An evaluation of the Australian Rotavirus Surveillance Program

April R Roberts-Witteveen, Mahomed S Patel, Paul W Roche

Abstract

The Australian Rotavirus Serotyping Program (ARSP) serotypes rotavirus isolates obtained from stool samples sent from Australian laboratories. In collaboration with ARSP, the Australian Government Department of Health and Ageing evaluated the program for its utility and capacity to monitor effectiveness of the rotavirus vaccines recently introduced into the Australian National Immunisation Program. The system was described using ARSP annual reports and staff interviews. The attributes of the system were assessed by adapting standard guidelines for evaluating a surveillance system. Email surveys or face to face interviews were conducted with staff of ARSP, participating laboratories, rotavirus vaccine manufacturing companies and representatives of the Communicable Diseases Network Australia. The ability of the ARSP to monitor changes in rotavirus serotype epidemiology was assessed. ARSP serotypes rotavirus isolates received from participating laboratories at least bi-annually, with results being reported at least as often. Serotype analyses have informed formulation of rotavirus vaccines and contributed to forecasting the extent of outbreaks caused by novel serotypes. The ARSP will be able to monitor changes in rotavirus serotype epidemiology and identify probable vaccination failures. Enhancement of the representativeness and sensitivity of the system are needed for the data to remain useful in the public health context. Methods for transferring data between the program and state and territory health departments need to be developed. *Commun Dis Intell* 2008;32:326–332.

Keywords: evaluation, rotavirus, vaccination

Introduction

Rotavirus is the most common cause of hospitalisations of children with diarrhoea worldwide.[1] The majority of infections occur in children under 5 years.[2] In both developing countries and developed countries rotavirus incidence is high in infants.[3,4] Worldwide, human infections are most often caused by Group A rotaviruses, which consist of a genome encased by three protein layers. The outer capsid layer is made of the VP7 protein which contains VP4 protein 'spikes'. The VP7 glycoprotein and VP4 protease-sensitive protein carry the G serotype and P serotype specific antigens respectively. The middle capsid layer, the VP6 protein, expresses an antigen which determines the group and subgroup of the virus.[5] The Australian Rotavirus Surveillance Program (ARSP) performs serotyping of VP4 and VP7 proteins of rotavirus isolates sent from laboratories in several Australian states and territories. Serotyping rotavirus isolates is important to monitor the emergence of new rotavirus serotypes.

In Australia in 2006, rotavirus infections were estimated to cause approximately 10,000 hospitalisations annually at an estimated cost of $19 million. An additional 22,000 emergency department (ED) visits and 150,000 general practitioner (GP) visits were attributed to acute rotavirus gastroenteritis, costing over $11 million.[6] Rotavirus vaccines, Rotarix and Rotateq, were licensed for use in Australia in 2006. From 1 July 2007, all children will receive either Rotarix or RotaTeq vaccination as part of the national childhood vaccination schedule. The vaccines have been designed to provide protection against severe diarrhoea caused by serotypes G1, G2, G3 and G4. These serotypes cause at least 90% of infections worldwide.[5] Rotarix (developed by GlaxoSmithKline) is based on a live attenuated monovalent virus (serotype P1A[8]G1). It has an overall clinical efficacy of 95.8% (95% C.I. 89.6–98.7) against severe rotavirus disease caused by serotypes P[8]G1, P[4]G2, P[8]G3, P[8]G4 and P[8]G9. RotaTeq (developed by Merck) is a live pentavalent bovine-human reassortant strain containing G1, G2, G3, G4 and P1A antigens.[7] Trials in 11 countries including the United States of America, Finland and South American countries[1] demonstrated a clinical efficacy of 98.2% (95% C.I. 89.6–100) against severe rotavirus disease caused by serotypes G1, G2, G3, G4 and G9. Both Rotarix and Rotateq are administered orally and unlike the earlier vaccine RotaShield, neither were associated with increased risk of intussusception in phase 3 trials.[7,8]

The ARSP and the Australian Government Department of Health and Ageing agreed to a collaborative evaluation of the ARSP to describe the surveillance system, to assess its attributes and to determine if the ARSP provides surveillance data appropriate for the vaccine era. This paper reports key findings of the evaluation.

Methods

Face-to-face interviews with key ARSP staff were used to gather information about serotyping

rotavirus isolates and reporting. A flow chart was constructed to describe how samples are received by the ARSP, how stool samples are serotyped in the ARSP, and how data are managed. This was verified as accurate by the laboratory director (Figure).

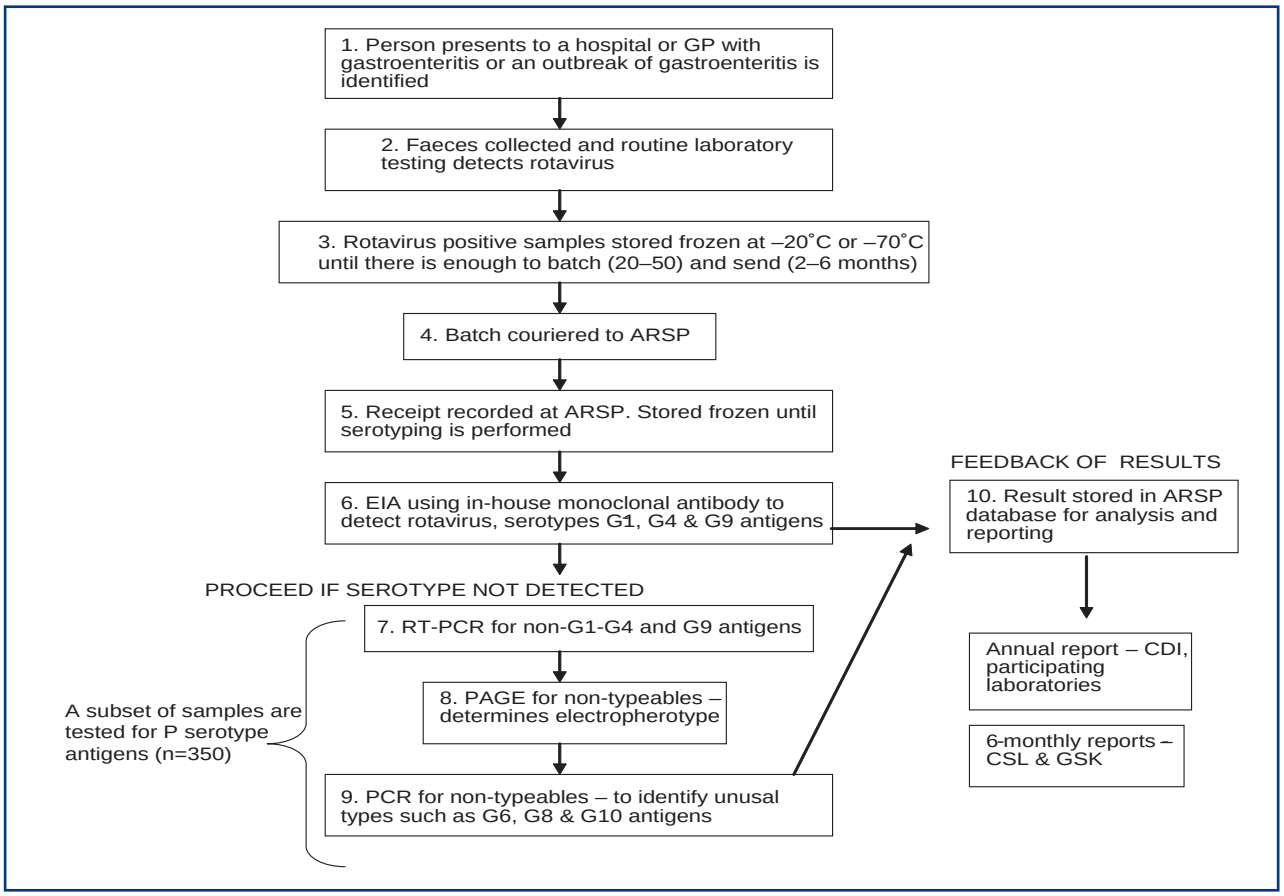
The assessment of the system attributes was adapted from the guidelines for the evaluation of the surveillance systems produced by the US Centers for Disease Control and Prevention.[9] Eleven attributes of the system were assessed. In this paper, the flexibility, sensitivity, representativeness, timeliness and usefulness of the ARSP will be reported, because of their relevance to the current situation of introduction of the rotavirus vaccines being introduced.

The 5 attributes of the ARSP system were defined as follows.

- Flexibility: the ability of the system to adapt to changing operating conditions and information and policy needs.
- Sensitivity: assessed for 3 different aspects of the ARSP:
  - the proportion of gastroenteritis stool samples that contained rotavirus;
  - the proportion of all rotavirus positive stool samples collected by each participating laboratory and which are sent to the ARSP for serotyping;
  - the ability of the ARSP to detect outbreaks, new or unusual strains, and infections acquired overseas.

  (Note: the ability of the ARSP to detect all rotavirus infections was not assessed as it was not a goal of the system.)
- Representativeness: how representative the isolates serotyped by the ARSP were of isolates from across Australia in terms of the age and location of the case from which the isolate was obtained and by comparing ARSP data to the:
  - published estimates of the number of cases of rotavirus occurring in Australia from hospitalisation data; and
  - number and age of rotavirus cases notified in the Northern Territory each year.
- Timeliness: the ability of the ARSP to produce results and reports in a manner which was judged as timely by stakeholders.
- Usefulness: the contribution of the ARSP to the prevention and control of rotavirus in Australia.

Figure. Flow chart of the system used by the Australian Rotavirus Surveillance Program to serotype rotavirus isolates and report on results



All stakeholders (Table) except ARSP staff were invited to participate in the evaluation by completing email surveys. Australian stakeholders were telephoned to ascertain if they would participate 1–2 days after the survey was emailed. If, after a specified return date, surveys were not completed, Australian participants were telephoned to determine if assistance was needed to complete the survey. International participants were contacted again via email.

Results

Description of the system

Participating laboratories sent stool samples to the ARSP with a unique sample code and the sex and age of the case from which it was obtained. This code allows samples to be linked to hospital data by the sending laboratory if needed.

Participating laboratories detect rotavirus using enzyme immunoassay (EIA) or latex agglutination tests. Samples of stool (0.05 mL–1.0 mL) containing rotavirus are sent to the ARSP. Nearly 60% (355/628) of samples are obtained from patients hospitalised with gastroenteritis though samples have been sent from non-hospitalised cases in outbreaks in the Northern Territory.

Upon receipt, the ARSP confirm that rotavirus is in the stool sample using an in-house monoclonal antibody (MAb) EIA, which also identifies common serotypes G1, G2, G3, G4 and G9. If rotavirus is not identified in the stool by the MAb EIA, there is no further testing. If rotavirus is detected but common serotypes are not identified, samples are genotyped by reverse-transcriptase polymerase chain reaction (RT-PCR).[10] If the serotype is not identified using EIA or RT-PCR, the RNA of the virus is analysed using polyacrylamide gel electrophoresis (PAGE) to determine if the electrophoretic pattern is similar to patterns of known serotypes.

The age and sex of a case, the date of specimen collection, the code associated with the sending laboratory and the EIA, RT-PCR and/or PAGE results are stored an Excel database. Stool samples are stored in locked freezers at the Royal Children's Hospital, Melbourne. The results of serotyping are published annually in *Communicable Diseases Intelligence* (CDI). The report is also forwarded to staff of vaccine manufacturing companies and participating laboratories. Data reported in the annual reports include the:

- number of stool samples received by ARSP (by month of receipt, and by collaborating laboratory);
- proportion and number of isolates of each serotype;
- age and gender of cases;
- geographic distribution of G serotypes in Australia, by state or territory; and
- whether isolates were associated with an outbreak.

Attributes

The proportion of staff from laboratories which contributed to the ARSP in 2004–05 who participated in the evaluation is shown in the Table. The low response rate from staff of laboratories who had previously participated in the program reflects that the questionnaire was sent to a retired laboratory staff or an expired email address, and that an appropriate participant from that laboratory could not be located.

Table. Stakeholders of the Australian Rotavirus Surveillance Program who were invited and surveyed, and attributes they assessed in the evaluation, 2006

Stakeholder	Number invited	Number participated	Attributes assessed
Staff from laboratories which currently participate	8	7	Flexibility, representativeness, timeliness, usefulness, sensitivity
Staff from laboratories which participated previously	5	2	Flexibility, representativeness, timeliness, usefulness, sensitivity
Vaccine manufacturing companies	2	2	Timeliness, usefulness
CDNA representatives of some states and territories*	3	3	Flexibility, representativeness, timeliness, usefulness, sensitivity
International experts in rotavirus surveillance	11	1	Flexibility, representativeness, timeliness, usefulness, sensitivity
ARSP staff (or annual reports)	NA	NA	Representativeness, flexibility, sensitivity, timeliness

* Communicable Diseases Network Australia representatives were asked to participate in states and territories where rotavirus was notifiable in 2006.

Flexibility

Based on experience, the ARSP laboratory director considers the current system as being flexible to adapt to changes in the number of laboratories participating, the number of samples serotyped, and the amount of funding received.

Between 1999 and 2004, the greatest number of laboratories participating in the ARSP was in 1999–2000 with 17 laboratories and 1,126 samples serotyped. The least number of laboratories participating was 7 in 2002–03 when 573 samples were serotyped. In the evaluation, 5 of 7 laboratories reported that ARSP can process as many samples as are sent, indicating that the participating laboratories perceived ARSP to be flexible.

Samples from outbreaks can be serotyped by ARSP whenever they are received. They are reported faster than results from routine serotyping, at no additional cost. The system is able to serotype new or unusual serotypes within 3 months by MAbs if these exist for the serotype, or by RT-PCR. The emergence of small numbers of the unusual serotypes G9 and G12 in 2001–02 and 2005–06 respectively was detected by the program.[4,10]

Representativeness

In 2004–05 only 5 of 8 Australian states and territories contributed to the ARSP. Representativeness of rural and remote locations could not be assessed in this study because the residential addresses of cases are not recorded by the ARSP. Stool specimens of cases occurring in rural and remote areas may be less likely to be tested by participating laboratories, which are mainly located in larger towns and cities.

The ARSP does not collect information on Indigenous status so neither the prevalence of serotypes, nor the burden of rotavirus disease in Indigenous populations could be estimated.

The proportion of hospital in-patients and out-patients from whom rotavirus samples were obtained was ascertained from laboratories involved in the Program in 2005. Of 7 laboratories, an average of 60% of rotavirus isolates came from in-patients. The proportion of in-patients and out-patients with samples tested by the ARSP was compared to estimations of the proportion of rotavirus hospital in-patients and out-patients in Australia. Galati estimated that for every case hospitalised for rotavirus, 2.2 visited an emergency department as an out-patient.[6] In the sample of rotavirus cases who had isolates serotyped by the ARSP, the ratio of hospitalisations to ED visits was 1:0.75. The ARSP therefore serotype a greater proportion of isolates from in-patients and may not be representative of non-hospitalised cases.

The age distribution of the hospitalised cases based on ARSP data differs from that of ICD-coded hospital separation data. In hospital separation data, most of the hospitalised cases (39.5%) were children aged between 12 and 23 months[6] while in ARSP data, most children (46.6%) were aged between 0 and 11 months. ARSP may not serotype a representative sample of children older than one year, who may be less likely to be hospitalised.

Differences reported by the ARSP and Galati[6] about the proportion of rotavirus cases that are hospitalised and the age distribution of cases, may be explained by differences in methods used to obtain the results and the populations sampled. Galati's estimates were based on hospitalisation and pathology data which were linked to obtain the rotavirus attributable fraction of all hospitalised gastroenteritis cases. This rotavirus attributable fraction was used to make estimations of the number of rotavirus cases, their ages, and the severity of their infection. This methodology may introduce misclassification biases associated with ICD coding. In contrast, the sample population of the ARSP is cases hospitalised, in mainly public hospitals, which are laboratory-confirmed.

The representativeness of the isolates received by the ARSP of all notified cases was assessed for cases in the Northern Territory. In 1999 and 2000, the proportion of notified rotavirus cases that had isolates serotyped by the ARSP ranged from between 18% and 20%, and from 2001 to 2005, between 39% and 60%.

The ARSP sample is representative of rotavirus from hospitalised cases in the areas where participating laboratories are located. It is not known if the isolates serotyped are representative of isolates causing disease in Indigenous populations, rural and remote areas and areas where there is no participating laboratory.

Sensitivity

Laboratories participating in 2004–05 detected rotavirus in between 3.3% and 17.6% of all stool samples they collected. Four of seven collaborating laboratories sent at least 90% of all stool samples that were positive for rotavirus to the ARSP for serotyping. One laboratory sent only 14% of stool samples in which rotavirus was detected. Overall, the ARSP received isolates from 63% of all rotavirus positive samples collected by participating laboratories in 2005. It is possible that a selection bias

was introduced into the sample of isolates sent by laboratories to be serotyped by the ARSP. It is not clear how this impacts the sensitivity of ARSP.

The sensitivity of the system to detect new or unusual serotypes of rotavirus is difficult to quantify because the true number of unusual serotypes circulating in Australia is not known. Nonetheless, in the last 5 years small numbers of serotypes G9 and G12 have been detected by the ARSP. These serotypes had not previously been observed in Australia.

The sensitivity of the ARSP surveillance system to provide information about whether a serotype was acquired overseas or is endemic in a particular Australian sub-population is limited. The ARSP does not collect data about travel, place of residence or Indigenous status for rotavirus cases. The ARSP does not have the sensitivity to detect rotavirus outbreaks independent of notification by public health or laboratory staff, as expected of laboratory surveillance. Outbreaks may be detected retrospectively by sorting data by date of collection and sending laboratory.

Timeliness

Timeliness of serotyping

As serotyping results do not affect the clinical management of patients, the time taken for results to reach the participating laboratory was not an important issue for stakeholders. On the other hand, the time taken to serotype samples collected during an outbreak increased the usefulness of results. The ARSP serotyped rotavirus isolates from two outbreaks in 2004–05 and reported on the results within 6–7 days. The relevant jurisdiction could then anticipate the extent and severity of the outbreak based on the uniqueness of the serotypes, and plan an appropriate response.

Timeliness of reporting

The ARSP annual report is published in CDI approximately 6 months after the end of the reporting period. A summary of serotyping results is prepared every 6 months and distributed to vaccine manufacturing companies.

Stakeholders were asked how frequently they would like reports of serotyping results after the introduction of the rotavirus vaccination program. Staff of participating laboratories who review the results only for information would like reports every 6 months. Communicable Diseases Network Australia representatives had different opinions about the requirements for reporting; 1 jurisdiction was satisfied with receiving serotyping results annually, 1 would find 6 monthly reports useful. Representatives of vaccine companies were satisfied with 6 monthly reports. The annual report was viewed as an important means of communication with international stakeholders.

Usefulness

In terms of usefulness in the control and prevention of the rotavirus in Australia, the ARSP has had relatively little impact to date. In the vaccine era however, the baseline prevalence data of rotavirus serotypes circulating in Australia collected by the ARSP in previous years will be used when vaccine effectiveness is assessed.

The perceived usefulness of ARSP results to stakeholders varies. One participating laboratory reported using the results to validate their own routine diagnostic test. One participant mentioned the usefulness of serotyping at the beginning of outbreaks to forecast the potential impact and extent of the outbreak according to if the serotype is new in a population. For vaccine companies, the most important use of ARSP data has been to inform the formulation of vaccines for use in Australia by determining if vaccine strains match circulating serotypes.

Discussion

The evaluation showed that, in the pre-vaccine era, the ARSP has provided baseline data on the serotypes of rotavirus causing hospitalisation in children in Australia with a sufficiently timely, flexible and sensitive system. Since mid-2007 vaccines have been available for use in preventing rotavirus infections in Australian children. In the vaccine era, national surveillance of rotavirus will provide notification data and information that could be used to assess the impact of vaccination, the rate of vaccination failures, changes in rotavirus epidemiology and the emergence of replacement serotypes. Data provided by the ARSP will contribute to the latter functions of national surveillance and will provide epidemiologists in Australia the unique opportunity to evaluate the impact of both Rotarix and RotaTeq in a single country.

Based on past experience of adapting to changing participation rates and new stakeholders, the ARSP will adapt to meet changing needs of stakeholders in the vaccine era and the greater demand for serotyping. Collaboration with new stakeholders such as public health personnel and staff of health departments will create new demands on the ARSP.

In order to provide valid data that could be used to assess the impact of rotavirus vaccines, representative sampling is required. Approaches to increasing the number of laboratories participating in the pro-

gram should implemented. Representative sampling of all states and territories, rural and remote areas, and Indigenous populations should be an aim of the program.

There was only limited patient demographic information available to the ARSP in the pre-vaccine era but data collected after rotavirus becomes a notifiable condition, will increase the value of serotyping data. Travel history information may explain the origin of unusual strains, locality information may be used to identify rotavirus outbreaks, and Indigenous status data will provide information data on the strains circulating in Indigenous populations. These data will also enable the effectiveness of vaccines to be determined in Australian sub-populations.

In the vaccine era, interest in rotavirus serotyping results will increase so results should be reported more often than currently. Isolates obtained from vaccinated children should be rapidly serotyped to enhance investigation of suspected vaccination failure. Timely identification of the serotypes in outbreaks will be important as rotavirus vaccine coverage increases, the incidence of disease decreases, and the risk of outbreaks caused by non-vaccine serotypes becomes increasingly important.

A key challenge is for the role of the ARSP to be clarified, clearly communicated to all stakeholders, and for the data it provides to be integrated into surveillance systems. Data flow from the ARSP to either public health units or state health departments should be developed in collaboration with each jurisdiction. If serotype data are matched to notification data, both the sensitivity of the ARSP system and the usefulness of the data for public health action will increase.

Conclusions

Australia is in the unique position of being able to evaluate the impact of two licensed vaccines in a population where the baseline epidemiology of rotavirus serotypes has been documented. The system is flexible, and can perform timely serotyping and reporting of data. The ARSP should strengthen the representativeness of its data in collaboration with state and territory public health systems to increase its sensitivity.

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Author details

Ms April R Roberts-Witteveen[1]
Dr Mahomed S Patel[2]
Dr Paul W Roche[3]

1. Master of Applied Epidemiology Scholar, Australian National University, Acton, Australian Capital Territory
2. Assoc Professor, National Centre for Epidemiology and Population Health, Australian National University, Australian Capital Territory
3. Senior Epidemiologist, Surveillance Policy and Systems Section, Australian Government Department of Health and Ageing, Canberra, Australian Capital Territory

Corresponding author: Mrs April Roberts-Witteveen, GPO Box 9848, Canberra, ACT 2601. Telephone: +61 2 6289 2721. Facsimile: +61 2 6289 2600. Email: lirpa_r@yahoo.com

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