

Systematic Review of the Safety and Efficacy of Rotavirus Vaccines March, 2007

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1 Background

This review underpins the recommendations on the use of rotavirus vaccines in Australia as made by the Australian Technical Advisory Group on Immunisation (ATAGI), and endorsed by the NHMRC, in the 9th edition of *The Australian Immunisation Handbook*. This review should be read in conjunction with sections of the 9th edition of *The Australian Immunisation Handbook*, Chapter 3.18 Rotavirus (available online at <http://immunise.health.gov.au/>).

2 Aim

The aim of this review is to assist in the development of recommendations for the use of rotavirus vaccines in Australia.

3 Methods

The following methods were used in this systematic review, according to NHMRC requirements.¹⁻³ This review is based on the following overall structured research question:

Is oral immunisation (vaccination) of infants with rotavirus vaccines (RotaTeq[®] or Rotarix[®]) effective and safe in preventing rotavirus gastroenteritis (RV-AGE), and the associated complications of RV-AGE, including severe dehydrating gastroenteritis requiring hospitalisation?

3.1 Systematic identification and review of the scientific literature

3.1.1 Search strategy: Databases and Period searched

The Cochrane Library (comprising the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, and the NHS Economic Evaluation Database) as at 18.9.2006 was searched to identify systematic reviews and randomised controlled trials relevant to the review questions. In addition, MEDLINE Daily Update (from 1966 to 17.09.06) and EMBASE (from 1980 to Week 37, 2006) as at 18.9.2006 were also searched to identify relevant randomised controlled trials.

To minimise the introduction of bias no limits with respect to date, language or abstract were used. Searches were limited to randomised controlled trials and systematic reviews. Search strategies varied slightly between databases depending on the availability of controlled vocabulary (thesaurus) terms and/or limits. A combination of thesaurus terms and truncated free text terms were utilised to maximise retrieval. The search terms and search strategies used are available in **Appendix C**.

3.1.2 Additional search methods

Additional search methods included interaction with expert sources, from the United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), checking and retrieval of studies in reference lists of identified clinical trials and review papers, and hand searching (relevant conference abstracts, and other sources).

Additional data supplied to ATAGI included commercial-in-confidence dossiers from the pharmaceutical companies, GlaxoSmithKline (GSK) and CSL Biotherapies/Merck & Co Inc, summarising unpublished data relevant to the licensure of the respective rotavirus vaccines, Rotarix and RotaTeq, examined in this review. However, unpublished data that remains commercial-in-confidence have not been included in this review.

3.1.3 Inclusion and exclusion criteria

The inclusion criteria were based on the study question as follows:

Population/problem:	Infants or children (healthy subjects)
Intervention:	Oral administration of live attenuated rotavirus vaccines
Comparator:	No immunisation (in healthy subjects) OR Placebo immunisation (in healthy subjects)
Outcomes:	Various measures of efficacy and safety (see below)
Study design:	Randomised controlled trials or systematic reviews
Languages:	Any

The following specific exclusion criteria were applied:

- randomised controlled clinical trials of the efficacy and safety of other rotavirus vaccine(s) that are not available in Australia (ie. not registered by the Therapeutic Goods Association, TGA);
- study data provided as ‘commercial-in-confidence’;
- review articles with no original data.

3.2 Questions specifically addressed in this systematic review

The following outcomes regarding rotavirus vaccine efficacy and safety in infants or children were reviewed:

Efficacy of rotavirus vaccination of infants or children:

- a) Prevention of rotavirus gastroenteritis of any severity
- b) Prevention of severe rotavirus gastroenteritis
- c) Prevention of hospitalisation due to rotavirus gastroenteritis
- d) Prevention of emergency department visits for rotavirus gastroenteritis
- e) Prevention of GP or clinic visits for rotavirus gastroenteritis
- f) Prevention of acute gastroenteritis of any cause
- g) Prevention of rotavirus gastroenteritis in premature infants (gestational age <36 weeks)

Safety of rotavirus vaccination of infants or children:

The following adverse events were reviewed:

- a) Intussusception
- b) Fever

- c) Gastrointestinal symptoms (diarrhoea, vomiting)
- d) General symptoms (irritability)
- e) Death
- f) Any serious adverse events
- g) Adverse events in premature infants (gestational age <36 weeks)

3.3 Questions which were not systematically reviewed

The immunogenicity of rotavirus vaccines has not been reviewed, as the purpose of this review was to review safety and efficacy. The immune correlates of protection following rotavirus infection and disease are not completely understood and, in vaccine studies, levels of serum or mucosal antibody have not been predictive of protection against disease. In addition, the two licensed vaccines are composed of different vaccine viruses and may afford protection by eliciting different immune responses.⁴

The cost-effectiveness of rotavirus vaccines has not been reviewed as this is not within the mandate of the Australian Technical Advisory Group on Immunisation. The cost-effectiveness of vaccines in Australia is assessed by the Pharmaceutical Benefits Advisory Committee.

In addition to the information presented in this systematic review, ATAGI reviewed the best available evidence on the clinical disease and epidemiology of rotavirus disease in Australia, the prevalence of specific rotavirus serotype disease, and information regarding a rotavirus vaccine previously licensed in the United States (Rotashield[®]). This and other information is presented in the 9th edition of *The Australian Immunisation Handbook*, Chapter 3.18 Rotavirus (**Appendix A**) and contributed to the development of recommendations on the use of rotavirus vaccines.

3.4 Appraisal of included studies

The appraisal of studies included in the review was performed as set out in the NHMRC toolkit publication: “How to review the evidence: systematic identification and review of the scientific literature”.¹ Data from each randomised controlled study included in the review was extracted into a standardised data extraction form (see **Appendix B**) and assessed using the critical appraisal checklist and descriptive comparisons as described in the NHMRC handbook “How to review the evidence: systematic identification and review of the scientific literature”. The quality appraisal tables, together with level of evidence and grading of the body of evidence tables, are shown in **Appendix B**.¹⁻³

3.5 Assessment and application of scientific evidence

Application of NHMRC dimensions of evidence of clinical importance and relevance were made to all primary outcomes in included studies (including NHMRC levels of evidence and a quality assessment) as set out in the NHMRC toolkit publication: “How to use the evidence: assessment and application of scientific evidence” – Section 1² (see also **Appendix B**).

3.6 Assessment of the body of scientific evidence and links with guideline recommendations

Assessment of the body of scientific evidence was performed by using the methods described by the NHMRC pilot program “NHMRC additional levels of evidence and grades for recommendations for developers of guidelines”

(<http://www.nhmrc.gov.au/consult/index.htm>)³ (**Appendix B**). The link between the evidence and the guideline recommendation is made in **Appendix A**, Chapter 3.18 Rotavirus of the 9th edition of *The Australian Immunisation Handbook*, by using reference to the systematic review throughout the chapter sections discussing the available vaccines, recommendations for use of the vaccines, and precautions and special considerations for use of rotavirus vaccines.

4 Results

4.1 Search results and studies identified

There were 669 records retrieved by the database searches (EMBASE n=234, MEDLINE n=252, Cochrane Library databases n =183). All available abstracts were independently reviewed by two study authors. Following the removal of duplicates and the application of inclusion and exclusion criteria, relevant and possibly relevant studies were retrieved and reviewed for inclusion (n=22). Of these, 12 studies were identified for inclusion in the review and are listed in **Table 1**. 10 studies were excluded from the review for the reasons stated in **Table 2**.

4.2 Appraisal of included studies

Table 3 provides a summary of the study design and quality assessment for each of the included studies.

4.3 Assessment and application of scientific evidence

Assessment of the applicability of the evidence is presented in **Tables 4a-f**, for the clinical questions regarding vaccine efficacy, and in **Tables 5a-f**, for the clinical questions regarding vaccine safety. Where possible, grading of both the clinical importance and relevance has been included. Where efficacy analysis reported outcomes for subgroups where there were small numbers of cases in both the vaccine and placebo groups, such as for analysis by different rotavirus strains (serotypes), assessment of clinical importance and relevance was not performed.

4.4 Assessment of the body of evidence

Assessment of the body of evidence is presented in **Tables 6a and 6b**, and refers to the routine use of rotavirus vaccines in infants in Australia (**Appendix A**).

As described in **Table 3**, there were no studies of the currently licensed rotavirus vaccines in older infants and children, with the exception of the study Vesikari 2004a,⁵ in which 26 study participants were young children, and 33 participants were adults. As described in **Appendix A**, Chapter 3.18 Rotavirus of the 9th edition of *The Australian Immunisation Handbook*, the large clinical trials of the efficacy and safety of the currently available rotavirus vaccines were restricted to administration in young infants, with lower and upper age limits for vaccine doses. The reason for age-restricted use of the current vaccines stems from the association of intussusception with a previously licensed rotavirus vaccine, RotaShield[®], when vaccine was administered to older infants and children in the United States.

The studies included in this systematic review did not contain data regarding the efficacy or safety of rotavirus vaccines in premature infants (specific outcome g, see Methods section 3.2). The recommendation for the use of rotavirus vaccines in this subset of infants has been based on expert opinion, limited data presented in other publications,⁶ and limited data that was either commercial-in-confidence or presented

in the product information (PI) for both vaccines.^{7,8} Assessment of the body of evidence underpinning the recommendation for use of rotavirus vaccines in premature infants is described in **Tables 7a and 7b**.

4.5 The link between the evidence and recommendations in the 9th edition of *The Australian Immunisation Handbook*

The guideline recommendations are shown in **Appendix A**, Chapter 3.18 Rotavirus of the 9th edition of *The Australian Immunisation Handbook*. The link between the evidence reviewed here is stated in the NHMRC Grades of Recommendation after each section in the recommendations regarding use of the vaccine.

5 References

1. National Health and Medical Research Council (NHMRC). How to review the evidence: systematic identification and review of the scientific literature. Canberra: NHMRC, 1999.
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4. Franco MA, Angel J, Greenberg HB. Immunity and correlates of protection for rotavirus vaccines. *Vaccine* 2006;24:2718-31.
5. Vesikari T, Karvonen A, Korhonen T, et al. Safety and immunogenicity of RIX4414 live attenuated human rotavirus vaccine in adults, toddlers and previously uninfected infants. *Vaccine* 2004;22:2836-42.
6. Parashar UD, Alexander JP, Glass RI. Prevention of rotavirus gastroenteritis among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP) 2927. *MMWR - Morbidity & Mortality Weekly Report* 2006;55(RR-12):1-13.
7. Merck and Co Inc. Rotateq[®] Product Information. 2006.
8. GlaxoSmithKline. Rotarix[®] Product Information. 2007.
9. Saari TN, American Academy of Pediatrics Committee on Infectious Diseases. Immunization of preterm and low birth weight infants. *Pediatrics* 2003;112:193-8.

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