

Rotavirus vaccination and risk of intussusception: A report of TGA's investigation of a possible safety signal

Summary

The TGA, working in collaboration with state health authorities, has undertaken an investigation of a possible association between the use of the rotavirus vaccines Rotarix® (GSK) and RotaTeq® (Merck/CSL) and the occurrence of a rare form of bowel obstruction known as intussusception (IS). Intussusception is a condition caused by the telescoping of one segment of the bowel into another. It is estimated to occur each year in around 80 per 100,000 children under 12 months of age, which represents approximately 200 cases per year in Australia. The peak incidence is in infants 5-10 months of age, with 80% of cases occurring before 24 months of age, and it is much more common in males than females.

IS was found to be a side effect of the first generation rotavirus vaccine (RotaShield®, Wyeth) that was available in the United States in 1998-1999. RotaShield was estimated to cause IS in 10-20 of every 100,000 doses given to infants, and was voluntarily withdrawn from the US market in October 1999.^{1,2} RotaShield was not used outside the US, however, as the historical incidence of IS is 2.5 to 3 times higher in infants in Australia than in the US, this would have translated to 25-60 cases of IS for every 100,000 doses of RotaShield if the vaccine had been used here.

Subsequently two new rotavirus vaccines, Rotarix and RotaTeq were developed, and both were tested in large studies designed to explore whether there was a risk of IS. In each of these placebo-controlled pre-registration studies, approximately 35,000 infants were given rotavirus vaccine, with no increased risk of IS observed.^{3,4} However, as large pre-registration safety studies may not always detect rare events, post-marketing studies have been undertaken in a number of countries.

In Australia, two post-marketing studies have been conducted to investigate whether the new rotavirus vaccines are associated with an increased risk of IS. The first study was conducted using two surveillance systems, the Paediatric Enhanced Disease Surveillance (PAEDS) with active surveillance of IS cases in 4 tertiary centres, and the Australian Paediatric Surveillance Unit (APSU) with national retrospective reporting of IS cases by paediatricians. This study, conducted in NSW, Victoria, Western Australia and South Australia, found an apparent four-fold increased risk of IS in babies within one week of being given the first dose of either vaccine, compared with historical data on hospitalisations coded as IS, but no overall increase in overall rates of IS up to the age of 9 months. This is much lower than the risk found with the earlier RotaShield vaccine.

Following this, a large self-controlled case series (SCCS) study using data on all hospitalised cases coded as IS from NSW, Victoria and Western Australia was commissioned by the TGA. This study found a statistically significant four-fold increase in the occurrence of IS in the first 1-7 days following the first dose of either Rotarix or RotaTeq compared with other time periods after vaccine receipt. This increase in risk translates to approximately 2 additional cases of IS occurring in every 100,000 first doses of vaccine administered, or 6 additional cases each year in children under 12 months of age in Australia. *These findings are preliminary, as the data are subject to confirmation.*

It is currently unclear whether this represents a true increase in overall risk of IS, or an early increase in risk of IS in infants which is compensated for by a subsequent decrease in risk leading to a reduction in cases of IS in older children. Longer term studies are required to clarify this.

Prior to the introduction of rotavirus vaccine, there were an estimated 10,000 hospitalisations annually in children under 5 years due to rotavirus gastroenteritis. Since the introduction of Rotarix and RotaTeq on to the National Immunisation Program (NIP) emergency department visits for acute gastroenteritis in young children have declined and hospitalisations for rotavirus gastroenteritis in the under 5 year age group have been reduced by over 70%^{5,6}. Based on the established benefits of rotavirus vaccination and the rare

occurrence of IS, both the World Health Organization (WHO) and the Australian Technical Advisory Group on Immunisation (ATAGI) have recommended the continued use of rotavirus vaccine for infants under the NIP.

Following is a more detailed report of the TGA's analysis of rotavirus vaccine and risk of IS. In addition, *Fact Sheets* for parents and immunisation providers about rotavirus vaccine and IS may be found here <LINK>

Introduction

Since the introduction of the first licensed vaccine for rotavirus in North America in the 1990s there have been concerns about a possible association between the receipt of rotavirus vaccine and the occurrence of intussusception (IS) in young infants. A previous vaccine (RotaShield[®], Wyeth) was withdrawn nine months after its introduction into the US National Immunization Program in 1998 following the identification of an association between the use of the vaccine and the occurrence of IS in a large case control study. The study identified an adjusted odds ratio of IS for days 3-7 after the first dose of RotaShield of 37 (95%CI 13 to 110), and an adjusted odds ratio of 4 (95%CI 1 to 14) following the second dose of RotaShield. Based on the estimated background incidence of IS in infants in the US, this translated to approximately 10 to 20 cases of IS in every 100,000 infant doses.^{1,2} RotaShield was not used outside the US, however, as the historical incidence of IS is 2.5 to 3 times higher in infants in Australia than in the US, this would have translated to 25-60 cases of IS for every 100,000 doses of RotaShield, if the vaccine had been used here.

More recently, two new rotavirus vaccines have been developed and introduced - RotaTeq[®] (Merck/CSL), which is administered in a 3-dose schedule at 2, 4 and 6 months of age, and Rotarix[®] (GlaxoSmithKline) which is administered in a 2-dose schedule at 2 and 4 months. An increased risk of IS in infant administered rotavirus vaccine was not identified in large-scale placebo controlled pre-registration clinical trials^{3,4} nor has this been identified in post-marketing surveillance data from the US⁷. Large self-controlled case-series studies have, observed a small, but statistically significant increase in risk of IS following the first dose of Rotarix in Mexico but not Brazil^{8,9}.

Data on cases of IS, obtained from New South Wales, Victoria, Western Australia and South Australia for the period between July 2007 and December 2008, have been collected by the Paediatric Enhanced Disease Surveillance (PAEDS), with active surveillance in 4 tertiary centres, and the Australian Paediatric Surveillance Unit (APSU), with national retrospective reporting by paediatricians. These data have provided evidence suggesting a four-fold increase in risk of IS following receipt of the first dose of each of the registered vaccines compared with historical rates of hospitalisation coded as IS between 1999 and 2006¹⁰.

TGA Analysis

To further investigate the possibility of an increased risk of IS following vaccination against rotavirus, the TGA, in collaboration with the State health departments in NSW, Victoria and WA, has undertaken an investigation to attempt to clarify the nature and extent of the apparent association. These three states collectively provided data on all ICD coded hospitalisations for IS, and the immunisation status of these cases. This enabled investigation of both registered vaccines, as Rotarix is supplied in New South Wales and has previously been used in Western Australia, while RotaTeq is currently used in Victoria and Western Australia.

The data included all children under the age of 12 months with a hospital discharge diagnosis of IS over the 2.5 year period from inclusion of the vaccine in the National Immunisation Program in July 2007 to December 2009. These cases were identified from hospital admission databases, and each child's immunisation status was determined through linkage to their immunisation history held in the Australian Childhood Immunisation Register (ACIR). The data were de-identified prior to analysis. Many of the same cases of IS included in the TGA analysis were also included in the PAEDS/APSU analysis.

To assess the strength of association between vaccination and IS risk, the data were analysed using a technique known as the *self-controlled case-series* method. Using this method the association between

vaccination and the outcome of interest (IS) is examined using a statistical model that compares the frequency of the outcome in periods of time following vaccination with unexposed time in the same child. The following exposure periods were used, on the basis of previously published literature on potential risk following rotavirus vaccination:

Risk period 1: 1-7 days post-vaccination

Risk period 2: 8-21 days post-vaccination

Results

A total of 274 cases coded as IS were identified (NSW 128, Victoria 108, WA 38). All three datasets included all cases of hospital admission for IS, together with linked information on the date of receipt of either of the rotavirus vaccines. To date, confirmation of the diagnosis by case record review has been completed for all cases included from NSW and for only some of the cases included from the other jurisdictions. Table 1 shows the geographical distribution of IS cases.

Table 1: Geographical distribution of IS cases

Age	NSW	VIC	WA	Total
No vaccinations reported	16	25	10	51
Rotarix	103	1	24	128
RotaTeq	5	73	3	81
Both vaccinations	0	4*	0	4
No ACIR linkage	4	5	1	10
Total	128	108	38	274

* These children were recorded on ACIR as having received one dose of Rotarix and at least one dose of RotaTeq.

Table 2 illustrates the temporal relationship between vaccine administration and onset of IS. Of the 274 cases of IS, 47 occurred within 21 days of vaccination and 227 occurred outside these periods.

Table 2: Temporal distribution of IS cases

Age	Rotarix				RotaTeq						Not within 21 days of any dose
	Dose 1		Dose 2		Dose 1		Dose 2		Dose 3		
	1-7 days	8-21 days	1-7 days	8-21 days	1-7 days	8-21 days	1-7 days	8-21 days	1-7 days	8-21 days	
1-<2 months											4
2-<3 months	3	4			3	4					8
3-<4 months			1			2					24
4->5 months	1		5	7			2	3			13
5-<6 months		1	1	2							25
6-<7 months	1			1				1		3	32
7-<8 months		1							1		32
8-<9 months											23
9-<10 months											22
10-<11 months											28
11-<12 months											16
Total	5	6	7	10	3	6	2	4	1	3	227

Table 3 illustrates the results of the case series analysis which measures the relative incidence (RI) of IS in specific time periods following receipt of rotavirus vaccine compared with all other time periods. It shows an elevated risk of IS in the 7 days following receipt of the first dose of both vaccines, with a RI of 3.89 (95%

confidence interval 1.53 - 9.89, p=0.004) for Rotarix and 4.12 (95% CI 1.26 - 13.48, p=0.02) for RotaTeq. There is also a suggestion that this elevated risk extends into the period 8-21 days post-vaccination with the first dose of RotaTeq and that an elevated risk of IS may also follow receipt of Dose 2 of Rotarix. However, case confirmation and further analyses are required to clarify this.

Table 3: Results of Case Series Analysis showing Relative Incidence of Intussusception

		RI	(95% CI)	P
Rotarix	Dose 1, 1-7 days	3.89	(1.53, 9.89)	0.004
RotaTeq	Dose 1, 1-7 days	4.12	(1.26, 13.48)	0.02

Interpretation of Results

These results must be interpreted with caution. The numbers of cases that have occurred within specific time periods are small and findings of statistical significance are vulnerable to small changes in classification of cases or timing of IS post vaccine receipt. For these reasons, confirmation of cases is important. Overall there is most consistency with respect to an increased risk of IS within 1-7 days of the first dose of either rotavirus vaccine as all cases occurring within this time period have been confirmed, and this observation is consistent with the findings of the PAEDS/APSU Australian study⁷ and with preliminary data from some overseas studies. Further investigation, involving confirmation of IS cases, and additional analyses are required to better assess risk of IS following dose 2 or other time periods following dose 1. Individual review of the remaining IS cases is being undertaken to confirm the diagnostic coding and ensure that each case meets standard diagnostic criteria for IS using the Brighton Collaboration definition of confirmed IS¹¹. This individual case review is ongoing and this report will be updated when that analysis is completed

Conclusion

This interim analysis provides evidence that both registered rotavirus vaccines are likely to be associated with an increase in risk of IS in the 7 days following the first dose of both Rotarix and RotaTeq. There is also a suggestion that an increased risk of IS may occur following the second dose of vaccine and that a lower level risk could extend into the second or third week beyond either dose of the vaccine, however case confirmation and alternate analyses are required to clarify this. Nevertheless, the findings of the study are broadly consistent with those of another Australian study which compared the incidence of IS following the first dose of rotavirus vaccine with historical rates of hospitalisation coded as IS from 1999 to 2006⁶. Based on the age specific incidence of IS, the relative risk of IS in the 7 days following dose 1 of rotavirus vaccine translates to approximately 2 additional cases of IS per 100,000 doses of vaccine administered. This is much lower than the risk found with the earlier RotaShield vaccine and it is possible that any short-term increase in risk is compensated for by a subsequent decrease in risk leading to a reduction in cases of IS in older children. Longer term studies are underway to clarify this.

Recent data from post-marketing surveillance of IS following administration of Rotarix in Mexico have also shown an increase in the risk of IS after the first dose of the vaccine but this finding has not been replicated in Brazil. The World Health Organization (WHO) issued a Statement on rotavirus vaccines and IS on 22 September 2010 (updated on January 28 2011) advising of the possibility of an increased risk of IS shortly after the first dose of rotavirus vaccination in some populations, but noting the substantial documented benefits of rotavirus vaccination, the suggestion in some studies of an overall long-term protective effect of the vaccine, and the ongoing surveillance in Latin America and elsewhere⁸.

Despite the identification of a small increase in risk of IS following the first dose of rotavirus vaccination, the TGA considers that the overall risk-benefit balance of both vaccines remains positive. Prior to the

introduction of rotavirus vaccine, an estimated 10,000 hospital admissions occurred annually in children under 5 years due to rotavirus gastroenteritis¹². Since the introduction of Rotarix and RotaTeq on to the National Immunisation Program (NIP) emergency department visits for acute gastroenteritis in young children have declined and hospitalisations for rotavirus gastroenteritis in the under 5 year age group have been reduced by over 70%^{5,6}. It is also important to note that both the World Health Organization (WHO) and the Australian Technical Advisory Group on Immunisation (ATAGI) have recommended the continued use of rotavirus vaccine for infants.

The Product Information documents for both vaccines will be amended to reflect these findings.

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