Observational Study

Medicine®

OPEN

The impact of rotavirus vaccination in the prevalence of gastroenteritis and comorbidities among children after suboptimal rotavirus vaccines implementation in Taiwan

A population-based study

Meng-Che Lu, MD[a], Ben-Chang Shia, PhD[b], Yi-Wei Kao, PhD[b,c], Sheng-Chieh Lin, MD PhD[a,d], Chuan-Yu Wang, MD, PhD[d,e], Wen-Chuan Lin, MD[d,f], Shih-Yen Chen, MD, PhD[g,*]

Abstract

In Taiwan, rotavirus vaccination was implemented in 2006 in the private sector. The population-based impact of rotavirus vaccination on gastroenteritis and comorbidities of children remains under-investigated.

We analyzed the annual prevalence of rotavirus-related disease, including gastroenteritis, convulsions, epilepsy, type I diabetes mellitus, intussusception, and biliary atresia among children under 5 years of age. Data were collected from Taiwan's National Health Insurance Research Database, a nationwide population-based database. A 16-year retrospective cohort study was conducted between 2000 and 2015.

Among children <5 years of age, the prevalence of gastroenteritis decreased after 2012 (44,259.69 per 100 thousands) and remained lower through 2015 (39,931.11 per 100 thousands, $P < .001$). The prevalence of convulsions rose steadily and significantly from 2007 (775.90 per 100 thousands) to 2015 (962.17 per 100 thousands, $P < .001$). The prevalence of epilepsy decreased significantly until reaching a nadir in 2013 (from 501.56 to 293.53 per 100 thousands, $P < .001$). The prevalence of biliary atresia tended upward, and surged suddenly in 2007 with a peak in 2013 (18.74 per 100 thousands). Among infants (<1 year of age) from 2000 to 2015, the prevalence of gastroenteritis declined steadily, and more rapidly after 2007 (22,513 to 17,285 per 100 thousands).

In Taiwan, after introducing rotavirus vaccination, gastroenteritis in young children decreased, especially in infancy. However, gastroenteritis is still common in children, given other emerging pathogens. Our results highlight the impact of rotavirus vaccines on children's health in Taiwan and provide indications for future preventive medicine and healthcare strategies in children.

Abbreviations: ICD = International Statistical Classification of Diseases and Related Health Problems, NHIRD = National Health Insurance Research Dataset.

Keywords: children's health, gastroenteritis, rotavirus vaccines, Taiwan

Editor: Ahmed Negida.

This research was supported by the New Faculty Research, grant TMU103-AE1-B22, from Taipei Medical University, Taipei, Taiwan.

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

[a] Division of Allergy, Asthma and Immunology, Department of Pediatrics, Shuang Ho Hospital, Taipei Medical University, New Taipei City, [b] Graduate Institute of Business Administration, College of Management, Fu Jen Catholic University, New Taipei City, [c] Research Center of Big Data, College of management, [d] Department of Pediatrics, School of Medicine, College of Medicine, Taipei Medical University, Taipei, [e] Division of Pediatric Neurology, Department of Pediatrics, Shuang Ho Hospital, Taipei Medical University, New Taipei City, [f] Division of Pediatric Infectious Disease, Department of Pediatrics, Shuang Ho Hospital, Taipei Medical University, New Taipei City, [g] Division of Pediatric Gastroenterology and Hepatology, Department of Pediatrics, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan.

[*] Correspondence: Shih-Yen Chen, Division of Pediatric Gastroenterology and Hepatology, Department of Pediatrics, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan (e-mail: 18159@s.tmu.edu.tw).

How to cite this article: Lu MC, Shia BC, Kao YW, Lin SC, Wang CY, Kuo YT, Lin WC, Chen SY. The impact of rotavirus vaccination in the prevalence of gastroenteritis and comorbidities among children after suboptimal rotavirus vaccines implementation in Taiwan: a population-based study. Medicine 2021;100:25(e25925).

Received: 15 July 2020 / Received in final form: 20 February 2021 / Accepted: 19 April 2021

http://dx.doi.org/10.1097/MD.0000000000025925

1. Introduction

Rotavirus is the most common cause of severe diarrhea among children younger than 5 years of age, and more than 85% of rotavirus deaths occur in developing countries.[1,2]

Before rotavirus vaccines were launched, there were about annually 611,000 rotavirus-related childhood deaths (interquartile range 454,000–705,000). Rotavirus vaccines have been demonstrated to have high efficacy in the USA and Europe.[3,4] In some developing countries, for instance those in Central America, Asia, and Africa, rotavirus vaccinations have also been proven to reduce rotavirus-associated mortality and disease severity.[3–6] In Taiwan, rotavirus vaccines have been used in the private sector since 2006. Even suboptimal use of rotavirus vaccines can have a modest impact on severe rotavirus gastroenteritis.[7] In Taiwan, the population-based impact of rotavirus vaccination on gastrointestinal diseases and children's health remains underinvestigated.

In addition to gastroenteritis, several extraintestinal symptoms and comorbidities are associated with rotavirus infections, including seizures and neurological disease.[8] Rotavirus vaccines have been shown to have beneficial effects against seizures and convulsions,[9,10] although 1 study did report that rotavirus vaccination had no impact on childhood seizure hospitalizations in England.[11] More studies are needed to clarify the effects of rotavirus vaccination on seizures and epileptic encephalopathy.

Autoimmune diseases related to rotavirus have also been a focus of interest in recent years and rotavirus has been recognized as an environmental trigger for autoimmune enteropathy and endocrinopathy.[12,13] A previous study found that rotavirus vaccination did not change the risk of type 1 diabetes mellitus or celiac disease.[14] The impact of rotavirus vaccination on children's endocrinopathy and autoimmune diseases remains undetermined. Animal models have linked rotavirus to the development of biliary atresia, but the evidence from human studies remains less conclusive and sample sizes in these studies are often limited.[15,16] A recent nationwide population-based study in Korea showed that rotavirus vaccination had no impact on the incidence of biliary atresia.[17] Although global clinical trials have shown no association between the current rotavirus vaccines and intussusception,[18,19] the incidence of intussusception following the launch of vaccines in Taiwan merits continued surveillance.

Our study aimed to figure out nationwide population-level trends in the prevalence of diseases related to rotavirus infection threatening children's health, including gastroenteritis, seizures, epilepsy, type 1 diabetes mellitus, biliary atresia, and intussusception among children under 5 years of age in Taiwan before and after the introduction of rotavirus vaccines.

2. Materials and methods

2.1. Ethics

This study was approved by the Review Board and Ethics Committee of Taipei Medical University, Taiwan (TMU-JIRB No.: N201802089). All applied methods were performed in accordance with the approved guidelines.

2.2. Patient enrollment and study population

We extracted data from the National Health Insurance Research Dataset (NHIRD), Taiwan. This database, established in 1995, is a population-based claims database containing current comprehensive health care data for over 99% of the Taiwanese population. The database includes the claims data of 23 million NHI enrollees from 2000 to 2015. All of the information in this database, including outpatient visits, admissions, and medications, has been verified. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes are applied to classify diagnoses.

Annual birth numbers and population numbers were obtained from demographic data on the website of the Ministry of the Interior. Data on implementation of the rotavirus vaccine in Taiwan from 2007 to 2013 were provided by the marketing departments of GlaxoSmithKline (Rixensart, Belgium) and Merck Sharp & Dohme (Whitehouse Station, New Jersey).

2.3. Measures

We analyzed the annual prevalence of rotavirus-related clinical features and diseases including gastroenteritis (ICD9: 558.9, 009.0), convulsions (ICD9: 780.3), epilepsy (ICD9: 345), type I diabetes mellitus (ICD9: 250.x1, 250.x3), intussusception (ICD9: 560.0), and biliary atresia (ICD9: 751.69) in children under 5 years old in the NHIRD from 2000 to 2015. The prevalence rate of various pathologies that mentioned above in 2006 in the NHIRD (prerotavirus vaccine introduction) were used as baseline prevalence rate to compare those in 2007 to 2015 (postrotavirus vaccine introduction) to see if there were any statistically significant differences. Poisson regression was used to calculate confidence intervals.

2.4. Statistical analysis

All statistical analyses were performed using SAS software v. 9.4 (SAS Institute, Inc., Cary, NC) and R 3.4.3 with $\alpha = 0.05$ as the threshold for statistical significance.

3. Results

3.1. Gastroenteritis and comorbidities in children under 5 years old

The total numbers of children under 5 years old in the NHIRD from 2000 to 2015 are shown in Table 1; the highest number was 1,489,242 in 2000 and the lowest was 956,990 in 2011. The numbers of newborn in Taiwan from 2007 to 2013 and the coverage of rotavirus vaccines were listed in the Table 2 and also with their coverage rate trend in Figure 1. The results of disease prevalence are shown in Table 3.

Compared to the baseline prevalence rate of gastroenteritis (40,331.83 cases per 100,000 people) among children under 5 in 2006, the prevalence of gastroenteritis was significantly higher ($P < .001$) in all years from 2007 to 2012, except in 2009. The highest prevalence rate of gastroenteritis was in 2012 (44,259.6 per 100,000 people). This trend reversed in 2013 to 2015, with the prevalence of gastroenteritis sustained at a significantly lower level (39,931.11per 100 thousands, $P < .001$) than the 2006 baseline.

The baseline prevalence rate of convulsions among children under 5 in 2006 was 681.23 per 100,000 people. The prevalence of convulsions rose steadily over time, from 775.90 per 100,000 people in 2007 to 929.64 per 100,000 people in 2015 ($P < .001$). The baseline prevalence rate of epilepsy in children under 5 in

Table 1

The total numbers of children under 5 years of age from 2000 to 2015 in Taiwan.

Age/Year	2000	2001	2002	2003	2004	2005	2006	2007
0–12 mo	292,724	246,381	236,687	217,456	206,936	195,331	192,887	192,021
13–24 mo	282,482	306,271	257,075	246,241	227,349	218,272	207,968	206,531
25–36 mo	267,563	282,885	306,554	257,200	246,452	227,492	218,499	208,288
37–48 mo	323,612	267,579	282,920	306,226	257,004	246,219	227,319	218,369
49–60 mo	322,861	323,643	267,593	282,780	306,198	257,041	246,269	227,376
Total	1,489,242	1,426,759	135,0829	1,309,903	1,243,939	1,144,355	109,2942	1,052,585
Age/Year	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
0–12 mo	187,568	182,599	157,282	187,442	218,944	183,744	199,275	201,523
13–24 mo	205,446	198,792	194,878	168,973	200,726	237,295	197,591	214,239
25–36 mo	206,660	205,828	199,174	195,292	169,383	201,101	237,780	197,973
37–48 mo	208,111	206,680	205,877	199,181	195,345	169,350	201,100	237,636
49–60 mo	218,421	208,261	206,882	206,102	199,285	195,461	169,380	201,084
Total	1,026,206	1,002,160	964,093	956,990	983,683	986,951	100,5126	1,052,455

2006 was 501.56 per 100,000 people. This rate decreased significantly following the launch of the vaccine and reached its lowest point in 2013 (293.53 per 100,000 people, $P < .001$). Overall, the prevalence of epilepsy among children under 5 showed a decreasing trend.

The baseline prevalence rate of type 1 diabetes mellitus among children under 5 in 2006 was 9.42 per 100,000 people; this prevalence rate remained steady without statistically significant deviations except in 2007, when the prevalence rate spiked (16.06 per 100,000 people). The prevalence of intussusception among children under 5 was 126.23 per 100,000 people in 2006. Following vaccine introduction, the prevalence of intussusception fluctuated between 2011 and 2015. In general, intussusception prevalence remained relatively steady from 2007 to 2015. The baseline prevalence of biliary atresia among children under 5 years in 2006 was 10.53 per 100,000 people. Biliary atresia prevalence surged suddenly in 2007 to 19.00 per 100,000 people, then reached another peak in 2013. The prevalence rates of biliary atresia increased every year from 2007 to 2015, except in 2012, and the overall trend of biliary atresia prevalence exhibited an upward tendency.

3.2. Disease prevalence in infants under 1 year of age

The prevalence of gastroenteritis, convulsions, epilepsy, intussusception, and biliary atresia among infants under 1 year of age from 2000 to 2015 are shown in Figure 1. Type 1 diabetes mellitus is not shown in this figure, owing to its extremely low rate of prevalence. The rotavirus vaccine coverage rates from 2006 to 2014 are also shown, illustrating the steady upward trend in vaccine coverage from 2007 to 2013.

Compared to the average prevalence of gastroenteritis in infancy from 2000 to 2015 (26,068.53 per 100,000 people), the prevalence of gastroenteritis steadily declined following the introduction of rotavirus vaccination, from 20,620 cases per 100,000 people in 2006 to 17,285 cases per 100,000 people in 2015 ($P < .001$). On average, the prevalence rate of convulsions in infants under 1 was 255.43 per 100,000 people. The prevalence of convulsions remained stable at this level before and after vaccine introduction. The average prevalence of epilepsy in infancy from 2000 to 2015 was 291.05 per 100,000 people. The prevalence of epilepsy steadily declined from 309 per 100,000 people in 2003, prior to the introduction of the vaccine, to 166 per 100,000 people in 2014 ($P < .001$). The prevalence of intussusception among infants remained steady at a lower level (53–66 per 100,000 people) after 2007 (85 per 100,000 people). The trend of biliary atresia prevalence among infants under 1 following introduction of the rotavirus vaccine was generally increasing. The highest rate of prevalence was 35 cases per 100,000 people in 2013, which is 2 to 3 times higher than the rates of prevalence before the introduction of the rotavirus vaccine (10.64 per 100,000 people on average) ($P < .001$).

Table 2

The numbers of newborns in Taiwan and the coverage of rotavirus vaccine from 2007 to 2013.

	Annual birth no.	Vaccine no.	Coverage rate%
2007	204,414	17,959	8.8
2008	198,733	39,083	19.7
2009	173,097	56,326	32.5
2010	166,886	52,068	31.2
2011	196,627	69,409	35.3
2012	229,481	87,432	38.1
2013	199,113	82,831	41.6

4. Discussion

Our population-based study found that the prevalence of gastroenteritis in infants under 1 year old steadily declined following introduction of the rotavirus vaccine. Among children under 5 years old, gastroenteritis prevalence peaked in 2012 before falling significantly and remaining steady at lower levels thereafter. The unusual prevalence peak in 2012 is likely attributable to outbreaks of norovirus gastroenteritis in Taiwan in 2011 to 2012.[20] After this disease outbreak, gastroenteritis prevalence dropped to a level that was significantly lower than before rotavirus vaccination. This trend is congruent with the results of a recent study showing that rotavirus vaccine reduced the rate of hospitalization for gastroenteritis, both that caused by rotavirus and all other causes.[21] In Taiwan, we found that rotavirus vaccination correlated with an immediate reduction in overall gastroenteritis among infants under 1 year old (after 2007) and with a more delayed reduction in overall gastroenteritis in children under 5 years old (after 2012).

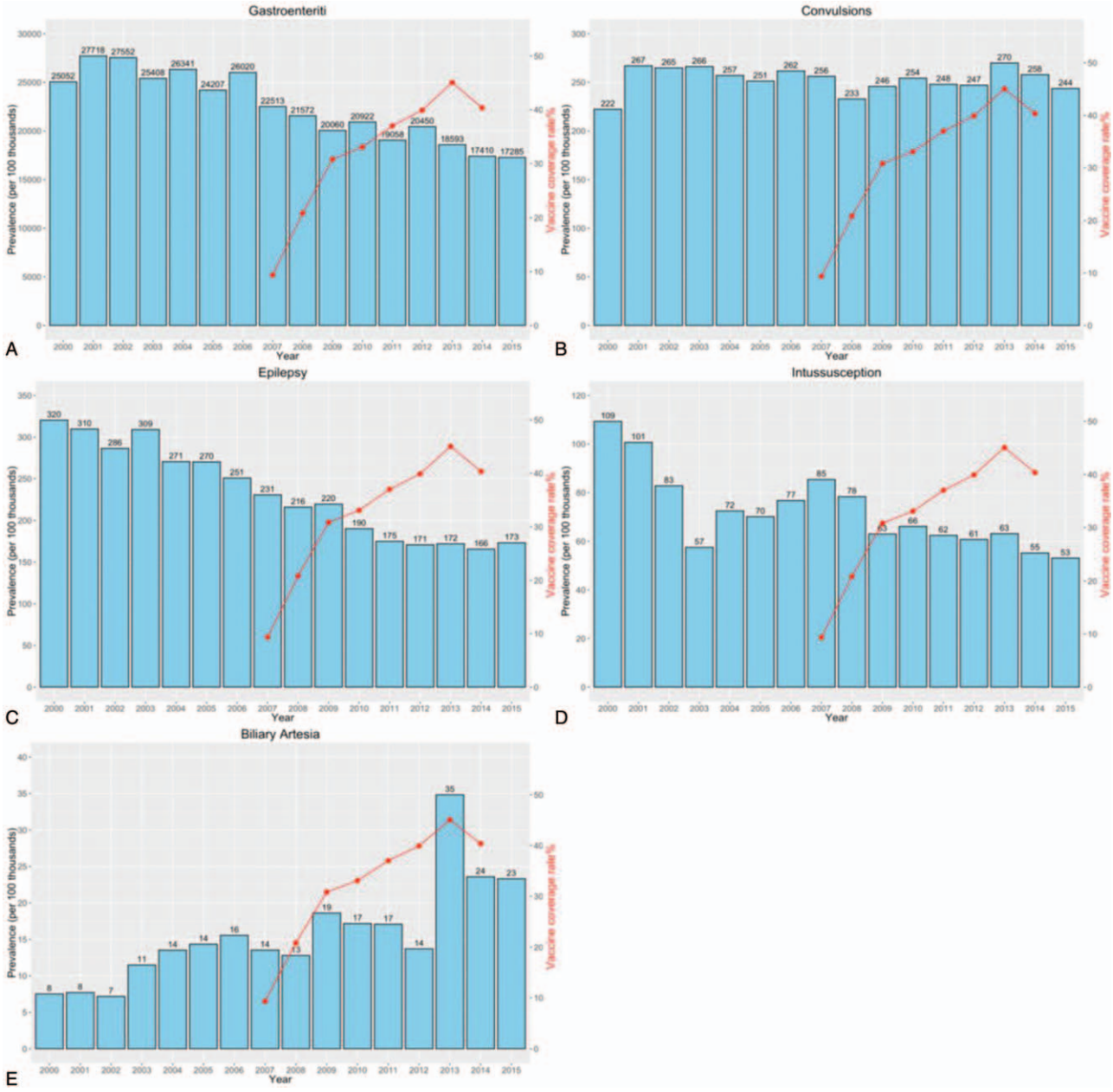

Figure 1. Annual prevalence of diseases among infants before 1 year old in Taiwan.

Previous research has shown that rotavirus vaccine implementation reduces the trend of hospitalization for convulsions.[22] However, another study reported that monovalent rotavirus vaccination had no impact on childhood seizure hospitalizations in England.[11] In the present study, the prevalence of convulsions among children under 5 exhibited an upward trend following introduction of the rotavirus vaccine, while the prevalence of convulsions among infants under 1 remained stable. It is probable that the upward trend in convulsions seen in children under 5 is attributable to outbreaks of other major etiologies or pathogens such as norovirus, as a significantly high incidence of convulsions has been reported to be associated with diarrheal diseases in children when emerging variants have circulated in Taiwan.[23,24] Epilepsy prevalence among infants and children under 5 shows a general downward trend following introduction of the rotavirus vaccine. Even though the etiology of epilepsy in children is complex, the downward trend of epilepsy prevalence in children observed after rotavirus vaccine introduction could be partly attributed to the suppression of rotavirus infection-associated encephalopathy.[25] It is interesting to note that the trends of epilepsy and seizures seem to be contradictory; our study provides different perspectives on the impact of rotavirus vaccinations on seizures and epilepsy.

The prevalence of type 1 diabetes mellitus among children under 5 remained steady without statistically significant changes after the introduction of rotavirus vaccination. In other words,

Table 3

Annual prevalence of disease among children under 5years of age in Taiwan before and after introduction of rotavirus vaccines.

Gastroenteritis	Prevalence (per 100 thousands)	95%CI	Rate ratio	95%CI	*P* value
Before introduction	40331.83	(40,247.31, 40,416.36)	1.00		
After introduction					
2007	42,229.84	(42,135.49, 42,324.20)	1.05	(1.04, 1.05)	<.001
2008	41,488.55	(41,393.22, 41,583.88)	1.03	(1.02, 1.03)	<.001
2009	40,288.58	(40,192.55, 40,384.60)	1.00	(0.99, 1.00)	.6087
2010	44,041.08	(43,941.99, 44,140.18)	1.09	(1.09, 1.10)	<.001
2011	42,328.76	(42,229.77, 42,427.75)	1.05	(1.05, 1.05)	<.001
2012	44,259.69	(4,4161.53, 44,357.84)	1.10	(1.09, 1.10)	<.001
2013	39,799.44	(39,702.87, 39,896.01)	0.99	(0.98, 0.99)	<.001
2014	39,538.53	(39,442.94, 39,634.11)	0.98	(0.98, 0.98)	<.001
2015	39,931.11	(39,837.55, 40,024.68)	0.99	(0.99, 0.99)	<.001
Convulsions	**Prevalence (per 100 thousands)**	**95%CI**	**Rate ratio**	**95%CI**	***P* value**
Before introduction	681.23	(667.06, 695.41)	1.00		
After introduction					
2007	775.90	(759.14, 792.66)	1.14	(1.11, 1.17)	<.001
2008	769.92	(753.01, 786.83)	1.13	(1.10, 1.17)	<.001
2009	723.64	(707.04, 740.23)	1.06	(1.03, 1.10)	<.001
2010	838.92	(820.72, 857.13)	1.23	(1.19, 1.27)	<.001
2011	874.72	(856.07, 893.38)	1.28	(1.25, 1.32)	<.001
2012	799.34	(781.75, 816.94)	1.17	(1.14, 1.21)	<.001
2013	880.69	(862.26, 899.12)	1.29	(1.26, 1.33)	<.001
2014	962.17	(943.08, 981.25)	1.41	(1.37, 1.45)	<.001
2015	929.64	(911.30, 947.97)	1.36	(1.33, 1.40)	<.001
Epilepsy	**Prevalence (per 100 thousands)**	**95%CI**	**Rate ratio**	**95%CI**	***P* value**
Before introduction	501.56	(489.39, 513.73)	1.00		
After introduction					
2007	394.17	(382.20, 406.14)	0.79	(0.76, 0.82)	<.001
2008	375.46	(363.63, 387.29)	0.75	(0.72, 0.78)	<.001
2009	346.75	(335.24, 358.26)	0.69	(0.66, 0.72)	<.001
2010	348.62	(336.85, 360.38)	0.70	(0.67, 0.72)	<.001
2011	326.13	(314.70, 337.55)	0.65	(0.62, 0.68)	<.001
2012	306.70	(295.78, 317.63)	0.61	(0.59, 0.64)	<.001
2013	293.53	(282.86, 304.20)	0.59	(0.56, 0.61)	<.001
2014	306.33	(295.53, 317.13)	0.61	(0.59, 0.64)	<.001
2015	297.49	(287.09, 307.90)	0.59	(0.57, 0.62)	<.001
Type I diabetes mellitus	Prevalence (per 100 thousands)	95%CI	Rate Ratio	95%CI	*P* value
Before introduction	9.42	(7.75, 11.09)	1.00		
After introduction					
2007	16.06	(13.64, 18.48)	1.70	(1.35, 2.15)	<.001
2008	8.28	(6.52, 10.04)	0.88	(0.67, 1.16)	.3635
2009	7.68	(5.97, 9.40)	0.82	(0.61, 1.09)	.1615
2010	9.96	(7.97, 11.95)	1.06	(0.81, 1.38)	.6826
2011	12.02	(9.82, 14.21)	1.28	(0.99, 1.65)	.0601
2012	9.76	(7.81, 11.71)	1.04	(0.79, 1.35)	.7937
2013	9.73	(7.78, 11.67)	1.03	(0.79, 1.35)	.8125
2014	8.46	(6.66, 10.25)	0.9	(0.68, 1.18)	.4463
2015	10.93	(8.93, 12.92)	1.16	(0.9, 1.5)	.2523
Intussusception	**Prevalence (per 100 thousands)**	**95%CI**	**Rate Ratio**	**95%CI**	***P* value**
Before introduction	126.23	(120.11, 132.35)	1.00		
After introduction					
2007	128.45	(121.60, 135.29)	1.02	(0.95, 1.09)	.6362
2008	125.51	(118.66, 132.36)	0.99	(0.92, 1.07)	.8779
2009	122.34	(115.49, 129.18)	0.97	(0.90, 1.04)	.4068
2010	124.16	(117.13, 131.19)	0.98	(0.91, 1.06)	.6634
2011	157.26	(149.32, 165.20)	1.25	(1.16, 1.34)	<.001
2012	106.74	(100.29, 113.19)	0.85	(0.78, 0.91)	<.001
2013	114.80	(108.12, 121.48)	0.91	(0.84, 0.98)	.014
2014	135.11	(127.93, 142.29)	1.07	(1.00, 1.15)	.0642
2015	111.07	(104.71, 117.44)	0.88	(0.82, 0.95)	<.001
Biliary Artesia	**Prevalence (per 100 thousands)**	**95%CI**	**Rate Ratio**	**95%CI**	***P* value**
Before introduction	10.53	(8.76, 12.30)	1.00		
After introduction					
2007	19.00	(16.37, 21.63)	1.80	(1.45, 2.24)	<.001
2008	15.10	(12.73, 17.48)	1.43	(1.14, 1.81)	.002
2009	15.47	(13.03, 17.90)	1.47	(1.17, 1.85)	.001
2010	16.91	(14.31, 19.50)	1.61	(1.28, 2.02)	<.001
2011	14.84	(12.40, 17.28)	1.41	(1.11, 1.78)	.0041
2012	13.11	(10.85, 15.38)	1.25	(0.98, 1.58)	.0737
2013	18.74	(16.04, 21.45)	1.78	(1.43, 2.22)	<.001
2014	17.81	(15.20, 20.42)	1.69	(1.35, 2.11)	<.001
2015	16.72	(14.25, 19.19)	1.59	(1.27, 1.99)	<.001

the introduction of rotavirus vaccines did not affect the prevalence rate of type 1 diabetes mellitus in Taiwan. Our results are consistent with those of Vaarala et al,[14] who showed that rotavirus vaccination did not change the risk of type 1 diabetes mellitus. Because the prevalence rate of type 1 diabetes mellitus among infants under 1 year of age was too low to determine the significance of any changes, more research is needed to clarify the possible impact on type 1 diabetes mellitus exerted by rotavirus vaccinations in infants.

Overall, the prevalence of biliary atresia among infants under 1 and children under 5 in Taiwan exhibited an upward trend, which may be related to the introduction of infant stool color card screening in 2004 and an updated version of infant stool color card screening in 2009. This screening program greatly reduced the mortality rate of biliary atresia in Taiwan.[26] It is probable that the consequent longer survival period in biliary atresia explains the upward trend in the prevalence of the disease. For this reason, it is hard to assess whether rotavirus vaccination impacted the rate of biliary atresia in Taiwan. More research is still needed to determine whether rotavirus vaccines have any impact on biliary atresia in Taiwan and other countries.

We also analyzed the association between the prevalence of intussusception and rotavirus vaccine. A recent study found that RotaTeq (RV5, a pentavalent vaccine) is associated with an increase of approximately 1.5 cases of intussusception per 100,000 recipients of the first dose, and that Rotarix (RV1, a monovalent vaccine) may also pose a potential risk for an increased rate of intussusception.[27] However, another investigation in 7 low-income sub-Saharan African countries revealed that the risk of intussusception with rotavirus vaccination was not higher than the background risk of intussusception.[28] In the present study, intussusception prevalence among infants under 1 year old showed a steady decline, while it remained relatively steady in children under 5 years of age.

There are some limitations in our study. First of all, it is difficult to conduct a case-targeting search study because we cannot approach the connection between the patient and the rotavirus vaccination implementation in the private sector. Furthermore, our study is an ecological study. The coding number of rotavirus-associated gastroenteritis can only be implemented in NHIRD when the pathogen is positively identified. In addition, the codes of gastroenteritis used in this study may not be fully specific to the infection. Finally, different types and causes of epilepsy or seizure cannot be determined by our coding system.

In conclusion, this population-based study showed that after rotavirus vaccines were introduced in Taiwan, the disease burden of gastroenteritis in young children decreased gradually, especially in infancy, in spite of suboptimal vaccine coverage. However, gastroenteritis is still common in children, especially that caused by emerging pathogens such as norovirus and enteric bacterium. In regard to comorbid diseases, rotavirus vaccines may reduce the rate of epilepsy in children somewhat, while further studies are needed to clarify the effects of rotavirus vaccination on seizures. Even though the number of patients was limited in this study, the data shows that rotavirus vaccines have no evident impact on the disease burden of type I diabetes mellitus, biliary atresia, or intussusception, indicating that these diseases are primarily associated with causes other than rotavirus infection. Rotavirus infection is one of the most important diseases threatening children's health around the world. The results of our study highlight the impacts of rotavirus vaccines on children's health in Taiwan, thus providing important references for future preventive medicine and children's health care strategy.

Acknowledgments

Thanks for allowing us to use materials from Taiwan National Health Insurance Research Dataset (NHIRD).

Author contributions

Conceptualization: Meng-Che Lu, Ben-Chang Shia, Shih-Yen Chen.
Data curation: Meng-Che Lu, Ben-Chang Shia, Yi-Wei Kao, Sheng-Chieh Lin, Chuan-Yu Wang, Wen-Chuan Lin, Shih-Yen Chen.
Formal analysis: Meng-Che Lu, Ben-Chang Shia, Sheng-Chieh Lin, Chuan-Yu Wang, Shih-Yen Chen.
Funding acquisition: Shih-Yen Chen.
Investigation: Meng-Che Lu, Yi-Wei Kao, Sheng-Chieh Lin, Chuan-Yu Wang, Wen-Chuan Lin, Shih-Yen Chen.
Methodology: Ben-Chang Shia, Yi-Wei Kao, Chuan-Yu Wang, Shih-Yen Chen.
Project administration: Meng-Che Lu, Ben-Chang Shia, Shih-Yen Chen.
Resources: Sheng-Chieh Lin, Chuan-Yu Wang, Wen-Chuan Lin, Shih-Yen Chen.
Software: Yi-Wei Kao.
Supervision: Wen-Chuan Lin.
Validation: Meng-Che Lu, Ben-Chang Shia, Yi-Wei Kao, Shih-Yen Chen.
Visualization: Meng-Che Lu, Sheng-Chieh Lin, Chuan-Yu Wang, Shih-Yen Chen.
Writing – original draft: Meng-Che Lu, Ben-Chang Shia, Yi-Wei Kao.
Writing – review & editing: Shih-Yen Chen.

References

[1] Glass RI, Parashar UD, Bresee JS, et al. Rotavirus vaccines: current prospects and future challenges. Lancet 2006;368:323–32.
[2] Parashar UD, Gibson CJ, Bresee JS, et al. Rotavirus and severe childhood diarrhea. Emerg Infect Dis 2006;12:304–6.
[3] Boom JA, Tate JE, Sahni LC, et al. Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States. Pediatrics 2010;125:e199–207.
[4] Martinon-Torres F, Bouzon Alejandro M, Redondo Collazo L, et al. Effectiveness of rotavirus vaccination in Spain. Hum Vaccin 2011;7: 757–61.
[5] Patel M, Pedreira C, De Oliveira LH, et al. Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among children in Nicaragua. JAMA 2009;301:2243–51.
[6] Troeger C, Khalil IA, Rao PC, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. JAMA Pediatr 2018;172:958–65.
[7] Chen SY, Tsai CN, Chen CL, et al. Severe viral gastroenteritis in children after suboptimal rotavirus immunization in Taiwan. Pediatr Infect Dis J 2013;32:1335–9.
[8] DiFazio MP, Braun L, Freedman S, et al. Rotavirus-induced seizures in childhood. J Child Neurol 2007;22:1367–70.
[9] Payne DC, Baggs J, Zerr DM, et al. Protective association between rotavirus vaccination and childhood seizures in the year following vaccination in US children. Clin Infect Dis 2014;58:173–7.
[10] Yeom JS, Kim YS, Kim RB, et al. Impact of rotavirus vaccine introduction on rotavirus-associated seizures and a related possible mechanism. J Child Neurol 2015;30:729–34.
[11] Biggart R, Finn A, Marlow R. Lack of impact of rotavirus vaccination on childhood seizure hospitalizations in England - an interrupted time series analysis. Vaccine 2018;36:4589–92.

[12] Gomez-Rial J, Sanchez-Batan S, Rivero-Calle I, et al. Rotavirus infection beyond the gut. Infect Drug Resist 2019;12:55–64.
[13] Vojdani A. A potential link between environmental triggers and autoimmunity. Autoimmune Dis 2014;2014:437231.
[14] Vaarala O, Jokinen J, Lahdenkari M, et al. Rotavirus vaccination and the risk of celiac disease or type 1 diabetes in finnish children at early life. Pediatr Infect Dis J 2017;36:674–5.
[15] Averbukh LD, Wu GY. Evidence for viral induction of biliary atresia: a review. J Clin Transl Hepatol 2018;6:410–9.
[16] Rauschenfels S, Krassmann M, Al-Masri AN, et al. Incidence of hepatotropic viruses in biliary atresia. Eur J Pediatr 2009;168: 469–76.
[17] Lee JH, Ahn HS, Han S, et al. Nationwide population-based study showed that the rotavirus vaccination had no impact on the incidence of biliary atresia in Korea. Acta Paediatr 2019;108:2278–84.
[18] Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354:11–22.
[19] Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006;354:23–33.
[20] Chen SY, Feng Y, Chao HC, et al. Emergence in Taiwan of novel norovirus GII.4 variants causing acute gastroenteritis and intestinal haemorrhage in children. J Med Microbiol 2015;64:544–50.
[21] Burnett E, Jonesteller CL, Tate JE, et al. Global impact of rotavirus vaccination on childhood hospitalizations and mortality from diarrhea. J Infect Dis 2017;215:1666–72.
[22] Pringle KD, Burke RM, Steiner CA, et al. Trends in rate of seizure-associated hospitalizations among children <5 years old before and after rotavirus vaccine introduction in the United Sates, 2000–2013. J Infect Dis 2018;217:581–8.
[23] Chen SY, Tsai CN, Lai MW, et al. Norovirus infection as a cause of diarrhea-associated benign infantile seizures. Clin Infect Dis 2009; 48:849–55.
[24] Chen YFE, Wang CY, Chiu CH, et al. Molecular epidemiology and clinical characteristics of norovirus gastroenteritis with seizures in children in Taiwan, 2006-2015. Medicine 2019;98:e17269.
[25] Fujita Y, Imai Y, Ishii W, et al. Improvement of intractable childhood epilepsy following acute viral infection. Brain Dev 2011;33:62–8.
[26] Lee M, Chen SC, Yang HY, et al. Infant stool color card screening helps reduce the hospitalization rate and mortality of biliary atresia: a 14-year nationwide cohort study in Taiwan. Medicine 2016;95:e3166. Erratum in: Medicine (Baltimore). 2016;95:e5673.
[27] Yih WK, Lieu TA, Kulldorff M, et al. Intussusception risk after rotavirus vaccination in U.S. infants. N Engl J Med 2014;370:503–12.
[28] Tate JE, Mwenda JM, Armah G, et al. Evaluation of intussusception after monovalent rotavirus vaccination in Africa. N Engl J Med 2018;378: 1521–8.