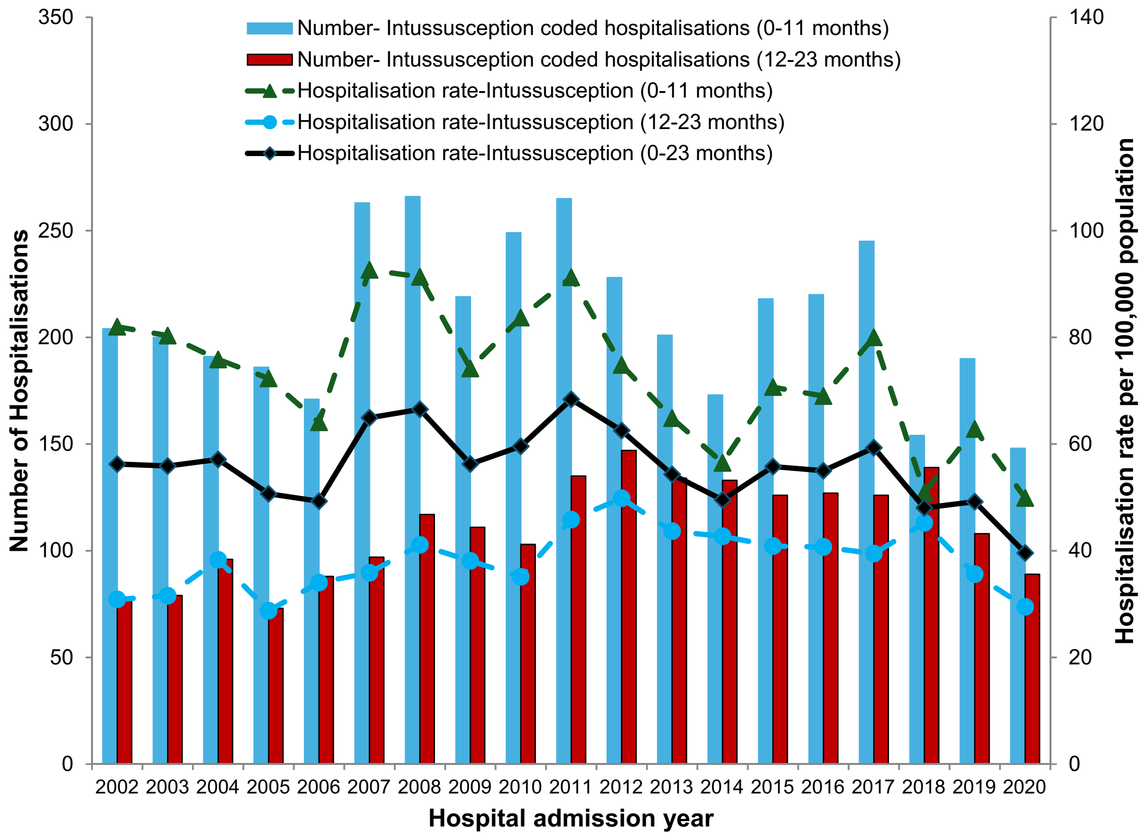

Fig. 2. Number and rate per 100,000 population per year of intussusception-coded hospitalisations* in children aged less than 2 years, Australia, January 2002 to December 2020.

1.08 (95% CI 0.89–1.31) as shown in Table 2. Intussusception-coded hospitalisation rates were also similar in the post-vaccine compared to pre-vaccine period in the age groups between 4 and <12 months, and infants aged 0 to 12 months combined (IRR 0.97; 95% CI 0.90–1.04) but higher in children aged 12 to <24 months (IRR 1.27; 95% CI 1.14–1.42) (Table 2). A significantly higher rate in infants 1–<4 months of age was observed in the early post-vaccine (2008–2013) compared to pre-vaccine period (IRR 1.28; 95% CI 1.04–1.57), but not in other age groups <12 months. However, more recently (2014–2019) there was no evidence of increased risk of intussusception in the 1–<4 months age group with an IRR of 0.89 (95% CI 0.71–1.12).

In the 2020 pandemic year, the intussusception-coded hospitalisation rate was substantially lower in children aged 0 to <12 months compared to both the pre-vaccine (2002–2006) (IRR 0.67, 95% CI 0.56–0.79) and 2008–2019 post-vaccine period (IRR 0.69; 95% CI 0.58–0.81).

In Indigenous children in the four jurisdictions (Queensland, Western Australia, South Australia and the Northern Territory) with >80% completeness of recording of Indigenous status there was no significant difference in intussusception hospitalisation rates in the post-vaccine (2008–2019) compared to pre-vaccine (2002–2006) period for those aged 0 to <12 months (IRR 0.97; 95% CI 0.51–1.84) or 12 to <24 months (IRR 1.19; 95% CI 0.48–2.94).

4.2. *Cohort analysis*

The cumulative percentage of intussusception-coded hospitalisations in children aged <1 year, by age in months, in pre-vaccine (2002–2006)

Table 2
Intussusception-coded hospitalisation rates by age in children aged <12 months, before (2002–2006) and after (2008–2019, 2020) the introduction of rotavirus vaccine, Australia.

Age in months	Pre-vaccine period (2002–2006)		Post-vaccine period (2008–2019)		Pandemic year (2020)		Incidence rate ratio (IRR) 2008–2019/ 2002–2006
	Total number	Mean annual rate*	Total number	Mean annual rate*	Total number	Mean annual rate*	IRR (confidence interval)
0–<12 months	952	74.7	2628	72.3	148	49.9	0.97 (0.90–1.04)
0- < 1 month	5	4.7	26	8.6	0	–	1.82 (0.70–4.75)
1- < 4 months	141	44.3	435	47.9	27	36.4	1.08 (0.89–1.31)
4–<7 months	338	106.1	855	94.1	26	35.1	0.89 (0.78–1.01)
7–<9 months	233	109.8	574	94.8	49	99.1	0.86 (0.74–1.01)
9–<12 months	235	73.8	738	81.2	46	62.0	1.10 (0.95–1.27)
12–<24 months	414	32.7	1506	41.5	89	29.5	1.27 (1.14–1.42)
0–<24 months	1366	53.8	4134	56.9	237	39.6	1.06 (1.00–1.13)

* Rate per 100,000 population per year.

and post-vaccine (2008–2019) periods are shown in Fig. 3. Infants in the first month of life accounted for 0.5% of intussusception-coded hospitalisations under one year in the pre-vaccine compared to 1.0% in the post-vaccine period, infants in the second month of life 6.8% compared to 10.6%, and infants in the third month of life for 15.3% compared to 17.5%. At 6 months of age, the cumulative percentage in the post-vaccine cohort (50.1%) crossed over to below that in the post-vaccine cohort (51.6%).

4.3. Deaths

We found no deaths with rotavirus AGE recorded as the underlying cause of death in children aged <5 years in the post-vaccine period (2008–2019) compared to 1–5 deaths in the pre-vaccine period (2002–2006). In individuals aged ≥5 years, there were 9 deaths with rotavirus AGE recorded as the underlying cause of death in the post-vaccine period compared to 1–5 deaths in the pre-vaccine period, with all in adults aged ≥65 years.

No deaths were recorded with intussusception as the underlying cause of death in children aged <5 years in either the pre-vaccine (2002–2006) or post-vaccine period (2008–2019).

5. Discussion

We found a sustained and substantial decline in rotavirus-coded AGE hospitalisations in children and adolescents during the 13-year post-rotavirus vaccine introduction period. The greatest impact was in children aged less than 5 years, with an 85% decline in rotavirus-coded gastroenteritis hospitalisations. In pre and post-licensure vaccine efficacy and effectiveness studies, including earlier studies in Australia, rotavirus vaccines have been shown to have greatest impact in preventing severe or hospitalised rotavirus-associated gastroenteritis [29–31]. No deaths due to rotavirus as the underlying cause were recorded in children aged <5 years in the 13 years following vaccine introduction, compared to 1–5 deaths (not reportable where number < 5) in the 5-year pre-vaccine period.

This substantial and sustained decline in hospitalised disease in Australia was associated with high and sustained rotavirus vaccine coverage (2 or 3 doses, depending on the vaccine type, assessed at age 12 months). Coverage increased rapidly following inclusion on the NIP and reached 92.5% by 2020 [11], despite recommended upper age limits for administration preventing uptake as higher as other vaccines scheduled in infancy, with coverage of 95% in 2020 [11].

Consistent with varying testing rates and limitations in test sensitivity, we found a considerable decline in hospitalisation rates for AGE not coded as rotavirus in children and adolescents. These reductions were proportionately smaller (46% for those <5 years), but larger numerically due to the higher incidence of non -rotavirus-coded AGE hospitalisations. More than one-third of other AGE hospitalisations were coded as unspecified (i.e. causative pathogen not identified), but many are likely due to undiagnosed rotavirus infection [32]. Conversely, the increase in hospitalisation rates for AGE coded as caused by other specific pathogens, such as norovirus and adenovirus, across all age groups in the post-vaccine period is likely due to increased laboratory stool testing using multiplex panels detecting nucleic acid for a range of pathogens by polymerase chain reaction (PCR) [33]. Furthermore, it is not certain why there are differences in the all-cause AGE hospitalisations among adults over 20 years of age when comparing principal diagnoses with other diagnostic fields. It may be due to increased availability of testing making specific pathogen diagnoses more certain. Access to testing data would assist in understanding this. The increase in rotavirus-coded AGE hospitalisation rates observed in adults aged ≥65 years is also likely due to increased use of PCR-based stool testing, noting that incidence in this age group was 30-fold lower than in children aged <5 years. A US study using similar coded hospitalisation data found an increased incidence of AGE in adults aged ≥60 years, but argued that this was not significant after adjustment [34], and a recent Japanese study reported lower incidence of AGE hospitalisation in older adults in regions where rotavirus vaccine uptake was higher, with some regions below 40%. [35] As rotavirus vaccine coverage in Australia was

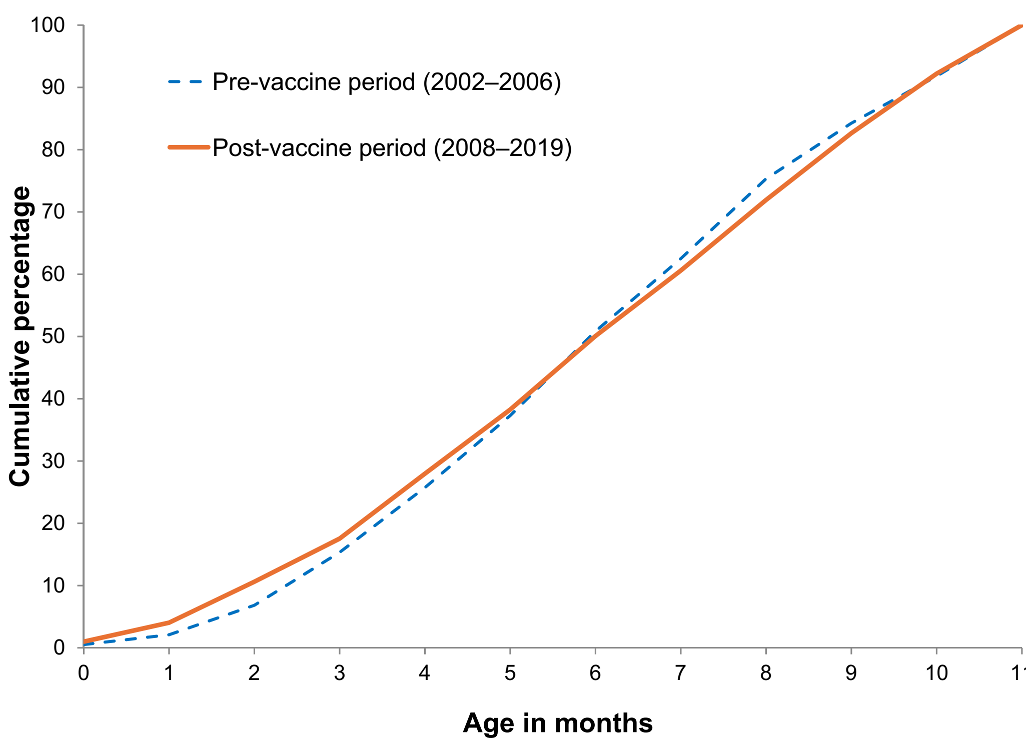

Fig. 3. Cumulative percentage of intussusception-coded hospitalisations in the first year of life using a cohort-based analysis by age in months, in children born before (2002–2006) and after (2008–2019) national rotavirus immunisation program introduction in Australia.

uniformly high, we could not examine the impact of low coverage but our data raise the possibility that the findings from Japan may be confounded by healthy vaccine effects, with factors promoting lower AGE hospitalisations also associated with higher childhood vaccine uptake.

We found intussusception hospitalisation rates by 12 months of age to be similar in the post- compared to pre-vaccine period (IRR 0.97; 95% CI 0.90–1.04). While the rate in infants aged 1–<4 months in the early post-vaccine period (2008–2013) was higher than in the pre-vaccine period, consistent with previous studies, [18,36] the rate in the more recent post-vaccine period (2014–2019) was similar to pre-vaccine. This is a reassuring observation that also lends support to the hypothesis that any increase in intussusception in the first few weeks immediately following vaccination could occur in infants intrinsically predisposed to developing intussusception i.e. those who would have otherwise developed intussusception due to viral infection or other environmental exposures at a later age. This apparent compensatory decline in incidence later in infancy, and data showing no increase in clinical severity of intussusception in vaccine proximate compared with non-vaccine proximate cases, [27,37] suggest that the impact of rotavirus vaccination on intussusception, if any, is so small that it is difficult to measure even at a population level. Recent systematic reviews and meta-analyses have found no evidence of increased intussusception with rotavirus vaccine. [22] [38]

While we found an increase in the intussusception hospitalisation rate in children aged 12–23 months in the post-vaccine compared to pre-vaccine period (IRR 1.27; 95% CI 1.14–1.42), changes were not significant overall when calculated for 0–23 months (IRR 1.06; 95% CI 1.00–1.13). A retrospective record linkage study of approximately 350,000 children born in Western Australia found a similarly higher rate over the 2008–2012 period among children aged 12–23 months, as well as children aged 2–4 years, but not for intussusception-coded hospitalisations associated with procedure codes, suggesting that application of intussusception coding may have become less specific over time [39]. We could not undertake similar analyses to assess the impact of procedure-related intussusception (e.g. following or related to other bowel surgery) as we did not have linked data, however this increased rate in older children appears unlikely to be related to vaccination.

While the rotavirus-coded AGE hospitalisation rate in Indigenous children aged <5 years was substantially lower in the post-vaccine than pre-vaccine period, the decline was less marked than in Australian children overall (61.4% versus 85.0%). This may be due to a number of factors, including lower vaccine effectiveness against rotavirus-related hospitalisation in Indigenous children [40], who often live in socioeconomically disadvantaged and crowded conditions [41] comparable to developing country settings where lower vaccine efficacy and effectiveness have been documented. We also found that the intussusception hospitalisation rate in Indigenous children was not significantly different in the post-vaccine compared to pre-vaccine period, across all age groups. Less stringent upper age limits, as well as an additional dose of rotavirus vaccine have been suggested as potential options to increase vaccine coverage among Indigenous Australian children [41,42] and children in low and middle-income countries [43], in order to maximise the public health benefits of rotavirus immunisation programs in such settings.

We identified a decline in rotavirus-coded AGE, other AGE and intussusception hospitalisation rates in 2020 in Australia, which could be due to the reduction in a range of infectious diseases associated with public health interventions during the COVID-19 pandemic. While viral infection has been implicated as a potential cause of intussusception [44], and a similar decline in intussusception hospitalisations observed in the United States of America in 2020 [45], it is also notable that the decline in intussusception hospitalisation was much less than the decline in rotavirus hospitalisation, suggesting a lesser role for infection in relation to intussusception.

We found no deaths with intussusception recorded as the underlying cause in children aged <5 years in either the pre- or post-vaccine period. Intussusception deaths temporally associated with rotavirus vaccination can cause significant concern and program disruption. For example, two deaths in France following intussusception in rotavirus vaccinated infants resulted in the suspension of the recommendation for rotavirus vaccination in 2015 [46], with the recommendation not reinstituted until 2022 [47].

There were a few limitations in our study. This was an ecological analysis using ICD-coded hospitalisation and death data, so we were unable to clinically verify these cases. ICD coding may vary in specificity and sensitivity [32] and coding practices may vary over time. Our results could have been influenced by factors such as changes in propensity to test and recording of the aetiology of gastroenteritis in medical records. Vaccination status is not captured routinely in hospitalisation data. We were unable to calculate vaccine effectiveness or relationship between vaccination and intussusception from this dataset but this has been done by other studies [31]. We were unable to account for the impact of potentially relevant variables not available in our dataset such as socioeconomic status indicators.

Strengths of this study include its longevity, with data over a 13-year period post-vaccine introduction, including all-age AGE hospitalisation and a detailed examination of intussusception in infants less than six months of age who are most intensively exposed to rotavirus vaccines.

In conclusion, we found substantial declines in rotavirus-coded and other AGE hospitalisations in Australia in children aged <5 years, with significant but lesser reductions in rotavirus and AGE hospitalisations in Aboriginal children, and no overall change in the risk of intussusception in infants. Few studies have examined all-age AGE. While we found statistically significant increases in AGE in adults older than 20 years, and especially in adults older than 65 years, increases were relatively small and likely due to increased use of PCR-based stool testing. Overall, the evidence from this study is consistent with the benefits of rotavirus vaccines far outweighing any risks and reinforces the findings of a previous study which found that the rotavirus immunisation program in Australia was cost-saving, based on data six years post-implementation [24]. These findings should increase the confidence of Australian policymakers, immunisation program staff and immunisation providers in promoting the individual and public health benefits of rotavirus vaccination and achieving as high levels of coverage as possible. Our findings can also inform updated economic evaluation of the Australian program and support other countries' decision-making around rotavirus vaccine introduction into their immunisation programs.

CRediT authorship contribution statement

Aditi Dey: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Joanne Jackson:** Writing – review & editing, Methodology, Conceptualization. **Han Wang:** Writing – review & editing, Formal analysis, Data curation. **Stephen B. Lambert:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Peter McIntyre:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Kristine Macartney:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Frank Beard:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. ICD-10-AM/ICD-10 codes

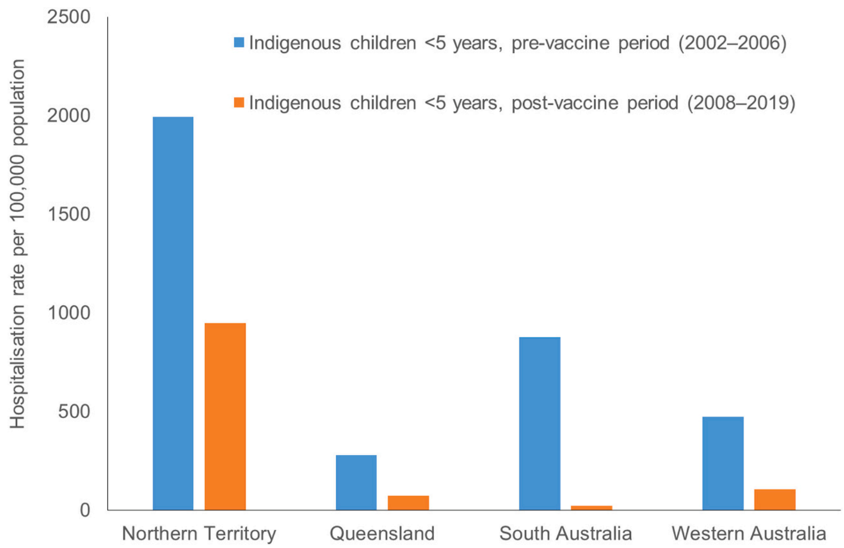
ICD-10-AM codes for rotavirus (A08.0), other acute gastroenteritis (K52 and A01 to A09, excluding A08.0) and intussusception (K56.1) included in the hospitalisation data from the AIHW.

	Code	Description
Rotavirus	A08.0	Rotaviral enteritis
Acute gastroenteritis	A01	Typhoid and paratyphoid fevers
	A02	Other salmonella infections
	A03	Shigellosis
	A04	Other bacterial intestinal infections
	A05	Other bacterial food-borne intoxications, not elsewhere classified
	A06	Amoebiasis
	A07	Other protozoal intestinal diseases
	A08.1	Acute gastroenteropathy due to Norovirus
	A08.2	Adenoviral enteritis
	A08.3	Other viral enteritis
	A08.4	Viral intestinal infection, unspecified
	A08.5	Other specified intestinal infections
	A09	Other gastroenteritis and colitis of infectious and unspecified origin
	K52	Other noninfective gastroenteritis and colitis
Intussusception	K56.1	Intussusception

Appendix B. Rotavirus-coded hospitalisation (all diagnosis fields) rates (all ages), by state and territory,* 2001 to 2020 (note: variation in y-axes scale)

*Note: Rotavirus vaccine was added to the Australian National Immunisation Program in July 2007.

Appendix C. Rotavirus-coded hospitalisation (all diagnosis fields) rates per 100,000 population per year in Indigenous children aged less than 5 years by jurisdiction (Northern Territory, Queensland, South Australia and Western Australia) before (2002–2006) versus after (2008–2019) rotavirus vaccine introduction, Australia



Appendix D. Incidence of coded hospitalisations (all diagnosis fields) for rotavirus and other causes of acute gastroenteritis by age group, Australia, 1 January 2002 to 31 December 2020

	0–<5 years				5–<20 years				20–<65years				≥65 years			
	Pre-vaccine period	Post-vaccine period	Post-vaccine period	Incidence rate ratio (IRR)	Pre-vaccine period	Post-vaccine period	Post-vaccine period	Incidence rate ratio (IRR)	Pre-vaccine period	Post-vaccine period	Post-vaccine period	Incidence rate ratio (IRR)	Pre-vaccine period	Post-vaccine period	Post-vaccine period	Incidence rate ratio (IRR)
	2002–2006	2008–2019	2020	2008–2019/2002–2006	2000–2006	2008–2019	2020	2008–2019 /2002–2006	2002–2006	2008–2019	2020	2008–2019 /2002–2006	2002–2006	2008–2019	2020	2008–2019 /2002–2006
	Rates	Rates	Rates	IRR (95% CI)	Rates	Rates	Rates	IRR (95% CI)	Rates	Rates	Rates	IRR (95% CI)	Rates	Rates	Rates	IRR (95% CI)
Rotavirus gastroenteritis (ICD-10-AM code A08.0)	275.1	50.1	10.9	0.18 (0.18–0.19)	7.8	4.5	0.8	0.57 (0.54–0.61)	0.3	1.0	0.4	3.13 (2.70–3.63)	2.1	5.7	1.7	2.75 (1.42–3.12)
Norovirus (ICD-10-AM code A08.1)	2.0	21.0	18.2	10.57 (8.86–12.62)	0.2	1.8	1.6	9.80 (7.05–13.61)	0.3	2.1	2.3	6.69 (5.78–7.74)	2.9	16.5	7.3	5.62 (5.07–6.24)
Adenoviral enteritis (ICD-10-AM code A08.2)	16.3	22.5	11.5	1.38 (1.29–1.47)	0.4	0.8	0.6	2.01 (1.60–2.54)	0.0	0.5	0.2	14.09 (9.23–21.51)	0.1	2.4	0.6	34.86 (18.09–67.20)
Other viral enteritis (ICD-10-AM code A08.3)	10.8	27.3	19.7	2.53 (2.34–2.74)	0.9	1.5	1.0	1.64 (1.40–1.92)	0.9	1.9	1.8	2.07 (1.89–2.26)	3.8	11.4	5.0	3.00 (2.73–3.29)
Viral intestinal infection, unspecified (ICD-10-AM code A08.4)	424.3	278.3	178.7	0.66 (0.65–0.67)	58.6	53.5	28.5	0.91 (0.89–0.93)	34.4	43.1	31.3	1.25 (1.23–1.27)	79.7	105.0	65.2	1.32 (1.29–1.35)
Acute gastroenteritis (ICD-10-AM code K52; A01 to A09 ***excluding*** A08.0)	1497.7	892.1	595.5	0.60 (0.59–0.60)	256.4	244.0	169.9	0.95 (0.94–0.96)	459.7	580.3	534.6	1.26 (1.26–1.27)	1504.0	2076.1	1812.0	1.38 (1.37–1.39)
All cause acute gastroenteritis (ICD-10-AM code K52; A01 to A09 ***including*** A08.0)	1772.8	942.2	606.4	0.53 (0.53–0.54)	264.2	248.5	170.7	0.94 (0.93–0.95)	460.0	581.4	535.0	1.26 (1.26–1.27)	1506.0	2081.8	1814.0	1.38 (1.38–1.39)

Note: Blue shaded boxes indicate pre-vaccine periods; green shaded boxes indicate statistically significant decrease in hospitalisation rates in the post-vaccine and pandemic period compared to the pre-vaccine period; grey shaded boxes indicate statistically significant increase in hospitalisation rates in the post-vaccine and pandemic period compared to the pre-vaccine period and those not shaded are where rates are no different in the pre-vaccine and post-vaccine period

Data availability

Data will be made available on request.

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